The First Chinese Microcirculation Week

October 28-30, 2016

Beijing, China

Co-President:

Professor Qi-Min Zhan

Professor You-Yi Zhang

President:

Professor Jing-Yan Han

第一届中国微循环周

2016 年 10 月 28-30 日

中国 北京

会议指南/论文摘要集

大会共同主席：

詹启敏 教授

张幼怡 教授

大会主席：

韩晶岩 教授

Contents

Dear Colleagues and Friends,

On behalf of the first Chinese microcirculation week organizing committee, I warmly welcome scientists, experts and scholars, to attend this conference.

Microvessels include arterioles, capillaries and venules, which form a network accounting for 90% of blood vessel system in the body, and represent a location wherein materials exchange between inside and outside the blood vessels takes place. Microcirculation is a collective word covering all the circulatory events present in the microvessels area, such as blood circulation, lymph circulation, circulation of water, gas, nutrition, and metabolites. Microcirculation disturbance is a critical scenario in a range of major diseases, including cardiac cerebral vascular diseases, diabetes vascular complication, cancer, trauma, shock, surgery injury, ischemia and reperfusion injury, burn, and crush injury, among others. Microcirculation disturbance is a multifaceted process involving altered blood velocity and vessel diameter, interaction between leukocytes and vascular endothelium, mast cell degranulation, plasma albumin leakage, hemorrhage, and thrombosis. Studies have shown that a wide spectrum of mechanisms participate in mediating of microcirculation disturbance, such as energy metabolism, oxidative stress, endoplasma reticulum stress, inflammatory cytokine release, expression of selectin, adhesive molecules,and receptors, signal transduction within cells, necrosis, apoptosis and autophage. This may explain why strategy using a single component targeting a single link is so far unsatisfied in clinic for treatment of microcirculation disturbance related diseases.
Chinese medicine is a medical system which has been applied in clinic for more than 2000 years with a theory effective for guiding clinic practice, a special diagnosis and therapy strategy (treatment based on syndrome differentiation). Compound Chinese medicine contains multiple ingredients and thus has a potential to interfere microcirculation disturbance by targeting multiple links. In China, Chinese medicines have been used in clinic to cope with microcirculation disturbance related diseases with obvious effectiveness, such as cardiac ischemia and reperfusion injury, ischemic stroke, diabetes vascular complication, shock and cancer. Some of compound Chinese medicines have passed phase II or III clinical trials of FDA in USA. The mechanisms for the effects of these medicines have been partly clarified

The first Chinese microcirculation week has been hold in Peking University Health Science Center, October 28-30, 2016, in the hope to construct a platform for exchange between microvesseles and large vesseles, microcirculation and system circulation, basic research and clinic practice, Chinese medicine and western medicine, and overseas and domestic, thus promoting spreading of the gain in the research of microcirculation and Chinese medicine. This conference is supported and sponsored by Chinese Society of Pathophysiology Microcirculation Professional Committee, Shock Professional Committee, and Vascular Disease Professional Committee, Chinese Society of Microcirculation Phlegm Stasis Professional Committee, Diabetes and Microcirculation Professional Committee, Peripheral Vascular Disease

Professional Committee, Shock Professional Committee, Cerebral Vascular Disease Professional Committee, Chinese Society of Integration of Chinese and Western Medicine Microcirculation Professional Committee, and World Federation of Chinese Medicine Societies Qi and Blood Professional Committee.

The participants of this conference come from various provinces of China, USA, UK, Hungary, Japan, Thailand, and Australia, among them 26 experts are invited for the Plenary Lecture, 3 experts will give education lecture, 45 experts and young scholars will present their works at 8 symposiums, 20 scholars are selected to give free oral presentation along with tens of posts for exchange.

I look forward to success of this conference in promoting exchange between Chinese and western medicine in microcirculation, as well as between overseas and domestic scholars.

Wish every attendee a happy time in Beijing.

Qi-Min Zhan M.D., Ph.D.
Co-President, the First Chinese Microcirculation Week
President, Peking University Health Science Center
President, Chinese Society of Microcirculation

You-Yi Zhang M.D., Ph.D.
Co-President, the First Chinese Microcirculation Week
Professor, Key Laboratory of Vascular Cardiovascular Sciences, Ministry of Education / Peking University Institute of Cardiovascular Sciences / Institute of Vascular Medicine. Peking University Third Hospital
President, Chinese Association of Pathophysiology

Jing-Yan Han M.D., Ph.D.
President, the First Chinese Microcirculation Week
Chairman and Professor, Department of Integration of Chinese and Western Medicine School of Basic Medical Sciences, Peking University
Vice-President, Chinese Society of Microcirculation

Organizer

Chinese Association of Pathophysiology

Professional Committee of Microcirculation

Society of Vascular Medicine

Society of Shock

Chinese Society of Microcirculation

Professional Committee of Phlegm-Statsis

Professional Committee of Diabetes and Microcirculation

Professional Committee of Vascular Disease

Society of Shock

Professional Committee of Vascular Disease

Chinese Association of Integraive Medicine

Professional Committee of Microcirculation

World Federation of Chinese Medicine Societies

Specialty Committee of Qi-Blood

Undertaker

Department of Integration of Chinese and Western Medicine, Peking University Health Science Center

Tasly Microcirculation Research Center, Peking University Health Science Center

主办团体	中国病理生理学会	微循环专业委员会
		血管医学专业委员会
		休克专业委员会
	中国微循环学会	痰瘀专业委员会
		糖尿病与微循环专业委员会
		周围血管疾病专业委员会
		休克专业委员会
		脑血管病专业委员会
	中国中西医结合学会	微循环专业委员会
	世界中医药学会联合会	气血专业委员会

承办单位 北京大学医学部中西医结合学系

北京大学医学部天士力微循环研究中心

Co-President：
Qi-Min Zhan, You-Yi Zhang

President：
Jing-Yan Han

Organizing Committee

Qi-Min Zhan, You-Yi Zhang, Er-Dan Dong, Ping Li, Nai-Feng Liu, Yu-Cheng Guo, Jing-Yan Han, Yong Jiang, Ke-Sheng Dai, Qiao-Bing Huang, Yue-Hong Zheng, Si-Feng Chen, Xue-Long Jin, Zi-Lin Sun, Qing-Fu Zhang, Xue-Jun Li

Scientific Committee

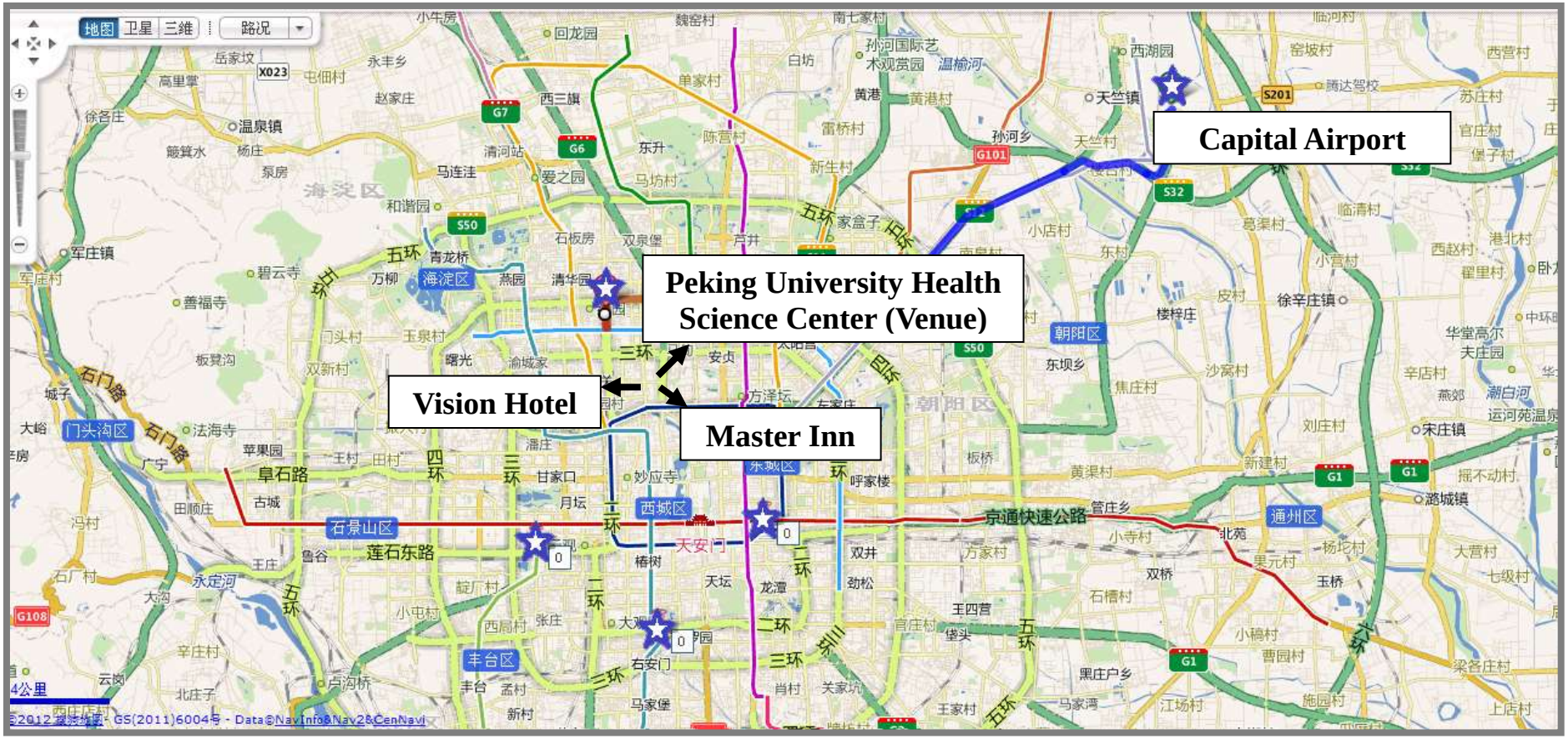
Yu-Ying Liu, Shi-Jun Wang, Yu-Zhen Li, Xian-Zhong Xiao, Liang-Ming Liu, Gang Jin, Gang-Min Ning, Chun-Yu Niu, Bao-Liang Sun, Fang-Tian Dong, Cheng-Xing Shen, Hai-Bin Gong, Jian-Qun Han, Shi-Shen Jiang, Ai-Ling Li, Dong-Ye Li, Lie-Ping Li, Xue-Qi Li, Yin-Qing Li, Zhong-Ming Xie, Jun Yang, Li Yang, Hua-Ye Zhang, Jian Zhang, Ju-Mei Li, Xian-Hua Zuo, Huai-Lian Guo, Jian-Bo Wu, Dong Han, Zi-Gang Zhao, Li Huang, Jian-Xun Liu, Da-Zhuo Shi, Ming-Jun Zhu, Hao Xu, Yan Lei, Shuang-Yan Zhang, Hua Zhang, Bao-Xue Yang, Ming Xu, Zi-Jian Li, Chuan-She Wang

International Scientific Committee

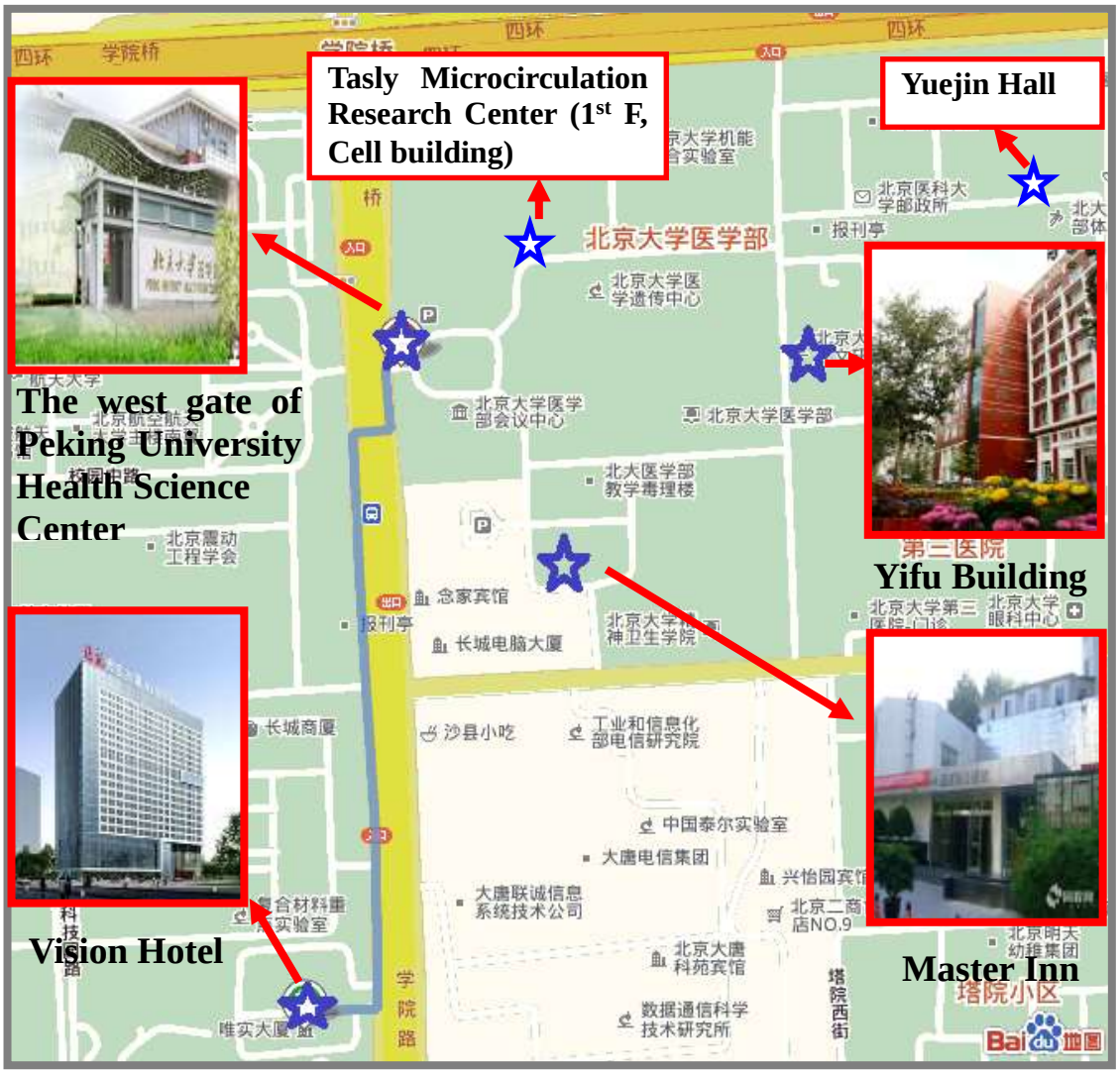
Qi-Min Zhan, You-Yi Zhang, Er-Dan Dong, Yu-Zhu, Ping Li, Nai-Feng Liu, Ceng-Yu Guo, Jing-Yan Han, Yong Jiang, Ke-Sheng Dai, Qiao-Bing Huang, Yue-Hong Zheng, Fang-Tian Dong, Jie Du, Yu Huang, Si-Feng Chen, Xue-Long Jin, Qing-Fu Zhang, Zi-Lin Sun, Jian-Gang Shen, Xian Wang, Xue-Jun Li, Gerald A. Meininger, Michael A. Hill, Giovanni E. Mann, Geraldine Clough, Nicola J. Brown, Akos Koller, Roland N. Pittman, Sarah Yuan, Jerome W. Breslin, Tailoi Chan-Ling, Suthiluk Patumuraj, Hidekazu Suzuki, Makoto Suematsu, Masato Yasui, Hirosi Nagata, Toshio Nakaki

Traffic

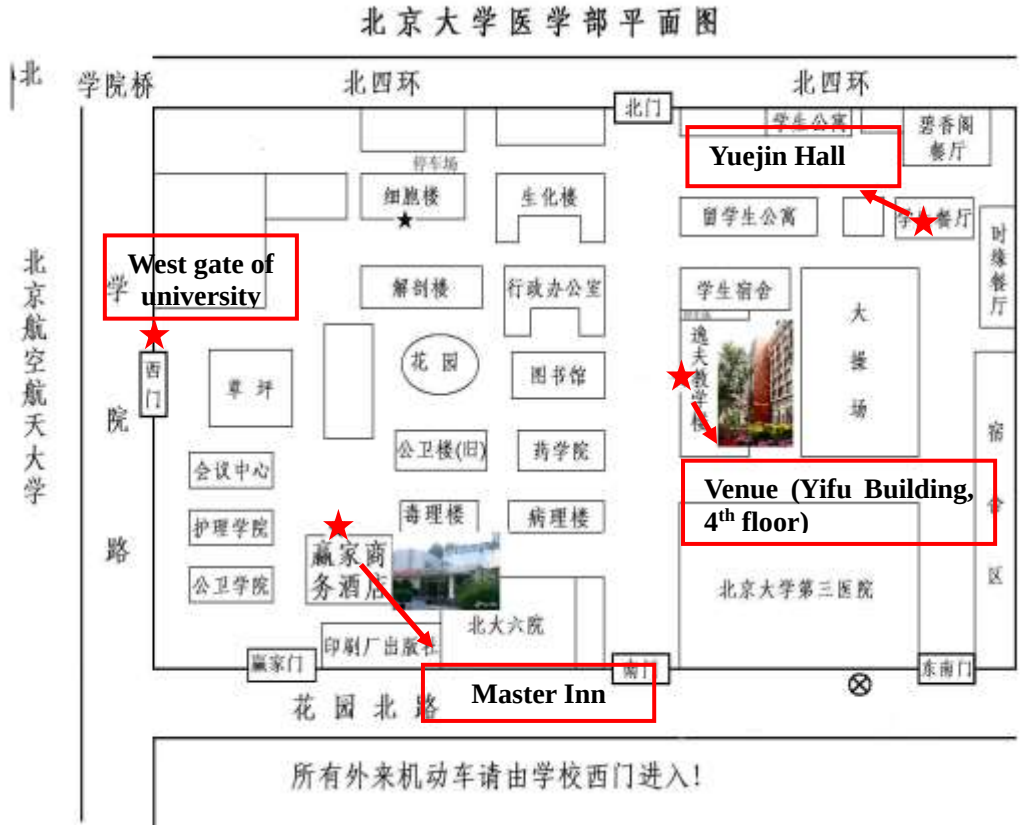
交 通 图

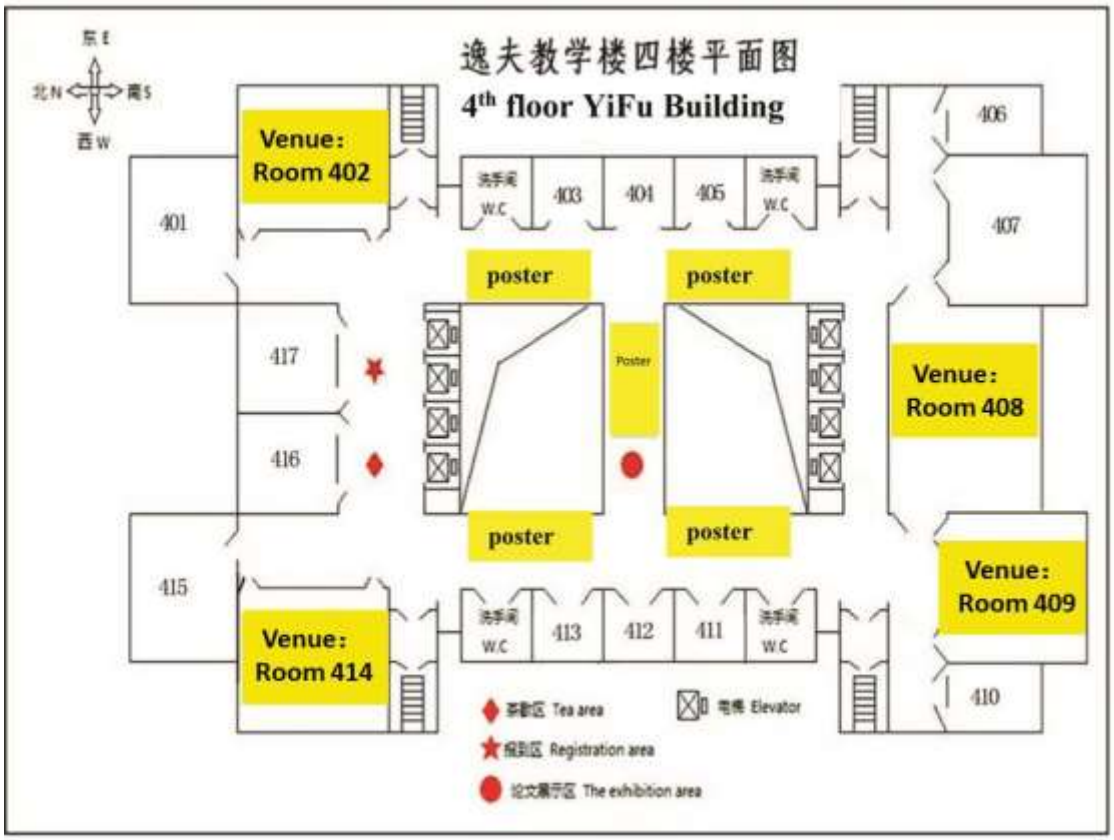

Capital Airport
Peking University Health Science Center (Venue)
Vision Hotel
Master Inn

Venue and Hotel
会场、宾馆、宴会地点



Peking University Health Science Center





Schedule

28th Oct Friday	**Room 414** Yifu Building, Campus of Peking University Health Science Center	**Room 402** Yifu Building, Campus of Peking University Health Science Center
10:00-12:00	**Registration**	
12:00-13:00	**Lunch** 2nd Floor Master Inn	
13:00-15:00	**Symposium 1** **Brain microcirculation and cerebral vascular diasease** Chair: Xue-Long Jin, Huai-Lian Guo S-1-1 Paul Fraser S-1-2 Xue-Long Jin S-1-3 Sheepsumon Viboolvorakul S-1-4 Lei-Lei Mao S-1-5 Yong-Bo Zhang S-1-6 Jing-Man Song	**Symposium 2** **Cardiovascular Disease and Coronary Microcirculation** Chair: Ming Xu Yu-Zhen Li S-2-1 Zi-Jian Li S-2-2 Ming Xu S-2-3 Xiao-Hong Wei S-2-4 Bao-Hong Jiang S-2-5 Wan-Li Shen
15:00-15:10	**Tea Break**	
15:10-15:40	**Plenary Lecture 1** **Hidekatsu Suzuki** Chair: Geraldine Clough	**Plenary Lecture 2** **Xue-Jun Li** Chair: You-Yi Zhang
15:40-16:10	**Plenary Lecture 3** **Huang An** Chair: Akos Koller	**Plenary Lecture 4** **Jerome W. Breslin** Chair: Bao-Xue Yang
16:10-16:40	**Plenary Lecture 5** **De-An Guo** Chair: Suthiluk Patumraj	**Plenary Lecture 6** **Roland N. Pittman** Chair: Tailoi Chan-Ling
16:40-17:10	**Plenary Lecture 7** **Nicola J. Brown** Chair: Gerald A. Meininger	**Plenary Lecture 8** **Ke-Sheng Dai** Chair: Nai-Feng Liu
17:15-17:20	**Group Photo** Out of 1st floor, Yifu Building	
18:00-19:30	**Opening Reception**	

19:40-20:10	**Council Meeting** Professional committee of the microcirculation, China pathophysiological society	
20:10-20:40		**Council Meeting** Specialty Committee of Qi-Blood, World Federation of Chinese Medicine Societies
20:40-21:10	**Council Meeting** Professional Committee of Phlegm-Stasis, China society of microcirculation	
21:10-21:40		**Council Meeting** Professional Committee of Microcirculation, Chinese Association of Integrative Medicine

29th Oct Sturday	**Room 414** Yifu Building, Campus of Peking University Health Science Center	**Room 402** Yifu Building, Campus of Peking University Health Science Center	**Room 408** Yifu Building, Campus of Peking University Health Science Center
8:00-10:00	**Symposium 3** **Shock** Chair: Yong Jiang Paul Fraser S-3-1 Hui Jin S-3-2 Li-Na Jiang S-3-3 Kai Sun S-3-4 Peng-Yun Li S-3-5 Yun-Pei Zhang S-3-6 Abbas Muhammad	**Symposium 4** **Hemorrhage-Thrombus** Chair: Ke-Sheng Dai Jian-Bo Wu S-4-1 Jin-Cai Luo S-4-2 Li-Qun Wang S-4-3 Rong Yan S-4-4 Guo-Qing Zheng S-4-5 Dong Zhao S-4-6 Qi Fang	**Free Oral Presentation 1** Chair: Bao-Liang Sun Yue-Hong Zheng O-1-1 Xiang-Yu Zhou O-1-2 Xiao-Hua Guo O-1-3 Lu Tie O-1-4 Wen Yu O-1-5 Ding Zhao O-1-6 Shuang-Shuang Zhang O-1-7 Wei-Ling Wang O-1-8 Sukpat Supakanda O-1-9 Zong-Yong Zhang O-1-10 Li-Min Zhang
10:00-10:10	**Tea Break**		
10:10-10:40	**Plenary Lecture 9** **Suthiluk Patumraj** Chair: Fu long Liao	**Plenary Lecture 10** **Yong Jiang** Chair: Nicola J. Brown	
10:40-11:10	**Plenary Lecture 11** **Qiao-Bing Huang** Chair: Jerome W. Breslin	**Plenary Lecture 12** **Geraldine Clough** Chair: Makoto Suematsu	
11:10-11:40	**Plenary Lecture 13** **Giovanni E. Mann** Chair: Toshio Nakaki	**Plenary Lecture 14** **Si-Feng Chen** Chair: Masato Yasui	
11:40-12:10	**Plenary Lecture 15** **Makoto Suematsu** Chair: Giovanni E. Mann	**Plenary Lecture 16** **Gianfranco D Alpini** Chair: Qiao-Bing Huang	
12:10-13:00	**Lunch** 3th Floor Yue-Jin Hall		
13:00-	**Poster**		

14:00	Yifu Building, Campus of Peking University Health Science Center		
14:00-16:00	**Symposium 5** **Diabetes and Microcirculation** Chair: Qiao-Bing Huang Akos Koller S-5-1 Fan-Yin Meng S-5-2 Amporn Jariyapongskul S-5-3 Bing-Chen Liu S-5-4 Lin Yao S-5-5 Ping Gu	**Symposium 6** **Qi-Blood** Chair: Shi-Jun Wang Hao Xu S-6-1 Yuan-Yuan Chen S-6-2 Hong-Li Wang S-6-3 Min Wang S-6-4 Yuan-Chen Cui S-6-5 Qian Hua	**14:00-14:30** **Education lecture 1** **脏器微循环的研究方法** **Yu-Ying Liu** Chair：Dong Han **14:30-15:30** **Education lecture 2** **心脑微循环障碍与中医药** **Jing-Yan Han** Chair：Yi-Ning Huang **15:30-16:00** **Education lecture 3** **Microcirculation 的投稿和常见问题** **Geraldine Clough** Chair: Jian-Bo Wu
16:10-16:20	**Tea Break**		
16:20-16:50	**Plenary Lecture 17** **Jing-Yan Han** Chair: Hiroshi Nagata	**Plenary Lecture 18** **Akos Koller** Chair: Roland N. Pittman	
16:50-17:20	**Plenary Lecture 19** **Gerald A. Meininger** Chair: Qi-Min Zhan	**Plenary Lecture 20** **Tailoi Chan-Ling** Chair: Yong Jiang	
17:40-19:40	**Dinner**		

30th Oct Sunday	**Room 408** Yifu Building, Campus of Peking University Health Science Center	**Room 402** Yifu Building, Campus of Peking University Health Science Center	**Room 409** Yifu Building, Campus of Peking University Health Science Center
8:00-10:00	**Symposium 7** **Blood stasis and Phlegm-stasis** Chair: Yan Zhu Yan Lei S-7-1 Mei-Xue S-7-2 Jing-Na Deng S-7-3 Yan Zhu S-7-4 Chun-Shui Pan S-7-5 Wei Li S-7-6 Lei Li	**Symposium 8** **New Technique** Chair: Gang-Min Ning Feng Han S-8-1 Feng Han S-8-2 Ruo-Fan Wang S-8-3 Xia-Bin Huang S-8-4 Jing Li S-8-5 Ming-Ming Gao S-8-6 Xiang Li	**Free Oral Presentation 2** Chair: Zi-Gang Zhao Qing-Fu Zhang O-2-1 Di Nan O-2-2 Ying-Li Yu O-2-3 Hou-Yuan Hu O-2-4 Yan Pan O-2-5 Lei Lei O-2-6 Yong-Xia Wang O-2-7 Xue-Hui Zhang O-2-8 Ya-Qian Huang O-2-9 Wen-Long Xue O-2-10 Shu-Xian Han
10:00-10:10	**Tea Break**		
10:10-10:40	**Plenary Lecture 21** **Hirosi Nagata** Chair: Hong-Quan Zhang	**Plenary Lecture 22** **Jian-Bo Wu** Chair: Jun-Bao Du	
10:40-11:10	**Plenary Lecture 23** **Michael A. Hill** Chair: Jian-Bo Wu	**Plenary Lecture 24** **Masato Yasui** Chair: Xue-Jun Li	
11:10-11:40	**Plenary Lecture 25** **Toshio Nakaki** Chair: Jing-Yan Han	**Plenary Lecture 26** **Gang-Min Ning** Chair: Ke-Sheng Dai	
11:40-12:10	**Closing Ceremony**		
12:10-13:10	**Lunch**		

Notice for attendees

1. Date: October 28 (Friday) – 30 (Sunday)
2. Venue: Room 402, 408, 409 & 414, Yifu Building, Peking University Health Science Center
3. Registration:
   1) Overseas attendees, and part of domestic attendees
      October 28 (Friday), 9:00-11:30
      Vision hotel, 1st floor, lobby (No.39, Xueyuan Road, Haidian District, Beijing.)
   2) Others of domestic attendees who need accommodation services.
      October 28 (Friday), 9:00-11:30
      Master Inn, 1st floor, lobby (No.38, Xueyuan Road, Haidian District, Beijing.)
   3) Attendees who do not need accommodation services or register after October 28
      October 28 (Friday), 12:20-17:00
      October 29 (Saturday), 7:40-17:00
      October 30 (Sunday), 7:40-17:00
      In front of room 402 and 414 on the 4th floor of Yifu Building, Peking University Health Science Center, No.38, Xueyuan Road, Haidian District, Beijing. (Contacts: Yang Zhang, Phone: 13810078145)
4. Conference fee
   1) Domestic attendees: 1200 RMB; Overseas attendees: 200US$
      Conference fee includes Conference Guide, Proceedings, Tea break, Welcome Reception, Lunches and Dinners
   2) Students: 600 RMB (with valid documentation)
   3) Payment: Cash only when registration. Remittance to the following account before October 21, please be sure to indicate your name, employer, phone number, The first Chinese Microcirculation week.
      Account Name: World Federation of Chinese Medicine Societies
      Deposit bank: Bank of communications, Beijing Hui Road Branch
      Account number: 110060971018002604480024
5. Hotel (at your own expense)
   1) Vision hotel (www.weishihotel.com, service@weishihotel.com)
      No.39, Xueyuan Road, Haidian District, Beijing. Phone: 0086-10-62308899

Rooms: Standard Room, Twin

One person: RMB 580/night (1 breakfast included)

Two person: RMB 650/night (2 breakfast included)

Deluxe Standard, One

One person: RMB 620/night (1 breakfast included)

2) Master Inn

No.38, Xueyuan Road, Haidian District, Beijing. Phone: 0086-10-82320101

Rooms: Standard Room, Twin

One person: RMB 268/night (breakfast included)

Two person: RMB 134/night/person (breakfast included)

Deluxe Standard, Twin

One person: RMB 388/night (breakfast included)

Two person: RMB 194/night/person (breakfast included)

3) Other hotel near Peking University Health Science Center

All season hotel (No.2, Zhixin Village, HuanYuan Road, Haidian District, Beijing, 010-82020101)

Hanting hotel (No.31, Xueyuan Road, Haidian District, Beijing, 010-82326688)

Haiyou hotel (No.265, Forth Ring South Road, Haidian District, Beijing.)

6. Repast:

1) October 28 (Friday)

Lunch: Master Inn (2nd floor), 12:00-12:50

Opening Reception: Master Inn (2nd floor), October 28 (Friday), 18:00 - 19:30

2) October 29 (Saturday)

Breakfast: In the accommodated hotel , 7:00-7:40 (with room card)

Lunch: Yuejing hall of Peking University Health Science Center (3rd floor), 12:00-13:00

3) October 30 (Sunday)

Breakfast: In the accommodated hotel, 7:00-7:40 (with room card)

Lunch: Master Inn (2nd floor), 12:00

7. Transport:

A. Airport to Vision hotel or Master Inn

By taxi: about RMB 110

B. Beijing railway station to Vision hotel or Master Inn

By taxi: about RMB 50

By subway: subway line No.2 to "Yong-he-gong lama temple" station, change line No.5 to "Hui-xin-xi-jie-nan-kou" station, change line No.10 to "Xi-tu-cheng" station, Vision hotel is about 100 m to the north, while Master Inn in Peking University Health Science Center is about 400 m to the north.

C. Beijing west railway station to Vision hotel or Master Inn

By taxi: about RMB 40

By bus: bus No.47 to "Xue-yuan-qiao east" station, the north gate of Peking University Health Science Center is on the opposite side of the road.

D. Beijing south railway station to Master Inn or Vision hotel

By taxi: about RMB 80

By subway: subway line No.4 to "Hai-dian-huang-zhuang" station, change line No.10 to "Xi-tu-cheng" station, ision hotel is about 100 m to the north, while Master Inn in Peking University Health Science Center is about 400 m to the north.

8. **Q&A:**

For people who would like to ask questions, please move to the venue microphone first, and then concisely ask questions after the approval of the moderator who informs your name and affiliation to the audience.

参会者须知

1、会议时间：2016 年 10 月 28 日（周五）——30 日（周日）

2、会场：北京大学医学部逸夫教学楼 4 楼的 414、402、408、409

3、报到：

1）唯实酒店住宿者的报到（海外参会者、部分国内参会者）

时间：10 月 28 日（周五）9:00－11:30

地点：唯实酒店一楼大厅（北京市海淀区学院路 39 号，电话：010-62308899）

2）赢家酒店住宿者的报到（部分国内需要住宿的参会者）

时间：10 月 28 日（周五）9:00－11:30

地点：北京大学医学部赢家酒店一楼大厅（北京市海淀区学院路 38 号，电话：010-82320101）

3）其他宾馆的住宿者和不住宿者、或 10 月 29 日、30 日（周六日）参会者的报到

时间：10 月 28 日（周五）12:20-

29 日（周六）7:40－

30 日（周日）7:40－

地点：北京大学医学部逸夫教学楼 402、414 室外（北京市海淀区学院路 38 号，张岩：13810078145）

4、会务费：

1）国内参会者 1200 元人民币/人，海外参会者 200 美元/人。

包括参会、会议指南和论文集一册、茶休、28 日和 29 日晚宴、29 日和 30 日中餐的费用。

2）在读的研究生 600 元人民币/人，凭有效证件。

3）缴费：报到仅接收现金。转账者请于 10 月 21 日前，汇到下述账户，**汇款时请务必注明本人姓名、单位（开发票使用）、手机号、第一届中国微循环周 ！**并将汇款收据拍照微信发给张岩（13810078145）。

分支机构名称：气血专业委员会

开户名称：世界中医药学会联合会

开户银行：交通银行北京育惠东路支行

银行账号：110060971018002604480024

5、住宿（费用自理）：

1）唯实酒店（北京市海淀区学院路 39 号，电话：62308899，www.weishihotel.com, service@weishihotel.com）

房间：普通标间，双床，1 人入住时，580 元人民币/日（含 1 人早餐费）。2 人入住时，650 元人民币/日（每人 325 人民币/日，含 2 人早餐费，自行组合）。

豪华房间，1 张大床。620 元人民币/日（含 1 人早餐费）。

2）赢家酒店（北京市海淀区学院路 38 号，电话：010-82320101）

房间：普通标间（双床/单床）。268 元人民币/日（双人入住时，每人 134 人民币/日，含早餐费，自行组合）。

豪华标间（双床/单床）。388 元人民币/日（含早餐）。双人入住时，每人 194 人民币/日，含早餐费，自行组合）。

3）距离会场较近的其他酒店

- 全季酒店（北京市海淀区花园路塔院志新村 2 号，010-82020101）
- 汉庭酒店（北京市海淀区学院路 31 号 6 号楼，010-82326688）
- 海友良品（北京市海淀区北四环中路 265 号，010-61196131）

说明：

1）由于 10 月底正值北京旅游高峰时段，北京大学医学部校园内和周边宾馆的入住情况较紧张，优惠较少。

2）距离会场较近的宾馆房屋有限，**请参会者尽快自行预订。**电话预定时，请说明是参加“第一届中国微循环周会议”者。

6、餐饮

1）10 月 28 日（周五）

午餐：12:00-12:50，赢家酒店二楼，（北京市海淀区学院路 38 号，电话：010-82320101,

交流晚会：18:00-19:30，赢家酒店二楼

2）10 月 29 日（周六）

早餐：在各自住宿的酒店内用餐，7:00-7:40（含在住宿费内）

自助午餐：北医跃进厅三楼，12:00-13:30

晚餐：北医跃进厅三楼，17:40-19:40

3）10 月 30 日（周日）

早餐：在各自住宿的酒店内用餐，7:00-7:40（含在住宿费内）

自助午餐：赢家酒店二楼，12:00-

凭代表证用午晚餐。

7、交通

1）飞机：

A、从首都机场乘出租车至北京大学医学部赢家酒店或者唯实酒店约 110 元（北京大学医学部在学院路东、唯实酒店在学院路西），北京大学医学部赢家酒店在北医三院西侧约 300 米。

B、从首都机场乘机场巴士 5 线至学院桥下，进北京大学医学部北门。

C、从首都机场乘地铁机场专线至三元桥换乘地铁 10 号线至西土城，东北出口往北 400 米为北京大学医学部西门，西北出口往北 100 米是唯实酒店。

2）火车：

A、北京站，乘出租车至北京大学医学部赢家酒店或者唯实酒店约 50 元（北京大学医学部在学院路东、唯实酒店在学院路西），北京大学医学部赢家酒店在北医三院西侧约 300 米。或在北京站乘地铁至积水潭换 331 路至北京航天航空大学站，前行 50 米是北京大学医学部西门；或北京站乘地铁至西直门站换乘 375 路至北京航天航空大学站。或者北京站乘

地铁 2 号线雍和宫站换乘 5 号线，惠新西街南口站换乘 10 号线至西土城站，东北出口往北 400 米为北京大学医学部西门，西北出口往北 100 米是唯实酒店。

B、北京西站，乘出租车至北京大学医学部赢家酒店约或者唯实酒店约 40 元（北京大学医学部在学院路东、唯实酒店在学院路西），北京大学医学部赢家酒店在北医三院西侧约 300 米。北京西站乘 47 路至学院桥站，马路对面是北京大学医学部北门。

C、北京南站，乘出租车至北京大学医学部赢家酒店约或者唯实酒店约 80 元（北京大学医学部在学院路东、唯实酒店在学院路西），北京大学医学部赢家酒店在北医三院西侧约 300 米。或者北京南站乘地铁 4 号线至海淀黄庄站换 10 号线至西土城站下，东北出口往北 400 米为北京大学医学部西门，西北出口往北 100 米是唯实酒店。

请参会者自行订购往返的车票或飞机票，根据“参会者须知”中的提示自行前往宾馆和会场（本次会议不安排接送站）。

8. 提问：请提问者预先站在会场内的话筒前，在征得主持人同意后，在通报您的姓名和所属单位后，简洁地提问。

Notice for speakers

1. Plenary Lecture: 25 minutes for presentation, 5 minutes for discussion.

2. Educational Lecture: Please prepare your report according to the conference notice.

3. Symposium: Please prepare your report according to the conference notice.

4. Oral report: 8 minutes for presentation, 4 minutes for discussion.

5. PC and projector are available in the conference hall. Speakers please hand over your Power Point or U-disk, mobile hard disk or notebook computer to the conference secretariat 120 minutes before your presentation. Secretariat is in front of the conference hall on the 4th floor of Yifu Building, who makes sure that your data will not be passed to others and deletes all your data after your report.

6. Poster: The posters should be prepared in English with a size of 90 (width) by 120 (height) cm. Please affix poster on your designated number before 13:00 pm on October 28 in the poster area on the 4th floor of Yifu Building of the Health Science Center Peking University. Poster communication time: 13:00-14:00 October 29. Under the auspices of the host, each poster speaker has 6 minutes for reporting, 4 minutes for discussion. Please withdraw your poster before 12:30 on October 30.

7. Each speaker please sat at the seat designated for the next speaker in the 1st row on the left when the one before you starts presenting. Please comply strictly the time.

报告者须知

1. 大会报告：25 分钟报告，5 分钟讨论。
2. 教育讲演：请按会议通知做准备。
3. 专题报告：请按会议通知做准备。
4. 口头报告，8 分报告，4 分讨论。
5. 本次大会的报告厅有报告专用的电脑，大会报告、教育讲演、专题报告、口头报告者，请将 Power Point（2003、2007）于报告前 120 分钟，将报告的 U 盘、移动硬盘或笔记本电脑）交给秘书处放映组（设在北京大学医学部逸夫教学楼四层，各报告厅门外）。秘书处放映组承诺不将报告内容拷给任何人，并在报告结束后完全清除提交的 PPT。
6. 壁报。会议向每份壁报提供 1 块 90×120cm 的展板。请报告者按上述尺寸准备壁报，于 10 月 28 日的 13:00 以前到北京大学医学部逸夫教学楼四层壁报区，按壁报号张贴壁报。壁报交流时间是 10 月 29 日 13:00－14:00。请在主持人的主持下，在壁报前报告 6 分钟、讨论 4 分钟。请于 10 月 30 日 12:30 以前撤出您的壁报。
7. 请大会报告、教育讲演、专题报告、头口报告者，在前一位报告开始后，在报告厅第一排左侧的“下一位报告者席”就坐。严格遵守报告时间。

Notice for the Chair

1. Please seat on the seat labeled as “the next host” on the right side of the first row of the hall before the last presentation is over.
2. The host of plenary lecture and educational lecture can make a brief remark to introduce the speakers, according to the speakers’ CV provided by the committee, and organize a discussion after the report. Please pay attention to control time.
3. Host of symposium should introduce the speakers’ names, affiliations and the titles of the reports only, and organize a discussion after the report within the time scheduled.
4. From 13:00 to 14:00 on October 29, host of the poster should organize the communications in the front of the appointed poster. Each paper should be reported for 6 minutes, then discussed for 4 minutes. And the host should hand in the best paper (only one) you chose to the secretariat poster group located at the 4th floor in the Yifu Building of Peking University Health Science Center before 15:00, October 29, including the title of the paper, the author’s name and affiliation.

主持人须知

1. 主持人请在前一场专场结束前，在报告厅第一排右侧的“下一位主持人席”就坐。
2. 大会报告的主持人，可简单地介绍报告者，严格掌控报告时间，组织讨论。
3. 教育讲演、专题报告的主持人，仅介绍报告人的姓名、单位和报告题目，严格掌控报告时间，组织讨论。
4. 口头报告的主持人，仅介绍报告人的姓名、单位和报告题目，严格掌控报告时间，组织讨论。
5. 壁报主持人于 10 月 29 日 13:00－14:00 间，在指定的壁报组前主持壁报交流。每份壁报报告 6 分钟，讨论 4 分钟。并于 10 月 29 日 15:00 点前将您选出的优秀论文（每组选 1 名）的题目、姓名、单位提交给设在北京大学医学部逸夫教学楼四层会场外的秘书处。

Award

1. The award will be set up in this conference.
2. The award will be selected among the posters.
3. The certificate and prize will be issued in closing ceremony at 12:00 in the October 30.

优秀论文奖

1. 本届会议设优秀论文奖。

2. 优秀论文奖从口头报告和壁报中产生。

3. 优秀论文奖的奖状和奖金，在 10 月 30 日 12:00 的闭幕式上颁发。未到场的获奖者，将按放弃理解。

中国病理生理学会微循环专业委员会全体会议

1. 时间：10 月 28 日 19:40－20:10
2. 地点：北京大学医学部逸夫教学楼 414 室
3. 主要议题：讨论专业委员会建设事宜、推选 2017 年度学术会议主办者、介绍 Microcirculation 投稿相关事宜等。

世界中医药学会联合会气血专业委员会全体会议

1. 时间：10 月 28 日 20:10－20:40
2. 地点：北京大学医学部逸夫教学楼 402 室
3. 主要议题：汇报专业委员会工作、推选 2017 年度学术会议主办者、介绍 Microcirculation 和 World Journal of Traditional Chinese Medicine 投稿相关事宜。

中国微循环学会痰瘀专业委员会全体会议

1. 时间：10 月 28 日 20:40－21:10
2. 地点：北京大学医学部逸夫教学楼 414 室
4. 主要议题：推荐 2017 年度学术会议主办者、介绍 Microcirculation 和 World Journal of Traditional Chinese Medicine 投稿相关事宜。

中国中西医结合学会微循环专业委员会全体会议

1. 时间：10 月 28 日 21:10－21:40
2. 地点：北京大学医学部逸夫教学楼 402 室
3. 主要议题：委员增选、2017 和 2018 年度学术会议筹备事宜、介绍 Microcirculation 和 World Journal of Traditional Chinese Medicine 投稿相关事宜。

大会秘书处人员及联系办法：

大会主席	韩晶岩	13910992907	hanjingyan@bjmu.edu.cn
会务负责人	王传社	13911003861	chuanshe@bjmu.edu.cn
报到及住宿	李娜	13810060510	weixunhuan@bjmu.edu.cn
	张岩	13810078145	tmrc@bjmu.edu.cn
财务	张岩	13810078145	

Programme

October 28 **Friday Room 414 Yifu Building**
Campus of Peking University Health Science Center

13:00-15:00 **Symposium 1**
Brain Microcirculation and Cerebral Vascular Diasease

Chairs: Xue-Long Jin
Department of physiology, Tianjin Medical University
Huai-Lian Guo
Department of Neurology, People's Hospital, Peking University

13:00-13:25 **The Role of Free Radical Generation in Increasing Cerebrovascular Permeability**
Paul Fraser
Cardiovascular Division Faculty of Life Sciences & Medicine King's College London

13:25-13:50 **A New Internal Capsule Hemorrhage Animal Model**
Xue-Long Jin
Department of physiology, Tianjin Medical University

13:50-14:15 **Exercise Training Ameliorates Age-induced Cerebral Microvascular Deterioration and VEGF Angiogenic Signaling in Rats**
Sheepsumon Viboolvorakul
Physiology Unit, Department of Medical Science, Faculty of Science, Rangsit University

14:15-14:30 **Adoptive Regulatory T Cell Therapy Protects Against Stroke-induced Cerebral Injury**
Lei-Lei Mao
Key Laboratory of Cerebral Microcirculation in Universities of Shandong, Taishan Medical University

14:30-14:45 **The Effects of Rho Kinase Inhibition on the Permeability of Blood-brain Barrier and Activation of Microglia After Cerebral Ischemia in Rats**
Yong-Bo Zhang
Department of Neurology, Beijing Friendship Hospital, Capital Medical University

14:45-15:00 **In vivo Observation of Cortical Astrocytes after Cerebral Hypoperfusion in Mice**
Jiang-Man Song
Department of Neurology, People's Hospital, Peking University

15:05-15:10 Tea Break

15:10-15:40 Plenary Lecture 1

Organ microcirculation and gastrointestinal (GI) disorders

Speaker: Hidekazu Suzuki, M.D., Ph.D., FACG, AGAF, RFF

President of Japanese Society for Microcirculation

Professor, Medical Education Center, Keio University School of Medicine

Chair: Geraldine Clough，M.D., Ph.D.

Professor, Institute of Developmental Sciences, Faculty of Medicine, University of Southampton

15:40-16:10 Plenary Lecture 3

Sexually Dimorphic Regulation of Cardiovascular Function: Roles of EETs/she

Speaker: An Huang, M.D., Ph.D.

Professor of Physiology, New York Medical College (NYMC), Valhalla, NY

Chair : Akos Koller, M.D., Ph.D.

Professor and Chairman of the Scientific Council, University of Physical Education, 1123 Budapest, Hungary

16:10-16:40 Plenary Lecture 5

Current Status and Future Perspectives in Modernization of Chinese Herbal Medicines

Speaker: De-An Guo, M.D., Ph.D.

Professor, Shanghai Research Center for TCM Modernization, Shanghai Institute of Materia Medica, Chinese Academy of Sciences

Chair : Suthiluk Patumraj, Ph.D.

Professor, Excellence Center for Microcirculation, Department of Physiology, Faculty of Medicine, Chulalongkorn University

16:40-17:10 Plenary Lecture 7

Role of the bone microvascular niche in the progression and treatment of tumour metastasis

Speaker: Nicola J. Brown, Ph.D.

President of British Microcirculation Society，

Professor of Department of Oncology & Metabolism，Microcirculation Research Group，Faculty of Medicine, Dentistry and Health，University of Sheffield

Chair : Gerald A. Meininger, M.D., Ph.D.

Professor, Dalton Cardiovascular Research Center

Department of Medical Pharmacology and Physiology

University of Missouri-Columbia

19:40-20:10 Council Meeting Room 414, Yifu Building, campus of Peking University Health Science Center

Professional committee of the microcirculation, China pathophysiological society

20:40-21:10 Council Meeting Room 414, Yifu Building, campus of Peking University Health Science Center

Professional Committee of Phlegm-Stasis, China society of microcirculation

October 28 Friday Room 402 Yifu Building
Campus of Peking University Health Science Center

13:00-15:00 Symposium 2
Cardiovascular Disease and Coronary Microcirculation

Chairs: Ming Xu
Department of Cardiology, Institute of Vascular Medicine, Peking University Third Hospital, Key Laboratory of Molecular
Yu-Zhen Li
Chinese PLA General Hospital

13:00-13:25 **HIP-55, A Novel Component of Pro-survival Signaling, and Cardiovascular Diseases**
Zi-Jian Li
Institute of Vascular Medicine, Peking University Third Hospital

13:25-13:50 **The Formation and Stabilization of G-quadruplex by Natural Small Molecule Down-Regulates miR-24 Expression**
Ming Xu
Department of Cardiology, Institute of Vascular Medicine, Peking University Third Hospital, Key Laboratory of Molecular

13:50-14:15 **Cardiotonic Pills Ameliorates Ischemia-reperfusion Induced Cardiac Injury in Rats, Relying on the Antioxidant Effect of 3, 4-dihydroxyl-phenyl Lactic Acid and Energy Regulation of Notoginsenoside R1**
Xiao-Hong Wei
Tasly Microcirculation Research Center, Peking University Health Science Center, Beijing, China

14:15-14:40 **Cardiovascular Protection of Salviae Miltiorrhizae and the Underlying Mechanism**
Bao-Hong Jiang
Shanghai Institute of Materia Medica, CAS

14:40-15:00 **Effects and Mechanisms of Tanshinone IIA Derivative on Ameliorating Myocardial Ischemia/Reperfusion Injury in Rats**
Wan-Li Shen
School of Pharmacy, Shihezi University

15:05-15:10 Tea Break

15:10-15:40 Plenary Lecture 2

Aquaporin-1 Translocation and Degradation Partially Mediates the Water Transportation Mechanism of Acetazolamide

Speaker: Xue-Jun Li, M.D., Ph.D.

Professor, Department of Pharmacology, School of Basic Medical Sciences, Peking University

Chair: You-Yi Zhang

Professor, Key Laboratory of Vascular Cardiovascular Sciences, Ministry of Education / Peking University Institute of Cardiovascular Sciences / Institute of Vascular Medicine. Peking University Third Hospital

15:40-16:10 Plenary Lecture 4

New Advances to Stop Microvascular Leakage During Inflammation

Speaker: Jerome W. Breslin, Ph.D.

Assistant Professor, Department of Molecular Pharmacology and Physiology, Morsani College of Medicine, University of South Florida

Chair : Bao-Xue Yang, M.D., Ph.D.

Professor, Department of Pharmacology, School of Basic Medical Sciences, Peking University

16:10-16:40 Plenary Lecture 6

Regulation of Microvascular Blood Flow and Oxygen Supply

Speaker: Roland N. Pittman, Ph.D.

Professor, Medical College of Virginia Campus

Virginia Commonwealth University

Chair : Tailoi Chan-Ling, M.D., Ph.D.

Professor, Discipline of Anatomy and Histology, Sydney Medical School, Bosch Institute, the University of Sydney

16:40-17:10 Plenary Lecture 8

Receptor-interacting protein kinase 3 promotes platelet activation and thrombosis

Speaker: Ke-Sheng Dai, M.D., Ph.D.

Professor, Deputy Director, Key Laboratory of Thrombosis and Hemostasis, Ministry of Health, Research Unit on Thrombosis and Hemostasis, Jiangsu Institute of Hematology, The First Affiliated Hospital of Soochow University

Chair : Nai-Feng Liu, M.D., Ph.D.

Professor of Medicine, Zhongda Hospital, Southeast University

17:15-17:20 Group photo Out of 1st floor, Yifu building

20:10-20:40 Council Meeting

Specialty Committee of Qi-Blood, World Federation of Chinese Medicine Societies

21:10-21:40 Council Meeting

Professional Committee of Microcirculation, Chinese Association of Integrative Medicine

October 29 Saturday Room 414 Yifu Building
Campus of Peking University Health Science Center

8:00-10:00 Symposium 3
Shock

Chairs: Yong Jiang
Department of Pathophysiology, School of Basic Medical Sciences, Southern Medical University
Paul Fraser
Cardiovascular Division Faculty of Life Sciences & Medicine King's College London

08:00-08:20 **Microcirculatory Disorders and Protective Role of Anti-oxidant in Severe Heat Stroke: A Rat Study**
Hui Jin
Department of Pathophysiology, Key Laboratory for Shock and Microcirculation Research, Southern Medical University (SMU)

08:20-08:40 **Effect of Post-hemorrhagic Shock Mesenteric Lymph on Murine CD4+ T cells**
Li-Na Jiang
Institute of Microcirculation, Hebei North University

08:40-09:00 **Yiqifumai Injection, A Traditional Chinese Compound Medicine, and Its Active Ingredient Ginsenoside Rb1 Ameliorate Microvascular Hyperpermeability Induced by Lipopolysaccharide**
Kai Sun
Tasly Microcirculation Research Center, Peking University Health Science Center

09:00-09:20 **Sirtuin 1/3 Prevents Low Vasoreactivity by Modulating Mitochondrial Function**
Peng-Yun Li
Key Laboratory of Medical Electrophysiology, and Institute of Cardiovascular Research, Southwest Medical University

09:20-09:40 **Catalpol Restores LPS-elicited Rat Microcirculation Disorder by Regulation of a Network of Signaling Involving Inhibition of TLR-4 and Src**
Yun-Pei Zhang
Department of Integration of Traditional Chinese and Western Medicine, School of Basic Medical Sciences, Peking University

09:40-10:00 **Hypoxia Induces Micro-lymphatic Endothelial Barrier Dysfunction Via Activation of ASK1/p38 MAPK Pathway**
Abbas Muhammad
Institute of Microcirculation, Hebei North University

10:00-10:10 Tea Break

10:10-10:40 Plenary Lecture 9

Acanthus ebracteatus Vahl suppresses hypoxia-induced angiogenesis via inhibition of HIF-1α/VEGF signaling pathway in cervical cancer implanted nude mice

Speaker: Suthiluk Patumraj, Ph.D.

Professor, Excellence Center for Microcirculation, Department of Physiology, Faculty of Medicine, Chulalongkorn University

Chair: Fu long Liao, Ph.D.

Professor, China Academy of Traditional Chinese Medicine

10:40-11:10 Plenary Lecture 11

Effects of Moesin Phosphorylation in Endothelial Dysfunction Induced by Advanced Glycation Endproducts

Speaker: Qiao-Bing Huang, M.D., Ph.D.

Professor, Department of Pathophysiology, School of Basic Medical Sciences, Southern Medical University

Chair : Jerome W. Breslin, Ph.D.

Assistant Professor, Department of Molecular Pharmacology and Physiology, Morsani College of Medicine, University of South Florida

11:10-11:40 Plenary Lecture 13

Metabolic programming of human fetal endothelial and smooth muscle cells in gestational diabetes

Speaker: Giovanni E. Mann, M.D., Ph.D.

Professor, Cardiovascular Division, British Heart Foundation Centre of Research Excellence, Faculty of Life Sciences & Medicine, King's College London

Chair : Toshio Nakaki, M.D., Ph.D.

Professor, Department of Pharmacology

Teikyo University School of Medicine

11:40-12:10 Plenary Lecture 15

CO-Responsive Heme Proteins Regulate Microcirculation and Cancer Proliferation

Speaker: Makoto Suematsu, M.D., Ph.D.

President, Japan Agency for Medical Research and Development

Chair : Giovanni E. Mann, M.D., Ph.D.

Professor, Cardiovascular Division, British Heart Foundation Centre of Research Excellence, Faculty of Life Sciences & Medicine, King's College London

12:10-13:00 Lunch 3th Floor Yue-Jin Hall

13:00-14:00 Poster Yifu Building, Peking University Health Science Center

14:00-16:00 **Symposium 5**
Diabetes and Microcirculation

Chairs: Qiao-Bing Huang
Department of Pathophysiology, School of Basic Medical Sciences, Southern Medical University
Akos Koller
University of Physical Education, Budapest, Department of Neurosurgery and Szentagothai Res Centre, University of Pecs, Hungary and Department of Physiology, New York Medical College

14:00-14:25 **Characterization of Angiogenesis and Endothelial Dysfunction in microRNA-34a Knockout Mice with Diabetic Liver Injury**

Fan-Yin Meng

Digestive Disease Research Center, Baylor Scott & White Healthcare, Texas A&M HSC College of Medicine

14:25-14:50 **Effects of Alpha Mangostin on Blood Brain Barrier Permeability in Type 2 Diabetic Rats**

Amporn Jariyapongskul

Department of Physiology, Faculty of Medicine, Srinakharinvirot University

14:50-15:15 **High Glucose Induces Podocyte Foot Process Effacement by Stimulating TRPC6**

Bing-Chen Liu

Department of Cardiology, the 4th Hospital of Harbin Medical University

15:15-15:40 **Obesity-induced Vascular Inflammation and Dysfunction Involves Elevated Arginase Activity.**

Lin Yao

Guangzhou University of Chinese Medicine

15:40-16:00 **Adipocyte SIRT1 Deletion Impaired Endothelial Function Via Reducing Brown Fat Phenotype in Perivascular Adipose Tissue**

Ping Gu

Department of Endocrinology, Jinling Hospital

16:10-16:20 Tea Break

16:20-16:50 Plenary Lecture 17

The mechanism for Chinese medicine to improve microvescular barrier and intestinal mucosa epithelial barrier.

Speaker: Jing-Yan Han, M.D., Ph.D.

Professor, Department of Integration of Chinese and Western Medicine, Peking University Health Science Center/Tasly Microcirculation Research Center, Peking University Health Science Center

Chair: Hiroshi Nagata, M.D.

Professor, Keiyu Hospital

16:50-17:20 Plenary Lecture 19

Remodeling of the Cytoskeleton and Adhesion are Fundamental Processes Coupled to Vascular Smooth Muscle Contraction and Relaxation

Speaker: Gerald A. Meininger, M.D., Ph.D.

Professor, Dalton Cardiovascular Research Center

Department of Medical Pharmacology and Physiology

University of Missouri-Columbia

Chair : Qi-Min Zhan, M.D., Ph.D.

President, Peking University Health Science Center

17:40-19:40 Dinner

October 29 Saturday Room 402 Yifu Building
Campus of Peking University Health Science Center

8:00-10:00 Symposium 4
Hemorrhage-Thrombus

Chairs: Ke-Sheng Dai
Jiangsu Institute of Haematology, The First Affiliated Hospital of Soochow University, Collaborative Innovation Center of Haematology, Key Laboratory of Thrombosis and Haemostasis, Ministry of Health
Jian-Bo Wu
Drug Discovery Research Center, Southwest Medical University

08:00-08:20 New Regulators of Endothelial Exocytosis and Their Roles in Vascular Hemostasis and Thrombosis
Jin-Cai Luo
Laboratory of Vascular Biology, Institute of Molecular Medicine, Beijing Key Laboratory of Cardiometabolic Molecular Medicine, Peking University

08:20-08:40 Glycation of Vitronectin Inhibits VEGF-induced Angiogenesis by Uncoupling VEGF Receptor-2-αvβ3 Integrin Cross-talk
Li-Qun Wang
Drug Discovery Research Center, Luzhou, Sichuan, People's Republic of China

08:40-09:00 Glycoprotein Ibα Clustering Induces Macrophage-mediated Platelet Clearance in the Liver
Rong Yan
Jiangsu Institute of Haematology, The First Affiliated Hospital of Soochow University, Collaborative Innovation Center of Haematology, Key Laboratory of Thrombosis and Haemostasis, Ministry of Health

09:00-09:20 Promoting Blood Circulation for Removing Blood Stasis Therapy for Acute Intracerebral Hemorrhage: A Systematic Review and Meta-analysis
Guo-Qing Zheng
Department of Neurology, The Second Affiliated Hospital & Yuying Children's Hospital of Wenzhou Medical University

09:20-09:40 The Effect of Connexin, Arteriole Membrane Potential and Endoplasmic Reticulum Stress-Induced Apoptosis Pathway on Delayed Cerebral Ischemia after Subarachnoid Hemorrhage
Dong Zhao
Department of Neurosurgery of the First Affiliated Hospital of Shihezi University School of Medicine

09:40-10:00 Research Progress on Cerebral Microcirculation
Qi Fang
The First Affiliated Hospital of Soochow Universit

10:00-10:10 Tea Break

10:10-10:40 Plenary Lecture 10

Future challenges for sepsis: novel strategies based on big data produced by Omics

Speaker: Yong Jiang, Ph.D.

Professor and Chairman of Department of Pathophysiology,

Director of Key laboratory of functional proteomics of Guangdong province, School of Basic Medical Sciences of Southern Medical University

Chair: Nicola J. Brown, Ph.D.

President of British Microcirculation Society，Professor of Department of Oncology & Metabolism，Microcirculation Research Group，Faculty of Medicine, Dentistry and Health，University of Sheffield

10:40-11:10 Plenary Lecture 12

Skin microvascular blood flow and oxygenation - adaptive outcomes in obesity and type 2 diabetes mellitus/insulin resistance

Speaker: Geraldine Frances Clough, BSc PhD FRSB

Professor, Institute of Developmental Sciences, Faculty of Medicine, University of Southampton

Chair : Makoto Suematsu, M.D., Ph.D.

President, Japan Agency for Medical Research and Development

11:10-11:40 Plenary Lecture 14

Exosomes and Cardiovascular Diseases

Speaker: Si-Feng Chen, BM, MM & MBA

Professor and Department Chairperson of Physiology and Pathophysiolgy at Fudan University College of Basic Medical Sciences,

Director of Kidney and Hypertension Research Center of Fudan University

Chair : Masato Yasui

Professor and Chair, Department of Pharmacology, School of Medicine, Keio University

11:40-12:10 Plenary Lecture 16

Vascular factors, angiogenesis and liver diseases

Speaker: Gianfranco D Alpini, M.D., Ph.D.

Professor, Dr. Nicholas C. Hightower Centennial Chair in Gastroenterology

Director，the Scott & White Digestive Disease Research Center

Olin E. Teague Medical Center

Chair : Qiao-Bing Huang, M.D., Ph.D.

Professor, Department of Pathophysiology, School of Basic Medical Sciences, Southern Medical University

12:10-13:00 Lunch 3th Floor Yue-Jin Hall

13:00-14:00 Poster Yifu Building, Peking University Health Science Center

14:00-16:00 **Symposium 6**
Qi-Blood

Chairs: Shi-Jun Wang
Shandong University of Traditional Chinese Medicine
Hao Xu
Peking UniversityThird Hospital

14:00-14:25 **QiShenYiQi Pills, a Compound in Chinese Medicine, Protects Against Pressure Overload-induced Cardiac Hypertrophy Through a Multicomponent and Multi-target mode**
Yuan-Yuan Chen
Department of Integration of Chinese and Western Medicine, School of Basic Medical Sciences, Peking University

14:25-14:50 **Regulation of Insulin Resistance by Multiple miRNAs Via Targeting the GLUT4 Signalling Pathway**
Li-Hong Wang
Department of Endocrinology, The Second affiliated Hospital of Harbin Medical University

14:50-15:15 **Elatoside C Protects the Heart from Ischaemia/Reperfusion Injury Through the Modulation of Oxidative Stress and Intracellular Ca2+ Homeostasis**
Min Wang
Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences & Peking Union Medical College

15:15-15:35 **Ginsenoside Rb1 Protects Against Ischemia/Reperfusion-induced Myocardial Injury Via Energy Metabolism Regulation Mediated by RhoA Signaling Pathway**
Yuan-Chen Cui
Department of Integration of Chinese and Western Medicine, School of Basic Medical Sciences, Peking University

15:35-16:00 **Angiogenesis Promoted by PNS Leading to a Neuroprotective Effects in AD-like Animal Models in a Modern Formula of Traditional Chinese Medicine Tong Luo Jiu Nao**
Qian Hua
Preclinical School of Medicine, Beijing University of Chinese Medicine

16:10-16:20 Tea Break

16:20-16:50 Plenary Lecture 18

Failure of the autoregulation of cerebral blood flow by hemodynamic forces

Speaker: Akos Koller, MD, PhD

Professor and Chairman of the Scientific Council, University of Physical Education, 1123 Budapest, Hungary

Chair: Roland N. Pittman, Ph.D.

Professor, Medical College of Virginia Campus

Virginia Commonwealth University

16:50-17:20 Plenary Lecture 20

The microvascular interface in the Central Nervous System: Normal function and relevance to pathology

Speaker: Tailoi Chan-Ling, M.D., Ph.D.

Professor, Discipline of Anatomy and Histology, Sydney Medical School

Bosch Institute, the University of Sydney

Chair : Yong Jiang, Ph.D.

Professor and Chairman of Department of Pathophysiology,

Director of Key laboratory of functional proteomics of Guangdong province,

School of Basic Medical Sciences of Southern Medical University

17:40-19:40 Dinner

October 29 Saturday Room 408 Yifu Building
Campus of Peking University Health Science Center

8:00-10:00 Free Oral Presentation 1
Chairs: Bao-Liang Sun
Key Lab of Cerebral Microcirculation in Universities of Shandong, Taishan Medical University

Yue-Hong Zheng
Department of vascular surgery, Peking Union Medical College Hospital

08:00-08:12 Screening and Functional Study of miRNAs in Arteriosclerosis Obliterans
Xiang-Yu Zhou
Department of Vascular and Thyroid Surgery, The Affiliated Hospital of SouthWest Medical University

08:12-08:24 The Involvement of Beta-catenin in AGE-induced Endothelial Hyperpermeability
Xiao-Hua Guo
Department of Pathophysiology, Key Laboratory for Shock and Microcirculation Research of Guangdong Province, Southern Medical University

08:24-08:36 Effects of FOXO1 Mediated Regulation of Mitochondrial Function in Diabetic Wound Healing
Lu Tie
State Key Laboratory of Natural & Biomimetic Drugs, Department of Pharmacology, School of Basic Medical Sciences, and Institute of System Biomedicine, Peking University

08:36-08:48 Sulfur Dioxide Protects against Pulmonary Artery Collagen Accumulation in Association with Downregulating TGF-β/Smad Pathway in Pulmonary Hypertensive Rats
Wen Yu
Department of Pediatrics, Peking University First Hospital

08:48-09:00 The Amelioration Effects of Berberine on Mesareic Vascular Damage in STZ - induced Diabetic Rats
Ding Zhao
School of Pharmacy & Institute of Integrated Traditional and Western Medicine, Hebei Medical University

09:00-09:12 **GLP-1 Inhibits the Receptor for Advanced Glycation Endproducts to Prevent Podocyte Apoptosis Induced by Advanced Oxidative Protein Products**

Shuang-Shuang Zhang

Department of Pathophysiology, Key Laboratory for Shock and Microcirculation Research of Guangdong Province, Southern Medical University

09:12-09:24 **Aquaporin-3 Deficiency Slows Renal Cystogenesis via Regulation of AMPK/ERK/mTOR Signaling**

Wei-Ling Wang

Department of Pharmacology, School of Basic Medical Sciences, Peking University, and State Key Laboratory of Natural and Biomimetic Drugs, Key Laboratory of Molecular Cardiovascular Sciences, Ministry of Education

09:24-09:36 **Effect of Low-dose Simvastatin on Therapeutic Efficacy of Mesenchymal Stem Cells (MSCs) Transplantation in Diabetic Wound Healing**

Sukpat Supakanda

Faculty of Medicine, Chulalongkorn University

09:36-09:48 **Enhanced Therapeutic Potential of Nano-curcumin Against Subarachnoid Hemorrhage-induced Blood-brain Barrier Disruption Through Inhibition of Inflammatory Response and Oxidative Stress**

Zong-Yong Zhang

Key Lab of Cerebral Microcirculation in Universities of Shandong, Taishan Medical University

09:48-10:00 **Estrogen Treatment Improves Lymphatic Contractility in Rats Following Hemorrhagic Shock**

Li-Min Zhang

Institute of Microcirculation, Hebei North University

12:10-13:00 **Lunch 3th Floor Yue-Jin Hall**

13:00-14:00 **Poster Yifu Building, Peking University Health Science Center**

14:00-14:30 Education Lecture 1

Methods for Study of the Organ Microcirculation

Speaker: Yu-ying Liu

Tasly Microcirculation Research Center, Peking University Health Science Center, Beijing, China

Chair: Dong Han

Professor, National Center for Nanoscience and Technology

14:30-15:30 Education Lecture 2

Attenuating effect and underlying mechanism of compound Chinese medicine on ischemia and reperfusion induced cerebral and cardiac microcirculation disturbance and organ injury

Speaker: Jing-Yan Han

Department of Integration of Chinese and Western Medicine, School of Basic Medical Sciences, Peking University

Chair: Yi-Ning Huang

Professor and Chairman, Department of Neurology, Peking University First Hospital

15:30-16:00 Education Lecture 3

An update of the journal Microcirculation

Speaker: Geraldine F Clough, Deputy Editor-in-Chief, Microcirculation

Professor, Vascular Physiology, Faculty of Medicine, University of Southampton, UK

Chair: Jian-Bo Wu

Professor, Drug Discovery Research Center, Southwest Medical University

October 30 Sunday Room 408 Yifu Building
Campus of Peking University Health Science Center

8:00-10:00 **Symposium 7**
Blood stasis and Phlegm-stasis

Chairs: Yan Zhu
Tianjin State Key Laboratory of Modern Chinese Medicine, Tianjin University of Traditional Chinese Medicine
Yan Lei
China Academy of Chinese Medical Sciences

08:00-08:20 **Panax Notoginseng Saponins Superior to Aspirin in Inhibiting Platelet Adhesion to Injured Endothelial Cells Through COX Pathway**
Mei-Xue
Xiyuan Hospital China Academy of Chinese Medical Sciences

08:20-08:40 **Deepure Tea Improves High Fat Diet-induced Insulin Resistance and Non-alcoholic Fatty Liver Disease**
Jing-Na Deng
Tasly Microcirculation Research Center, Peking University Health Science Center

08:40-09:00 **Coordinated Activation of VEGF/VEGFR-2 and PPARD Pathways by a Multi-component Chinese Medicine DHI Accelerated Recovery from Peripheral Arterial Disease in Type 2 Diabetic Mice**
Yan Zhu
Tianjin State Key Laboratory of Modern Chinese Medicine, Tianjin University of Traditional Chinese Medicine

09:00-09:20 **Post-treatment with Ma-Huang-Tang Ameliorates Cold-warm-cycles Induced Rat Lung Injury**
Chun-Shui Pan
Tasly Microcirculation Research Center, Peking University Health Science Center

09:20-09:40 **Protective Effect of Curcumin Against Cerebral Ischemia-reperfusion Injury in Rats**
Wei Li
Department of Physiology, Faculty of Medicine, Chulalongkorn University

09:40-10:00 **Pharmacological assessment of the efficacy of traditional Chinese medicine for coronary heart disease of phlegm-stasis syndrome**
Lei Li
Institute of Basic Medical Sciences of Xiyuan Hospital, China Academy of Chinese Medical Sciences

10:00-10:10 **Tea Break**

10:10-10:40 **Plenary Lecture 21**

Migration of Lymphoid and Cancer Cell in Gut-Associated Lymphoid Tissue

Speaker: Hiroshi Nagata, M.D.

Professor, Keiyu Hospital

Chair: Hong-Quan Zhang, M.D., Ph.D.

Professor and Head Department of Anatomy, Histology and Embryology Peking University Health Science Center Director, Laboratory of Molecular Cell Biology and Tumor Biology, School of Basic Medical Sciences Peking University Health Science Center

10:40-11:10 **Plenary Lecture 23**

Contribution of At1r Mechanoactivation to the Arterial Myogenic Response and its Regulation by Rgs5 Protein in Skeletal Muscle Arterioles

Speaker: Michael A. Hill, M.D., Ph.D.

Professor, Medical Pharmacology and Physiology,

Dalton Cardiovascular Research Center, University of Missouri

Chair : Jian-Bo Wu, M.D., Ph.D.

Professor, Drug Discovery Research Center, Southwest Medical University

11:10-11:40 **Plenary Lecture 25**

Micro RNA in regulating oxidative stress in neurons

Speaker: Toshio Nakaki, M.D., Ph.D.

Professor, Department of Pharmacology

Teikyo University School of Medicine

Chair : Jing-Yan Han, M.D., Ph.D.

Professor, Department of Integration of Chinese and Western Medicine, Peking University Health Science Center/Tasly Microcirculation Research Center, Peking University Health Science Center

11:40-12:10 **Closing Ceremony**

12:10-13:10 **Lunch**

October 30 Sunday Room 402 Yifu Building
Campus of Peking University Health Science Center

8:00-10:00 Symposium 8
New Technique

Chairs: Gang-Min Ning
Department of Biomedical Engineering, MOE Key Laboratory of Biomedical Engineering, Zhejiang University
Feng Han
Institute of Pharmacology and Toxicology, Zhejiang University

08:00-08:20 Visualization of the Inflammatory Response During Neurovascular Damage: Communication Between Microvessel and Microglia
Feng Han
Institute of Pharmacology and Toxicology, Zhejiang University

08:20-08:40 A Mathematical Model for the Interaction of Nitric Oxide and Oxygen in the Microcirculation Network
Ruo-Fan Wang
Department of Biomedical Engineering, MOE Key Laboratory of Biomedical Engineering, Zhejiang University

08:40-09:00 Tissue Viability Imaging for Reconstructive Plastic Surgery
Xia-Bing Huang
Moor Instruments

09:00-09:20 High-speed Atomic Force Microscopy for Nano-visualization of Living Biological Samples
Jing Li
National Center for Nanoscience and Technology

09:20-09:40 Generation of Human-like Small Rodent Models for Dyslipidemic and Atherosclerotic Studies: CRISPR/Cas9 Mediated Gene Targeting of Syrian Golden Hamsters
Ming-Ming Gao
Basic medical college of hebei medical university

09:40-10:00 Deep RNA Sequencing Elucidates MicroRNA Regulated Molecular Pathways in Ischemic Cardiomyopathy (ICM) And Non Ischemic Cardiomyopathy (NICM)
Xiang Li
National Center for Nanoscience and Technology

10:00-10:10 Tea Break

10:10-10:40 Plenary Lecture 22

Regulation of Plasminogen Activator Inhibitor-1 in vessel maturation

Speaker: Jian-Bo Wu, M.D., Ph.D..

Professor, Drug Discovery Research Center, Southwest Medical University

Chair: Jun-Bao Du, M.D., Ph.D.

Professor, Department of Pediatrics, Peking University First Hospital

10:40-11:10 Plenary Lecture 24

Aquaporins in brain disorders

Speaker: Masato Yasui, M.D., Ph.D.

Professor, Department. of Pharmacology, School of Medicine, Keio University, Tokyo, Japan

Chair : Xue-Jun Li, M.D., Ph.D.

Professor, Department of Pharmacology, School of Basic Medical Sciences, Peking University

11:10-11:40 Plenary Lecture 26

Modelling the Flow Pulsatility in Microcirculation Network

Speaker: Gang-min Ning, M.D., Ph.D.

Professor, Department of Biomedical Engineering, Zhejiang University

Chair : Ke-Sheng Dai, M.D., Ph.D.

Professor, Deputy Director, Key Laboratory of Thrombosis and Hemostasis, Ministry of Health, Research Unit on Thrombosis and Hemostasis, Jiangsu Institute of Hematology, The First Affiliated Hospital of Soochow University

11:40-12:10 Closing Ceremony

12:10-13:10 Lunch

October 30 Sunday Room 409 Yifu Building
Campus of Peking University Health Science Center

8:00-10:00 Free Oral Presentation 2

Chairs: Zi-Gang Zhao
Institute of Microcirculation, Hebei North University
Qing-Fu Zhang
The first hospital of Hebei Medical University

08:00-08:12 In Vivo Morphological Observation of Cortical Vessel in Cerebral Hypoperfusion Mice
Di Nan
Department of Neurology, People's Hospital, Peking University

08:12-08:24 Cardioprotective Effects of Gypenoside XVII on Endoplasmic Reticulum Stress–Mitochondrial Damage Crosstalk after Ischemia–reperfusion Injury through PI3K/AKT and P38 Signalling Pathways
Yingli Yu
Institute of Medicinal Plant Development, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing

08:24-08:36 Staphylococcal SSL5-induced Platelet Microparticles Provoke Proinflammatory Responses Via the CD40/TRAF6/NFκB Signaling Pathway in Monocytes
Hou-Yuan Hu
Department of Cardiology, Southwest Hospital

08:36-08:48 Role of Vimentin in the Inhibitory Effects of Low-Molecular-Weight Heparin on PC-3M Cell Adhesion to, and Migration through, Endothelium
Yan Pan
Department of Pharmacology, School of Basic Medical, Peking University Health Science Center

08:48-09:00 AQP3 protects against Renal Ischemia/Reperfusion Injury by promoting MAPK Signaling
Lei Lei
Department of Pharmacology, School of Basic Medical Sciences, Peking University

09:00-09:12 **Density and Kinetics of Ito、IK1、IKs and IKr in Guinea Pig ventricular Myocytes：Implications for Arrhythmogenesis in Humans**

Yong-Xia Wang

The first affiliated hospital of Henan University of traditional Chinese medicine

09:12-09:24 **Cardioprotective Effects of Rosa Rugosa Flavoniods on Myocardial Ischemia Reperfusion Injury in Mice**

Xue-Hui Zhang

Pharmacy school, Shihezi University

09:24-09:36 **Endogenous sulfur dioxide alleviates collagen remodeling via inhibiting TGF-β/Smad pathway in vascular smooth muscle cells**

Ya-Qian Huang

Department of Pediatrics, Peking University First Hospital

09:36-09:48 **H_2S regulates endothelial nitric oxide synthase protein stability by promotingmicroRNA-455-3p expression**

Wen-Long Xue

Shanghai Key Laboratory of Bioactive Small Molecules, Department of Physiology and Pathophysiology, Shanghai Medical College, Fudan University

09:48-10:00 **The effect and mechanism of XST capsule inhibiting THP-HUVECs adhesion under different flow conditions**

Shu-Xian Han

Institute of Chinese Materia Medica China Academy of Chinese Medical Science

Poster 1　Heart and Brain

Chair: Shuang-Yan Zhang
The Fourth Affiliated Hospital of Harbin Medical University

13:00-13:10　P-1-1
Effects of exercise training on microvascular degeneration and oxidative stress in aging rat brain
Channipa Chanpakdee
Inter-Department of Physiology, Graduate School, Chulalongkorn University

13:10-13:20　P-1-2
Diagnostic potential of lncRNA H19 in ischemic stroke and modulation of HDAC-dependent microglial activation
Jue Wang
Cerebrovascular Diseases Research Institute, Xuanwu Hospital of Capital Medical University

13:20-13:30　P-1-3
Ruscogenin Attenuates Cerebral Ischemia-Induced Blood-Brain Barrier Dysfunction by Suppressing TXNIP/NLRP3 Inflammasome Activation and the MAPK Pathway
Guo-Sheng Cao
Jiangsu Key Laboratory of Traditional Chinese Medicine Evaluation and Translational Research, Department of Complex Prescription of Traditional Chinese Medicine, China Pharmaceutical University

13:30-13:40　P-1-4
Kindlin-2 complexes with α-actinin-2 and β1 integrin to maintain the integrity of Z-disc in cardiac muscles
Li-Hua Qi
Department of Human Anatomy, Histology and Embryology, Peking University Health Science Center

13:40-13:50　P-1-5
Calcium homeostasis and endoplasmic reticulum stress are involved in Salvianolic acid B-offered protection against cardiac toxicity of arsenic trioxide
Jing-Yi Zhang
Institute of Medicinal Plant Development, Peking Union Medical College and Chinese Academy of Medical Sciences

13:50-14:00　P-1-6

Poster 2 Kidney

Chair: Bao-Xue Yang
Department of Pharmacology, School of Basic Medical Sciences, Peking University

13:00-13:10 P-2-1

Repulsive Guidance Molecule b Inhibits Renal Cyst Development Through the Bone Morphogenetic Protein Signaling Pathway

Jiang-Feng Liu

Department of Pharmacology, School of Basic Medical Sciences, Peking University

13:10-13:20 P-2-2

Low Molecular Weight Fucoidan Protects Renal Tubular Cells From Injury Induced by Albumin Overload

Ying-Li Jia

Department of Pharmacology, School of Basic Medical Sciences, Peking University

13:20-13:30 P-2-3

Generation and Phenotypic Analysis of Mice Lacking all Urea Transporters

Ying-Jie Li

Department of Pharmacology, School of Basic Medical Sciences, Peking University

13:30-13:40 P-2-4

The Knockout of Urea Transporter-B Improves the Hemorheological Properties of Erythrocyte

Xiao-Qiang Geng

Department of Pharmacology, School of Basic Medical Sciences, Peking University Health Science Center

13:40-13:50 P-2-5

Ganoderma Triterpenes Inhibit Renal Cysts Development by Down-regulating Ras/MAPK Signal Pathway

Li-Min Su

Department of Pharmacology, School of Basic Medical Sciences, Peking University Health Science Center

13:50-14:00 P-2-6

Ganoderma Lucidum Polysaccharide Peptide Prevents Renal Ischemia Reperfusion Injury via Reducing Oxidative Stress

Dan-Dan Zhong

Department of Pharmacology, School of Basic Medical Sciences, Peking University

Poster 3 Shock

Chair: Zi-Gang Zhao
Institute of Microcirculation, Hebei North University

13:00-13:10 P-3-1

Resveratrol enhances vascular reactivity in mice following lipopolysaccharide challenge through RhoA-ROCK-MLCP pathway

Yu-Ping Zhang
Institute of Microcirculation, Hebei North University

13:10-13:20 P-3-2

Post-hemorrhagic shock mesenteric lymph induces splenic dendritic cells dysfunction

Li-Na Jiang
Institute of Microcirculation, Hebei North University

13:20-13:30 P-3-3

Post-hemorrhagic shock mesenteric lymph enhances permeability of thoracic aorta vascular endothelial cells

Ya-Xiong Guo
Institute of Microcirculation, Hebei North University

13:30-13:40 P-3-4

Estrogen treatment enhances the vascular hypo-reactivity in mice following hemorrhagic shock

Li-Min Zhang
Institute of Microcirculation, Hebei North University

13:40-13:50 P-3-5

Resveratrol improves blood rheological properties in LPS-challenged rats

Niu-Niu Feng
Institute of Microcirculation, Hebei North University

13:50-14:00 P-3-6

ω-3PUFAs alleviates hemorrhagic shock-induced acute lung injury through inhibiting autophagy in rats

Chen Zhao
Institute of Microcirculation, Hebei North University

Poster 4 Traditional Medicine

Chair: Fei Ye

Institute of Materia Medica, Chinese Academy of Medical Sciences & Peking Union Medical College

13:00-13:10 P-4-1

Establishment and Evaluation of Qi Deficiency Syndrome Model in Mice

Jun-Guo Ren

Institute of Basic Medical Sciences of Xiyuan Hospital, Key Laboratory of Pharmacology of Chinese Materia in Beijing

13:10-13:20 P-4-2

The establishment and evaluation of a rat model with syndrome of dampness retention due to spleen deficiency

Cui Ning

College of Basic Medical Sciences, Shandong University of Traditional Chinese Medicine

13:20-13:30 P-4-3

The anti-tumor and anti-angiogenesis effects of crude extract of Acanthus ebracteatus Vahl on HPV16-induced cervical cancer in nude mice xenograft model

Liao T

Center of Excellence for Microcirculation, Department of Physiology, Faculty of Medicine, Chulalongkorn University

13:30-13:40 P-4-4

Catalpol Protects the desruction of BMECs tight junctions induced by LPS based on Rho / ROCK pathway

Li Zou

College of Pharmaceutical Sciences & Chinese Medicine, Southwest University

13:40-13:50 P-4-5

Study on the effect and mechanism of JTD on Diabetic Nephropathy

Jin-Ni Hong

Integrated laboratory of Traditional Chinese Medicine and Western Medicine, Peking University First Hospital

13:50-14:00 P-4-6

Glucocorticoid-like effect found in geniposide but accompanied with a selective function

Qi Zhang

Preclinical School of Medicine, Beijing University of Chinese Medicine

Poster 5 Other

Chair: Lu Tie

State Key Laboratory of Natural & Biomimetic Drugs, Department of Pharmacology, School of Basic Medical Sciences, and Institute of System Biomedicine, Peking University

13:00-13:10 P-5-1

Silibinin capsules improve high fat diet-induced nonalcoholic fatty liver disease through hepatic de novo lipogenesis and fatty acid oxidation pathways in hamsters

Chun-Xue Cui

Tasly Microcirculation Research Center, Peking University Health Science Center

13:10-13:20 P-5-2

The association of diabetic kidney disease and diabetic cardiovascular autonomic neuropathy of type 2 diabetic patients

Fang-Fang Zeng

Department of endocrinology of North Huashan Hospital

13:20-13:30 P-5-3

Nordihydroguaiaretic acid impairs prostate cancer cell migration and tumor metastasis by suppressing neuropilin 1

Xin Li

Department of Pharmacology, School of Basic Medical Sciences, Peking University

13:30-13:40 P-5-4

An *in vivo* study of the biodistribution of gold nanoparticles after intervaginal spaces injection in the tarsal tunnel

Xiao-Li Shi

CAS Center of Excellence in Nanoscience, National Center for Nanoscience and Technology

13:40-13:50 P-5-5

H&K Quantum Chip, a brand new Microcirculation enhancement device
Open a new Era for Microcirculation Biotherapy

Tien-Fung Wu

Chinese International MicroCirculation Association Taipei

13:50-14:00

Plenary Lecture 1

15:10-15:40 October 28 Friday

Room 414 Yifu Building

Organ microcirculation and gastrointestinal (GI) disorders

Hidekazu Suzuki, M.D., Ph.D., FACG, AGAF, RFF

President of Japanese Society for Microcirculation

Professor, Medical Education Center, Keio University School of Medicine

Chair: Geraldine Clough，M.D., Ph.D.

Professor, Institute of Developmental Sciences, Faculty of Medicine, University of Southampton

PL-1

Organ microcirculation and gastrointestinal (GI) disorders

Hidekazu Suzuki, MD, PhD, FACG, AGAF, RFF

President of Japanese Society for Microcirculation;
Professor, Medical Education Center, Keio University School of Medicine, Tokyo, Japan

In the multifactorial mechanisms involved in the development of gut mucosal inflammation, derangement of microcirculation is a common initial pathway. In response to gut luminal antigens such as bacteria and food factors, the microvascular endothelium transduces signals to circulating cells. For example, Helicobacter pylori (H. pylori) colonization induces a significant level of leukocyte recruitment to the gastric mucosa as a result of the sequential pathological processes in microcirculatory system (Microcirculation 16:547-558, 2009). This bacterial infection is associated with a variety of clinical outcomes. After H. pylori inoculation, the bacteria colonize the surface epithelium, after which numerous leukocytes rolling or adhering to the endothelial cells can be observed in the venules of the gastric mucosa. These leukocytes invade the gastric mucosa and produce reactive oxygen species such as O2-, OCl-, which is produced by PMNs; and NH2Cl, which is a cytotoxic reaction product with NH3 originating from H. pylori (Am. J. Physiol. 263:G719-725, 1992; Am. J. Physiol. 275:G712-G716, 1998). On the other hand, functional GI disorders (FGIDs) is a syndrome characterized by chronic and recurrent GI symptoms in the absence of any organic, systemic or metabolic disease that is likely to explain the symptoms. FD is remarkably common, can be disabling, and can pose a major social and economic burden (Gastroenterology 150:1380-1392, 2016). Although the pathophysiology of FGIDs is likely complex and multifactorial, and not completely elucidated, not only GI motor and sensory dysfunction, impaired mucosal integrity or local bacterial infection (Nature Rev. Gastroenterol. Hepatol. 12:556-557, 2015, Nature Rev. Gastroenterol. Hepatol. 10:168-74, 2013), but also low-grade inflammation that may be initiated by local infection and microcirculatory damage are considered as implicated etiologies. Then, organ microcirculatory system is more or less involved in these pathophysiologies.

CURRICULUM VITAE

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CURRENT ACADEMIC POSITION:

Professor,
Medical Education Center
Keio University School of Medicine, Tokyo, Japan
Phone: +81-3-5363-3914 Fax: +81-3-5363-3967

EDUCATION

1983-1995 Keio University, Premedical Course, Tokyo, Japan.
1985-1989 Keio University School of Medicine, Tokyo, Japan (M.D. June, 1989)
1989-1993 Keio University, Postgraduate Course of Medicine, Tokyo, Japan
1994 Ph.D.
1993-1995 Postdoctoral Research Fellow, Institute for Biomedical Engineering, University of California at San Diego, La Jolla, California, U.S.A.
1995-2003 Instructor, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan
2003-2016 Visiting Assistant Professor, Department of Internal Medicine, Tokyo Dental College
2007-2015 Head of Outpatient Clinic, Division of Gastroenterology and Hepatology, Keio University Hospital
2011-2015 Associate Professor, Department of Internal Medicine, Keio University School of
2015-present Professor, Medical Education Center, Keio University School of Medicine
2015-present Professor, Keio University Graduate School of Medicine

Associate Editor :

"American Journal of Gastroenterology" (Nature publishing group, 2010-2015)
"Microvascular Communications and Review" (Elsevier, 2006-)
"Digestive Endoscopy" (Wiley, 2012- 2015)
"Frontiers in non-coding RNA" (Frontiers)
"Frontiers in Molecular Biosciences" (Frontiers, 2010-)
"Journal of Gastroenterology" (Springer, 2006-2009)

MEMBERSHIPS IN MEDICAL AND SCIENTIFIC SOCIETIES:

International

2012-present Asian Neurogastroenterology and Motility Association (ANMA, **Executive Director**)
2016-present ILCM member

Domestic

1990-present. The Japanese Society of Gastroenterology (2003-, **Executive member**)
1991-presnet. The Japanese Society of Gastroenterological Endoscopy (2006-, **Executive member**)
1989-present. The Japanses Society for Microcirculation (2016-, **President**)
1992-present. The Japanese Society of Autonomic Nervous System (1998-, **Executive member**)
1993-present. The Japanese Society of Ulcer Research (2015-, **Executive Director**)
1994-present. The Japanese Society of Helicobacter Research (2014- **Executive Director**)
1993-present. Society for Free Radical Research, Japan (2001-, **Executive member**)
2001-present The Japanese Society of Clinical Chinease Medicine (2013-, **Executive Director**)
2002-present. The Japanese Society of Neurogastroenterology (2015-, **Executive Director**)
2004-present. The Japanese Gastroenterological Association (2009-, **Executive member**)
2012-present. The Japanese Association for Cancer Prevention (2012-, **Executive member**)

Plenary Lecture 2

15:10-15:40 October 28 Friday

Room 402 Yifu Building

Aquaporin-1 Translocation and Degradation Partially Mediates the Water Transportation Mechanism of Acetazolamide

Xue-Jun Li, M.D., Ph.D.

Professor, Department of Pharmacology, School of Basic Medical Sciences, Peking University

Chair: You-Yi Zhang

Professor, Key Laboratory of Vascular Cardiovascular Sciences, Ministry of Education / Peking University Institute of Cardiovascular Sciences / Institute of Vascular Medicine. Peking University Third Hospital

PL-14

Aquaporin-1 Translocation and Degradation Partially Mediates the Water Transportation Mechanism of Acetazolamide

Xue-Jun Li
Department of Pharmacology, School of Basic Medical Sciences, Peking University, Beijing 100083, China

Acetazolamide (AZA), a prototype of carbonic anhydrase (CA) inhibitor. It is a sulfonamide derivatives and acts as an diuretic agent with its site of action on renal proximal tubules. This nephron segment also contain aquaporin-1(AQP1) water channels as well, which is required for the formation of concentrated urine. Therefore we hypothesized that AZA may inhibit water transportation mediated by AQP1. In 2002, we confirmed that AZA inhibited the tumor growth and metastasis and the action was accompanied by the down-regulation of AQP1 protein. Later, we found that the inhibition of tumor angiogenesis of AZA was related to decreasing the expression of AQP1 protein in 2004. Further we proved that AZA could inhibit AQP1 water transportation by microinjected AQP1 cRNA into Xenopus laevis oocytes. However some laboratories failed to confirm the direct inhibitory effect of AZA on AQP1 by applying other approaches. In 2013, Seeliger D used AZA as positive control for discovery of new AQP1 inhibitors, they found that AZA significantly inhibited the water transporting function after transfer of the AQP1 gene in Xenopus oocytes, but AZA not acting on the functional sites in AQP1 which they proposed.

In the present study we found that the AZA increased the urine volume from 8 hrs to 14 days in mice. However, total CAs activity was decreased within 8 hrs and then gradually recovered to the normal level and the CAs protein expression was increased at the beginning of AZA treatment. AQP1 expression was significantly reduced after AZA administration for 7 days. When combined with NaHCO3, AZA had a more pronounced diuretic effect. But it didn't induce CA isozymes expression and the CAs activity anymore. However, AQP1 expression was still inhibited from day 7th. AZA increased AQP1 ubiquitination in the HK-2 cell membrane followed by the degradation induced by proteasome. We found that AZA facilitated AQP1 translocation onto cell membrane by promoting the interaction of AQP1 and myosin heavy chain (MHC). And this process was mediated by ERK and myosin light chain kinase (MLCK) pathway. These findings indicate that AZA promotes AQP1 translocation and degradation, which may partially mediates the effect of AZA.

In summary, acetazolamide may regulate AQP1 through a variety of ways by down regulating its expression, suppressing the function, and promote AQP1 ubiquitination and degradation.

• **Job Title**

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Professor Li Xue-Jun currently is a Professor of Pharmacology， School of Basic Medical Sciences, Peking University. She graduated from the Faculty of Medicine, Peking University and then worked in the Dept. of Pharmacology. Between 1992 and 1994, she studied in the Rockefeller University of USA as a Post doctoral fellow. In June of 1996, she was promoted to Professor. From 2003 to July 2008 she worked as Associate Dean of School of Basic Medical Sciences, and for more than 10 years, she chaired the Department Pharmacology. Presently, she serves as Vice President of Chinese Pharmacological Society. Her current research interest focuses on molecular pharmacology and anticancer drug discovery. Up to date she has published more than 200 scientific articles and obtained more than 10 research funds from Chinese government and Rockefeller Foundation of USA.

Plenary Lecture 3

15:40-16:10 October 28 Friday

Room 414 Yifu Building

Sexually Dimorphic Regulation of Cardiovascular Function: Roles of EETs/sEH

An Huang, M.D., Ph.D.

Professor of Physiology, New York Medical College (NYMC), Valhalla, NY

Chair: Akos Koller, M.D., Ph.D.

Professor and Chairman of the Scientific Council, University of Physical Education, 1123 Budapest, Hungary

PL-3

Sexually Dimorphic Regulation of Cardiovascular Function: Roles of EETs/she

An Huang
Department of Physiology, New York Medical College, Valhalla NY

The estrogen-dependent potentiation of cardiovascular function via NO-mediated pathway has been extensively studies, whereas studies pertaining to roles of epoxyeicosatrienoic acids (EETs), specifically soluble epoxy hydrolase (sEH) responsible for catalyzing EETs to DHETs in the mediation of estrogen-dependent cardioprotective actions are less explored. We hypothesized that female sex favors microvascular function via increases in EETs, as a function of suppressing sEH, to attenuate pressure-induced myogenic vasoconstriction (MC) and augment flow/shear stress-induced vasodilation (FID) in arterioles that were isolated from of male (M) and female (F) mice genetically knockout of sEH gene (sEH-KO) and their wild type (WT) control mice. **Results 1:** Myogenic vasoconstriction (MC): Pressure-diameter relationships were assessed in isolated and cannulated coronary arteries (~150μm in diameter). All vessels constricted in response to increases in intraluminal pressure from 60 to 120 mmHg. MC was significantly attenuated, associated with higher cardiac level of EETs in M-KO and F-KO, as well as F-WT mice compared to M-WT controls. Blockade of EETs with 14,15-EEZE (an EET antagonist) prevented the attenuated MC in sEH-KO mice, suggesting an EET-mediated attenuation of myogenic response. In the presence of 14,15-EEZE, pressure-diameter curves of females (F-WT and F-KO) shifted upward from those of males (M-WT and M-KO), manifesting a sex-different phenotype. Additional administration of L-NAME eliminated the sex-difference, suggesting a NO-mediated attenuation of myogenic response in females. Moreover, cardiac expression of sEH was downregulated in F-WT mice. **Conclusion 1**: In combination with NO, the increased EET bioavailability as a function of genetic deletion and/or downregulation of sEH accounts for the female-favorable attenuation of pressure-induced constriction. **Results 2:** Flow-induced vasodilation (FID): isolated gracilis muscle arterioles (~120μm in diameter) were cannulated at 80 mmHg, and increases in diameter as a function of increases in perfusate flow (5, 10, 15, 20 and 25 μl/min) were recorded. The magnitude of FID was significantly greater in arterioles of F-WT than M-WT mice, revealing a female-favorable FID. This sex-difference was abolished by deletion of the sEH gene, as evidenced by an enhanced FID in M-KO mice to a level comparable to those observed in F-KO and F-WT mice. These three groups of mice coincidentally exhibited an increased endothelial sensitivity to shear stress. Protein expression of sEH was downregulated by approximately 4-fold in vessels of F-WT compared to M-WT mice, paralleled with greater vascular EET levels that were comparable to those observed in sEH-KO mice. **Conclusion 2**: Female-specific downregulation of sEH accounts for the sex difference in FID, characterized as an enhanced FID in female WT mice to a comparable level as those of sEH-KO mice. (These studies were supported by National Institutes of Health Grant HL070653, USA)

An Huang

Present Position: Professor of Physiology, New York Medical College (NYMC), Valhalla, NY. **Education**: MD., Ph.D. Shanghai Second Medical University, PR China (1982-1991, Surgery). **Postdoctoral:** NYMC Dept. of Physiology (1992-1994). **Professional Societies**: Microcirculatory Society since 1994, American Physiological Society since 1994, and American Heart/Stroke Association (2013-2014). **Research:** My research has been focusing on the sex/gender difference in the regulation of vascular function since 1995 when I was first awarded a Grant-in-Aid by the American Heart Association (AHA) NY, Affiliate, entitled "Estrogen and microvascular tone in hypertension" (PI: An Huang, 07/1995-06/1997). In these studies, I explored the actions of estrogen in the regulation of microvascular tone and their potential role in hypertension. Supported by a National AHA Scientist Development Grant entitled "Estrogen and coronary arteriolar tone" in 1999 (PI: An Huang, 01/1999-12/2003), I began studying the specific role of estrogen in the regulation of coronary arteriolar function. During these studies, I was able to demonstrate that in physiological conditions, estrogen benefits endothelial function by an upregulation of NO synthase. I concluded that this could be one of the underlying mechanisms responsible for the lower incidence of cardiovascular diseases and delayed appearance of increases in peripheral resistance during the development of hypertension in women compared with that of men. On the other hand, in some pathological situations, such as hypertension or heart failure, vasodilator mechanisms are impaired due to a reduced NO bioavailability. To this end, I extended my research in recent years to focus on estrogen-dependent regulation of vascular function when NO bioavailability is impaired. Supported by National Institute of Health (NIH) RO1 since 2003 (PI: An Huang, 07/01/2003-03/31/2018), I have been working on the project, entitled "Estrogen and EDHF (endothelium-derived hyperpolarizing factors) in NO Deficiency". In these studies, I have been able to demonstrate that estrogen-dependent upregulation of epoxyeicosatrienoic acids (EETs) metabolites of arachidonic acid via cytochrome P450, are responsible for the EDHF-induced vasodilation in female microvessels under conditions of NO deficiency. A current publication entitled "soluble epoxide hydrolase-dependent regulation of myogenic response and blood pressure" was developed into a podcast by recording an interview with both an Associate Editor of AJP and Dr. David Harder, a recognized expert in the field via audio Skype conference call. This podcast has been posted on http://ajpheart.podbean.com/e/the-role-of-eets-in-pressure-induced-vasoconstriction/.

Plenary Lecture 4

15:40-16:10 October 28 Friday

Room 402 Yifu Building

New Advances to Stop Microvascular Leakage During Inflammation

Jerome W. Breslin, Ph.D.

Assistant Professor, Department of Molecular Pharmacology and Physiology, Morsani College of Medicine, University of South Florida

Chair: Bao-Xue Yang, M.D., Ph.D.

Professor, Department of Pharmacology, School of Basic Medical Sciences, Peking University

PL-4

New Advances to Stop Microvascular Leakage During Inflammation

Jerome W. Breslin, PhD

Associate Professor of Molecular Pharmacology and Physiology

Morsani College of Medicine

University of South Florida

Tampa, FL, USA

Microvascular hyperpermeability and edema formation are hallmarks of inflammation. Although excessive microvascular leakage has long been recognized to exacerbate chronic inflammatory states, therapeutic strategies to stop microvascular leakage have not developed. In the last decade, rapid advances in biochemical analysis, genetic manipulation, microscopic imaging, and recombinant protein biosensors have significantly expanded our understanding of the cellular and molecular mechanisms that control the barrier function of the microvascular wall. Our laboratory focused efforts on detecting time-dependent signaling events and structural changes within individual endothelial cells in response to stimuli that are known to modulate endothelial permeability. The most striking finding from this work was the discovery of local lamellipodia that determine the degree of contact between adjacent endothelial cells and promote integrity of cell-cell junctions. From this work, we found that sphingosine-1-phosphate (S1P) and cyclic AMP analogs robustly promote local lamellipodia formation in endothelial cells, which temporally correlates with enhanced barrier function. In addition, tests by multiple lab groups, including our own, suggest that S1P and other agonists of S1P receptors can reduce microvascular hyperpermeability in a variety of *in vivo* models. These findings offer promise of a new, additional strategy to supplement current anti-inflammatory therapies. In addition, the use of S1P receptor agonists may open new horizons for chronic microvascular hyperpermeability that currently have limited treatment options.

Jerome W. Breslin, Ph.D.

Associate Professor of Molecular Pharmacology and Physiology,
Morsani College of Medicine, University of South Florida

Education:

B.A., 1993 Rutgers University, New Brunswick, NJ; Biological Sciences
M.S., 1998 Seton Hall University, South Orange, NJ; Biology
Ph.D., 2002 Rutgers University (formerly University of Medicine and Dentistry of New Jersey), Newark, NJ; Pharmacology and Physiology
Postdoc, 2002-2004 Dept. of Surgery, Texas A&M University College of Medicine; Scott and White Memorial Hospital, Temple, TX
Postdoc, 2004-2007 Dept. of Surgery, University of California, Davis, School of Medicine, Sacramento, CA

Academic Appointments:

10/2007 – 9/2012 Assistant Professor (Tenure-Track) of Physiology, School of Medicine, Louisiana State,University Health Sciences Center, New Orleans, LA
10/2012 – present Associate Professor (Tenure granted 7/2013) of Molecular Pharmacology and Physiology, Morsani College of Medicine, University of South Florida, Tampa, FL

Membership in Professional Organizations:

The Microcirculatory Society, Inc.; American Physiological Society; American Heart Association; American Society for Cell Biology

Teaching Accomplishment:

2015 – present Course Director for Medical Sciences 4: GI, Renal, and Endocrine Systems (Medical School)
2013 – present Course Director for Cardiovascular Regulation (Graduate School)

Current Grant Support:

7/15/16 – 4/30/20 S1P-fluid therapy to reduce hemorrhagic shock & intoxication-induced injury
NIH/NIGMS R01GM120774
Role: PI

7/1/15 – 6/30/17 Signaling Mechanisms Controlling Sphingosine-1 Phosphate-Induced Microvascular Barrier Enhancement
American Heart Association 15PRE25710193; PI: Xun Zhang
Role: Sponsor

Other Professional Activities:

6/1/2013 – present Associate Editor, *Microcirculation*
9/1/2014 – present Academic Editor, *PLOS One*
2013 – present Reviewer on NIH PAR panels ZRG1 DKUS-A (57), DKUS-D (57), DKUS-E (57), and DKUS-C(58). Topic: Lymphatics in Health and Disease
2014 Reviewer on NIH/NHLBI Special Emphasis Panel ZHL1 CSR-O (S1) "Blood and Vascular Systems Response to Sepsis (R01)"
2016 Reviewer, Natural Sciences and Engineering Research Council of Canada Discovery Grants Peer-reviewer for many journals including *Journal of Clinical Investigation, Journal of Physiology (London), Circulation Research, American Journal of Physiology, Scientific Reports,* and others.

Recent Publications:

Zhang XE, Adderley SP, **Breslin JW**. Activation of RhoA, but not Rac1, mediates early stages of S1P-induced endothelial barrier enhancement. *PLOS One* 11: e0155490, 2016. PMID: 27187066 PMCID: PMC4871357

Breslin JW, Daines DA, Doggett TM, Kurtz KM, Souza-Smith FM, Wu MH, Yuan SY. Rnd3 as a novel target to ameliorate microvascular leakage. *J. Am. Heart. Assoc.* 5: e003336, 2016. PMID: 27048969

Adderley SP, Lawrence C, Madonia E, Olubadewo JO, **Breslin JW**. Histamine activates p38 MAP kinase and alters
local lamellipodia dynamics, reducing endothelial barrier integrity and eliciting central movement of actin fibers. *Am. J.*
Physiol. Cell Physiol. 309: C51-C59, 2015. PMID: 25948734 PMCID: PMC4490326

Breslin JW, Zhang XE, Worthylake RA, Souza-Smith FS. Involvement of local lamellipodia in endothelial barrier function. *PLOS One*. 10: e0117970, 2015. PMID: 25658915 PMCID: PMC4320108

Adderley SP, Zhang XE, **Breslin JW**. Involvement of the H1 histamine receptor, p38 MAP kinase, MLCK, and Rho/ROCK in histamine-induced endothelial barrier dysfunction. *Microcirculation*. 22: 237-248, 2015.

Plenary Lecture 5

16:10-16:40 October 28 Saturday

Room 414 Yifu Building

Current Status and Future Perspectives in Modernization of Chinese Herbal Medicines

De-An Guo, M.D., Ph.D.

Professor, Shanghai Research Center for TCM Modernization, Shanghai Institute of Materia Medica, Chinese Academy of Sciences

Chair: Suthiluk Patumraj, Ph.D.

Professor, Excellence Center for Microcirculation, Department of Physiology, Faculty of Medicine, Chulalongkorn University

PL-5

Current Status and Future Perspectives in Modernization of Chinese Herbal Medicines

De-an Guo (Shanghai Research Center for TCM Modernization, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, P.R. China; daguo@simm.ac.cn)

Traditional Chinese medicine (TCM) has over 3000 years of history and played important role in the peoples' health and social development in Chinese history. In the past 50 years, Chinese scientists have made great effort to modernize TCM to make it an evidence-based medicine from the experience-based origin. The current review has summarized the recent advances in the modern research on the various respects of TCM including the resources investigation, GAP cultivation, phytochemistry, quality assessment, safety issues, metabolic investigation, pharmacology, systems biology etc. It was pointed out that GAP for Chinese herbs is the first and key step in the quality control cycle of traditional Chinese medicine. In addition, the research on TCM active principles and quality control methods were also summarized. Over 12,000 chemical constituents have been isolated from over 600 species of traditional Chinese medicines, among which over 3000 new compounds were discovered, which laid a solid foundation for clarifying the material basis of action and providing reference substances for the quality control of TCM. Systems biology approach is now being actively practiced for the action mechanism studies of TCMs and their active principles, which provided a valuable approach for complex TCM systems. Currently, genomics, preotenomics and metabolomics have obtained good application in TCM studies. Inaddition, the progress of TCM new drug research and development has been outlined. Several famous new drugs from TCM or based on TCM have been successfully marketed. Examples are artemisinin, artemether, hupzine A, etc. Other types of new drugs include Fufang Danshen Dripping Pill, Diao Xinxuekang, etc. Finally, the existing challenges and opportunities will be outlines and future perspectives will be projected.

Dr. De-An Guo serves as director of the Shanghai Research Center for TCM Modernization at the Shanghai Institute of Materia Medica, Chinese Academy of Sciences. He is currently the President of GP-TCM Research Association (London) and Chair, Vice chair or expert committee member of Chinese Pharmacopoeia, United States Pharmacopoeia and European Pharmacopoeia. At present, he is Editor-in-chief, vice editor or editorial board member of 18 international journals. He is mainly engaging TCM analysis and quality research and received a number of renowned national and international awards including Second Prize of National Natural Science Award (2012), Wujieping Medical and Pharmaceutical Innovation Award (2013), American Botanical Council Norman Farnsworth Excellence Award in Botanical Research (2013), Cheung An Tak International Award for Outstanding Contribution to Chinese Medicine (2015), American Society of Phamacognosy Varo Tyler Prize (2016), and Second Prize of National Science and Technology Advancement Award (2016). To date, he has published 380 SCI papers with over 7000 SCI citations.

Plenary Lecture 6

16:10-16:40 October 28 Saturday

Room 402 Yifu Building

Regulation of Microvascular Blood Flow and Oxygen Supply

Roland N. Pittman, Ph.D.

Professor, Medical College of Virginia Campus

Virginia Commonwealth University

Chair: Tailoi Chan-Ling, M.D., Ph.D.

Professor, Discipline of Anatomy and Histology, Sydney Medical School

Bosch Institute, the University of Sydney

PL-6

Regulation of Microvascular Blood Flow and Oxygen Supply

Roland N. Pittman and Aleksander S. Golub

Department of Physiology and Biophysics, Medical College of Virginia Campus, Virginia Commonwealth University, Richmond, Virginia, USA

Mammalian cells rely on a continuous, adequate supply of oxygen to the tissues for survival. When the activity of a tissue increases, blood flow increases (functional hyperemia) to match the oxygen supply to oxygen demand. Over the past 140 years, several mechanisms have been proposed to account for metabolically-linked matching of oxygen supply to demand. The classic metabolic hypothesis is based on the elaboration of vasodilator compounds from hypoxic tissue. Precisely how a multitude of vasodilator substances are able to interact simultaneously to match oxygen supply to demand remains a mystery. In the mid-1990s two new hypotheses were proposed in which the red blood cells (RBCs) acted as mobile oxygen sensors and released either ATP or nitric oxide (NO) in response to a decrease in the oxygenation of hemoglobin. Although a number of steps in these proposals have been tested experimentally, in neither case has the entire sequence of molecular events been satisfactorily integrated into a viable explanation of functional hyperemia. More recently a new hypothesis, involving production and interaction of the two signaling radicals, NO and superoxide (O_2^-), has been proposed to account for functional hyperemia in skeletal muscle, due in part to their localized production and their rapid and selective chemical reaction, which neutralizes NO in the ISF and reduces its vasodilator action. The primary sources of these radicals are eNOS in endothelial cells for NO and NAD(P)H oxidase in nearby parenchymal cells for O_2^-. When the activity of the parenchymal cells increases, oxygen consumption (VO_2) increases to produce the needed ATP, oxygen tension (PO_2) in the active cells and interstitial fluid (ISF) decreases, leading to a reduction in O_2^- emitted into the ISF and an elevation of NO. The resulting vasodilation of the arterioles and functional hyperemia persist until the parenchymal cell activity declines toward the baseline state. Recent results of real-time measurements of [NO] during muscle contraction, using a fluorescent NO indicator in the ISF, showed that the kinetics of NO changes were as predicted by a mathematical model.

Because the goal of the NO/O_2^- radical pair hypothesis of local blood flow regulation is to provide an adequate, but not excessive, supply of oxygen to meet the tissue's energy needs, the relationship between oxygen consumption and PO_2 is a key element of the integrated oxygen transport/regulatory system. The classic view, supported by decades of in vitro studies on isolated cell and mitochondrial suspensions, is that VO_2 is virtually independent of PO_2 until the PO_2 falls to near or below 1 mmHg; i.e., mitochondrial respiration is quite insensitive to oxygen over the physiological PO_2 range. Recent results from the first in situ measurements of the PO_2 dependence of VO_2 demonstrated a dramatic departure from this view: the PO_2 for half-maximal VO_2 (k_m) was found to be 10 mmHg, more than an order of magnitude higher than the previous in vitro results. A possible explanation for this discrepancy was that the chemical environment of mitochondria in situ was sufficiently different from that of the in vitro experiments to account for the difference. Following the in situ findings another group repeated the in vitro measurement of the PO_2 dependence of mitochondrial VO_2 with a finding of k_m = 12 mmHg, in agreement with the in situ result. Thus, it appears that cellular respiration is indeed sensitive to oxygen over most of the in vivo range of PO_2, a new finding that should be considered in the interpretation of future studies of oxygen transport in organs and tissues.

Incorporation of these new results into our understanding of oxygen transport and its regulation can be facilitated with the use of electrical circuit analogies which combine convective and diffusive transport of oxygen with a control system utilizing the NO/O_2^- radical pair hypothesis, describing oxygen's role in the local regulation of blood flow and oxygen supply. Because of the essential need for oxygen in the normal function of all cells, a reduction in oxygen supply is often associated with pathological conditions. The expansion of these studies to common disease states in which oxygen is known to be a limiting factor in tissue or organ function may reveal new ideas for early detection and treatment of these conditions.

Roland N. Pittman, Ph.D.
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Education

State University of New York, Stony Brook, New York, Ph.D. (Physics) 1971
Massachusetts Institute of Technology, Cambridge, Massachusetts, S.B. (Physics) 1966

Faculty Positions

1974-78: Asst Prof of Physiology, Virginia Commonwealth Univ, Richmond, Virginia
1978-87: Assoc Prof of Physiology, Virginia Commonwealth Univ, Richmond, Virginia
1987-present: Prof of Physiology, Virginia Commonwealth Univ, Richmond, Virginia
1992-present: Prof of Biomedical Engineering, Virginia Commonwealth Univ, Richmond, Virginia
2000-present: Prof of Emergency Medicine, Virginia Commonwealth Univ, Richmond, Virginia

Honors

Microcirculatory Society Travel Award, 1976; Finalist, Louis N. Katz Basic Science Research Prize for Young Investigators, AHA, 1979; Instrumentation for Physiology and Medicine, Inc. Innovative Instrumentation Award, Microcirculatory Society, 1989; Fellow, American Physiological Society, Cardiovascular Section, 1991; President, Microcirculatory Society, 1993-1994; Senior Member, Biomedical Engineering Society, 1995; Fellow, American Institute of Medical and Biological Engineering, 1999; Eugene M. Landis Research Award, Microcirculatory Society, 2012.

Publications (selected from 150)

Pittman RN, Duling, BR. Measurement of percent oxyhemoglobin in the microvasculature. J. Appl. Physiol. 38:321-327, 1975.

Kuo L, **Pittman RN.** Effect of hemodilution on oxygen transport in arteriolar networks of hamster striated muscle. Amer. J. Physiol. 254:H331-H339, 1988.

Japee SA, **Pittman RN**, Ellis CG. A new video image analysis system to study red blood cell dynamics and oxygenation in capillary networks. Microcirculation 12:489-506, 2005.

Golub AS, **Pittman RN.** Erythrocyte-associated transients in PO_2 revealed in capillaries of rat mesentery. Am. J. Physiol. Heart Circ. Physiol. 288:H2735-H2743, 2005.

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Golub AS, **Pittman RN.** PO_2 measurements in the microcirculation using phosphorescence quenching microscopy at high magnification. Am. J. Physiol. Heart Circ. Physiol. 294:H2905-H2916, 2008.

Chen K, **Pittman RN**, Popel AS. Nitric oxide in the vasculature: Where does it come from, and where does it go? A quantitative perspective. Antiox. Redox Signal., 10:1185-1198, 2008.

Pittman RN. Oxygen gradients in the microcirculation. Acta Physiologica 202:311-322, 2011.

Golub AS, Song BK, **Pittman RN.** The rate of oxygen loss from mesenteric arterioles is not unusually high. Am J Physiol Heart Circ Physiol. 301:H737-745, 2011.

Pittman RN. Oxygen gradients in the microcirculation. Acta Physiologica 202:311-322, 2011.

Golub, AS, Song, BK, **Pittman, RN.** The rate of oxygen loss from mesenteric arterioles is not unusually high. Am J Physiol Heart Circ Physiol. 301:H737-745, 2011.

Golub, AS, **Pittman, RN.** Oxygen dependence of respiration in rat spinotrapezius muscle in situ. Am. J. Physiol. Heart Circ. Physiol. 303:H47-H56, 2012.

Pittman RN. Oxygen transport in the microcirculation and its regulation. Microcirculation 20:117-137, 2013.

Golub, AS, **Pittman, RN.** Bang-bang model for regulation of local blood flow. Microcirc 20:455-483, 2013.

Golub, AS, **Pittman, RN**. A paradigm shift for local blood flow regulation. J. Appl. Physiol. 116:703-705, 2014.

Plenary Lecture 7

16:40-17:10 October 28 Saturday

Room 414 Yifu Building

Role of the bone microvascular niche in the progression and treatment of tumour metastasis

Nicola J. Brown, Ph.D.

President of British Microcirculation Society，

Professor of Department of Oncology & Metabolism，Microcirculation Research Group， Faculty of Medicine, Dentistry and Health， University of Sheffield

Chair: Gerald A. Meininger, M.D., Ph.D.

Professor, Dalton Cardiovascular Research Center

Department of Medical Pharmacology and Physiology

University of Missouri-Columbia

PL-7

Role of the bone microvascular niche in the progression and treatment of tumour metastasis

Nicola J Brown[1], Jamie K Hobbs[2], Ingunn Holen[1], Jacob Albon[2], Kimberley J Reeves[1] , Marie-Therese Haider[1], Gloria Allocca[1]

Microcirculation Research Group, Departments of Oncology[1] and Physics and Astonomy[2], University of Sheffield, UK.

This talk will overview our current knowledge of the regulation of bone angiogenesis, the involvement and targeting of microvessels in cancer-induced bone disease, and experimental developments for the monitoring of bone-endothelial-tumour interactions both *in vitro* and *in vivo.*

Blood vessels are crucial for regulating physiological tissue development and homeostasis, in addition to being involved in detrimental responses induced by aging and disease processes. In the skeleton, control of the microvascular network growth is thought to be via bone cells (osteoblasts, osteoclasts) and chondrocytes in concert with other cell-types including the endothelium in the bone microenvironment. The angiogenic mitogen, vascular endothelial growth factor (VEGF) is the most well-characterised of these angiogenic mitogens. However, our understanding of the functional, molecular and structural control of the bone microvasculature is limited in both healthy tissue and disease processes such as cancer. This is largely due to the technical limitations surrounding 3D longitudinal real-time non-invasive imaging of bone in preclinical models.

Primary prostate and breast cancers demonstrate a high rate of secondary spread to the skeleton, with bone metastasis inducing significant morbidity such as pain and fractures. However currently there is no curative treatment for patients with advanced disease. Cells of the bone microenvironment including both haematopoietic and vascular cells express a range of receptors including VEGFR2, cMET and integrin receptors and may therefore be responsive to therapy, targeting such receptors. Clinically, patients with advanced disease are responsive to anti-resorptive agents, which reduce the frequency of bone lesions in addition to strengthening the bone structures and have been shown to also modulate angiogenesis. We have used a combination of *in vivo* and *in vitro* models, therapeutic agents and imaging modalities to investigate the response of metastatic tumour cell homing, localisation, colonisation and adhesion within the bone microenvironment and have determined the involvement of the bone microvasculature in this process. Our findings indicate that the bone microvasculature is central to the metastatic process, has biological and mechanical components, can be manipulated to reduce tumour cell colonisation and both the bone and tumour microvasculature are responsive to combination vascular-targeted therapy with chemotherapeutic or biological agents, leading to enhanced treatment efficacy.

We gratefully acknowledge the support of Cancer Research UK, Breast Cancer Campaign, Breast Cancer Now and the British Association for Cancer Research

Nicola J Brown Biosketch

Nicola Brown was appointed Professor of Microcirculation Biology in 2003 at the University of Sheffield. She is currently a senior principal investigator within the Department of Oncology and Metabolism, in the Faculty of Medicine, Dentistry and Health at the University of Sheffield, where she is Director of the Microcirculation Research Group which she established in 1991 and is also Head of the Academic Surgical Oncology Unit within the Department. Professor Brown has over 25 years of laboratory-based cancer research experience which has been funded largely by PI project grant funding primarily from cancer charities including CRUK , in addition to CoI programme and project grant funding from Research Councils (EPSRC, BBSRC) and charities. Professor Brown has published more than 130 original research articles and is a named inventor on three patents, in addition to supervising more than 30 PhD students and 15 postdoctoral research scientists, many of whom have secured academic positions. Professor Brown is a member of the editorial board of the Journal of Vascular Research, Journal of Photochemistry and Photobiology and an associate editor for Frontiers in Vascular Physiology; she has served on the Medical Research Council Fellowships and Training Panel, and the scientific advisory board for the Breast Cancer Campaign, in addition to being an Executive committee member for the British Association for Cancer Research (BACR) and on the Training and Meetings Committee. Professor Brown has been an active member of the British Microcirculation Society for 25 years, first as a committee member, then Treasurer, and is currently President of the society The main strategic aims of the Microcirculation Research Group is to use a multidisciplinary and translational approach to further understand the molecular mechanisms controlling angiogenesis in both wound biology and tumour progression and metastasis, and to develop novel and repurposing existing therapies targeting the microvasculature for angiogenesis-dependent disorders primarily using sophisticated *in vivo* models and imaging, including conventional, confocal, multiphoton and atomic force microscopy. In addition to her research activities Professor Brown contributes to University teaching at both undergraduate and postgraduate levels, has a special interest in mentoring junior researchers, and chairs a number of administrative committees.

Plenary Lecture 8

16:40-17:10 October 28 Saturday

Room 402 Yifu Building

Receptor-interacting protein kinase 3 promotes platelet activation and thrombosis

Ke-Sheng Dai, M.D., Ph.D.

Professor, Deputy Director, Key Laboratory of Thrombosis and Hemostasis, Ministry of Health, Research Unit on Thrombosis and Hemostasis, Jiangsu Institute of Hematology, The First Affiliated Hospital of Soochow University

Chair : Nai-Feng Liu, M.D., Ph.D.

Professor of Medicine, Zhongda Hospital, Southeast University

PL-8

Receptor-interacting protein kinase 3 promotes platelet activation and thrombosis

Kesheng Dai
Jiangsu Institute of Hematology, The First Affiliated Hospital, The Cyrus Tang Hematology Center, and Collaborative Innovation Center of Hematology, Soochow University, Key Laboratory of Thrombosis and Hemostasis, Ministry of Health, Suzhou, China.
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Previous studies have shown that receptor-interacting protein kinase 3 (RIP3) is involved in many important biological processes such as necroptosis, apoptosis, and inflammation. Here we show that RIP3 plays a critical role in regulating platelet functions and *in vivo* thrombosis and hemostasis. We showed that RIP3-knockout ($RIP3^{-/-}$) mice had tail-bleeding times that were significantly increased compared with their wild-type littermates. In an *in vivo* model of arteriole thrombosis, mice lacking RIP3 exhibited prolonged occlusion times. Wild-type mice repopulated with $RIP3^{-/-}$ bone marrow-derived cells had longer occlusion times than $RIP3^{-/-}$ mice repopulated with wild-type bone marrow-derived cells, suggesting a role of RIP3-deficient platelets in arterial thrombosis. Consistent with these findings, we observed that RIP3 was expressed in both human and mice platelets. Deletion of RIP3 in mouse platelets caused a marked defect in aggregation and attenuated dense granule secretion in response to low doses of thrombin or a thromboxane A_2 analogue, U46619. Phosphorylation of Akt induced by U46619 or thrombin was diminished in $RIP3^{-/-}$ platelets. Moreover, we found that RIP3 interacted with $G\alpha_{13}$. Spreading on fibrinogen and clot retraction were impaired in RIP3-deficient platelets. A RIP3 inhibitor dose-dependently inhibited platelet aggregation *in vitro* and prevented arterial thrombus formation *in vivo***.** These data demonstrate a novel role for RIP3 in promoting *in vivo* thrombosis and hemostasis by amplifying platelet activation. RIP3 may represent a novel promising therapeutic target for thrombotic diseases.

Kesheng Dai, Ph.D., M.D.

Kesheng Dai received his PhD in hematology from Soochow University, China, and postdoctoral training in Department of pharmacology from University of Illinios, USA. Dr. Dai is Professor and Deputy Director, Key Laboratory of Thrombosis and Hemostasis, Ministry of Health, Research Unit on Thrombosis and Hemostasis, Jiangsu Institute of Hematology, The First Affiliated Hospital of Soochow University. He was previously Professor in space life-science, Beihang University, China. Research directions in his lab include signaling and regulatory mechanisms of a platelet adhesion receptor glycoprotein Ib-IX complex, the signaling cascades leading to the activation of the platelet integrin alpha IIb/beta 3, and signaling and regulatory mechanisms of platelet apoptosis and glycoprotein Ib alpha shedding. He has opened an important new field of research with interest both for basic and applied research and may explain why astronauts are not experiencing thromboembolism despite extensive sitting during their spaceflights. He has published about 100 articles in leading journals in thrombosis and haemostasis, 31 articles are cited by SCI, including Blood, Circulation Research, J Thromb Haemost. He is the principal Investigator of the National Natural Science Funds (national key project).

Plenary Lecture 9

10:10-10:40 October 29 Saturday

Room 414 Yifu Building

Acanthus ebracteatus Vahl suppresses hypoxia-induced angiogenesis via inhibition of HIF-1α/VEGF signaling pathway in cervical cancer implanted nude mice

Suthiluk Patumraj, Ph.D.

Professor, Excellence Center for Microcirculation, Department of Physiology, Faculty of Medicine, Chulalongkorn University

Chair: Fu long Liao**, Ph.D.**

Professor, China Academy of Traditional Chinese Medicine

PL-9

Acanthus ebracteatus Vahl suppresses hypoxia-induced angiogenesis via inhibition of HIF-1α/VEGF signaling pathway in cervical cancer implanted nude mice

Suthiluk Patumraj[1], Natchaya Wongeakin[1], Toshiki Watanabe[2], Parvapan Bhattarakosol[3]

[1] Excellence Center for Microcirculation, Department of Physiology, Faculty of Medicine, Chulalongkorn University, Bangkok, 10330, Thailand

[2] Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan

[3] Department of Microbiology, Faculty of Medicine, Chulalongkorn University, Bangkok, 10330, Thailand

Abstract:

Background: Recently, it has been reported that *Acanthus ebracteatus* Vahl (AE) crude extract exhibit antitumor effects in cervical cancer implanted nude mice. However, the mechanisms of antitumor effects of AE still remain unclear. Therefore, the study aimed to investigate mechanisms of anti-angiogenic effect of AE related to HIF-1α/VEGF signaling pathway by using CaSki (HPV-16 positive) implanted nude mice model.

Methods: All nude mice were divided in to 3 major groups; 1) control group, 2) HPV-treated-vehicle group (HPV), 3) HPV-treated-with AE group (AE). After tumor bud in each mouse is approximately 0.5*0.5 cm^3, mice were given AE dose 3,000 mg/kg BW by gavage daily. After treatment for 7, 14 and 28 days, the tumor bud was measure by caliper. Capillary vascularity (CV) was determined using laser scanning confocal microscopy and then percentage of CV was calculated for each confocal image by using Image Software. Tumor tissue was collected from each mouse to evaluate HIF-1α and VEGF expressions by immunohistochemistry.

Results: The results showed that % CV in both AE14D and AE28D decreased significantly as compared to HPV14D and HPV28D, respectively. Moreover, the HIF-1α expression in AE14D decreased significantly as compared to HPV14D. Nevertheless, there were significant differences in VEGF expressions between HPV and AE at 14 days.

Conclusion: The findings of study demonstrated that AE extract seem to have the inhibitory effect on tumor angiogenesis with closed correlation to HIF-1α/VEGF-dependent pathways.

Suthiluk Patumraj (Professor in Physiology)

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Educational Background

Degree	Subject	University	Year
B.Sc.	Biochemistry	Chulalongkorn University	1981
M.Sc.	Biomedical Engineering	New Jersey Institute of Technology, USA	1985
Ph.D.	Physiology	University of Medicine and Dentistry of New Jersey, USA	1990

Area of Specialization: Microcirculation

Current Position:

- Professor Department of Physiology, Faculty of Medicine, Chulalongkorn University
- Assistant Dean for Academic Affairs, Faculty of Medicine, Chulalongkorn University
- Editorial board of Asian biomedicine
- Editorial board of Clinical Hemorheology and Microcirculation
- President of Thai Society for Microcirculation
- International Liaison Committee for Microcirculation

Past Position:

● Assistant to the President for Research Affairs, Chulalongkorn University
● Assistant Dean for Graduate Affairs, Faculty of Medicine, Chulalongkorn University
● Secretary General for the Organizing Committee of the 3rd Asian Congress for Microcirculation
● Secretary General for the Organizing Committee of the 8th Asian Congress for Microcirculation

Awards:

American Heart Fellowship, New Jersey, USA. 1987-1989.
Young Investigator Award. The First Asian Congress for Microcirculation, 1993. Osaka, Japan.

Research Articles (last 3 years]

1. Yoysungnoen-Chintana, P, Bhattarakosol, P, **Patumraj, S.** Antitumor and antiangiogenic activities of curcumin in cervical cancer xenografts in nude mice. BioMed Research International, **2014**, 817972
2. Viboolvorakul S, and **Patumraj S.** Exercise training could improve age-related changes in cerebral blood flow and capillary vascularity through the upregulation of VEGF and eNOS. Biomed Res Int. 2014. Article ID 230791, 12 pages
3. Wongeakin N, Bhattarakosol P, and **Patumraj S.** Molecular Mechanisms of Curcumin on Diabetes-Induced Endothelial Dysfunctions: Txnip, ICAM-1, and NOX2 Expressions. Biomed Res Int. Volume **2014**, Article ID 161346, 10 pages. http://dx.doi.org/10.1155/2014/161346
4. Khemthongcharoen, N., Ruangpracha, A., Sarapukdee, P., (...), **Patumraj, S.,** Piyawattanametha, W. Novel p16 binding peptide development for p16-overexpressing cancer cell detection using phage display. Journal of Peptide Science, **2015**. 21 (4), pp. 265-27
5. Yoysungnoen, B, Bhattarakosol, P, **Patumraj, S**, Changtam, C. Effects of tetrahydrocurcumin on hypoxia-inducible factor-1 α and vascular endothelial growth factor expression in cervical cancer cell-induced angiogenesis in nude mice. BioMed Research International, **2015**, 391748
6. Yoysungnoen, B, Bhattarakosol, P, Changtam, C and **Patumraj, S.** Effects of tetrahydrocurcumin on tumor growth and cellular signaling in cervical cancer xenografts in nude mice. Biomed Res International, Published online **2016** Jan 4. doi:10.1155/2016/1781208.
7. Wei Li, Suwanavela N.C., **Patumraj S.** Pre-reperfusion of curcumin could protect blood-brain barrier against I/R injury associated with Nrf2, and NF-kappa-B expressions in transient MCAO rat model. Microvas Res. **2016.** 106, pp. 117-127.

Plenary Lecture 10

10:10-10:40 October 29 Saturday

Room 402 Yifu Building

Future challenges for sepsis: novel strategies based on big data produced by Omics

Yong Jiang, Ph.D.

Professor and Chairman of Department of Pathophysiology, Director of Key laboratory of functional proteomics of Guangdong province, School of Basic Medical Sciences of Southern Medical University

Chair: Nicola J. Brown, Ph.D.

President of British Microcirculation Society，

Professor of Department of Oncology & Metabolism，Microcirculation Research Group， Faculty of Medicine, Dentistry and Health， University of Sheffield

PL-10

Future challenges for sepsis: novel strategies based on big data produced by Omics

Yong Jiang

Guangdong Provincial Key Laboratory of Proteomics, Key Laboratory of Transcriptomics and Proteomics of Ministry of Education of China, State Key Laboratory of Organ Failure Research, Southern Medical University, Guangzhou 510515, China

Every medical advances will have a significant impact on the survival quality and life time of human beings. The invention of microscope made it possible for humans to observe and understand the microcosmic world associated with diseases. The success of vaccine and the synthesis of antibiotics have greatly extended the life of human beings. Since the 20th century, modern medicine has made a revolutionary progress on the interpretation of gene and protein functions, which also helps us to understand and aware the development process of life and disease in a great leap forward. As the human genome project (HGP) finished, various data produced by Omics have generated in great quantities, which makes life science and medicine for the first time into the era of big data. The basic research of life science and clinical medical practice is undergoing major changes. It is going to realize the change of theory exploration primarily driven by big data with auxiliary experiments. This will not only change the basic medical research model, but also has profound influence on new drug research and development process (R&D), including target detection, compound screening and function optimization. Sepsis and multiple organ dysfunction (MODS) brought by sepsis have a severe effect on human health, but still lack of effective drug treatment. In this paper, we introduce how to use a new generation high-throughput sequencing technologies (next generation sequencing, NGS) and quantitative proteomic techniques to explore the law of occurrence and development of sepsis and novel therapeutic strategies.

CURRICULUM VITAE

Yong Jiang, M.D., Ph.D.

Current Position:

Professor and Chairman of Department of Pathophysiology,
Director of Key laboratory of functional proteomics of Guangdong province,
School of Basic Medical Sciences of Southern Medical University.
E-mail: jiang48231@163.com

Education:

The First Military Medical University, Guangzhou, China, 1985, M.D., Specialty in Medicine.
The First Military Medical University, Guangzhou, China, 1990, M.S., Specialty in Pathophysiology.
Chinese Academy of Military Medical Sciences, Beijing, China, 1997, Ph.D., Specialty in Molecular Biology.

Research and Professional Experience

1987 –1990: Research Fellow, Department of Pathophysiology, The First Military Medical University, Guangzhou, China.
1990 –1994: Lecturer, Key Lab for Shock and Microcirculation of PLA, Department of Pathophysiology, The First Military Medical University, Guangzhou, China.
1995 –1997: Research Associate, Department of Immunology, The Scripps Research Institute, La Jolla, CA, USA
1997 –1998: Associate Professor and Vice Director, Key Lab for Shock and Microcirculation of PLA, Department of Pathophysiology, The First Military Medical University, Guangzhou, China.
1998 –1999: Professor and Director, Key Lab for Shock and Microcirculation of PLA, Department of Pathophysiology, The First Military Medical University, Guangzhou, China.
1999 –2001: Visiting Professor, Dept. of Internal Medicine, University of Iowa College of Medicine, Iowa, USA.
2001 – 2004: Professor and Chairman, Key Lab for Shock and Microcirculation of PLA, Department of Pathophysiology, The First Military Medical University, Guangzhou, China.
2004 –2011: Professor and Director, Key Laboratory of Functional Proteomics of Guangdong Province, Department of Pathophysiology, Southern Medical University, Guangzhou, China.
2011 –2012: Visiting Professor, Department of Surgery, School of Medicine, University of Pittsburgh, Pittsburgh, USA
2012 – up to now: Professor and Director, Key Laboratory of Functional Proteomics of Guangdong Province; Chairman of Department of Pathophysiology, Southern Medical University, Guangzhou, China.

Awards and Honors:

Award for Yong Investigators of Shock Society of China, 1992
Scholarship of Zeng Xianzhi, 1997
Award for Yong Investigators of Shock Society of China, 1998
China Youth Award of Science and Technology, 1998
First Award for the Advance in Science & Technology of PLA, 2000
Qiushi Outstanding Youth Award, 2001
Zhu Jiang Scholar, 2006 Program
Chang Jiang Scholar, 2010 Program

Plenary Lecture 11

10:40-11:10 October 29 Saturday

Room 414 Yifu Building

Effects of Moesin Phosphorylation in Endothelial Dysfunction Induced by Advanced Glycation Endproducts

Qiao-Bing Huang, M.D., Ph.D.

Professor, Department of Pathophysiology, School of Basic Medical Sciences, Southern Medical University

Chair: Jerome W. Breslin, Ph.D.

Assistant Professor, Department of Molecular Pharmacology and Physiology, Morsani College of Medicine, University of South Florida

PL-11

Effects of Moesin Phosphorylation in Endothelial Dysfunction Induced by Advanced Glycation Endproducts

Qiao-Bing Huang, Xiao-Hua Guo
Department of Pathophysiology, School of Basic Medical Sciences, Southern Medical University, Guangzhou, China, 510515

Aim: To investigate the effects and the cellular signaling mechanisms of phosphorylation of ERM protein, especially moesin, in endothelial dysfunction induced by advanced glycation endproducts (AGEs).
Methods: Human umbilical vein endothelial cells (HUVECs) or human dermal microvascular endothelial cells (HMVECs) was used in the study. AGE modified-human, bovine, or even mouse serum albumin (AGE-HSA, AGE-BSA, or AGE-MSA) were produced by incubating D-glucose and relative albumin for 8 weeks. Moesin expression and phosphorylation were detected using western blotting. The manipulations of moesin expression and phosphorylation in endothelial cells were conducted with siRNA or mutant plasmids. The manipulation of signaling activities of AGE receptor (RAGE), mitogen-activated protein kinase (MAPK) and Rho-associated protein kinase (ROCK) were induced by antibody, inhibitors or recombinant adenovirus, respectively. The endothelial barrier function was tested using TEER or albumin flux. The proliferation, migration, in vitro vasculogenesis activities of HUVECs were measured with CKK-8 kit, wound healing and transwell chamber assay, as well as Matrigel cell culture. AGE-treated mice were peritoneally injected with AGE-MSA for certain time accordingly.
Results: AGEs induced the phosphorylation of moesin by binding with RAGE. The AGE/RAGE-induced activation of RhoA/ROCK and p38 MAPK pathway were the upstream signals that phosphorylated moesin. The AGE-induced phosphorylation of moesin resulted in morphological and functional alterations in endothelial cells, leading to endothelial barrier dysfunction and vascular hyperpermeability. AGEs could also enhanced the proliferation, migration and in vitro vasculogenesis. Again, moesin phosphorylation played a role in this AGE-induced angiogenesis. The data also demonstrated that oxidative stress and endoplasmic reticulum stress also exerted their influences on AGE-induced endothelial dysfunction.
Conclusion: Moesin and its phosphorylation are critical in AGE-induced endothelial dysfunction.

Qiao-Bing Huang

Professor, Department of Pathophysiology, School of Basic Medical Sciences, Southern Medical University.

Research interest: The activation and dysfunction of endothelial cells in the development of cardiovascular diseases.

Ongoing projects: ①To investigate the effects and the cellular signaling mechanisms of phosphorylation of ERM protein, especially moesin, in endothelial dysfunction induced by advanced glycation endproducts (AGEs). ②To explore the mechanisms of angiogenesis and neovessel immaturation in proliferative diabetic retinopathy, and to prove that AGEs could induce excessive neovascularization, as well as insufficient neovessel maturation by phosphorylating moesin. ③To address the double influences and the mechanisms of S1P and its receptors in endothelial functional modulation during the development of acute and chronic inflammatory diseases.

Publications: Over 100 papers published in English and Chinese, including in journals such as AJP Cell, AJP Heart and Circ Physiol, Sci Rep, Shock, Exp Physiol, Brain Res, Burns, and Cardiovasc Diabetol, etc.

Societies: Regular member of American Society of Physiology, and Microcirculatory Society. Standing committee member of Chinese Society of Microcirculation, the vice chairman of Diabetes and Microcirculation Specialized Committee in Chinese Society of Microcirculation, the vice chairman of Microcirculation Specialized Committee, and Shock Specialized Committee in Chinese Association of Pathophysiology.

Editorial board: World Journal of Traditional Chinese Medicine, Chin J Traumatol, Chinese Journal of Pathophysiology, Journal of Microcirculation (Chinese). Invited reviewer for AJP Heart Circ, Microcirculation, Burns and Shock, etc.

Plenary Lecture 12

10:40-11:10 October 29 Saturday

Room 402 Yifu Building

Skin microvascular blood flow and oxygenation - adaptive outcomes in obesity and type 2 diabetes mellitus/insulin resistance

Geraldine Frances Clough, BSc PhD FRSB

Professor, Institute of Developmental Sciences, Faculty of Medicine, University of Southampton

Chair: Makoto Suematsu, M.D., Ph.D.

President, Japan Agency for Medical Research and Development (AMED)

PL-12

Skin microvascular blood flow and oxygenation - adaptive outcomes in obesity and type 2 diabetes mellitus/insulin resistance

Geraldine F Clough

Institute of Developmental Sciences, Faculty of Medicine, University of Southampton, Southampton SO16 6YD, UK.

Deficits in peripheral vascular structure and function are an independent risk determinant in cardio-metabolic disease. Changes in micro-vascular function may be detected early, often before the onset of macro-vascular disease and the development of the end organ damage common to hypertension and obesity-associated clinical disorders (1). Much attention has been focused on genotype and on lifestyle factors such as inactivity, smoking and high caloric intake as being the major contributors to the development of cardiovascular disease and the metabolic syndrome. In developed countries approximately 15% of the adult population over the age of 20 years have metabolic syndrome, and the incidence is increasing markedly in young people as a result of increasing obesity. However, large-scale genome-wide associations have yet to provide strong evidence for a major genomic component in the predisposition to the metabolic syndrome in the general population and mounting evidence now indicates that the rising incidence of cardio-metabolic disease may have its origins in an individual's pre- and peri-natal environment (2). Further, treatment strategies in the form of lifestyle interventions (diet and exercise) which are often advised alongside pharmacological treatment have varied in their efficacy to reduce disease burden.

Evidence that disturbances in the microvasculature play a key role in the patho-physiological manifestations of cardio-metabolic disease comes from longitudinal and cross sectional studies in human cohorts and from studies in animal models. The majority of studies that suggest a contributory role of the microcirculation to the development and progression of cardio-metabolic disease are confined to measurements in accessible vascular beds such as the skin and retina in which changes in structure and function have been found to correlate negatively with insulin resistance, obesity and type 2 diabetes, both at rest and during increased metabolic demand (3,4).

Adequate delivery of oxygen and nutrients is essential for tissue health and dependent on matching of the tissue's requirements (demand) and microvascular perfusion. Regulation of microvascular perfusion is predominately achieved through changes in network conductance, which is in turn modulated at a local level by myogenic, endothelial and neurological regulatory mechanisms. Impairment of spatial and temporal regulation of network perfusion by these local mechanisms gives rise to a mismatch between perfusion and demand, particularly at times of elevated metabolic activity. The consequence of such inadequate perfusion control is a compromised tissue function, as that associated with features of the metabolic syndrome, leading to retinopathy, neuropathy, skin ulcers and difficult to heal wounds.

Our recent studies in cohorts at risk of, or with, cardio-metabolic disease have been focused on the multi-scale behaviour of accessible microvascular networks and the spatial and temporal characteristics of the local regulatory mechanisms associated with perfusion control and tissue oxygenation. The extent to which such studies can inform the diagnosis of micro-vasculopathies and treatment efficacy will be discussed.

1. Krentz AJ, Clough G and Byrne CD. Vascular Disease in the Metabolic Syndrome: Do We Need to Target the Microcirculation to Treat Large Vessel Disease? J Vasc Res 46: 515-526, 2009.
2. Clough GF Developmental Conditioning of the Vasculature. Comprehensive Physiology Vol 5 ed R Hester. America Physiological Society. Wiley 2015.
3. Clough GF, L'Esperance V, Turzyniecka M, Walter L, Chipperfield AJ, Gamble J, Krentz AJ, Byrne CD. Functional dilator capacity is independently associated with insulin sensitivity and age in central obesity and is not improved by high dose statin treatment. Microcirculation 2011 18(1); 74-84.
4. McCormick KG, Scorletti E, Bhatia L, Calder PC, Griffin MJ, Clough GF, Byrne CD. Impact of high dose n-3 polyunsaturated fatty acid treatment on measures of microvascular function and vibration perception in non-alcoholic fatty liver disease: results from the randomised WELCOME trial. Diabetologia. 2015 58(8):1916-25.

Geraldine Frances Clough BSc PhD FRSB

Institute of Developmental Sciences, Faculty of Medicine, University of Southampton, Southampton SO16 6YD. (G.F.Clough@southampton.ac.uk)

Geraldine Clough is Professor of Vascular Physiology in the Faculty of Medicine at the University of Southampton where her research focuses on the life course determinants of vascular dysfunction and particularly the microcirculation. She is a Visiting Professor in the BHF Centre of Research Excellence at King's College London (2014-). Research funding for her current and recent research activities is from UK research councils, charities, NIHR, DoH and industry. Professor Clough has served as member of Council of the Physiological Society, Senior Editor of the Journal of Physiology, and member of the Executive Committee of the Journal of Physiology. Geraldine Clough has also served as President of the British Microcirculation Society and as a member of the European Society of Microcirculation Executive and Awards panel and the International Liaison Committee. She is currently deputy Editor-in-Chief of Microcirculation and serves on several editorial boards. Geraldine Clough has been a Visiting Professor at Southern University China (2008-2011) and is a Consultant for the World Federation of Chinese Medicine Societies (2014-).

Geraldine Clough has published over 140 research and review articles and book chapters. She has been an invited speaker at national and international scientific meetings. She currently acts as primary or co-supervisor to 6 PhD students across the faculties of Medicine and Engineering Sciences in the University of Southampton.

Selected Recent Publications

1. Clough GF, McCormick KG, Scorletti E, Bhatia L, Calder PC, Griffin MJ, Byrne CD. Higher body fat percentage is associated with enhanced temperature perception in NAFLD: results from the randomised Wessex Evaluation of fatty Liver and Cardiovascular markers in NAFLD with OMacor thErapy trial (WELCOME) trial. Diabetologia. 2016 Apr 22. [Epub ahead of print]
2. Stead R, Musa MG, Bryant CL, Lanham SA, Johnston DA, Reynolds R, Torrens C, Fraser PA, Clough GF. Developmental conditioning of endothelium-derived hyperpolarizing factor-mediated vasorelaxation. J Hypertens. 2016 Mar;34(3):452-63.
3. Hanson MA, Cooper C, Sayer AA, Eendebak R, Clough GF, Beard JR. Developmental Aspects of a Life Course Approach to Healthy Ageing. J Physiol. 2016 594(8):2147-60.
4. McCormick KG, Scorletti E, Bhatia L, Calder PC, Griffin MJ, Clough GF, Byrne CD. Impact of high dose n-3 polyunsaturated fatty acid treatment on measures of microvascular function and vibration perception in non-alcoholic fatty liver disease: results from the randomised WELCOME trial. Diabetologia. 2015 58(8):1916-25.
5. Bhatia L, Scorletti E, Curzen N, Clough GF, Calder PC, Byrne CD. Improvement in non-alcoholic fatty liver disease severity is associated with a reduction in carotid intima-media thickness progression. Atherosclerosis. 2015 Dec 24;246:13-20.
6. Patel HP, White MC, Westbury L, Syddall HE, Stephens PJ, Clough GF, Cooper C, Sayer AA. Skeletal muscle morphology in sarcopenia defined using the EWGSOP criteria: findings from the Hertfordshire Sarcopenia Study (HSS). BMC Geriatr. 2015 Dec 18;15:171
7. Scorletti E, West AL, Bhatia L, Hoile SP, McCormick KG, Burdge GC, Lillycrop KA, Clough GF, Calder PC, Byrne CD. Treating liver fat and serum triglyceride levels in NAFLD, effects of PNPLA3 and TM6SF2 genotypes: Results from the WELCOME trial. J Hepatol. 2015 Dec;63(6):1476-83.
8. Pontes IE, Agra KF, Silva Jr JR, Borges PSN, Clough GF, Alves JGB. Microvascular reactivity in women with gestational diabetes mellitus studied during pregnancy. Diabetol Metab Syndr. 2015 ;7:27.
9. Clough GF Developmental Conditioning of the Vasculature. Comprehensive Physiology Vol 5 ed R Hester. America Physiological Society. Wiley 2015.
10. Musa M, Torrens C, Clough GF. The Microvasculature: A Target for Nutritional Programming and Later Risk of Cardio-Metabolic Disease. Acta Physiol (Oxf). 2014 Jan;210(1):31-45.
11. Scorletti E, Bhatia L, McCormick KG, Clough GF, Nash K, Hodson L, Moyses HE, Calder PC, Byrne CD; on behalf of the WELCOME Study Investigators. Effects of purified eicosapentaenoic and docosahexaenoic acids in non-alcoholic fatty liver disease: Results from the *WELCOME study. Hepatology. 2014 Oct;60(4):1211-21.
12. Kuliga KZ, McDonald EF, Gush R, Michel C, Chipperfield AJ, Clough GF. Dynamics of microvascular blood flow and oxygenation measured simultaneously in human skin. Microcirculation. 2014 Aug;21(6):562-73.
13. Valletta JJ, Chipperfield AJ, Clough GF, Byrne CD. Daily energy expenditure, cardiorespiratory fitness and glycaemic control in people with type 1 diabetes. PLoS One. 2014 May 14;9(5):e97534.
14. Gill C, Parkinson E, Church MK, Skipp P, Scott D, White AJ, O'Connor D and Clough GF. A qualitative and quantitative proteomic study of human microdialysate and the cutaneous response to injury. AAPS Journal 2011;13(2):309-17.
15. Clough GF, L'Esperance V, Turzyniecka M, Walter L, Chipperfield AJ, Gamble J, Krentz AJ, Byrne CD. Functional dilator capacity is independently associated with insulin sensitivity and age in central obesity and is not improved by high dose statin treatment. Microcirculation 2011 18(1); 74-84.
16. Clough GF, Turzyniecka M, Walter L, Krentz AJ, Wild SH, Chipperfield AJ, Gamble J, Byrne. Muscle microvascular dysfunction in central obesity is related to muscle insulin insensitivity but is not reversed by high-dose statin treatment. Diabetes. 2009 May;58(5):1185-91.
17. Turzyniecka M, Wild SH, Krentz AJ, Chipperfield AJ, Gamble J, Clough GF, Byrne CD. Skeletal muscle microvascular exchange capacity is associated with hyperglycaemia in subjects with central obesity. Diabet Med. 2009 Nov;26(11):1112-9.

Plenary Lecture 13

11:10-11:40 October 29 Saturday

Room 414 Yifu Building

Metabolic programming of human fetal endothelial and smooth muscle cells in gestational diabetes

Giovanni E. Mann, M.D., Ph.D.

Professor, Cardiovascular Division, British Heart Foundation Centre of Research Excellence, Faculty of Life Sciences & Medicine, King's College London

Chair: Toshio Nakaki, M.D., Ph.D.

Professor, Department of Pharmacology

Teikyo University School of Medicine

PL-13

Metabolic programming of human fetal endothelial and smooth muscle cells in gestational diabetes
Giovanni E. Mann

Cardiovascular Division, British Heart Foundation Centre of Research Excellence, Faculty of Life Sciences & Medicine, King's College London, 150 Stamford Street, London SE1 9NH, UK

Gestational diabetes mellitus (GDM) is defined as glucose intolerance with first recognition during pregnancy (Lappas *et al.*, 2011). Offspring from GDM pregnancies have a higher risk of cardiovascular diseases in later life, most likely as a consequence of foetal programming (Barker *et al.*, 2002; Lappas *et al.*, 2011) . Previously, we have reported that Nrf2 regulated redox signaling in fetal umbilical vein endothelial cells is impaired as a result of increased oxidative stress in GDM (Cheng *et al.*, 2013).

In the present study, the redox phenotype and gene expression were characterised using fetal umbilical artery smooth muscle cells (HUASMC) isolated from normal (n=63) and GDM (n=32) pregnancies (International Association of the Diabetes and Pregnancy Study Groups (IADPSG) criteria). Proliferation of GDM HUASMC was slower than normal HUASMC (n=5 normal vs 4 GDM donors), while the cellular redox status, as determined by mitochondrial superoxide generation, intracellular glutathione (GSH) and basal protein carbonylation, were similar in normal and GDM cells (n= 5-11 normal vs 5-11 GDM donors). A microarray analysis of gene expression from normal (n=9) and GDM (n=7) HUASMC cultures identified 176 differentially expressed genes, associated with *in utero* embryonic development, lipid metabolism, proliferation, cellular responses to stresses, proteolysis, chromatin organisation, RNA processing, transcription, and other intracellular signalling pathways. In particular, as validated by qPCR, the expression of several imprinted genes in the imprinting region 11p15.5 showed differential expression between normal and GDM HUASMC. Notably, the expression of cyclin-dependent kinase inhibitor 1C (CDKN1C), an inhibitor of cell proliferation and with important function in foetal growth, was increased by 3-fold in GDM HUASMC ($P<0.005$, Mann-Whitney *U* test).

In addition, validation of microarray findings by qPCR identified a 1.5-fold upregulation ($P<0.05$) of glutathione-*S*-transferase A4 (GSTA4), the key enzyme responsible for the detoxification of 4-hydroxynonenal (HNE), a lipid peroxidation product increased in GDM. Moreover, accumulation of HNE protein adducts after HNE treatment (20μM, 4h) was significantly elevated in GDM HUASMC (221 ± 74 μg/mg protein, n=5) compared to normal HUASMC (125 ± 37 μg/mg protein, n=5, mean ± S.E.M., $P<0.01$, two-way ANOVA), while induction of the antioxidant stress protein heme oxygenase 1 by HNE (20 μM, 4h-8h) was lower in GDM HUASMC ($P<0.05$). Furthermore, a pathological concentration of HNE (100 μM, 24h) induced apoptosis in normal HUASMC (13 ± 3 %, n=6), which was significantly enhanced in GDM HUASMC (32 ± 9 %, n=6, mean ± S.E.M., $P<0.05$).

Our ongoing research provides convincing evidence that GDM alters gene expression and the phenotype of fetal vascular endothelial (Cheng et al., 2013) and smooth muscle cells, providing valuable insights for the developmental origins of health and disease in offspring from pregnancies affected by oxidative stress.

Supported by British Heart Foundation

Barker DJ, Eriksson JG, Forsen T & Osmond C. (2002). *Int J Epidemiol* **31,** 1235-1239.

Cheng X, Chapple SJ, Patel B, Puszyk W, Sugden D, Yin X, Mayr M, Siow RC & Mann GE. (2013). *Diabetes* **62,** 4088-4097

Lappas M, Hiden U, Desoye G, Froehlich J, Hauguel-de Mouzon S & Jawerbaum A. (2011). ional di *Antioxid Redox Signal* **15,** 3061-3100.

Giovanni E. Mann, Ph.D.

Professor of Vascular Physiology
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Career and Research Profile

Giovanni Mann obtained his PhD in Physiology (1978) from University College London, UK and was subsequently appointed to a 4-year Postdoctoral Research Fellowship at Queen Elizabeth College, London, a Lectureship in Physiology (1981), Readership in Physiology (1992) and then as Professor of Vascular Physiology at King's College London in 1997. He is currently President of the Society for Free Radical Research-Europe (SFRR-E) and General Secretary of the Society of Free Radical Research-International (SFRR-I), and previously served as Chairman of The Physiological Society, President of the British Microcirculation Society, President of the European Microcirculation Society, a Council Member of the Physiological Society, SFRR-Europe, European Society for Microcirculation and International Liaison Committee for Microcirculation.

He serves as an Associate and Reviews Editor for Free Radical Biology & Medicine and a member of the Editorial Boards of Journal of Physiology, Microcirculation and Editorial Advisor for the Biochemical Journal. He recently served as Chair of Heart Research UK Translational Sciences Panel and Chair of the Medical Panel of The Henry Smith Charity, and is currently a member of the Basic Science Panel of Heart Research UK, Board of External Referees for the Biotechnology & Biological Sciences Research Council and College of Experts and the Medical Research Council - Physiological Systems & Clinical Sciences.

His vascular biology research group at King's College London is investigating signalling cascades involved the transcriptional activation of antioxidant defence genes in endothelial and smooth muscle cells in oxidative stress.

We are particularly interested in vascular dysfunction induced by oxidative stress in diseases such as atherosclerosis, gestational diabetes and stroke, and the health benefits of dietary inducers of the redox sensitive transcription factor Nrf2 involved the upregulation of endogenous antioxidant defences.

He has published more than150 primary papers and a selection of references relevant to the symposium are listed below.

Relevant publications:

- Bach1 differentially regulates distinct Nrf2-dependent genes in human venous and coronary artery endothelial cells adapted to physiological oxygen levels. Chapple SJ, Keeley TP, Mastronicola D, Arno M, Vizcay-Barrena G, Fleck R, Siow RC, Mann GE. Free Radic Biol Med. 2015 Dec 15. pii: S0891-5849(15)01166-1
- Heme oxygenase-1-derived bilirubin protects endothelial cells against high glucose-induced damage. He M, Nitti M, Piras S, Lisa Furfaro A, Traverso N, Pronzato MA, Mann GE. Free Radic Biol Med. 2015 Dec;89:91-8.
- Keap1-Nrf2 regulated redox signaling in utero: Priming of disease susceptibility in offspring. Chapple SJ, Puszyk WM, Mann GE. Free Radic Biol Med. 2015 Nov;88(Pt B):212-20.
- Redox status in mammalian cells and stem cells during culture in vitro: critical roles of Nrf2 and cystine transporter activity in the maintenance of redox balance. Ishii T, Mann GE. Redox Biol. 2014 Apr 18;2:786-94.
- Deficiency of p62/Sequestosome 1 causes hyperphagia due to leptin resistance in the brain. Harada H, Warabi E, Matsuki T, Yanagawa T, Okada K, Uwayama J, Ikeda A, Nakaso K, Kirii K, Noguchi N, Bukawa H, Siow RC, Mann GE, Shoda J, Ishii T, Sakurai T. J Neurosci. 2013 Sep 11;33(37):14767-77.
- Sulforaphane preconditioning of the Nrf2/HO-1 defense pathway protects the cerebral vasculature against blood-brain barrier disruption and neurological deficits in stroke. Alfieri A, Srivastava S, Siow RC, Cash D, Modo M,Duchen MR, Fraser PA, Williams SC, Mann GE. Free Radic Biol Med. 2013 Dec;65:1012-22.
- Gestational diabetes mellitus impairs Nrf2-mediated adaptive antioxidant defenses and redox signaling in fetal endothelial cells in utero. Cheng X, Chapple SJ, Patel B, Puszyk W, Sugden D, Yin X, Mayr M, Siow RC, Mann GE. Diabetes. 2013 Dec;62(12):4088-97.
- Sequestosome1/p62: a regulator of redox-sensitive voltage-activated potassium channels, arterial remodeling, inflammation, and neurite outgrowth. Ishii T, Warabi E, Siow RC, Mann GE. Free Radic Biol Med. 2013 Dec;65:102-16.
- Enhanced neointimal hyperplasia and carotid artery remodelling in sequestosome 1 deficient mice. Sugimoto R, Warabi E, Katayanagi S, Sakai S, Uwayama J, Yanagawa T, Watanabe A, Harada H, Kitamura K, Noguchi N, Yoshida H, Siow RC, Mann GE, Ishii T. J Cell Mol Med. 2010 Jun;14(6B):1546-54.
- Role of Nrf2 in the regulation of CD36 and stress protein expression in murine macrophages: activation by oxidatively modified LDL and 4-hydroxynonenal. Ishii T, Itoh K, Ruiz E, Leake DS, Unoki H, Yamamoto M, Mann GE. Circ Res. 2004 Mar 19;94(5):609-16.

Plenary Lecture 14

11:10-11:40 October 29 Saturday

Room 402 Yifu Building

Exosomes and Cardiovascular Diseases

Si-Feng Chen, BM, MM & MBA

Professor and Department Chairperson of Physiology and Pathophysiolgy at Fudan University College of Basic Medical Sciences,

Director of Kidney and Hypertension Research Center of Fudan University

Chair: Masato Yasui

Professor and Chair, Department of Pharmacology, School of Medicine, Keio University

PL-14

Exosomes and cardiovascular diseases

Si-Feng Chen

Department of Physiology and Pathophysiology, Fudan University College of Basic Medical Sciences, Shanghai, China

Exosomes are small membrane vesicles of 30–100 nm in diameter resemble to the internal vesicles present in multivesicular endosomes. They are released from a variety of different cell types and have been found in various body fluids such as blood plasma. They recruit various cellular proteins and RNAs, and therefore play an important role in cell-cell interactions.

Exosomes from stem cells, including mesenchymal stem cells, hematopoietic stem cells, induced pluripotent stem cells and myocardial progenitor cells, selectively contain a large amount of proteins required for vigorous cells and are beneficial for myocardial infarction and endothelial injury. In contrast, exosomes from lymphocytes, platelets and macrophages are mainly harmful for atherosclerosis. The effect of exosomes from mesenchymal stem cells on myocardial infarction was demonstrated by decreased infarction size and approved left ventricular ejection fraction, left ventricular fraction shortening, end-diastolic volume, and end-systolic volume.

Atherosclerosis primarily involved systemic arteries. Luminal surface, a monolayer of endothelial cells, of artery directly exposes to blood and is susceptible to active substances in the blood. Thus, it is expected that exosomes in the blood may contribute to atherosclerosis by affecting endothelial cells. We analyzed the relationship of blood exosome proteins and atherosclerosis. Patients and healthy subjects were divided into two comparisons: healthy subject vs atherosclerosis (HS vs AS), and hypertension vs hypertension plus atherosclerosis (HT vs HT+AS). Serum exosomes were decoded by protein mass spectrometry. The protein profile and function were analyzed by gene ontology (GO). It was found that 5 differentiated child terms appeared in both comparisons under the biological process GO terms of “response to stimulus” and “immune system process”. They are “positive regulation of innate immune response”, “immune response-activating signal transduction”, “activation of innate immune response”, “innate immune response-activating signal transduction” and “innate immune response activating cell surface receptor signaling pathway”. Two differentiated child terms emerged in both comparisons in the molecular function category of “binding”: “antigen binding” and “enzyme binding”. In addition, three differentiated proteins, PSMA6, PSMA7 and annexin A2, appeared in both comparisons. Thus, the innate immune system contributes to AS development. PSMA6, PSMA7 and annexin A2 may be new target proteins for AS prevention and treatment.

In conclusion, exosomes can either be beneficial or detrimental to cardiovascular diseases depending on their cellular origin,

Si-Feng Chen,BM,MM & MBA

Si-Feng Chen, received degrees with honors from Second Military Medical University. He is currently profesor and department chairperson of physiology and pathophysiolgy at Fudan University College of Basic Medical Sciences. He is also the director of Kidney and Hypertension Research Center of Fudan University. His research has ranged over a wide field from mechanisms to stem cell and immune therapy for variable non-infectious chronic diseases. He is currently served as principal investigator of Great Research and Development Plan Grant from Ministry of Sciences and Technology of China, Key International Cooperation Grant and Great Research Plan Grant from Natural and Scientific Foundation of China (NSFC). As principal investigator, Dr. Chen has finished one 973 project and 5 NSFC grants including a key grant. He has published over 65 papers in SCI-cited journals including those in Cir Res、JEM、PNAS、JASN and AJT.

After graduation in 1988, Dr. Chen continued to work at Department of Pathophysiology, Second Military Medical University as an assistant professor, associate professor and deputed department chairperson until being awarded by Humboldt Foundation of Germany to work at University of Magdeburg, Germany in 1997. After finishing his Humboldt fellowship in October of 1998, he became a postdoctoral research associate at Department of Medicine, University of Florida and was promoted to assistant scientist soon after. He served as Assistant Professor of Medicine, University of Alabama at Birmingham from 2004 to 2007. He started his career at Department of Physiology and Pathophysiology of Fudan University in 2006. During his career in the U.S., he was supported by 5 NIH research grants as PI and Co-PI.

Dr. Chen has had many honors including standing committee members of Chinese Association for Microcirculation, Chinese Association for Physiological Sciences (CAPS) and Chinese Association for Pathophysiology (CAP). He is vice-president of CAPS Study Section of Circulation, CAP Study Section of Microcirculation, Shanghai Association for Physiological Sciences and Shanghai Association for Pathophysiology. He frequently served in review sections of NSFC and Ministry of Sciences and Technology of China

Plenary Lecture 15

11:40-12:10 October 29 Saturday

Room 414 Yifu Building

CO-Responsive Heme Proteins Regulate Microcirculation and Cancer Proliferation

Makoto Suematsu, M.D., Ph.D.

President, Japan Agency for Medical Research and Development (AMED)

Chair: Giovanni E. Mann, M.D., Ph.D.

Professor, Cardiovascular Division, British Heart Foundation Centre of Research Excellence, Faculty of Life Sciences & Medicine, King's College London

PL-15

CO-Responsive Heme Proteins Regulate Microcirculation and Cancer Proliferation

Makoto Suematsu, MD, PhD (gasbiology@keio.jp)

Department of Biochemistry, Keio University School of Medicine, Tokyo 160-8582

Gases constitute a group of smallest metabolites in biological systems. Among gases, carbon monoxide (CO) is generated by heme oxygenase that is inducible in cancer cells in response to exposure to stimuli such as radiation, hypoxia and anti-cancer reagents. We have explored CO-responsive macromolecules through two different methods; metabolomics analyses and heme-conjugated affinity nano-beads. The former method allowed us to find lists of metabolites that are up- or down-regulated in response to CO-inducing conditions, since CO has the ability to bind to proteins with metal-centered prosthetic groups, that is, enzymes. Cystathionine β-synthase (CBS) is such a CO-responsive protein that regulates remethylation and transsulfuration pathways. CBS is also H_2S-generating enzyme that abundantly occurs in astrocytes that belong to neurovascular units. In brain, hypoxia suppresses neural CO generation and unlocks its ability to inhibit CBS and resultantly induces H_2S generation to relax microvessels. CO induction or CBS knockdown turned out to down-regulate methylation of PFKFB3, a key enzyme regulating PFK1, and resultantly up-regulate glucose bio-transformation towards pentose phosphate pathway. Such responses benefit increases in NADPH/GSH system to enhance cancer survival against anti-cancer reagents[1)]. On the other hand, the latter method allowed us to mine up progesterone receptor membrane component 1 (PGRMC1), a heme-containing protein also known as the sigma-2 receptor that is highly expressed among different types of solid tumors [2-4)]. According to our crystallographic analyses, the heme iron is five-coordinated by Tyr113 alone. PGRMC1 dimerizes by stacking interactions of two heme molecules protruding from each monomer, and this heme-mediated dimerization is essential for its function. Physiologic levels of CO interfere with PGRMC1 dimerization by forming a six-coordinated CO complex. Inhibition of PGRMC1 dimerization prevents its interaction with EGFR and cytochromes P450, limiting cancer proliferation and confers chemosensitivity to anticancer drugs. These results collectively demonstrate that CO-responsive CBS and/or PGRMC1 serve as novel molecular targets for controlling microcirculation and cancer development.

1. Kabe Y, et al. Haem-dependent dimerization of PGRMC1/sigma-2 receptor facilitates cancer proliferation and chemoresistance. **Nature Commun.** 2016; 7:11030. doi: 10.1038 /ncomms11030.

2. Yamamoto, T. et al. Reduced methylation of PFKFB3 in cancer cells shunts glucose towards the pentose phosphate pathway. **Nature Commun.** 2014; 5, 3480.

3. Suematsu, M. et al. Carbon monoxide: an endogenous modulator of sinusoidal tone in the perfused rat liver. **J Clin Invest.** 1995; 96: 2431-2437.

4. Morikawa T, et al. Hypoxic regulation of the cerebral microcirculation is mediated by a carbon monoxide-sensitive hydrogen sulfide pathway. **Proc Natl Acad Sci USA.** 2012;109(4), 1293-1298.

Makoto Suematsu, MD, PhD

President, Japan Agency for Medical Research and Development

Nationality: Japan. Birthday: November 30, 1957 (59 years old)

March 1983 Graduated from Keio University School of Medicine (MD)

1984-1988 Post-graduate School, Keio University School of Medicine (PhD)（Gastroenterology and Microvascular Physiology）

May 1991 Bioengineer Step IV, Institute for Biomedical Engineering, University of California San Diego (Supervised by Professor Benjamin W Zweifach and Professor Geert W Schmid-Schoenbein)

April 2001 Professor and Chair, Department of Biochemistry and Integrative Medical Biology, Keio University School of Medicine

April 2003 Leader, National Leading Project for Biosimulation by Ministry of Edication, Sciences and Technology

June 2007 Leader, Global Center of Exellence for Life Sciences, Human Metabolomic Systems Biology from MEXT

October 2007-March 2015 Dean, School of Medicine, Keio University

October 2009-present Leader, JST, ERATO, Suematsu Gas Biology Project

April 2015 Founding President, Japan Agency for Medical Research and Development (AMED)

June 2015 Member, Heads of International Research Organization (HIROs)

March 2016 The International Selection Panel, National Institute of Health Research Biomedical Research Centres & Units (NIHR-BRC/Us), UK

September 2016 International Abvisory Board, Vilunius University Faculty of Medicine, Luthuania

Main Research Interests

Gas Biology and Medicine, Microcirculatory physiology, Development of Imaging MS spectrometry. Exploring disease-specific biomarker molecules by metabolomics

Contributions to Academic Communities

President, Japanese Society for Microcirculation

President, 10th World Congress for Microcirculation (Kyoto, September 2015)

Lists of Major Publication

1. Takubo K, --Suematsu M, Suda T. Regulation of glycolysis by pdk functions as a metabolic checkpoint for cell cycle quiescence in hematopoietic stem cells. **Cell Stem Cell** 2013, 12(1), 49-61.
2. Yamamoto T, --Suematsu M. Reduced methylation of PFKFB3 in cancer cells shunts glucose towards the pentose phosphate pathway. **Nat Commun** 2014, 5, 3480. doi:10.1038/ncomms4480.
3. Tohyama S, --Suematsu M, Fukuda K. Glutamine oxidation is indispensable for survival of human pluripotent stem cells. **Cell Metabolism** in press 2016.
4. Kabe Y, --Suematsu M. Haem-dependent dimerization of PGRMC1/sigma-2 receptor facilitates cancer proliferation and chemoresistance. **Nat Commun** 7:11030 .2016.

Plenary Lecture 16

11:40-12:10 October 29 Saturday

Room 402 Yifu Building

Vascular factors, angiogenesis and liver diseases

Gianfranco D Alpini, M.D., Ph.D.

Professor, Dr. Nicholas C. Hightower Centennial Chair in Gastroenterology

Director，the Scott & White Digestive Disease Research Center

Olin E. Teague Medical Center

Chair: Qiao-Bing Huang, M.D., Ph.D.

Professor, Department of Pathophysiology, School of Basic Medical Sciences, Southern Medical University

PL-16

Vascular factors, angiogenesis and liver diseases

Gianfranco Alpini, Ph.D, Distinguished Professor and Director
Baylor Scott & White Digestive Disease Research Center, Texas A&M HSC College of Medicine, Central Texas Veteran Healthcare System, Temple, Texas 76504, U.S.A.

The overall focus of our program is to analyze the underlying signaling pathways and cellular responses regulating various hepatic injuries and diseases. Specifically, our research emphasizes diseased states that are centered around cholangiocytes, the cells that line the intra- and extra-hepatic bile ducts. The bile ducts serve as conduits and modify bile (by a series of secretory/reabsorptive events) that is excreted from hepatocytes before being delivered to the duodenum. Work from our group has shown that cholangiocytes have a significant link to the peribiliary vascular plexus, which secretes several angiogenic factors and composes the microvascular architecture of the biliary tree. Based on their close proximity, the peribiliary vascular plexus acts as the main nutritional source for cholangiocytes as we have shown that crosstalk between these two cell types is key for the maintenance of liver homeostasis. Our group provided the first evidence that: (i) cholangiocytes express the mRNA and secrete vascular endothelial growth factor (VEGF)-A and VEGF-C; and (ii) expression and secretion of these factors is significantly increased following bile duct ligation (BDL, a model of obstructive cholestasis). Furthermore, cholangiocytes express both VEGF receptor 2 (VEGFR-2) and VEGFR-3, which is increased following BDL, and have a proliferative response following stimulation of these receptors. To prove that cholangiocyte proliferation is VEGF dependent, we treated normal rats with recombinant-VEGF-A or recombinant-VEGF-C and found that cholangiocyte proliferation and ductal secretion was increased. This demonstrates that cholangiocyte-derived VEGF plays an autocrine role in the regulation of cholangiocyte proliferation during cholestasis-induced injury. Conversely, treatment with antibodies against either VEGF-A or VEGF-C diminished BDL-induced cholangiocyte proliferation. Aside from autocrine regulation, cholangiocyte-derived VEGF can act in a paracrine manner on the peribiliary vascular plexus. Our lab has shown that following BDL, the peribiliary vascular plexus expands to compensate for the enhanced nutritional need of the cholangiocytes. However, BDL rats that underwent hepatic artery ligation (HAL), to decrease blood-derived nourishment, exhibited disappearance of the peribiliary vascular plexus, alongside impaired cholangiocyte proliferation and VEGF secretion. HAL-induced defects were prevented following treatment with recombinant-VEGF-A. Based on our research it is apparent that VEGF levels need to be tightly regulated to allow for homeostasis between cholangiocytes and the peribiliary vascular plexus. We have further shown that BDL rats that receive hepatic artery ischemia reperfusion (IR) have damaged cholangiocytes with reduced proliferation and function. Furthermore, IR increased cholangiocyte expression of VEGF-A/C, VEGFR-2/3, angiopoietin (Ang)-1/2, and the angiopoietin receptors (Tie-1/2). Here we show that the functional damage of cholangiocytes by IR is associated with increased expression of angiogenic factors, presumable due to a compensatory mechanism in response to biliary damage. Overall, we have shown that enhanced expression of angiogenic factors can be detrimental to the liver by inducing biliary hyperplasia and hepatic fibrosis; however, loss of angiogenic factors, such as VEGF, can diminish the peribiliary vascular plexus and result in cholangiocyte apoptosis. These findings further solidify the concept that maintenance of the peribiliary vascular plexus and cholangiocyte proliferation depends on crosstalk between these two cell types. Aside from VEGF and Ang, our lab has also shown that cholangiocytes can express and secrete platelet-derived growth factor (PDGF)-B and its receptor β subunit, and expression and secretion of these factors is significantly increased following BDL-induced cholestasis. These results show another cholangiocyte-specific autocrine loop similar to that of VEGF/VEGFR. Further, since PDGF-B can enhance growth of endothelial cells, and our lab has shown that the peribiliary vascular plexus expands during cholestatic injury, it is intuitive that cholangiocyte-derived PDGF-B can modulate the growth of the peribiliary vascular plexus following injury. Angiogenesis and the expression of vascular factors are closely involved in the regulation of cholangiocyte damage. Hepatic inflammatory diseases, such as primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC), tend to have enhanced vessel formation and expression of angiogenic factors that can lead to increased fibrosis. Modulation of these factors and pathways may be key to ameliorating damage associated with these devastating cholangiopathies.

Gianfranco D Alpini, Ph.D
Distinguished Professor of Internal Medicine
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Education and Training

Institution and Location	Degree	MM/YY	Field of Study
Terenzio Mamiani, Rome, Italy	B.S.	1976	Classical Studies
University of Rome "La Sapienza", Rome, Italy	Ph.D.	1984	Chemistry
Mount Sinai Medical Center, New York, NY	Postdoc	1985-1988	Hepatology
Albert Einstein Yeshiva University, NY	Postdoc	1988-1991	Hepatology
Mayo Clinic, Rochester, MN	Postdoc	1991-1994	Digestive Disease

Research Interests

My research focuses on the pathophysiology of intrahepatic bile duct epithelial cells or cholangiocytes, which line the intrahepatic biliary tree inside the liver. Cholangiocytes play a key role in the modification of the bile (secreted by hepatocytes) by a series of reabsorptive and secretory processes under both spontaneous and hormone-regulated conditions. Cholangiocytes have also the capacity to selectively proliferate following the application of pathological perturbations, such as bile duct ligation. Cholangiocyte proliferation is observed in virtually all-human cholestatic liver diseases. The Two Major Objectives of my research program are: (i) to identify and functionally characterize the different sized segments of the intrahepatic biliary tree which are differentially involved in secretory and proliferative processes under normal and pathophysiological states which is of particular importance since cholangiocyte proliferation in human cholestatic liver disease is restricted to specific-sized ducts; and (ii) to define the coordinated and complex series of factors which regulate cholangiocyte proliferation in liver disease. The program projects are supported by four R01s (PIs) from NIH/NIDDK and one VA Merit Award.

Positions and Employment

1994-2000 Assistant Professor, Medicine and Medical Physiology, Central Texas Veterans Health Care System and Texas A & M University System Health Science Center, College of Medicine.

2000-2003 Associate Professor, Medicine and Medical Physiology, Central Texas Veterans HCS and Texas A & M University HSC, College of Medicine.

2004-Present Distinguished Professor, Medicine and Medical Physiology, Central Texas Veterans HCS, Texas A & M University HSC. Dr. Nicholas C. Hightower Centennial Chair of Gastroenterology. Director of the Scott & White Digestive Disease Research Center.

Service to Professional Journals

Associate Editors: Hepatology, Digestive Liver Disease, PLOSONE, BMC Research Notes, BMC Gastroenterology.

Editorial Board Member: J Hepatol, J Biol Chem, Am J Physiol, Am J Pathol, Laboratory Investigation

Honors

1993-1994 Grant Award from the American-Italian Cancer Foundation.

2004-present Department of Veterans Affairs, Senior Research Career Scientist.

Centennial Hightower Chair for Gastroenterology at Scott & White, Texas A&M HSC.

Recipient, association of military surgeons of the United States (AMSUS) research and development award, 2011.

Director of the Scott & White Digestive Disease Research Center (DDRC).

Award in Excellence in Research, Texas A&M HSC COM, 2008

Plenary Lecture 17

16:20-16:50 October 29 Saturday

Room 414 Yifu Building

The mechanism for Chinese medicine to improve microvescular barrier and intestinal mucosa epithelial barrier.

Jing-Yan Han, M.D., Ph.D.

Professor, Department of Integration of Chinese and Western Medicine, Peking University Health Science Center/Tasly Microcirculation Research Center, Peking University Health Science Center

Chair: Hiroshi Nagata, M.D.

Professor, Keiyu Hospital

PL-17

The mechanism for Chinese medicine to improve microvescular barrier and intestinal mucosa epithelial barrier.

Jing-Yan Han

Department of Integration of Chinese and Western Medicine, School of Basic Medical Sciences, Peking University

Microvascular barrier of venules and capillaries is maintained by vascular endothelial caveolae, junctions between endothelial cells, base lamina and periocytes around the vessels, injury in which underlays the pathology for microvascular hyperpermeability and albumin leakage. Intestinal mucosa epithelial barrier is regulated by inter-epithelial cell junctions, which takes part in the pathogenesis of occurrence and recurrence of intestinal inflammatory disease .
As one of the basic theory of Chinese medicine, Qi is consisted of oxygen and dietary essence, being a resource for ATP production. Ischemia, deficiency in dietary essence or decreased activity of ATP synthase in mitochondria result in reduced ATP production, leading to degradation of F-actin, which in vascular endothelial cells causes rearrangement of cell junction proteins, expanding of inter-cellular gaps and albumin flowing out of vessels, while in intestinal mucosa epithelial cells provokes rearrangement of junction proteins, widening of inter-epithelial cell gaps that damages intestinal barrier leading to occurrence or recurrence of intestinal inflammatory diseases. The Chinese medicines with potential of tonifying qi exhibit superiority in clinic for treatment of conditions that involve barrier disorder in vascular endothelium or intestinal epithelium, however, the underlying mechanism is sofar unclear.
This report presented evidences showing that QiShenYiQi pills, a compound Chinese medicine with potential of tonifying qi and activating blood, is able to protect rat cardiac microvascular barrier; that HuangQiJianzhong decoction improves energy metabolism disorder of rat intestine, restores F-actin and junction proteins disarrangement in rat intestinal epithelial cells, promoting repairing of injured intestinal mucosa.
The reporter will elaborate the the role and mechanism for Chinese medicine to protect against dysfunction in microvascular and intestinal mucosa epithelial barrier.

Jing-Yan Han

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Professor Jing-Yan Han is a professor and chairman of department of integration of Chinese and western medicine, Peking university health science Center, directs the tasly microcirculation research center, Peking university health science center.

He has published 56 original articles and reviews in the last 10 years. These studied explored the process of blood stasis and the ameliorating effects of traditional Chinese medicine (TCM), especially compound traditional Chinese preparation. He has evaluated important concepts in blood stasis including characterization of different blood stasis, differentiation strategy for treatment of blood stasis, the therapeutic effects of TCM and underlying mechanisms. In particular, he has demonstrated the pivotal role of microcirculatory disturbances rather than macrovascular deficits in the whole pathological course of blood stasis related diseases.

He is a vice-president of Chinese society for microcirculation, president of the professional committee of phlegm-stasis, China society of microcirculation, president of the specialty committee of Qi-Blood, World Federation of Chinese Medicine Societies, president of professional committee of microcirculation, China pathophysiological society, councilor member of international liaison committee for microcirculation, co-editor of the world journal of TCM and associate editor of microcirculation.

Plenary Lecture 18

16:20-16:50 October 29 Saturday

Room 402 Yifu Building

Failure of the autoregulation of cerebral blood flow by hemodynamic forces

Akos Koller, MD, PhD

Professor and Chairman of the Scientific Council, University of Physical Education, 1123 Budapest, Hungary

Chair: Roland N. Pittman, Ph.D.

Professor, Medical College of Virginia Campus

Virginia Commonwealth University

PL-18

Failure of the autoregulation of cerebral blood flow by hemodynamic forces

Akos Koller

University of Physical Education, Budapest, Department of Neurosurgery and Szentagothai Res Centre, University of Pecs, Hungary and Department of Physiology, New York Medical College, Valhalla, NY, USA

The brain has a very efficient autoregulation because the cerebral vascular network is enclosed in the rigid cranium thus increases in pressures and/or volumes could elicit increases intracranial pressure, endangering the maintenance of appropriate blood flow to the brain tissues. Thus it is logical to assume that autoregulation is coupled to changes in hemodynamic forces and the vascular wall itself.

Pressure sensitive vasomotor response: Autoregulation of CBF first has been explained by the pressure-induced myogenic - smooth muscle dependent - responses of cerebral arteries. This response of vessels was first described by W. Bayliss early in the 20^{th} century. Accordingly, when systemic blood pressure increases cerebral vessels constrict, which elevates cerebrovascular resistance. Because flow relates to the 4^{th} power of radius the increased resistance maintains CBF close to the original level, despite elevation in pressure. In contrast, when systemic pressure decreases, dilation of cerebral vessels reduce cerebrovascular resistance, thereby maintaining relatively constant blood flow.

Flow sensitive vasomotor response: During increases in systemic pressure blood flow to the brain increases, as well. This led to the hypothesis that there is a vascular mechanism, which is sensitive to changes in blood flow. Indeed, our recent studies support this idea. We have found in the isolated middle cerebral arteries that - in the presence of constant pressure - increases in flow elicited constrictions. The constrictions are mediated by 20-HETE (20-hydroxieicosatetraenoic acid, a constrictor metabolite of arachidonic acid synthesized by cytochrome P450 hydroxylases) and reactive oxygen species (ROS). Thus simultaneous increases of hemodynamic forces amplify their action to protect the brain from high pressure and volume.

Pathological conditions: Unfortunately, these mechanisms are not always working properly, especially in hypertension, aging and after traumatic brain injury, which could be responsible for the development of stroke and brain edema. Elucidating the vasomotor pathomechanisms and their molecular basis would help to develop prevention of secondary brain damage after stroke and traumatic brain injury.

Support: National Research, Development and Innovation (NKFI) Fund Hungary (OTKA) K108444, OTKA K104984, FP7- Marie Skłodowska-Curie ***"SmArteR***" project and Hungarian Hypertension Society 2013-2015.

Name: Akos Koller
Birth Date: 1951 / 02 / 03 Nationality: Hungarian
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Position: Professor

Educational Background
Semmelweis University, Budapest, Hungary
Major: MD, General Medicine. From 1969/ 09 to 1975 / 08
Degrees: MD, PhD, DSci (Physiology)

Selected Publications

- **Koller, A.** and G. Kaley. Prostaglandins mediate arteriolar dilation to increase blood flow velocity in skeletal muscle microcirculation. Circ. Res. 67:529-534, 1990.
- **Koller, A.,** D. Sun and G. Kaley. Role of shear stress and endothelial prostaglandins in flow- and viscosity-induced dilation of arterioles in vitro. Circ. Res. 72:1276-1284, 1993.
- **Koller, A.,** A. Huang, D. Sun and G. Kaley. Exercise training augments flow-dependent dilation in rat skeletal muscle arterioles. Role of endothelial nitric oxide and prostaglandins. Circ. Res.76: 544-550, 1995.
- Vaccarino V, Badimon L, Corti R, de Wit C, Dorobantu M, Manfrini O, **Koller A,** Pries A, Cenko E, Bugiardini R. Presentation, management, and outcomes of ischaemic heart disease in women. Nat Rev Cardiol. 10:(9) 508-518, 2013.
- Toth P, Csiszar A, Sosnowska D, Tucsek Z, Cseplo P, Springo Z, Tarantini S, Sonntag WE, Ungvari Z, **Koller A**. Treatment with the cytochrome P450 omega-hydroxylase inhibitor HET0016 attenuates cerebrovascular inflammation, oxidative stress and improves vasomotor function in spontaneously hypertensive rats. Br J Pharmacol. Apr;168(8):1878-88, 2013.
- Toth P, Tucsek Z, Sosnowska D, Gautam T, Mitschelen M, Tarantini S, Deak F, **Koller A**, Sonntag WE, Csiszar A, Ungvari Z. Age-related autoregulatory dysfunction and cerebromicrovascular injury in mice with angiotensin II-induced hypertension. J Cereb Blood Flow Metab. 2013.
- Nemeth Z, Cziraki A, Szabados S, Horvath I, **Koller A**. Pericardial fluid of cardiac patients elicits arterial constriction: role of endothelin-1. Can J Physiol Pharmacol. 2015 Sep;93(9):779-785.
- Cseplo P, V ámos Z, Torok O, Ivic I, Toth A, Buki A, **Koller A**. Hemolysed blood elicits calcium antagonist and high CO2 reversible constrictions via elevation of Ca2+ in isolated cerebral arteries. J Neurotrauma. 2016 Mar 28.
- Ivic I, Vamos Z, Cseplo P, **Koller A**. From Newborn to Senescence Morphological and Functional Remodeling Leads to Increased Contractile Capacity of Arteries. J Gerontol A Biol Sci Med Sci. 2016 May 17.

Work Experience:
Department of Physiology, New York Medical College, Valhalla, NY, USA: Professor
Dept. of Pathophysiology, Semmelweis University, Budapest, Hungary: Professor and Vice Dean
Dept. of Pathophysiology, Medical school, University of Pecs, Hungary: Head of the Department and Vice Dean
Institute of Natural Sciences, University of Physical Education, Budapest, Hungary: Professor and Vice Rector

Research Topics: Physiology, Exercise Physiology, and Pathophysiology of the Cardiovascular System.

Plenary Lecture 19

16:50-17:20 October 29 Saturday

Room 414 Yifu Building

Remodeling of the Cytoskeleton and Adhesion are Fundamental Processes Coupled to Vascular Smooth Muscle Contraction and Relaxation

Gerald A. Meininger, M.D., Ph.D.

Professor, Dalton Cardiovascular Research Center

Department of Medical Pharmacology and Physiology

University of Missouri-Columbia

Chair: Qi-Min Zhan, M.D., Ph.D.

President, Peking University Health Science Center

PL-19

Remodeling of the Cytoskeleton and Adhesion are Fundamental Processes Coupled to Vascular Smooth Muscle Contraction and Relaxation

Gerald A. Meininger[1,2] , Zhe Sun[1,2], Michael A. Hill[1,2], and Luis A. Martinez-Lemus[1,2]

[1]Dalton Cardiovascular Research Center and [2]Department of Medical Pharmacology and Physiology, University of Missouri, Columbia, MO 65211

The actin cytoskeleton is fundamental to the structure and contraction of vascular smooth muscle cells (VSMC). Growing evidence indicates coordination of actin-myosin based contraction with rapid remodeling and reorganization of the actin cytoskeleton. The process of remodeling in VSMC is dynamic occurring in parallel with contraction and relaxation and involves rapid cytoskeletal F-actin polymerization and/or depolymerization. The process is triggered by mechanical forces and agonists alike, which induce contraction or relaxation, respectively. This remodeling is very apparent in the cellular compartment containing cortical actin stress fibers. Along with cytoskeletal remodeling, we have found that integrin-dependent VSMC-extracellular matrix adhesions and N-cadherin based cell-cell adhesions rapidly up-regulate with contraction and down-regulate with relaxation. Collectively, this demonstrates that VSMC contractility, and the force transmission axis of the cell, are highly adaptive and responsive to the state of vascular contractile tone. The remodeling of the cytoskeleton appears linked to the cellular and vascular remodeling that occurs in the vasculature during aging and disease, e.g. hypertension. Together, the coordinated behavior of the cytoskeleton with adhesion supports an active view of VSMC contraction involving a range of cellular processes.

Gerald A. Meininger

Gerald A. Meininger is Past Director of the Dalton Cardiovascular Research Center. He is currently a Senior Investigator at the Dalton Cardiovascular Research Center and a Margaret Mulligan Endowed Professor in Medical Research. He is appointed as Professor in the Department of Medical Pharmacology and Physiology, School of Medicine with adjunct Professorial appointments in the Departments of Biomedical Sciences, College of Veterinary Medicine and Department of Biological Engineering, College of Engineering at the University of Missouri-Columbia. Prior to assuming the Directorship, Dr. Meininger was a Regents Professor and Associate Head of the Department of Medical Physiology and Director of the Division of Vascular Biology at Texas A&M University System HSC. Dr. Meininger obtained his B.S (1974) and M.S. (1976) degrees from Central Michigan University and his Ph.D. degree in 1981 from the University of Missouri-Columbia. Dr. Meininger's research career has focused on mechanisms of microvascular control and mechanotransduction in vascular cells. He has extensively published on the myogenic response, and the microvasculature during hypertension, aging, microvessel remodeling and local mechanisms for regulation of vascular smooth muscle function. Recent research efforts are directed at understanding the mechanisms by which vascular smooth muscle cells sense and respond to mechanical forces. His investigations are focused on the extracellular matrix-integrin-cytoskeletal axis and cell-cell interactions and they have provided strong evidence supporting an active role for integrins and cadherins in vascular control. In other recent work Dr. Meininger is interested in understanding the detailed architectural microstructure/organization of extracellualar matrix proteins in the vascular wall. Dr. Meininger has been very active in promotin application of new technologies for study of the cell biology of the vascular wall. Examples have included use of fluorescent calcium indicators in intact microvessels, three-dimensional imaging of cells in the microvessel wall and application of atomic force microscopy for study of the adhesive interactions between extracellular matrix proteins and integrins in cardiovascular cells and in particular vascular smooth muscle.

Plenary Lecture 20

16:50-17:20 October 29 Saturday

Room 402 Yifu Building

The microvascular interface in the Central Nervous System: Normal function and relevance to pathology

Tailoi Chan-Ling, M.D., Ph.D.

Professor, Discipline of Anatomy and Histology, Sydney Medical School

Bosch Institute, the University of Sydney

Chair: Yong Jiang, Ph.D.

Professor and Chairman of Department of Pathophysiology,
Director of Key laboratory of functional proteomics of Guangdong province, School of Basic Medical Sciences of Southern Medical University

PL-20

The microvascular interface in the Central Nervous System: Normal function and relevance to pathology

Tailoi Chan-Ling[1], Samuel J Adamson[1], Louise C Baxter[1], Mark E Koina[2], Frank Arfuso[1,3] and Ping Hu[1]

1. Discipline of Anatomy & Histology, Sydney Medical School, Bosch Institute, The University of Sydney Sydney Australia. 2. Department of Anatomical Pathology, ACT Pathology, The Canberra Hospital, Garran, Australian Capital Territory, Australia 3. School of Anatomy, Physiology and Human Biology, Faculty of Science, The University of Western Australia, Crawley, Western Australia, Australia

Embryologically, the retina is an extension of the midbrain where the optic stalk buds from the diencephalon. As such any understanding of the processes of vasculogenesis, angiogenesis, vascular stability and neovascularisation gained by studying the retinal vasculature have wider applicability to the vessels of the CNS. However, unlike the vessels of the brain which is encased inside the cranium, with it's complex 3-dimensional architecture requiring sectioning and serial reconstruction, the retinal vascular bed can be examined as a wholemount, where normal cell-cell interactions are maintained, permitting detailed examination of glial-neuronal, vascular interactions in intact CNS tissue.

As a consequence, the eye has been dubbed 'the window to the brain' because it is the one place where we can see the health of the blood vessels in the brain non-invasively, with recent improvements in technology permitting high resolution imaging of retinal vasculature using fundus cameras and OCT. For these reasons, much of our insights about vascular biology have been gained by the study of the retinal vascular bed.

During embryological development, the retina is an avascular neuroepithelium. Vascular lineage cells appear at the optic nerve head at 14 weeks gestation, before differentiation, proliferation and transformation into solid vascular cords. These vessels are closely ensheathed by both astrocytes (whose functions include induction of the blood-brain barrier) and pericytes (with functional roles including regulating blood flow and vessel stability). To determine the contribution of pericytes to vessel stability during normal development and in the kitten model of retinopathy of prematurity (ROP), we established the desmin ensheathment ratio [DER- relative occurrence of desmin (pericytes) to lectin (endothelium)], and found a DER of <0.9, indicating an actively remodeling or unstable vascular bed. Further, the DER is low when the retinal vasculature is responsive to the expression and withdrawal of VEGF165. The pericyte/endothelial ratio (PER- number of pericytes per capillary length) was reduced in aging rat retinal vasculature, most likely leading to increased angiogenesis and vessel instability (including blood-retinal-barrier breakdown). We suggest that this loss of vessel stability is associated with increased angiogenic activity.

Astrocyte loss during the proliferative stage of ROP exemplifies their susceptibility to hypoxia-induced cell death. Where astrocytic ensheathment of blood vessels is lost and the glia limitans (formed by astrocytes and Muller cells) is breached, pathological, pre-retinal new vessel formation can occur. Taken together, these studies demonstrate the importance of perivascular cell dynamics in determining the functional characteristic of the various vascular beds in the normal CNS and in pathology.

Tailoi Chan-Ling

Professor Chan-Ling has made a sustained contribution to the understanding of glial-vascular biology during normal development of the retina, as well as understanding to the disease processes in Retinopathy of Prematurity (the leading cause of infant blindness in the world), multiple sclerosis, cerebral malaria and experimental inflammation using experimental models of disease. Tailoi's work aims to shed light on the earliest initiating events in diseases affecting sight and the central nervous system, with the aim of developing therapies that attack the cause of disease rather than treating the symptoms. She is the author of over 100 highly cited peer reviewed publications (h index 45, with over 6500 citations).

Tailoi Chan-Ling is Professor of Neurobiology and Visual Science in the discipline of Anatomy, School of Medical Sciences, Faculty of Medicine, Bosch Institute, The University of Sydney. She is also an Adjunct Professor of Ophthalmic Science (Ophthalmology), Harkness Eye Institute, Columbia University Medical Center, New York. She is on the editorial board of 3 International peer review journals and is a regular invited speaker at key international meetings on angiogenesis, vascular biology, Glial biology and Retinal biology. She is currently the Secretary of the International Society for Eye Research and Chair-elect of the International Liaison Committee for Microcirculation. She serves in a number of capacities within the University including, Executive Leadership Group of the Bosch Institute; University of Sydney, Harassment and Discrimination Support Officer; Honorary Research Associate: Institute of Clinical Neurosciences, Royal Prince Alfred Hospital; Academic Board Nominee, University of Sydney: Consortium leader: Replacement of Confocal Microscope Bosch Advanced Imaging Core Facility. Dr Chan-Ling maintains a large number of international and national collaborations expanding the types of research opportunities/experience available in her laboratory and has trained numerous highly successful young investigators. She is Chair of the Young Investigator Committee of the International Society for Eye Research, and is a strong advocate for enhancing career opportunities for young investigators worldwide.

Plenary Lecture 21

10:10-10:40 October 30 Sunday

Room 414 Yifu Building

Migration of Lymphoid and Cancer Cell in Gut-Associated Lymphoid Tissue

Hiroshi Nagata, M.D.

Professor, Keiyu Hospital

Chair: Hong-Quan Zhang**, M.D., Ph.D.**

Professor and Head Department of Anatomy, Histology and Embryology Peking University Health Science Center Director, Laboratory of Molecular Cell Biology and Tumor Biology, School of Basic Medical Sciences Peking University Health Science Center

PL-21

Migration of Lymphoid and Cancer Cell in Gut-Associated Lymphoid Tissue

Hiroshi Nagata

Department of Internal Medicine, Keiyu Hospital

3-7-3, Minatomirai, Nishi-ku, Yokohama City, Kanagawa 220-8521, Japan

Lymphocytes and dendritic cells continue to patrol the gut-associated lymphoid tissue (GALT) for immune surveillance. Cancer cells also flow through the same pathway for metastasis. The purpose of this study was to visualize migration behavior of these cells in GALT of rats, using in vivo microscopy. There was a dense network of efferent lymphatic vessels in the perifollicular and interfollicular area of Peyer's patches. The efferent lymphatic vessels in the perifollicular area were filled with lymphocytes. Numerous lymphocytes flowed through lymphatic vessels in the mesentery and reached the lymph node. Dendritic cells were found to flow with lymphocytes through the lymphatic vessels in the mesentery. From the terminal of the afferent lymphatic vessels, lymphocytes flowed out and entered the marginal sinus in the mesenteric lymph node. There was no direct passage of the lymphocytes through the medullary sinus to efferent lymphatic vessels. The lymphocytes were eventually arrested in the marginal sinus. Macrophages were lying beneath the marginal sinus with pseudopods extending through the endothelium. Upon incorporation of foreign bodies or cancer cells, these macrophages migrated through the marginal sinus or the lymph node parenchyma toward the medulla. In conclusion, the lymphatic vessel in the Peyer’s patch and the marginal sinus in the mesenteric lymph node have the potential capacity for storage of lymphocytes to modulate their migration. The marginal sinus constitutes a mechanical barrier by arresting migrant foreign bodies and cancer cells.

Hiroshi Nagata, MD

Born in June 13, 1952 (63 years old)

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Education and Professional Experience:

March, 1977 graduated from School of Medicine, Keio University, MD

March, 1981 graduated from Post-Graduate School of Medicine, Keio University (Gastroenterology)

April, 1981 Post doctoral fellow, CURE (Center for Ulcer Research and Education) and University of California, Los Angeles (Supervised by Professor Paul H. Guth)

August, 1983 Attending Physician, Department of Internal Medicine, Saiseikai Central Hospital

April, 1990 Visiting Assistant Professor, Department of Internal Medicine, School of Medicine, Keio University

April, 1993 Instructor, Department of Internal Medicine, Saiseikai Central Hospital

January, 1997 Chief, Department of Internal Medicine, Saiseikai Central Hospital

October, 1998 Assistant Professor, Department of Internal Medicine, School of Medicine, Keio University

April, 2001 Associate Professor, Department of Internal Medicine, School of Medicine, Keio University

April, 2007 Vice president, Keiyu Hospital

April, 2009-present President, Keiyu Hospital

Membership

Director of Japanese Society for Microcirculation

Councilor of Japanese Society of Lymphology

Councilor of Japanese Society of Experimental Ulcer Research*

Councilor of Japanese Society of Gastroenterology

Member of Japan Society of Hepatology

International Member of American Gastroenterological Association

Plenary Lecture 22

10:10-10:40 October 30 Sunday

Room 402 Yifu Building

Regulation of Plasminogen Activator Inhibitor-1 in vessel maturation

Jian-Bo Wu, M.D., Ph.D.

Professor, Drug Discovery Research Center, Southwest Medical University

Chair: Jun-Bao Du**,** M.D., Ph.D.

Professor, Department of Pediatrics, Peking University First Hospital

PL-22

Regulation of Plasminogen Activator Inhibitor-1 in vessel maturation

Jian-Bo Wu

Drug Discovery Research Center, Southwest Medical University, Luzhou, Sichuan, China

Plasminogen activator inhibitor-1 (PAI-1) is the primary inhibitor of urinary-type and tissue-type plasminogen activators and a key regulator of fibrinolysis. PAI-1 also regulates the function of vascular cells, including vascular smooth muscle cells (VSMCs). PAI-1 inhibits VSMC migration by inhibiting plasmin formation and preventing degradation of extracellular matrix (ECM) and elastic laminae. PAI-1 binds vitronectin (VN), an ECM protein whose PAI-1 binding site overlaps with those on VN for integrin $\alpha_V\beta_3$ and u-PA receptor (uPAR), cell surface proteins that control VSMC migration. Therefore, PAI-1 can competitively block VSMC-VN interactions and inhibit migration. However, PAI-1 can also promote VSMC migration by binding to uPAR-bound u-PA, leading to conformational changes in PAI-1 and exposure of its high-affinity binding site for LDL receptor-related protein (LRP). Binding of PAI-1 to LRP triggers internalization of PAI-1, along with associated u-PA, uPAR, and integrin. This internalization process, which appears to occur predominantly at the trailing edge of cells, allows VSMCs to detach from the ECM, a process necessary for migration. PAI-1 has been shown to exhibit both pro- and anti-angiogenic activities. Based on available data, it is hypothesized that the pro-angiogenic effect of PAI-1 is mediated by stabilizing the ECM through inhibition of plasmin-mediated proteolysis, whereas the anti-angiogenic effects of PAI-1 are mediated by inhibition of VN-dependent cell adhesion. Therefore, that the pharmacologic inhibition of elevated PAI-1 might restore the impairments in neovasculature observed in type II diabetes.

Jianbo Wu
Director of Drug Discovery Research Center
Southwest Medical University, Luzhou, Sichuan, China

2008 ATVB Merit Awards for Young Investigators
2008 Finalist Kenneth M. Brinkhous Young Investigator Prize in Thrombosis
2010 Member of American Heart Association Peer Review Committee
2010 AHA ATVB Travel Award for Young Investigators (Junior Faculty)

Personal Statement

This interest now focuses on vessel maturation and function under physiological and pathophysiological conditions. Further we have a particular interest on how vascular cells interact with the extracellular matrix and, in the diabetes context, how this is affected by protein glycation. Our work in the diabetes area has involved the use of experimental animal models as well as the in vitro modification of proteins; including that of extracellular matrix.

Select Publications

1. Yang Y, Xiao L, Chen N, Li Y, Deng X, Wang L, Sun H, **Wu J***. Platelet-derived factor V promotes angiogenesis in a mouse hind limb ischemia model. J Vasc Surg. 2016 pii: S0741-5214(16)30038-6. (*, as corresponding author).
2. Xiao L, Yan K, Yang Y, Chen N, Li Y, Deng X, Wang L, Liu Y, Mu L, Li R, Luo M, Ren M, **Wu J***. Anti-vascular endothelial growth factor treatment induces blood flow recovery through vascular remodeling in high-fat diet induced diabetic mice. Microvasc Res. 2016; 105: 70.
3. Hong K, Lee S, Li R, Yang Y, Tanner MA, **Wu J**, Hill MA. Adiponectin Receptor Agonist, AdipoRon, Causes Vasorelaxation Predominantly Via a Direct Smooth Muscle Action. Microcirculation. 2016;23(3):207-20.
4. Chen N, Ren M, Li R, Deng X, Li Y, Yan K, Xiao L, Yang Y, Wang L, Luo M, Fay WP, **Wu J***. Bevacizumab promotes venous thromboembolism through the induction of PAI-1 in a mouse xenograft model of human lung carcinoma. *Mol Cancer*. 2015;14:140.
5. Wang L, Zhang X, Pang L, Xiao L, Li Y, Chen N, Ren M, Deng X, **Wu J*.** Glycation of Vitronectin Inhibits VEGF-induced Angiogenesis by Uncoupling VEGF Receptor-2-αvβ3 Integrin Cross-talk. *Cell Death Dis.* 2015 ;6:e1796.
6. Luo M, Li R, Deng X, Ren M, Chen N, Zeng M, Yan K, Xia J, Liu F, Ma W, Yang Y, Wan Q, **Wu J*** . Platelet-derived miR-103b as a novel biomarker for the early diagnosis of type 2 diabetes. *Acta Diabetol*. 2015;52(5):943-9.
7. **Wu J***, Strawn TL, Luo M, Wang L, Li R, Ren M, Xia J, Zhang Z, Ma W, Luo T, Lawrence DA, Fay WP. Plasminogen activator inhibitor-1 inhibits angiogenic signaling by uncoupling vascular endothelial growth factor receptor-2-αVβ3 integrin cross talk. *Arterioscler Thromb Vasc Biol*. 2015;35(1):111-120.
8. Ren M, Li R, Luo M, Chen N, Deng X, Yan K, Zeng M, **Wu J***. Endothelial cells but not platelets are the major source of Toll-like receptor 4 in the arterial thrombosis and tissue factor expression in mice. *Am J Physiol.* 2014;307(7):R901-907.
9. Li R. Luo M. Ren M. Chen N. Xia J. Deng X. Zeng M. Yan K. Luo T. **Wu J***. Vitronectin regulation of vascular endothelial growth factor-mediated angiogenesis. *J Vasc Res*. 2014; 51:110-117.
10. Li R, Ren M, Chen N , Luo M, Deng X, Xia J, Yu G, Liu J, He B, Zhang X, Zhang Z, Zhang X, Ran B and **Wu J***. Presence of intratumoral platelets is associated with tumor vessel structure and metastasis. *BMC Cancer* 2014; 14:167.
11. Zhang Z, Yang Y, Hill MA, **Wu J***. Does C-reactive protein contribute to atherothrombosis via oxidant-mediated release of pro-thrombotic factors and activation of platelets? *Front Physiol*. 2012;3:433.
12. Li R, Ren M, Chen N, Luo M, Zhang Z, **Wu J***. Vitronectin increases vascular permeability by promoting VE-cadherin internalization at cell junctions. PLoS One. 2012;7(5):e37195.
13. Li R, Ren M, Luo M, Chen N, Zhang Z, Luo B, **Wu J***. Monomeric C-reactive protein alters fibrin clot properties on endothelial cells. *Thromb Res*. 2012;129(5):e251-6.
14. Garg N, Goyal N, Strawn TL, **Wu J**, Mann KM, Lawrence DA, Fay WP. Plasminogen activator inhibitor-1 and vitronectin expression level and stoichiometry regulate vascular smooth muscle cell migration through physiological collagen matrices. *J Thromb Haemost*. 2010; 8: 1847-1854.
15. Yang Y, Wu X, Gui P, **Wu J**, Sheng JZ, Ling S, Braun P, Davis GE, Davis MJ. α5β1 integrin engagement increases BK channel current and Ca^{2+} sensitivity through c-Src mediated channel phosphorylation. *J Biol Chem*. 2010 ; 285(1):131-141.
16. **Wu J***, Peng L, McMahon GA, Rabbani AB, Lawrence DA, Fay WP. Recombinant plasminogen activator Inhibitor-1 inhibits intimal hyperplasia. *Arterioscler Thromb Vasc Biol*. 2009; 29(10):1565-1570.

Plenary Lecture 23

10:40-11:10 October 30 Sunday

Room 414 Yifu Building

Contribution of At1r Mechanoactivation to the Arterial Myogenic Response and its Regulation by Rgs5 Protein in Skeletal Muscle Arterioles

Michael A. Hill, M.D., Ph.D.

Professor, Medical Pharmacology and Physiology,

Dalton Cardiovascular Research Center, University of Missouri

Chair: Jian-Bo Wu, M.D., Ph.D.

Professor, Drug Discovery Research Center, Southwest Medical University

PL-23

Contribution of At1r Mechanoactivation to the Arterial Myogenic Response and its Regulation by Rgs5 Protein in Skeletal Muscle Arterioles

Michael A. Hill[1], Kwangseok Hong[1], Gerald A. Meininger[1], Guiling Zhao[2], Z. Hong[1], Philip S. Clifford[2] Zhe Sun[1] and Yan Yang[1].

[1]Dalton Cardiovascular Research Center and Department of Medical Pharmacology and Physiology, University of Missouri, Columbia, MO 65211, USA. [2]College of Applied Health Sciences, University of Illinois at Chicago, Chicago, Illinois 60612, USA.

The arteriolar myogenic response, or pressure-induced vasoconstriction, is a major factor in the local regulation of hemodynamics. Although intracellular mechanisms underlying the arteriolar myogenic response have been well-defined, the mechanotransduction events transducing the mechanical stimulus remain unclear. Recently, ligand-independent activation of G protein-coupled receptors (in particular, the angiotensin II type 1 receptor; AT1R) has been suggested to play a major role in vascular smooth muscle mechanotransduction, thereby contributing to myogenic constriction. However, the downstream pathways following ligand-independent activation of the AT1R have not been clearly elucidated. Using isolated and pressurized small artery preparations our studies provide pharmacological evidence that the mechanically activated AT1R generates diacylglycerol, which in turn activates PKC that subsequently induces actin cytoskeleton reorganization for myogenic constriction. Actin polymerization was quantified using blotting. Further, using atomic force microscopy on single smooth muscle cells we showed thickening of cortical actin fibers in response to hypotonic buffer (a mechanical stimulus) and that this was attenuated by the AT1R blocker, candesartan. In terms of physiological roles, the arterial myogenic response acts to generate vascular tone, prevent capillaries from being damaged, and reduce edema due to high capillary hydrostatic pressure. Thus, an exaggerated AT1R-mediated myogenic constriction could conceivably contribute to vascular disorders. As a result, small arteries likely exhibit negative feedback regulatory mechanisms to prevent such an exaggerated myogenic response. In regard to this, we discovered that ligand-dependent or -independent activation of the AT1R causes trafficking of an important regulatory molecule, RGS5 (Regulators of G protein Signaling) protein, which may modulate Ang II or myogenic-mediated constriction by terminating Gq/11 protein-dependent signaling. Collectively, these data provide further evidence supporting the mechanosensitivity of the AT1R and that its actions occur in concert with appropriate regulatory mechanisms.

Michael A. Hill, Ph.D.
Professor of Physiology and Interim Director
Dalton Cardiovascular Research Ctr
University of Missouri
Columbia, MO 65211, USA.

Training:

MSc. (1988) University of Melbourne, Melbourne, Australia

Ph.D. (1988) University of Melbourne, Melbourne, Australia

Positions and Employment

1988-1991 Postdoctoral Fellow/Assistant Research Scientist, Medical Physiology, Texas A&M Univ, College Station, Texas, USA

1991-1996 Assistant/Assoc Professor, Physiology and Surgery, Eastern Virginia Medical School, Norfolk, Virginia, USA

1997-2001 Professor and Head of Department, Human Biology and Movement Science, Royal Melbourne Institute of Technology University, Bundoora, Victoria, Australia

1997-2004 Inaugural Chair, Physiology, Royal Melbourne Institute of Technology Univ, Bundoora, Victoria, Australia

2000-2004 Associate Dean (Research and Development), Faculty of Life Sciences, Royal Melbourne Institute of Technology University, Bundoora, Victoria, Australia

2004-2006 Professor and Chair, Physiology; Head, Physiology and Pharmacology, School of Medical Sciences, Faculty of Medicine, University of New South Wales, Kensington, Australia

2006-present Professor (tenured), Medical Pharmacology and Physiology, University of Missouri-Columbia 2006-present, Associate Director (2008-2015); Interim Director (9/2015 – present), Dalton Cardiovascular Research Center, University of Missouri-Columbia

Representative Publications

- Clifford PS, Ella SR, Yang Y, Davis MJ, Meininger GA, **Hill MA**. Spatial distribution and mechanical function of elastin in resistance arteries - a role in bearing longitudinal stress. Arterio Thromb Vasc Biol, 2011;31:2889-96. PMCID: PMC3380608.
- McCurley A, Pires PW, Bender SB, Aronovitz M, Zhao MJ, Metzger D, Chambon P, **Hill MA**, Dorrance AM, Mendelsohn ME, Jaffe IZ. Direct regulation of blood pressure by smooth muscle cell mineralocorticoid receptors. Nat Med, 2012;18:1429-33. PMCID: PMC3491085
- DuPont, J.J., **Hill, M.A.**, Bender, S.B., Jaisser, F. and Jaffe, I.Z. Aldosterone and mineralcorticoid receptors: regulators of ion channels beyond the kidney. Hypertension 63:632-637, 2014. PMID: 24379184.
- Moreno-Dominguez A, Colinas O, El-Yazbi A, Walsh EJ, **Hill MA**, Walsh MP, Cole WC. Role of calcium sensitization and dynamic cytoskeletal reorganization in the myogenic response of skeletal muscle resistance arteries to intravascular pressure. J Physiol, 591:1235-50, 2013. PMCID: PMC3607868.
- Nourian, Z., Li, M., Yang, Y., Davis, M.J., Braun, A.P. and **Hill, M.A.** Large Conductance, Ca^{2+}-activated, K^+ Channels (BK) a-subunit variants in resistance arteries from rat cerebral and skeletal muscle vasculature. PLOS One 9:e98863, 2014.
- Lee, S., Yang, Y., Tanner, M.A., Li, M. and **Hill, M.A**. Heterogeneity in Kv7 channel function in the cerebral and coronary circulation. Microcirculation 22:109-21, 2015
- Hong, K., Zhao,G., Clifford, P.S., Meininger, G.A. and **Hill, M.A.** Ligand-independent activation of angiotensin II type 1 receptors evokes diacylglycerol/protein kinase C-mediated actin cytoskeleton remodeling and contributes to arteriolar myogenic constriction. J. Physiol. (Accepted for publication)
- **Hill, M.A.**, Nourian, Z., Ho, I., Clifford, P.S., Martinez-Lemus, L. and Meininger, G.A. Small artery extracellular matrix architecture – focus on the three dimensional organization of elastin. Microcirculation 2016 (Accepted for publication).

Plenary Lecture 24

10:40-11:10 October 30 Sunday

Room 402 Yifu Building

Aquaporins in brain disorders

Masato Yasui, M.D., Ph.D.

Professor, Department. of Pharmacology, School of Medicine, Keio University, Tokyo, Japan

Chair: Xue-Jun Li, M.D., Ph.D.

Professor, Department of Pharmacology, School of Basic Medical Sciences, Peking University

PL-24

Aquaporins in brain disorders

Masato Yasui

Dept. of Pharmacology, School of Medicine, Keio University, Tokyo, JAPAN

Aquaporin-4 (AQP4) is the main water channel in mammalian brain, and is distributed with highest density in the perivascular and subpial astrocyte end-feet. AQP4 has been implicated in several neurologic conditions, such as brain edema, seizure and even mood disorders. Here we discuss about the mechanisms how AQP4 is dynamically regulated at different levels; channel gating, subcellular distribution, phosphorylation, protein-protein interactions and orthogonal array formation. Interestingly, AQP4 has been identified as a target antigen of autoimmune attack in neuromyelitis optica (NMO). NMO is characterized by extensive necrotic lesions preferentially involving the optic nerves and spinal cord. However, previous *in vivo* experimental models injecting human anti-AQP4 antibodies only resulted in mild spinal cord lesions compared to NMO autopsied cases. We made a high affinity anti-AQP4 monoclonal antibody (E5415A), recognizing extracellular domain of AQP4 by using baculovirus display method. By injecting this monoclonal antibody, we have established a severe experimental NMO rat model with highly clinical exacerbation and extensive tissue destructive lesions typically observed in NMO patients. Our data suggest that the pathogenic antibodies could induce immune mediated astrocytopathy with mobilized neutrophils, resulted in early lesion expansion of NMO lesion with vacuolation and other tissue damages.

Masato Yasui

Personal

Birth date: June 28, 1964
Birth place: Tokyo, Japan
Citizenship: Japanese
Residence: 2-2-14 Sasuke, Kamakura, Kanagawa, 248-0017 JAPAN

Education

1989 Medical License (M.D.), Graduated from School of Medicine, Keio University (Tokyo, Japan)
1997 Doctor of Philosophy (Ph. D.) at the Karolinska Institute (Stockholm, Sweden). Thesis Title: Expression and Regulation of water channels and ion transpoters (Ontogenic Aspects)
1998 Doctor of Medical Science (Ph.D.) at School of Medicine,Keio University

Clinical Training

1989-1992 Clinical Resident of Pediatrics, St. Luke's International Hospital, Tokyo, Japan
1992 Clinical Fellow of Neonatolgy, Tokyo Women's Medical University, Tokyo, Japan

Research Training

1992 Guest Researcher, Dept. of Molecular NeurobiologyUniversity of Tokyo, Japan
1993-1997 Postgraduate Student, Dept of Woman and Child Health, Pediatric Unit, Karolinska Institute,
1997-2000 Postdoctoral Research Fellow, Dept. of Biological Chemistry, Johns Hopkins Univ. School of Medicine, Baltimore, USA (Prof. Peter Agre)

Academic Positions

2000-2001 Instructor, Dept. of Biol. Chem., Johns Hopkins School of Medicine,Baltimore, Maryland, USA
2001- Assistant Professor, Depts of Pediatrics and Biological Chemistry, Johns Hopkins School of Medicine, Baltimore, Maryland, USA
2006- Professor and Chair, Department of Pharmacology, Keio University School of Medicine, Japan

Honors

1997 Society for Pediatric Research, Student Award
1998 Human Frontier Science Program, Long-term Fellowship Award, American Heart Association MDA Fellowship Award
2000 Johns Hopkins Young Investigators Day, A. McGehee Harvey Prize for Post-doctoral research
2002 Keio Medical School, Alumni Assoiciation Award, Tokyo
2004 S&R Foundation Award, Washington, D.C.

Society Memberships

American Society of Nephrology, USA
American Heart Association, USA
Japanese Society of Pharmacology, Japan
American Society of Neuroscience American Society of Biophysics

Selected Publications

- Yasui M, Kwon TH, Knepper MA, Nielsen S and Agre P. Aquaporin-6: An intracellular vesicle water channel protein in renal epithelia. Proc. Natl. Acad. Sci. USA. 96(10):5808-13. (1999)
- Yasui M, Hazama A, Kwon TH, Nielsen S, Guggino WB and Agre P. Rapid gating and anion permeability of an intracellular aquaporin. Nature. 402(6758): 184-7. (1999)
- Yasui M. Molecular mechanisms and drug development in aquaporin water channel diseases: structure and function of aquaporins. J. Pharmacol. Sci. 96(3): 260-3. (2004)
- Liu K, Kozono D, Kato Y, Agre P, Hazama A and Yasui M. Conversion of aquaporin-6 from an anion channel to a water-selective channel by a single amino acid substitution. Proc. Natl. Acad. Sci. USA. 102(6): 2192-7. (2005)
- Nuriya M, Fukushima S, Momotake A, Shinotsuka T, Yasui M and Arai T. Multimodal two-photon imaging using a second harmonic generation-specific dye. Nat Commun. 7:11557. (2016)

Plenary Lecture 25

11:10-11:40 October 30 Sunday

Room 414 Yifu Building

Micro RNA in regulating oxidative stress in neurons

Toshio Nakaki, M.D., Ph.D.

Professor, Department of Pharmacology
Teikyo University School of Medicine

Chair: Jing-Yan Han, M.D., Ph.D.

Professor, Department of Integration of Chinese and Western Medicine, Peking University Health Science Center/Tasly Microcirculation Research Center, Peking University Health Science Center

PL-25

Micro RNA in regulating oxidative stress in neurons

Toshio Nakaki

Department of Pharmacology, Teikyo University School of Medicine,

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Glutathione (GSH) is the key antioxidant that plays an important neuroprotective role in the brain. Decreased GSH levels are associated with neurodegenerative diseases. Circadian involvement in neurodegenerative diseases has long been suggested, but evidence is still elusive. We found that a diurnal fluctuation of the GSH level is correlated with neuroprotective activity against oxidative stress in dopaminergic cells. In addition, the protein level of excitatory amino acid carrier 1 (EAAC1), a transporter of cysteine for neuronal GSH synthesis, is negatively regulated by a micro RNA, miR-96-5p, which exhibits a diurnal rhythm. The intracerebroventricular administration of miR-96-5p inhibitor increased the EAAC1 expression, the GSH level and neuroprotection against oxidative stress in the mouse substantia nigra. A clinical report shows patients with a neurodegenerative disease, multiple system atrophy, to exhibit an increase in miR-96-5p in the brain. An amino acid, taurine, is known to play a role of neuroprotection of neurons and miR-96-5p is reported to negatively regulate taurine transporter. Our results together with other reports demonstrate miR-96-5p to be the key regulator of oxidative stress via EAAC1 and taurine transporter and to play a role in pathogenesis of multiple system atrophy.

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Education:
1979 Graduated from Keio University School of Medicine, Japan
1979 M.D., Keio University
1983 Ph. D., Keio University, Pharmacology

Board Certification:
License of Medical Practice (Japan)
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Professional Experience:

1983-89	Assistant Prof., Keio University School of Medicine
1983-85	Postdoctoral Fellow of NIH (U.S.A.)
1989-96	Assistant Prof., Keio University School of Medicine
1996-2000	Associate Professor, Teikyo University School of Medicine
2000-present	Professor and Chairman, Department of Pharmacology, Teikyo University School of Medicine

Awards:
1992 Kitasato Award
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Major Research Interest

Defense mechanism against oxidative stress, Nitric oxide biology, Parkinson's disease

Plenary Lecture 26

11:10-11:40 October 30 Sunday

Room 402 Yifu Building

Modelling the Flow Pulsatility in Microcirculation Network

Gang-min Ning, M.D., Ph.D.

Professor, Department of Biomedical Engineering, Zhejiang University

Chair: Ke-Sheng Dai, M.D., Ph.D.

Professor, Deputy Director, Key Laboratory of Thrombosis and Hemostasis, Ministry of Health, Research Unit on Thrombosis and Hemostasis, Jiangsu Institute of Hematology, The First Affiliated Hospital of Soochow University

PL-26

Modelling the Flow Pulsatility in Microcirculation Network

Gang-Min Ning

Department of Biomedical Engineering, Zhejiang University

The modelling techniques for microvascular hemodynamics have been developed for decades. However, most of the microcirculatory models are utilized as steady flow approaches. The physiological significance of pressure pulsatility in microcirculation is acknowledged and its understanding asked for dynamic models. We supposed a multi-scale dynamic model to describe the dynamic behavior of microvascular blood flow. The model allows the simulation of the dynamic properties of blood flow in microcirculatory networks, including the pressure pulsatility and pulse wave velocity etc. Meanwhile, the pulsatility involved regulations, e.g. the production of nitric oxide and the induced vasodilatation, are investigated. The model was validated in real mesenteric network of rats. The simulation results suggest that the present model may facilitate exploring the dynamic behaviors and mechanisms of pulsatility in complex microvascular networks.

Gang-Min Ning

Gang-Min Ning received the B. Sc. and M. Sc. degree in biomedical engineering from the Zhejiang University, China, in 1987 and 1990, and the Dr.-Ing. degree in biomedical engineering from the Technische Universität Ilmenau, Germany, in 2001. He is currently a professor in the Department of Biomedical Engineering, Zhejiang University, China. He was the scholarship holder of German Academic Exchange Service (DAAD) and the visiting professor at Charité Medicine Center, Berlin, Germany. His research interests cover the modelling and simulation of cardiovascular system, design of biomedical devices and individual treatment strategy in clinic, with over 80 academic publications and contributions to the conferences.

Education Lecture 1

14:00-14:30 October 29 Saturday

Room 408 Yifu Building

Methods for Study of the Organ Microcirculation

Yu-Ying Liu

Tasly Microcirculation Research Center, Peking University Health Science Center, Beijing, China

Chair: Dong Han

Professor, National Center for Nanoscience and Technology

Education Lecture 1

Methods for Study of the Organ Microcirculation

Yu-Ying Liu

Tasly Microcirculation Research Center, Peking University Health Science Center, Beijing, China

Microcirculation study is an important means for evaluating the organ pathophysiology and exploring underlying mechanism in experimental study. The approach of microcirculation study varies depending on the organ concerned. This lecture provides a brief introduction for the approach used in research of microcirculation of mesentery, heart, brain, liver and lungs of small animals, including vascular configuration of different organs, selection of micro-vessels, blood flow velocity measurement, the label methods of leukocytes, cell adhesion, the determination of peroxide, mast cells degranulation and counting, and the determination of tissue blood flow.

Education Lecture 2

14:30-15:30 October 29 Saturday

Room 408 Yifu Building

Attenuating effect and underlying mechanism of compound Chinese medicine on ischemia and reperfusion induced cerebral and cardiac microcirculation disturbance and organ injury

Jing-Yan Han

Department of Integration of Chinese and Western Medicine, School of Basic Medical Sciences, Peking University

Chair: Yi-Ning Huang

Professor and Chairman, Department of Neurology, Peking University First Hospital

Education Lecture 2

Attenuating effect and underlying mechanism of compound Chinese medicine on ischemia and reperfusion induced cerebral and cardiac microcirculation disturbance and organ injury

Jing-Yan Han
Department of Integration of Chinese and Western Medicine, School of Basic Medical Sciences, Peking University

Ischemia and reperfusion (I/R)-induced microcirculation disturbance and organ injury occurs frequently following intervention, thrombolysis, and major surgery. Ischemia and hypoxia in ischemic phase and peroxides produced in reperfusion phase result in various pathological manifestations, including expression of E-selectin and adhesive molecules in vascular endothelial cells; expression of L-selectin and adhesive molecules in leukocytes; leukocytes rolling on, adhesion to and migration from micovessel wall; monocyte migration out of microvessels; and necrosis, apoptosis and fibrosis that occur in perivascular interstitial. Clearly, I/R-induced microcirculation disturbance and organ injury involve a complex pathological process, to attenuate which an intervention targeting multiple links is required.

Chinese medicine, particularly compound Chinese medicine, is a preparation consisted of multiple ingredients. Clinical research revealed obvious superiority of compound Chinese medicines in dealing with I/R-induced cerebral and cardiac injury. Using dynamic visualized technique, histology and histochemistry, cellular and molecule biology and systematic biology, the reporter systematically explored the beneficial role of cerebralcare granules in I/R- induced rat cerebral microcirculation disturbance and neuron injury, gained insight into the mechanism by which cerebral care granules ameliorated I/R-induced injury in hippocampus and cotex neurons. Explored were also QiShenYiQi pills and its major ingredients astragaloside IV, danshensu and notoginsenoside R1 as to their role and mechanism in I/R-induced energy metabolism disorder, microcirculation disturbance and injury in rat myocardium, highlighting QiShenYiQi pills as a multi-components-multi-targeting medicine that acts at a network of pathways.

The present report will systematically introduce the related results.

Education Lecture 3

15:30-16:00 October 29 Saturday

Room 408 Yifu Building

An update of the journal Microcirculation

Geraldine F Clough

Deputy Editor-in-Chief, Microcirculation
Professor, Vascular Physiology, Faculty of Medicine, University of Southampton, UK

Chair: Jian-Bo Wu
Professor, Drug Discovery Research Center, Southwest Medical University

Education Lecture 3

An update of the journal *Microcirculation*: Report to the 1st Chinese Microcirculation Week

Geraldine F Clough, Deputy Editor-in-Chief, Microcirculation

The journal *Microcirculation* features original contributions that are the result of investigations contributing significant new information relating to the vascular and lymphatic microcirculation addressed at the intact animal, organ, cellular, or molecular level. Papers describe applications of the methods of physiology, biophysics, bioengineering, genetics, cell biology, biochemistry, and molecular biology to problems in microcirculation.

Microcirculation also publishes state-of-the-art reviews that address frontier areas or new advances in technology in the fields of microcirculatory disease and function. Specific areas of interest include: Angiogenesis, growth and remodeling; Transport and exchange of gasses and solutes; Rheology and biorheology; Endothelial cell biology and metabolism; Interactions between endothelium, smooth muscle, parenchymal cells, leukocytes and platelets; Regulation of vasomotor tone; and Microvascular structures, imaging and morphometry. Papers also describe innovations in experimental techniques and instrumentation for studying all aspects of microcirculatory structure and function.

The journal is published by Wiley and is currently the official journal of the Microcirculatory Society Inc., the British Microcirculation Society, the Australia and New Zealand Microcirculation Society and the Japanese Society for Microcirculation.

http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1549-8719

Symposium 1

13:00-15:00 October 28 Friday Room 414 Yifu Building

Brain Microcirculation and Cerebral Vascular Diasease

Chairs:

Xue-Long Jin
Department of physiology, Tianjin Medical University
Huai-Lian Guo
Department of Neurology, People's Hospital, Peking University

S-1-1 The Role of Free Radical Generation in Increasing Cerebrovascular Permeability
Paul Fraser
Cardiovascular Division Faculty of Life Sciences & Medicine King's College London

S-1-2 A New Internal Capsule Hemorrhage Animal Model
Xue-Long Jin
Department of physiology, Tianjin Medical University

S-1-3 Exercise Training Ameliorates Age-Induced Cerebral Microvascular Deterioration and VEGF Angiogenic Signaling in Rats
Sheepsumon Viboolvorakul
Physiology Unit, Department of Medical Science, Faculty of Science, Rangsit University

S-1-4 Adoptive Regulatory T Cell Therapy Protects Against Stroke-induced Cerebral Injury
Lei-Lei Mao
Key Laboratory of Cerebral Microcirculation in Universities of Shandong, Taishan Medical University

S-1-5 The Effects of Rho Kinase Inhibition on the Permeability of Blood-brain Barrier and Activation of Microglia After Cerebral Ischemia in Rats
Yong-Bo Zhang
Department of Neurology, Beijing Friendship Hospital, Capital Medical University

S-1-6 In vivo Observation of Cortical Astrocytes after Cerebral Hypoperfusion in Mice
Jiang-Man Song
Department of Neurology, People's Hospital, Peking University

S-1-1

The Role of Free Radical Generation in Increasing Cerebrovascular Permeability

The brain endothelium constitutes a barrier to the passive movement of substances from the blood into the cerebral microenvironment, and disruption of this barrier after a stroke or trauma has potentially fatal consequences. Reactive oxygen species (ROS), which are formed during these cerebrovascular accidents, have a key role in this disruption. ROS are formed constitutively by mitochondria and also by the activation of cell receptors that transduce signals from inflammatory mediators, e.g., activated phospholipase A2 forms arachidonic acid that interacts with cyclooxygenase and lipoxygenase to generate ROS. Endothelial NADPH oxidase, activated by cytokines, also contributes to ROS. There is a surge in ROS following reperfusion after cerebral ischemia and the interaction of the signalling pathways plays a role in this.

There is a surge in ROS generation when tissue is reperfused following a blockage, as in ischemic stroke, and the evidence that this originates from the endothelium itself will be discussed.

S-1-2

A New Internal Capsule Hemorrhage Animal Model

Xue-Long Jin [1], Zhao-Qiang Zhang [1], Jin Hu [2]

1. Department of physiology, Tianjin Medical University, Tianjin 300070, China.
2. Department of the Integrated Traditional Chinese and Western Medicine, Hunan university of Chinese medicine, Hunan 410208, China.

Objective: To study and evaluate a new internal capsule hemorrhage animal model.

Methods: We established an internal capsule hemorrhage animal model using Horseley-Clarke technique. Internal capsule was orientated referring to Sawyer rabbit brain stereotaxic atlas. The model was duplicated by injecting 0.5 ml autologous arterial blood into hind limb of internal capsule. We used HE stain to observe the changes of brain tissues. Then somatosensory evoked potential and intracranial pressure were measured.

Results: Obvious hematoma was detected in brain tissues under light microscopes. The latency of N1 and P1 in somatosensory evoked potential prolonged and the peak-to-peak value of N2-P1 decreased. Meantime intracranial pressure increased.

Conclusion: We established an internal capsule hemorrhage animal model successfully. Histopathologic changes of the brain tissues and abnormal somatosensory evoked potential were found. We observed an increase in intracrnial pressure. These can provide the reference for the study of intracerebral hemorrhage.

S-1-3

Exercise Training Ameliorates Age-induced Cerebral Microvascular Deterioration and VEGF Angiogenic Signaling in Rats

Sheepsumon Viboolvorakul[1,*] and Suthiluk Patumraj[2].

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*Corresponding author

Background: Reductions of basal blood flow and capillary density in the brain contributes tissue perfusion insufficiency with advanced age. Microvascular loss in aged tissues appears to be related to downregulation of vascular endothelial growth factor (VEGF) signaling. Regular exercise has been reported to have beneficial effects to brain health in aging individuals. Therefore, the present study aimed to investigate effect of exercise training on age-induced cerebromicrovascular alteration with modulation of VEGF angiogenic signaling.
Methods: Male Wistar rats were divided into 3 groups; sedentary-young, sedentary-aged (and exercised-aged. Exercise program included swimming training 5 days/week for 8 weeks. *In situ study* of brain microvascular networks was performed to determine regional blood flow (rCBF) (by Doppler flowmetry) and microvascular vascularity (MV) (using a laser scanning confocal fluorescent microscopy). Level of VEGF, VEGFR2, PI3K, Akt and eNOS in isolated brain microvessels were determined by immunoassay.
Results: MV and rCBF was significantly lower in the sedentary-aged rats compared with the sedentary-young rats, whereas that in the exercised-aged rat was significantly higher than the sedentary-aged rats. The levels of VEGF, VEGFR2 and eNOS were significantly lower in the sedentary-aged rats compared with the sedentary-young rats, whereas those in the exercised-aged rats were significantly higher than those in the sedentary-aged rats. The expression of phosphorylated Akt and PI3K corresponded to the alterations in the VEGF, VEGFR2 and eNOS levels.
Conclusion: These findings suggest that exercise training could improve brain microvascular alteration partly associated to VEGF signaling in aging rats.

S-1-4

Adoptive Regulatory T Cell Therapy Protects Against Stroke-induced Cerebral Injury

Lei-Lei Mao[1,2], Guo-Qing Zhou[1], Pei-Ying Li[2], Xiao-Ming Hu[2], Ming-Feng Yang[1], *Jun Chen[2], Xiao-Yi Yang[1], *Bao-Liang Sun[1]

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[2]State Key Laboratory of Medical Neurobiology and Institute of Brain Sciences, Fudan University, Shanghai 200032, China

Objective: The pathology of ischemic stroke and the mechanism of thrombolytic therapy induced lethal hemorrhagic transformation (HT) involve disruption of the blood brain barrier (BBB) . This study evaluated the effect of regulatory T cells (Tregs) transfer on ischemic stroke and rtPA-enhanced HT . In addition, we further investigated the mechanism underlying Treg-afforded BBB protection.

Methods and Results: Cerebral ischemia was induced in mouse by suture middle cerebral artery occlusion (MCAO) for 1h , or for 2h followed by intravenous rtPA infusion leading to HT. Systemic administration of purified Tregs at 2, 6, or 24 hours after the surgery, resulted in marked reduction of brain infarct and rtPA-induced cerebral hemorrhage. Treg-afforded neuroprotection was accompanied by attenuated blood–brain barrier (BBB) disruption during early stages of ischemia in these two different model types. Further studies suggested that Tregs inhibited the elevation of matrix metallopeptidase-9 (MMP9) and chemokine (C-C motif) ligand 2 (CCL2) expression after stroke , thus preventing proteolytic damage of the BBB. Using MMP9 knockout and CCL2 knockout mice, we found that both molecules partially contribute to the protective actions of Tregs. Using *In vitro* model of BBB, we confirmed that Tregs inhibited tPA-induced endothelial expression of CCL2 and protected BBB against ischemic challenge. Clinical data revealed a significant decrease in the number of circulating Tregs upon stroke onset. The prolonged loss of circulating Tregs is correlated with poor stroke outcomes.

Conclusions: Tregs reduces ischemia and rtPA-induced BBB damage by two inhibitory mechanisms targeting both CCL2 and MMP9. Tregs may represent a potent cell-based therapy to decrease the brain infarct and increase the safety of thrombolytic treatment for stroke.

S-1-5

The Effects of Rho Kinase Inhibition on the Permeability of Blood-brain Barrier and Activation of Microglia After Cerebral Ischemia in Rats

Yong-Bo Zhang*，Qin Zhang, Qing-Hong Cui et al.

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* Correspondence: Dr. Yongbo Zhang

Rho kinase inhibitor fasudil has been shown to reduce cerebral vasospasm, to inhibit inflammation and apoptosis and to promote the recovery of neurological function after stroke. The integrity of the blood-brain barrier (BBB) and the activation of microglia play an important role in ischemic stroke. This study sought to explore the effects of fasudil on BBB permeability and microglia activation and mutual transformation between M1 phenotype and M2 phenotype after focal cerebral ischemia/reperfusion in rats. A focal cerebral ischemia/reperfusion model was established using the intraluminal suture technique. Fasudil (15 mg/kg) was intraperitoneally injected once a day. Neurological deficit was evaluated using Longa's method. Change in permeability of BBB was measured using Evans blue. The microglia markers of M1 phenotype and M2 phenotype were detected within ischemic penumbra by real time quantitative PCR. GAP-43 and claudin-5 were detected by immunohistochemistry and Western blotting analysis. Results revealed that fasudil noticeably contributed to the recovery of neurological function, improved the function of BBB, inhibited and upregulated GAP-43 and claudin-5 protein expression following cerebral ischemia/reperfusion. We also demonstrated that fasudil promoted microglia transfer from M1 phenotype to M2 phenotype. Results indicated that Rho kinase exhibits a certain effect on neurovascular damage and the activation of microglia following cerebral ischemia/reperfusion. Intervention targeted Rho kinase might be a new therapeutic target in the treatment of cerebral ischemia/reperfusion.

S-1-6

In vivo Observation of Cortical Astrocytes after Cerebral Hypoperfusion in Mice

Jiang-Man Song [1], Huai-Lian Guo [1], Di Nan [1], Qi-Hua He [2], Lu Yang [1]
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Abstract
Objective Cerebral hypoperfusion caused by atherosclerosis could induce astrocyte activation characterized with proliferation, hypertrophy and anomalous gene expression. Evidence suggests that the degree of astrocyte activation is heterogeneous, which depends on the distance from the edge of the ischemic core. In this work, we explored the astrocyte activation at different locations of neocortex in the live mouse brain under hypoperfusion.
Methods Tie2-GFP transgenic mice with Sulforhodamine 101 labeling plasma were used in this study. To mimic cerebral hypoperfusion, mice were subjected to modified unilateral common carotid arteries occlusion (UCCAO) operation, permanent left common carotid occlusion combined with twice transient right common carotid occlusion. Two-photon confocal laser-scanning microscope and three-dimensional reconstruction technology were applied to investigate astrocytes and vessels in vivo.
Results We found that astrocytes located around cortical capillaries and penetrating arteries underwent different degrees of activation, including proliferation and hypertrophy. The density of astrocytes around cortical capillaries was (2.169±0.06933×104/mm3) significantly higher than control group (1.699±0.1115×104/mm3) after hypoperfusion (p=0.0056). The mean volume of astrocyte somas around cortical capillaries (482.5±19.29μm3) was significantly increased compared to control group (359.0±21.03μm3) (p=0.0013). Around penetrating artery, the density of astrocytes in hypoperfusion and control group was 1.699±0.1260×104/mm3 and 1.569±0.06920×104/mm3 (p=0.3676) respectively. The mean volume of astrocytes around penetrating arteries was 434.5±31.51μm3 in hypoperfusion group, and 381.8±28.60μm3 in control group (p = 0.2492). Additionally, the average distance between penetrating artery and the nearest astrocyte soma in hypoperfusion group (17.75±1.033μm) was significantly shorter (p=0.0109) than sham group (26.34±2.432μm).
Conclusion Our results provide a suggestion that the cortical vessels of different types may affect the degree of astrocyte activation, and the astrocyte activation in turn contributes to angiogenesis in process of forming a new vessel network in hypoperfusion injury.
Key Words
Cerebral hypoperfusion; Astrocyte activation; Penetrating artery; Cortical capillary; Two-photon confocal laser-scanning microscopy

Symposium 2

13:00-15:00 October 28 Friday Room 402 Yifu Building

Cardiovascular Disease and Coronary Microcirculation

Chairs:

Ming Xu

Department of Cardiology, Institute of Vascular Medicine, Peking University Third Hospital, Key Laboratory of Molecular

Yu-Zhen Li

Chinese PLA General Hospital

S-2-1 **HIP-55, A Novel Component of Pro-survival Signaling, and Cardiovascular Diseases**

Zi-Jian Li

Institute of Vascular Medicine, Peking University Third Hospital

S-2-2 **The Formation and Stabilization of G-quadruplex by Natural Small Molecule Down-Regulates miR-24 Expression**

Ming Xu

Department of Cardiology, Institute of Vascular Medicine, Peking University Third Hospital, Key Laboratory of Molecular

S-2-3 **Cardiotonic Pills Ameliorates Ischemia-reperfusion Induced Cardiac Injury in Rats, Relying on the Antioxidant Effect of 3, 4-dihydroxyl-phenyl Lactic Acid and Energy Regulation of Notoginsenoside R1**

Xiao-Hong Wei

Tasly Microcirculation Research Center, Peking University Health Science Center, Beijing, China

S-2-4 **Cardiovascular Protection of Salviae Miltiorrhizae and the Underlying Mechanism**

Bao-Hong Jiang

Shanghai Institute of Materia Medica, CAS

S-2-5 **Effects and Mechanisms of Tanshinone IIA Derivative on Ameliorating Myocardial Ischemia/Reperfusion Injury in Rats**

Wan-Li Shen

School of Pharmacy, Shihezi University

S-2-1

HIP-55, A Novel Component of Pro-survival Signaling, and Cardiovascular Diseases

Zi-Jian Li

Institute of Vascular Medicine, Peking University Third Hospital, Key Laboratory of Cardiovascular Molecular Biology and Regulatory Peptides, Ministry of Health, Key Laboratory of Molecular Cardiovascular Sciences, Ministry of Education and Beijing Key Laboratory of Cardiovasicular Receptors Research Beijing 100191, China.

HIP-55 (hematopoietic progenitor kinase 1 [HPK1]-interacting protein of 55 kDa) is a multidomain protein that contains an actin-binding domain at its N terminus and an SH3 domain at its C terminus. It functions in part through controlling the HPK1 function, which appears to be important for organ development and immune response. Here, we found expression of HIP-55 up-regulated significantly after myocardial infarction. HIP-55 deficiency caused the apparent increase in myocardial infarction and death. Over-expression of HIP-55 leads to decrease significantly myocardial infarction and death. Those results indicated that HIP-55 protected against injure after myocardial infarction and promoted cell survival. Furthermore, we identified of a novel HIP-55 partner protein, 14-3-3, with a proteomic approach and found that the HIP-55/14-3-3 interaction is controlled by Akt. Mutational analysis revealed Ser-269 and Thr-291 as critical sites for Akt phosphorylation, which are essential for mediating 14-3-3 binding. While HIP-55WT(wide-type) decreased the kinase activity of HPK1, mutant HIP-55 that is defective in Akt phosphorylation and 14-3-3 binding failed to inhibit HPK1. HPK1 is key kinase which mediates cell death pathway. HIP-55 can protect against injure after myocardial infarction and promoted cell survival through HIP-55/14-3-3 complex inhibition of HPK1 cell death pathway. This study couples the HIP-55/HPK1 regulatory axis to an Akt-mediated signaling pathway and identifies a novel mechanism by which HIP-55 suppresses HPK1 in an Akt/14-3-3-dependent manner.

S-2-2

The Formation and Stabilization of G-quadruplex by Natural Small Molecule Down-Regulates miR-24 Expression

Juan Gao, You-Yi Zhang, Ming Xu

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MicroRNA-24

(miR-24) is a small non-coding RNA with 22 nucleotides, which has extensive biological effects, such as promoting cell proliferation and differentiation, promoting tumor cell invasion and migration, limitting vascular inflammation, and so on. In the process of heart failure (HF), miR-24 reduces the Excitation-contracti on (E-C) coupling efficiency by down regulate the membrane coupling protein Junctophilin2 (JP2), which anchors cell membrane and sarcoplasmic reticulum, an d promotes the development of heart failure. So, limiting the expression of miR-24 is important for the prevention and treatment of heart failure. Bioinformatics analys is revealed that upstream of genomic mir-24-1 harbored a potential G-quadruplex sequence(PQS), which may potentially fold into a G-quadruplex structure. Hence, this study is to detect the influence of PQS on expression of miR-24 and further explore the regulation mechanism. Here we show the deletion of PQS leads to increased expression of miR-24 and down-regulated expression of JP2 in neonatal rat myocardial cells (NRCM). In KO rats, the deletion of PQS leads to decreased left ventricular systolic function. The PQS formed G-quadruplex structure in vitro and can be stabilized by natural small molecule tetrandrine. The formation and stabilization of G-quadruplex down-regulates the expression of miR-24 in vivo. Our results suggest that the PQS of mir-24-1 possess ability of regulating the expression of miR-24 and cardiac contractile function.

S-2-3

Cardiotonic Pills Ameliorates Ischemia-reperfusion Induced Cardiac Injury in Rats, Relying on the Antioxidant Effect of 3, 4-dihydroxyl-phenyl Lactic Acid and Energy Regulation of Notoginsenoside R1

Xiao-Hong Wei,[1,3,4] Ke He,[1,3,4] Xiao-Yuan Yang,[1,3,4] Li Yan,[1,3,4] Na Zhao,[1,3,4] Yu-Ying Liu,[1,3,4] Chun-Shui Pan,[1,3,4] Yuan-Chen Cui,[1,3,4] Quan Li,[1,3,4] Bai-He Hu,[1,3,4] Xin Chang,[1,3,4] Kai Sun,[1,3,4] Jing-Yu Fan,[1,3,4] Chuan-She Wang,[1,2,3,4] and Jing-Yan Han[1,2,3,4]

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Cardiac ischemia-reperfusion (I/R) injury remains a challenge for clinicians, which increases the risk of mortality of percutaneous coronary intervention. Cardiotonic pill (CP), consisting of Salvia miltiorrhiza, Panax notoginseng, and Borneol, is a widely used traditional Chinese medicine in China for treating ischemic angina pectoris, which has underwent phase III clinical trials for prevention and treatment of ischemic cardiovascular diseases by the US Food and Drug Administration in 2016. The present report aimed to introduce the protective effect of CP and its main ingredients (3, 4-dihydroxyl-phenyl lactic acid, DLA and notoginsenoside R1, NR1) on I/R induced cardiac injury and underlying mechanism.

Male Sprague-Dawley rats were subjected to left anterior descending coronary artery occlusion for 30 min followed by reperfusion with or without CP, DLA and R1 administration. Myocardial microcirculatory disturbance, heart function, cardiac infarct and fibrosis size, myocardial apoptosis, myocardial histology and ultrastructure were evaluated. Inflammatory factors, apoptosis-related proteins, oxidative stress, energy metabolism were assessed.

Results showed that a single administration of CP pretreatment at 0.8 g/kg attenuates I/R-induced myocardial injury and cardiac microcirculatory disturbance. However, multiple administration of CP at doses ranging from 0.1 to 0.8 g/kg protected against rat heart I/R injury. Posttreatment with CP starting from 3 hour after reperfusion until day 6 ameliorated I/R-induced myocardial fibrosis. DLA, binding to and activating Sirtuin 1, restored I/R-induced decrease in NDUFA 10 expression, improved Complex I activity and mitochondrial function. NR1 was able to inhibit Rho kinase and enhance mitochondrial ATP synthase δ-subunits.

These results suggested that CP could ameliorate rat I/R-induced myocardial microcirculatory disturbance, myocardial infarct and myocardial fibrosis, which was due to the antioxidant effect of DLA and energy regulation of R1.

S-2-4

Cardiovascular Protection of Salviae Miltiorrhizae and the Underlying Mechanism

Bao-Hong Jiang

Shanghai Institute of Materia Medica, CAS

Salviae miltiorrhizae, one of the most important traditional herbal medicines, has been widely used in clinic in China for the treatment of cardiovascular diseases. Our study contained extract, active compounds, and the combination of active compounds from *Salviae miltiorrhizae*. Salvianolic acids, the water-soluble extract containing salvianolic acid A (SalA), salvianolic acid B (SalB), rosmarinic acid and other phenolic acids, significantly reduced doxorubicin-induced cardiomyopathy in mice, and decreased infarct size, improved LV function in rat with acute myocardial infarction (AMI). SalA prevented endothelial dysfunction, cardiac remodeling and vascular remodeling in spontaneously hypertensive rats; attenuated aortic aneurysm formation in apolipoprotein E-deficient mice. SalB functioned as a competitive inhibitor of matrix metalloproteinase-9 (MMP-9), attenuated cardiac fibroblast migration, collagen and cytoking secretion, and further efficiently prevented cardiac remodeling. The herb pair, derived from roots of *Salviae miltiorrhizae* and *Panax notoginseng*, has been widely used for improving coronary or cerebral circulation in China. Our study evaluated the cardioprotection of combined SalB and ginsenoside Rg1 (Rg1) against myocardial ischemia/reperfusion injury. SalB-Rg1 combination was found to maintain mitochondrial membrane potential and resist apoptosis and necrosis in H9c2 cell. SalB-Rg1 combination down-regulateed myocardial infarct size, maintained myocardium structure and cardiac function and improved the viability of cardiac myocytes other than cardiac fibroblasts in rats with ischemia/reperfusion injury. All of these founding elucidated the cardioprotection of the active components from *Salviae miltiorrhizae* and the underlying mechanism.

S-2-5

Effects and Mechanisms of Tanshinone IIA Derivative on Ameliorating Myocardial Ischemia/Reperfusion Injury in Rats

Wan-Li Shen[a], Fei Yu[c], Lu Xu[b], Cong Chen[b], Yi-Ni Cao[b], Shu Liu[a], Chao Wang[c] and Rong Qi[*, a, b]

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c School of Pharmaceutical Sciences, Peking University, Beijing 100191, China

Aim: Ischemia/reperfusion (I/R) injury is the main cause of myocardial damage and dysfunction. Tanshinone IIA (TSIIA) is the major bioactive constituent of Salvia miltiorrhiza Bunge, a Chinese herbal medicine, which has definite cardioprotective effects on myocardial ischemia/reperfusion (MIR) injury. However, due to its poor water solubility, the therapeutic effects of TSIIA was unstable and therefore, its clinical use was limited. The objective of this study was to investigate whether the glycosylated TSIIA, a water-soluble derivative of TSIIA (TD), had comparable cardioprotective effects on MIR injury as TSIIA and its related mechanisms.

Methods: Sprague Dawley (SD) rats were randomly divided into several groups with 7 rats in each group. With Danshen Dropping Pill (DDP, 135 mg/kg) as a positive control drug, TSIIA (7.912 mg/kg) or TD (7.912 mg/kg) was intragastrically administrated to the rats for 7 days. Then all rats received 45 min of ischemia by complete ligation of the left ascending coronary artery, followed by reperfusion for 2 h. After then, the infarct size and several consequences of MIR including microstructure disorder, myocardial zymogram, oxidant and inflammatory status of the rats were evaluated.

Results: Compared to the saline-treated MIR group, treating the rats with DDP, TSIIA or TD dramatically reduced the infarct size from 42.91 ± 3.34 to 29.93 ± 1.52%, 24.91 ± 5.25% or 20.49 ± 3.80%, respectively. And myocardial fibers were relatively uniform in the cross-sectional area with less edema, inflammatory infiltration and cardiac necrosis in the DDP-, TSIIA- or TD- treated groups. Pre-treatment of the rats with DDP, TSIIA or TD could significantly reduce the activities of lactate dehydrogenase (LDH) in serum and total superoxide dismutase (T-SOD) in myocardium, and significantly decrease the malondialdehyde (MDA) level and the mRNA expression of nuclear factor-κ-gene binding (NF-κB) and upregulate the mRNA expression of heme oxygenase (HO-1) and superoxide dismutase (SOD-1) in the infarcted myocardium.

Conclusions: This study suggest that TD as a water soluble derivative of TSIIA had comparable protective effects on MIR injury as TSIIA and DDP, which was through attenuating oxidative stress and inflammatory responses. Therefore, TD could be potentially used as an alternative of TSIIA in clinic for MIR treatment.

Key words: Tanshinone IIA Derivative, myocardial ischemia/reperfusion, inflammation, oxidative stress

Symposium 3

8:00-10:00 October 29 Saturday Room 414 Yifu Building

Shock

Chairs:

Yong Jiang

Department of Pathophysiology, School of Basic Medical Sciences, Southern Medical University

Paul Fraser

Cardiovascular Division Faculty of Life Sciences & Medicine King's College London

S-3-1 Microcirculatory Disorders and Protective Role of Anti-oxidant in Severe Heat Stroke: A Rat Study

Hui Jin

Department of Pathophysiology, Key Laboratory for Shock and Microcirculation Research, Southern Medical University (SMU)

S-3-2 Effect of Post-hemorrhagic Shock Mesenteric Lymph on Murine CD4+ T cells

Li-Na Jiang

Institute of Microcirculation, Hebei North University

S-3-3 Yiqifumai Injection, A Traditional Chinese Compound Medicine, and Its Active Ingredient Ginsenoside Rb1 Ameliorate Microvascular Hyperpermeability Induced by Lipopolysaccharide

Kai Sun

Tasly Microcirculation Research Center, Peking University Health Science Center

S-3-4 Sirtuin 1/3 Prevents Low Vasoreactivity by Modulating Mitochondrial Function

Peng-Yun Li

Key Laboratory of Medical Electrophysiology, and Institute of Cardiovascular Research, Southwest Medical Universit

S-3-5 Catalpol Restores LPS-elicited Rat Microcirculation Disorder by Regulation of a Network of Signaling Involving Inhibition of TLR-4 and Src

Yun-Pei Zhang

Department of Integration of Traditional Chinese and Western Medicine, School of Basic Medical Sciences, Peking University

S-3-6 Hypoxia Induces Micro-lymphatic Endothelial Barrier Dysfunction Via Activation of ASK1/p38 MAPK Pathway

Abbas Muhammad

Institute of Microcirculation, Hebei North University

S-3-1

Microcirculatory Disorders and Protective Role of Anti-oxidant in Severe Heat Stroke: A Rat Study

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Abstract: This study aims to examine microcirculation and systemic hemodynamic disturbances in severe heat stroke (HS).147 rats were divided into heat stroke group (HS), pre-treated with SOD (SOD+HS) group and pre-treated with normal saline (NS+HS) group. Heat-stress was induced by incubating the animals in certain temperatures. Blood flow and vascular reactivity were monitored dynamically with intravital microscopy. Pulmonary permeability was reflected by wet-to-dry weight ratio, the concentration of Evans Blue and histopathology of lung. The results showed that heat stress could induce blood flow rate reduced, SOD exhibited better protective role in blood flow rate. The arteriolar reactivity threshold to norepinephrine was markedly reduced at Tc=41ºC, but no significant decrease occurred in SOD+HS group. Water content and Evans Blue concentration in lung tissue in HS group were increased along with temperature rise. SOD treatment could attenuate those changes. The pathological lung injury caused by heat stress was also milder in SOD+HS group than that in other two groups. MAP decreased at early stages of heat stress, but there's no decrease in SOD+HS group. There was a significant body weight loss during heat stress in all groups. Survival time in SOD+HS group was longer than that in other two groups. These results suggest that microcirculation disturbance occurs not only at the early stage but also before systemic hemodynamic disorder, monitoring microcirculation following heat stroke is of prognostic value, intervention with anti-oxidative agents may have certain protecting effects in severe heat stroke.
Key Words: Heat Stroke, Microcirculation Blood Flow, Microvascular Reactivity, Microvascular Permeability, Oxidative Stress, Anti-oxidant

S-3-2

Effect of Post-hemorrhagic Shock Mesenteric Lymph on Murine CD4+ T Cells

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Abstract

The immune dysfunction is associated with inflammation following hemorrhagic shock, which involves post-hemorrhagic shock mesenteric lymph (PHSML) return. This study was conducted to investigate the effects of PHSML on the proliferation of CD4+ T lymphocytes in vivo and ex vivo. We firstly observed the effect of PHSML drainage on the spleen CD4+ T lymphocytes in the established mouse model of hemorrhagic shock [(40±2) mmHg for 60 min, follow by fluid resuscitation]. Secondly, drained normal mesenteric lymph (NML), PHSML during hypotension (PHSML-H) or from 0 h to 3 h after resuscitation (PHSML-R) were incubated with normal spleen CD4+ T lymphocytes to verify its direct proliferation effect. The results showed that hemorrhagic shock resulted in decreased proliferation of CD4+ T lymphocytes to ConA, expressions of IL-2 and IL-2 receptor (IL-2R) mRNA in CD4+ T lymphocytes, and the levels of IL-2, IFN-γ levels in supernatants, whereas IL-4 level was increased. These effects were reversed by PHSML drainage. In vitro, NML incubation promoted CD4+ T lymphocytes proliferation while PHSML-H and PHSML-R treatment had an enhanced effect at early stage and inhibitory efftct at later stage on CD4+ T lymphocytes proliferation, respectively. NML had no significant effect on expression of IL-2, IFN-γ and IL-4. However, PHSML-H increased expression of IL-2 at 12 h, but decreased expression of both IL-2 and IFN-γ at 24 h. In contrast, PHSML-R induced significant increases in IL-2, IL-4, and IFN-γ at 24 h. Expression of IL-4 in CD4+ T lymphocytes was decreased at 12 h, but increased at 24 h after either PHSML-H or PHSML-R treatment. These results indicate that PHSML has a direct effect on CD4+ T lymphocytes proliferation that induces inflammatory response during cellular immune dysfunction following hemorrhagic shock. This work was supported by the Key Research Program of Education Department in Hebei Province (ZH2012004) and the Research Program of Health Department in Hebei Province (20130042).

S-3-3

Yiqifumai Injection, A Traditional Chinese Compound Medicine, and Its Active Ingredient Ginsenoside Rb1 Ameliorate Microvascular Hyperpermeability Induced by Lipopolysaccharide

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Abstract

Background: Microvascular hyperpermeability is one of the common pathological processes of multiple disease states. This study evaluated whether Yiqifumai injection (YQFM), a traditional Chinese compound medicine, and its active ingredient ginsenoside Rb1 (Rb1) have beneficial effects on LPS-induced microvascular hyperpermeability and the underlying mechanisms.

Methods: Male Wistar rats were continuously infused with LPS (5 mg/kg/hr) via the left jugular vein for 90 min. In some rats, YQFM (5, 30, 80 mg/kg/hr) or Rb1 (5 mg/kg/hr) was administrated through the left jugular vein 30 min before or after LPS infusion, respectively. The dynamics of fluorescein isothiocynate (FITC)-labeled albumin leakage from mesentery venules was observed by intravital microscopy. Intestinal tissue edema was evaluated by hematoxylin and eosin staining. The number of caveolae in endothelium of microvessels was examined by electron microscopy. Confocal microscopy and Western blotting were applied to detect caveolin-1 (Cav-1) expression, Cav-1 phosphorylation, VE-Cadherin phosphorylation, ZO-1 degradation, and concerning signaling proteins in human umbilical vein endothelial cells (HUVECs).

Results: LPS infusion evoked an increased albumin leakage from mesentery venules, which was significantly ameliorated by YQFM and Rb1. Intestinal edema around microvessels were also reduced by Rb1. In addition, Rb1 decreased caveolae number in endothelium of microvessels. Cav-1 expression and phosphorylation, VE-Cadherin phosphorylation, ZO-1 degradation, nuclear factor-kappa B (NF-κB) activation and Src kinase phosphorylation were inhibited by Rb1 as well.

Conclusion: YQFM and its major active ingredient Rb1 ameliorated microvascular hyperpermeability induced by LPS, improving intestinal edema via regulating both trans- and paracellular pathway, which was correlated to suppression of NF-κB and Src activation. These results provide scientific evidence for YQFM and its major active ingredient as potential therapeutic strategies for LPS-induced microvascular hyperpermeability related diseases.

S-3-4

Sirtuin 1/3 Prevents Low Vasoreactivity by Modulating Mitochondrial Function

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[2] Guangdong Key Laboratory of Shock and Microcirculation Research, Department of Pathophysiology, Southern Medical University, Guangzhou, 510515, China

Vascular hyporeactivity is one of the major causes responsible for refractory hypotension and associated mortality in vascular hypoxemia disease. Mitochondrial permeability transition (MPT) pore opening in arteriolar smooth muscle cells (ASMCs) is involved in the pathogenesis of vascular hyporeactivity. However, the molecular mechanism underlying mitochondria injury in ASMCs during shock is not well understood. Our previous studies have demonstrated that resveratrol (RSV), a selective SIRT1 activator, improved vasoreactivity in vivo. Here we used an in vitro model of hypoxia/reoxygenation (H/R) injury to examine the vasoprotective effect of sirtuin$_{1/3}$, and explore its possible mechanism in vivo. We found that SIRT$_{1/3}$ protein levels and deacetylase activities were decreased in ASMCs exposed to HR. Immunofluorescence staining revealed a reduced accumulation of SIRT$_1$ in the nucleus and of SIRT$_3$ in the mitochondria. Overexpression of SIRT$_1$ preserved SIRT$_3$ deacetylase activity in human ASMCs exposed to HR, while knockdown of SIRT$_3$ abrogated SIRT1-mediated deacetylation of cyclophilin D (CyPD), a component of MPT pore. SIRT$_1$ activators suppressed MPT pore opening and ameliorated mitochondrial injury in ASMCs after HR. Our data suggest that epigenetic mechanisms, mostly histone post-translational modifications, are involved in regulation of MPT by SIRT$_1$/SIRT$_3$- mediated deacetylation of CyPD. SIRT$_{1/3}$ is a promising therapeutic target for approach for the treatment of vascular diseases connected with cytopathic hypoxia

S-3-5

Catalpol restores LPS-elicited rat microcirculation disorder by regulation of a network of signaling involving inhibition of TLR-4 and Src

Yun-Pei Zhang,[1, 2, 3, 4, 5] Chun-Shui Pan,[2, 3, 4, 5] Li Yan,[2, 3, 4, 5] Yu-Ying Liu,[2, 3, 4, 5] Bai-He Hu,[2, 3, 4, 5] Xin Chang,[2, 3, 4, 5] Quan Li,[2, 3, 4, 5] Dan-Dan Huang,[1, 2, 3, 4, 5] Hao-Yu Sun,[1, 2, 3, 4, 5] Ge Fu,[6] Kai Sun,[2, 3, 4, 5] Jing-Yu Fan,[2] and Jing-Yan Han[1, 2, 3, 4, 5]*

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Abstract

Lipopolysaccharide (LPS)-induced microvascular hyperpermeability and hemorrhage play a key role in the development of sepsis, attenuation of which might be an important strategy to prevent sepsis. However, present clinical therapies are proved to be inefficient in improving the final survival rate for the patients with sepsis. Catalpol, an iridoid glycoside extracted from the roots of Rehmannia, has been reported able to protect against LPS-induced acute lung injury through Toll-like Receptor-4 (TLR-4) mediated NF-κB signaling pathway. However, it is still unknown whether Catalpol is effective to ameliorate the LPS-induced microvascular disorder. The present study was aimed to investigate the impact of Catalpol on LPS-induced mesenteric microvascular disorder and its underlying mechanism. Male Wistar rats were challenged by infusion of LPS (10 mg/kg/h) through left femoral vein for 120 min. Post-treatment with Catalpol (10 mg/kg) alleviated the LPS-induced microvascular hyperpermeability and hemorrhage, reduced mortality, ameliorated the alteration in distribution of claudin-5 and JAM-1, and the degradation of collagen IV and laminin, attenuated the increase of TLR-4 level, phosphorylations of Src tyrosine kinase, phosphatidyl inositol 3-kinase, focal adhesion kinase, and Cathepsin B activation. In vitro study in human umbilical vein endothelial cells verified these results and further revealed that inhibition of TLR-4 and Src each simulated some but not all effects Catalpol exerted. Besides, surface plasmon resonance showed that Catalpol could directly bind to TLR-4 and Src. These results demonstrated that Catalpol was able to ameliorate the LPS-induced microvascular barrier damage and hemorrhage by targeting both TLR-4 and Src thus attenuating the phosphorylation of Src kinase, phosphatidyl inositol 3-kinase and focal adhesion kinase, as well as Cathepsin B activation.

S-3-6

Hypoxia Induces Micro-lymphatic Endothelial Barrier Dysfunction Via Activation of ASK1/p38 MAPK Pathway

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Abstract

Severe hemorrhagic shock-induced sepsis has much high mortality rate, which is related to the lymphatic dysfunction. The activation of apoptosis signal regulating kinase 1 (ASK1) / p38 mitogen activated protein kinase (p38MAPK) involved in the process of hemorrhagic shock-induced inflammation. In the present study, our hypothesis was that hemorrhagic shock causes lymphatic endothelial barrier dysfunction by the ASK1/p38 MAPK signaling pathway. Therefore, the present research established a cell hypoxia model instead of hemorrhagic shocked animal model, and observed the effect of hypoxia on the expressions of ASK1 and p38 MAPK in human dermal lymphatic endothelial cells (HDLECs), the role of ASK1/p38 MAPK signaling pathway in hypoxia inducing monolayer barrier dysfunction and expressions of cytoskeleton protein F-actin, adhesion junction protein VE-cadherin, tight junction proteins ZO-1, claudin-1, along with application of ASK1 and p38 MAPK inhibitors. The present results showed that hypoxia increased the expressions of ASK1 and p38 MAPK phosphorylated proteins, decreased the trans-epithelial electrical resistance (TEER) of monolayer cells, increased the FITC-Albumin permeability, reduced the expressions of F-actin, VE-cadherin, ZO-1, claudin-1, and induced morphological damage of HDLECs; the above effects of hypoxia on HDLECs were abolished by Trx1 (ASK1 inhibitor) or SB203580 (p38 MAPK inhibitor) treatment, suggested that lymphatic endothelial barrier dysfunction was alleviated. In summary, these results indicated that hypoxia caused lymphatic endothelial cell injury, reduced the expressions of cytoskeletal and connexin proteins, and resulted in lymphatic endothelial barrier dysfunction via the activation of ASK1 / p38 MAPK signal pathway. This work was supported by the Natural Science Foundation of China (30370561, 81500380).

Symposium 4

8:00-10:00 October 29 Saturday Room 402 Yifu Building

Hemorrhage-Thrombus

Chairs:

Ke-Sheng Dai

Jiangsu Institute of Haematology, The First Affiliated Hospital of Soochow University, Collaborative Innovation Center of Haematology, Key Laboratory of Thrombosis and Haemostasis, Ministry of Health

Jian-Bo Wu

Drug Discovery Research Center, Southwest Medical University

S-4-1 New Regulators of Endothelial Exocytosis and Their Roles in Vascular Hemostasis and Thrombosis

Jin-Cai Luo

Laboratory of Vascular Biology, Institute of Molecular Medicine, Beijing Key Laboratory of Cardiometabolic Molecular Medicine, Peking University

S-4-2 Glycation of Vitronectin Inhibits VEGF-induced Angiogenesis by Uncoupling VEGF Receptor-2-αvβ3 Integrin Cross-talk

Li-Qun Wang

Drug Discovery Research Center, Luzhou, Sichuan, People's Republic of China

S-4-3 Glycoprotein Ibα Clustering Induces Macrophage-mediated Platelet Clearance in the Liver

Rong Yan

Jiangsu Institute of Haematology, The First Affiliated Hospital of Soochow University, Collaborative Innovation Center of Haematology, Key Laboratory of Thrombosis and Haemostasis, Ministry of Health

S-4-4 Promoting Blood Circulation for Removing Blood Stasis Therapy for Acute Intracerebral Hemorrhage: A Systematic Review and Meta-analysis

Guo-Qing Zheng

Department of Neurology, The Second Affiliated Hospital & Yuying Children's Hospital of Wenzhou Medical University

S-4-5 The Effect of Connexin, Arteriole Membrane Potential and Endoplasmic Reticulum Stress-induced Apoptosis Pathway on Delayed Cerebral Ischemia after Subarachnoid Hemorrhage

Dong Zhao

Department of Neurosurgery of the First Affiliated Hospital of Shihezi University School of Medicine

S-4-6 Research Progress on Cerebral Microcirculation

Qi Fang

The First Affiliated Hospital of Soochow University

S-4-1

New Regulators of Endothelial Exocytosis and Their Roles in Vascular Hemostasis and Thrombosis

Jin-Cai Luo

Laboratory of Vascular Biology, Institute of Molecular Medicine, Beijing Key Laboratory of Cardiometabolic Molecular Medicine, Peking University, Beijing 100871, China

AIM: Vascular endothelial exocytosis acts as one of the first lines of defense against vascular injury through regulation of the release of von Willebrand factor (VWF), interleukin-8, p-selectin from endothelium-specific granules called Weibel-Palade Bodies (WPBs). The molecular mechanism underlying endothelial exocytosis in the final stages remains unclear.

Methods: 1) Using shRNA screening, we searched for the new regulators of endothelial vWF secretion from the regulatory components in focal adhesions; 2) using most advanced super resolution nanoscopy (high NA TIRF-SIM), we explored the cellular and molecular mechanisms of new endothelial secretion regulators; 3) using gene knockout and disease models, we investigated the physiological role of new secretion regulators in vascular thrombosis and hemostasis.

Results: We have successfully identified several new regulators of endothelial vWF secretion from primary cultured human endothelial cells stimulated by cAMP agonists. Gene-deficient mice exhibit impaired epinephrine-stimulated VWF release, prolonged bleeding time and thrombosis. Consistently, cAMP agonist-induced WPB exocytosis was impaired in the endothelial cells isolated from gene knockout mice. Using live cell super-resolution microscopy, we visualize previously unappreciated assembly of actin-coats from locally pre-existing actin filaments around WPBs undergoing exocytosis, dependent on the actin crosslinker α-actinin.

Conclusions: Our findings not only identify novel physiological regulators of endothelial exocytosis, but also reveal a fusion-independent actin coating from local actin network in the final stages of exocytosis.

S-4-2

Glycation of Vitronectin Inhibits VEGF-induced Angiogenesis by Uncoupling VEGF Receptor-2-αvβ3 Integrin Cross-talk

Li-Qun Wang[1], Xu Zhang[1], Ning-Bo Pang[1], La-Mei Xiao[1], Yong-Jie Li[1], Ni Chen[1], Mei-Ping Ren[1], Xin Deng[1], Jian-Bo Wu[1,2]

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[2]Department of Medicine, University of Missouri School of Medicine, Columbia, MO, USA

Objective: The goal of this study was to investigate the effects of methylglyoxal (MGO)-glycated vitronectin (VN) on VEGF-induced angiogenesis.

Methods: We synthesized glycated VN by incubating VN with methylglyoxal (MGO) *in vitro* and identified the formation of glycated VN by an LC-ESI-MS/MS based method. Unmodified and MGO-glycated VN were used as substrates for human umbilical vein cells (HUVECs). The effects of glycated VN on VEGF signaling in HUVECs were investigated.

Results: Normal VN-positive bands (65/75 kDa) vanished in multimeric VN and monomeric VN in the presence of MGO and multimeric-VN treated by MGO clearly shifted to a higher molecular mass, which indicated the changes in glycosylation and the existence of covalently cross-linked products. The glycation of VN inhibited VEGF-induced phosphorylation of VEGFR-2 and the intracellular signaling pathway downstream of VEGFR-2. Glycated VN inhibited the binding of VEGFR-2 to β3 integrin and inhibited the phosphorylation of β3 integrin. Furthermore, glycation of VN significantly decreased VEGF-induced migration of HUVECs *in vitro* and vessel outgrowth in an *ex vivo* angiogenesis model.

Conclusions: Collectively, these data indicate that the glycation of VN inhibits VEGF-induced VEGFR-2 activation by uncoupling VEGFR-2-αvβ3 integrin cross-talk. The glycation of VN causes a reduction in the migration of endothelial cells and vessel outgrowth. This may provide a mechanism for the failure of collateral sprouting in diabetic microangiopathy.

S-4-3

Glycoprotein Ib Clustering Induces Macrophage-Mediated Platelet Clearance in the Liver

Rong Yan

Jiangsu Institute of Haematology, The First Affiliated Hospital of Soochow University, Collaborative Innovation Center of Haematology, Key Laboratory of Thrombosis and Haemostasis, Ministry of Health, Suzhou, China

Many immune thrombocytopenia (ITP) patients, particularly patients with anti-glycoprotein (GP) Ib-IX autoantibodies, do not respond to the conventional treatments such as splenectomy. However, the underlying mechanism remains unclear. Here we found that anti-GPIb N-terminus antibody AN51, but not other anti-GPIb antibodies (AK2, HIP1, VM16d, or WM23), induced GPIb clustering that led to integrin $_{IIb}$ $_{3}$-dependent platelet aggregation. After intravenous injection, AN51 dose-dependently induced thrombocytopenia in guinea pigs, and the platelets were mainly removed by macrophages in the liver. The inhibitor of integrin receptor $_{M}$ $_{2}$ of hepatic macrophages, N-acetyl-D-glucosamine, but not sialidase inhibitor, dose-dependently rescued AN51-induced platelet destruction. Furthermore, AN51 but not VM16d, induced rapid platelet clearance in the liver of cynomolgus macaques. Five of twenty-two chronic ITP patients had anti-GPIb autoantibodies, and the autoantibodies from four of the five patients competed with AN51 for binding to platelets. These data indicate that GPIb clustering induced by anti-GPIb N-terminus antibody causes integrin $_{IIb}$ $_{3}$-dependent platelet aggregation, phagocytosis, and rapid platelet clearance in the liver. Our findings reveal a novel Fc-independent mechanism underlying the pathogenesis of ITP, and suggest new therapeutic strategies for ITP patients with anti-GPIb autoantibodies.

S-4-4

Promoting Blood Circulation for Removing Blood Stasis Therapy for Acute Intracerebral Hemorrhage: A Systematic Review and Meta-analysis

Guo-Qing Zheng,

Department of Neurology, The Second Affiliated Hospital & Yuying Children's Hospital of Wenzhou Medical University, Wenzhou 325027, China.

AIM: Spontaneous intracerebral hemorrhage (ICH) is one of the most detrimental subtypes of stroke. However, currently no specific therapies or treatments improve the outcome after ICH. Thus, the objective of this study is to conduct a systematic review and meta-analysis to assess the current evidence available regarding the promoting blood circulation and removing blood stasis (PBCRBS) therapy for Chinese patients with acute intracerebral hemorrhage (ICH).

METHODS: Six databases were searched from their inception to November 2013. The studies assessed in ≥ 4 domains with 'yes' were selected for detailed assessment and meta-analysis. The herbal compositions for PBCRBS therapy for acute ICH patients were also assessed. The risk of bias was assessed using the 7 criteria recommended by the Cochrane Handbook.All data analyses were performed using Review Manager 5.1.0.

RESULTS: From the 6 databases, 292 studies claimed randomized-controlled clinical trials (RCTs). Nine studies with 798 individuals were assessed in ≥ 4 domains with 'yes' by using the Cochrane RoB tool. Meta-analysis showed that PBCRBS monotherapy and adjuvant therapy for acute ICH could improve the neurological function deficit, reduce the volume of hematoma and perihematomal edema, and lower the mortality rate and dependency. Moreover, there were fewer adverse effects when compared with Western conventional medication controls. Xueshuantong Injection and Fufang Danshen Injection, Buyang Huanwu Decoction and Liangxue Tongyu formula, and three herbs (danshen root, sanqi and leech) were the most commonly used Chinese herbal patent injections, herbal prescriptions and single herbs, respectively.

CONCLUSION: Despite the apparently positive findings, it is premature to conclude that there is sufficient efficacy and safety of PBCRBS for ICH because of the high clinical heterogeneity of the included studies and small number of trials in the meta-analysis. This work identifies some key areas for further research. Further large sample-sizes and rigorously designed RCTs are needed.

Keywords: acute intracerebral hemorrhage, traditional Chinese medicine, promoting blood circulation for removing blood stasis, systematic review, meta-analysis

S-4-5

The Effect of Connexin, Arteriole Membrane Potential and Endoplasmic Reticulum Stress-induced Apoptosis Pathway on Delayed Cerebral Ischemia After Subarachnoid Hemorrhage

Dong Zhao

Department of Neurosurgery of the First Affiliated Hospital of Shihezi University School of Medicine

Objective： To investigate alteration of connexins in basilar artery, asymmetric dimethylarginine in cerebrospinal fluid and basilar artery diameter in SAH model rats, and study the effect of 18β-GA on ADMA, connexins and CVS after SAH; To investigate alteration of membrance potential and membrane input conductance in arteriole;To investigate alteration of GRP78 and CHOP protein expression, caspase-12 mRNA and neuron apoptosis in the hippocampus tissue, and confirm endoplasmic reticulum stress-induced apoptosis pathway, and neuron apoptosis mechanism after SAH.

Methods： Sprague-Dawley rats were divided into the control group, sham, SAH, and SAH+18β-GA group. The neurological score, basilar artery diameter, connexin protein and ADMA were measured using Kaoutzanis scoring system, pressure myograph, Western blot and enzyme linked immunosorbent assay kit, respectively, 1, 3, 5, 7, and 14 days after SAH;Groups were divided similar above. The basilar artery diameter, membrance potential and membrane input conductance in arteriole were measured using pressure myograph and whole cell patch clamp technique; Sprague–Dawley rats were divided into the control group, sham, and SAH groups. GRP78 and CHOP protein, caspase-12 mRNA, apoptosis and ultrastructure neuron cell in CA1 region were measured using Western blot, Real Time-PCR, terminal deoxynucleotidy1 transferase-mediated dUTP nick-end labeling staining (TUNEL) and electron microscopes, respectively,at 1, 6, 24, 48 and72 h after SAH. Pearson correlation coefficients were used to examine correlation.

Results： The neurological score significantly decreased on days 3, 5, 7, and 14 after SAH. The basilar artery diameter significantly decreased on day 1, 3, 5, 7, and 14, and was lowest on day 7. Cx37 was not detected. The Cx40 expression decreased compared with the other groups on days 3, 5, 7 and 14, and was lowest on day 7. The Cx43 and Cx45 expression increased on all days , peaked on day 7. The ADMA levels increased at the 5 timepoints, and peaked on day 5.Positive correlation between basilar artery diameter and Cx40, and opposite between the basilar artery diameter and Cx43 or Cx45; The membrane potential substantially increased on days 3, 5, and 7and membrane input conductance significantly increased at the five time-points in the SAH group. Change of the above indicators were inhibited by 18β-GA group. The negative correlation between the basilar artery diameter and the membrane potential;The GRP78 expression in the SAH group significantly increased at 1 h, substantially increased compared with that of the other groups at 6, 24, 48 and 72 h, and was highest at 24 h. The CHOP expression significantly increased at all time-points, peaked at 24h. The caspase-12 mRNA levels increased at 6, 24 and 48 h, and peaked at 24 h. Apoptosis changed at 24h;edematous and cytoplasmic rarefaction were found at 48 h, ER was observed at 72 h. Positive correlation between apoptotic neurons and GRP78、 CHOP、 caspase-12 mRNA.

Conclution： Cx40, Cx43, Cx45 and ADMA involve CVS after SAH.ADMA is probably involved in the pathophysiological events of CVS after SAH by affecting Cx43;Vasospasm of arterioles may be correlated with enhancement of cell membrance permeability. 18β-GA could alleviate alteration of electrophysiological characteristics of arteriole. Subsequently, endoplasmic reticulum stress-induced apoptosis pathway is activated and cause neurons apoptosis. In endoplasmic reticulum stress-induced apoptosis pathway, CHOP signaling and caspase signaling have demonstr- ated a direct involvement of neurons apoptosis after SAH.

S-4-6

Research Progress on Cerebral Microcirculation

Qi Fang

The First Affiliated Hospital of Soochow University, Suzhou, China

Abstract: Cerebral microcirculation is the center to obtain oxygen and glucose, which can substance necessary exchange and information in physiological condition to nerve cell metabolism. It's known that vascular wall, extravascular and intravascular factors can all affect Microcirculation. Perfusion disorder may show no-reflow, delayed low perfusion state after cerebral ischemia, as well as reperfusion damage. Cerebral microcirculation can be evaluated by study of nail fold microcirculation and imageological examination, including TPLSM、PWI、DWI、T2W1、FLAIR etc. Furthermore, it is certified that the following methods can improve the perfusion of microcirculation:(1)control tiny thrombus;(2)strengthen collateral circulation; (3)mild hypothermia therapy; (4)suppression of inflammation.

Symposium 5

14:00-16:00 October 29 Saturday Room 414 Yifu Building

Diabetes and Microcirculation

Chairs:

Qiao-Bing Huang

Department of Pathophysiology, School of Basic Medical Sciences, Southern Medical University

Akos Koller

University of Physical Education, Budapest, Department of Neurosurgery and Szentagothai Res Centre, University of Pecs, Hungary and Department of Physiology, New York Medical College

S-5-1 Characterization of Angiogenesis and Endothelial Dysfunction in microRNA-34a Knockout Mice with Diabetic Liver Injury

Fan-Yin Meng

Digestive Disease Research Center, Baylor Scott & White Healthcare, Texas A&M HSC College of Medicine

S-5-2 Effects of Alpha Mangostin on Blood Brain Barrier Permeability in Type 2 Diabetic Rats

Amporn Jariyapongskul

Department of Physiology, Faculty of Medicine, Srinakharinvirot University

S-5-3 High Glucose Induces Podocyte Foot Process Effacement by Stimulating TRPC6

Bing-Chen Liu

Department of Cardiology, the 4th Hospital of Harbin Medical University

S-5-4 Obesity-induced Vascular Inflammation and Dysfunction Involves Elevated Arginase Activity.

Lin Yao

Guangzhou University of Chinese Medicine

S-5-5 Adipocyte SIRT1 Deletion Impaired Endothelial Function Via Reducing Brown Fat Phenotype in Perivascular Adipose Tissue

Ping Gu

Department of Endocrinology, Jinling Hospital

S-5-1

Characterization of Angiogenesis and Endothelial Dysfunction in microRNA-34a Knockout Mice with Diabetic Liver Injury

Fan-Yin Meng, Ph.D
Digestive Disease Research Center, Baylor Scott & White Healthcare, Texas A&M HSC College of Medicine, Temple, Texas 76504, U.S.A

Aim: Sinusoidal endothelial dysfunction (SED) has been found to be an early event in diabetic liver injury (DLI) but the molecular mechanisms underlying its causation remains unclear. DLI associated portal hypertension is induced by an increased intrahepatic resistance, a major consequence of liver cirrhosis. Endothelial dysfunction in liver sinusoidal endothelial cells (LSECs) decreases the production of vasodilators, such as nitric oxide (NO) and favors vasoconstriction. Recent studies have shown demonstrated microRNAs as pharmacological targets in endothelial cell function and dysfunction. We aimed to characterize microRNA regulated endothelial dysfunction in the mice model of diabetic liver injury.

Methods: Diabetic liver injury (DLI) was induced in mice by 170% overnutrition in calories using intragastric overfeeding of high fat diet with alcohol. The upstream modulators and downstream mediators of sinusoidal injury were defined in miR-34a knockout mice *in vivo* and cultured human hepatic sinusoidal endothelial cells with miR-34a modifications *in vitro* by real-time PCR array/assay, immunohistochemistry and Western blot analysis. Liver angiogenesis, macrophage infiltration, and hypoxia were assessed by way of CD31, CD68 and hypoxia-inducible factor-1alpha immunostaining. The *in vivo* SED effects were also evaluated in toll like receptor 4 (TLR-4) knockout mice or the morpholino antisense oligomer against miR-34a (miR-34a Morpho/AS) treated mice with DLI. **Results:** Using obesity-alcohol synergism mouse model of diabetic liver injury, results showed the synergistic increase in serum ALT and miR-34a, hyperglycaemia, severe steatosis, pericellular fibrosis, and intensified nitrosative stress induced by a 32-fold induction of nitric oxide synthase (Nos2). The upregulation of miR-34a in human sinusoidal endothelial cells led to a time-dependent repression of its target protein Sirt1 levels as shown by western blot analyses, and a significant increase of the expression of NOS2. SED markers ICAM-1, VEGFR-2, and E-selectin as assessed by immunofluorescence microscopy were significantly up regulated in the progressive phases of DLI. Lack of miR-34a in vivo, reversed the serum ALT level, and restored the levels of Sirt1 coupled with decreased NOS2 mRNA expression as well as SED dysfunction markers. Depletion of miR-34a in vivo also decreased overall vessel formation. This was significant in portal areas of DLI mice and was associated with a significant increase of liver collagen by 29%, and up-regulation of profibrogenic genes and matrix metalloproteinases. Interestingly, in mice lacking TLR-4 with DLI, significantly reduced miR-34a levels, increased Sirt1 repression and decreased NOS2 mRNA expression were observed. In isolated sinusoidal endothelial cells, Kupffer cells and hepatic stellate cells by laser capture microdissection (LCM) from DLI mice, enhanced expression of miR-34a was seen in hepatic stellate cells, sinusoidal injury was significantly higher in all cell types while endothelial dysfunction was present in sinusoidal endothelial cells. Finally miR-34a morpholino treatment in DLI mice also showed reduced NOS2 mRNA level and reversed SED.

Conclusion: Our experimental results described here show a close association of LPS-induced miR-34a in aiding sinusoidal injury and endothelial dysfunction in diabetic liver disorders. The discovery that the activation of miR-34a plays a significant role in the process of diabetic liver injury through sinusoidal endothelial dysfunction for an exciting field in which the epigenomic microRNAs of hepatic endothelial cells may be manipulated with potential therapeutic benefits.

S-5-2

Effects of Alpha Mangostin on Blood Brain Barrier Permeability in Type 2 Diabetic Rats

Assist.Prof.Dr. Amporn Jariyapongskul

Department of Physiology, Faculty of Medicine, Srinakharinvirot University

Objective: The present study examined effects of alpha-mangostin (α-MG) supplementation on cerebral blood flow (CBF), and blood-brain barrier (BBB) permeability in type 2 diabetic (DM2) rat model.

Materials and Methods: Male Sprague-Dawley rats were divided into 2 experimental sets . Each set of animal was devided into four sub groups: normal control and diabetes with or without α -MG supplementation. Daily gavage feeding of alpha-MG (α-MG ; 200 mg/kg BW) was performed for 8 and 40 weeks. The effect of α-MG on 1) metabolic changes; blood glucose (BG), hemoglobin A1C (HbA1C) blood cholesterol (CHOL), trglyceride (TG), serum insulin and calculated HOMA-IR and 2) hemodynamics changes; mean arterial pressure (MAP), cerebral blood flow (CBF) and leakage of BBB were investigated. Additionally, levels of cerebral malondialdehyde (MDA) and advance glycation end products (AGEs) were evaluated.

Results: The elevated blood glucose, HbA1c, cholesterol, triglyceride were observed in DM2 rats. Our results showed that insulin resistance, an important characteristic in human DM2 occurred at 8 weeks after inducing DM2, as evaluated by an increasing in S.insulin and HOMA-IR index while the S.insulin and the calculated HOMA-IR of 40 weeks DM2 rats was lower than control group. The α-MG supplementation was able to decrease HOMA-IR levels particularly in the 8 weeks DM2-α-MG rats. Additional, DM2 rats had significantly decreased CBF, but statistically increased MAP and leakage of the BBB both 8 and 40 weeks supplementation. α-MG supplementation significantly increased CBF while decreased MAP and leakage of BBB. In DM2 rats, the cerebral cortex MDA and AGEs levels were significantly higher than those in the normal control rats. Interestingly, alpha-MG gave good effects of treatment in DM2-α-MG rats, achieving about 63.25% and 40.9% reductions in MDA and AGE respectively.

Conclusion: Alpha mangostin supplementation could improved CBF and BBB permeability through its anti-hyperglycemia and antioxidant activities.

Keyword: Alpha mangostin, cerebral blood flow, blood brain barrier, type2 diabetes mellitus

S-5-3

High Glucose Induces Podocyte Foot Process Effacement by Stimulating TRPC6

(Early responses of diabetic nephropathy)

Bing-Chen Liu

[1]Department of Cardiology, the 4th Hospital of Harbin Medical University, Harbin, China

Objectives: We have previously shown that high glucose causes podocyte apoptosis by stimulating TRPC6 channels. The present study aims at determining how TRPC6 and its downstream signaling molecules mediate the early responses of podocytes to high glucose.

Methods: We used immortalized human podocyte cell line and TRPC6 knockdown podocyte in which TRPC6 was knocked down by TRPC6 silencing short hairpin RNA (shRNA) combined with a variety of experimental methods (Scanning ion conductance microscopy (SICM), Western blot and Confocal microscopy) to illuminate TRPC6 involved mechanism of podocyte foot process effacement induced by high glucose.

Results: Our scanning ion conductance microscopy data show that high glucose induced foot process effacement of cultured podocytes and that the induction was attenuated by a TRPC6 channel blocker. Western blot data show that high glucose increased TRPC6 expression, but decreased podocin expression, and that hyperforin, a TRPC6 activator, also decreased podocin expression in control podocytes, but not in podocytes treated with TRPC6 shRNA. Confocal microscopy data show that both high glucose and hyperforin elevated the availability of free cholesterol and caused the accumulation of Zonulaoccludens protein 1 (ZO-1), a tight junction protein, in the area of effaced podocyte foot process. Interestingly, exogenous cholesterol mimicked high glucose-induced effacement of podocyte foot processes. Since podocin is a cholesterol-binding protein, theoretically, a decrease in podocin should result in the release of cholesterol. Our previous studies have shown that cholesterol controls ZO-1 levels in tight junction area of cortical collecting duct principal cells.

Conclusions: Therefore, these data suggest that high glucose may activate a sequential signaling pathway, which stimulates TRPC6, decreases podocin, elevates cholesterol, and finally attract ZO-1 to podocyte foot processes to cause their effacement.

S-5-4

Obesity-induced Vascular Inflammation and Dysfunction Involves Elevated Arginase Activity.

Lin Yao[1], Anil Bhatta[2], Zhimin Xu[2] Yuqing Huo[2], Ruth B. Caldwell[2], Robert W. Caldwell[2]

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[2] Medical College of Georgia, Augusta University, Georgia, USA

Obesity-induced cardiovascular dysfunction involves increased inflammation and oxidative stress due to pathological expansion of visceral adipose tissue (VAT). We hypothesized that increases in endothelial cell arginase 1 (EC-A1) is centrally involved in this pathology. Elevated arginase activity can reduce availability of L-arginine to NO synthase, resulting in decreased NO production, increased oxidative stress, and leukocyte attachment and vascular macrophage infiltration.

Our study utilized wild type (WT) and EC-A1 knockout (EC-A1-KO) mice made obese and diabetic by high fat/high sucrose (HFHS) diet (6 mos, N=6/group). In WT mice, HFHS diet increased body weight (38%), fasting blood glucose (82%), postprandial plasma insulin (3.8 fold) and vascular arginase activity (2.3 fold), and impaired aortic EC-dependent relaxation (32%). In aorta and VAT, respectively, HFHS increased mRNA levels of TNF-(2.3 and 4.4 fold), MCP-1 (1.9 and 4.6 fold), and VCAM-1 (1.7 and 1.9 fold). There also were elevated levels of circulating inflammatory monocytes (2.1 fold). Within VAT, infiltration of macrophages was increased 4.6 fold. Within these macrophage, the inflammatory macrophage (*M1)* rose by 5.1 fold, while the reparative macrophage (*M2)* fell by 4.9 fold. These effects of HFHS diet, except for body weight and blood glucose, were prevented or significantly reduced in mice treated with arginase inhibitor ABH (8 mg/kg/day) or those lacking EC-A1. In isolated mouse aortic EC, 6 hr exposure to high glucose (25 mM) and palmitate (200μM) reduced NO production (48%), increased mRNA levels of A1, A2, TNF-a, ICAM-1 and MCP-1, and increased adhesion of isolated monocytes to MAEC by 2.1 fold ($p<0.05$). Deletion of EC-A1 or treatment with ABH (100μM) prevented these effects.

In conclusion, vascular dysfunction and VAT inflammation induced by HFHS diet is mediated by EC-A1 expression. Furthermore, activation and inflammation of ECs by high glucose and palmitate also involves increased arginase 1 activation. Limiting arginase activity appears to be a therapeutic means to control obesity-induced vascular pathology

S-5-5

Adipocyte SIRT1 Deletion Impaired Endothelial Function Via Reducing Brown Fat Phenotype in Perivascular Adipose Tissue

Ping Gu, Bin Lu, Jian Ma, Cui-Hua Yang, Jia-Qing Shao

Department of Endocrinology, Jinling Hospital
Nanjing General Hospital of Nanjing Military Command, Nanjing University School of Medicine, Nanjing, Jiangsu Province

Objectives: Perivascular adipose tissue (PVAT) is the fat depot surrounding blood vessels. It has long been regarded as merely structural support for vasculature but evidence has been emerging that PVAT is actually playing indispensable roles in maintaining the normal function of cardiovascular systems. But the underlying mechanism how PVAT achieves its cardio-protective function is unknown. The aim of this study is to investigate whether obesity induces endothelial dysfunction via PVAT and elucidate the underlying mechanisms.

Methods: Six weeks old wild type (WT) and adipocyte-specific SIRT1 knockout mice (AKO) were fed with either standard chow or high fat diet for 12 weeks. The obese mice were exposure to cold environment (4℃) for 6 days. The aortic rings either without or with PVAT were isolated and the endothelial-dependent relaxation (EDR) of aorta in response to acetylcholine was measured by wire myograph. Expression of the brown adipocyte markers including UCP-1 and PGC1α were evaluated by western blotting, immunohistochemistry and/or qPCR. DHE staining and lucigenin assay were used to measure superoxide levels.

Results: Compared to the lean mice, the EDR was significantly impaired in aorta from obese mice in the presence of PVAT. We also found that the browning level of PVAT was significantly decreased in obese mice. Interestingly, mice with SIRT1 deletion in adipocytes suffered from a further decline of PVAT browning and exacerbation of endothelial dysfunction. Furthermore, cold induced upregulation of the browning marker and thereby improved EDR readily observed in PVAT from wildtype mice by reducing superoxide production , but the effect was abolished in SIRT1 knockout mice.

Conclusions: Our studies demonstrated that enhanced PVAT browning showed strong superoxide chelating ability and thereby improves endothelial dysfunction in mice. SIRT1 plays a pivotal role in controlling PVAT browning, which in turn causes decreased superoxide production.

Symposium 6

14:00-16:00 October 29 Saturday Room 402 Yifu Building

Qi-Blood

Chairs:

Shi-Jun Wang

Shandong University of Traditional Chinese Medicine

Hao Xu

Xiyuan Hospital

S-6-1 QiShenYiQi Pills, a Compound in Chinese Medicine, Protects Against Pressure Overload-induced Cardiac Hypertrophy Through a Multicomponent and Multi-target Mode

Yuan-Yuan Chen

Department of Integration of Chinese and Western Medicine, School of Basic Medical Sciences, Peking University

S-6-2 Regulation of Insulin Resistance by Multiple miRNAs Via Targeting the GLUT4 Signalling Pathway

Li-Hong Wang

Department of Endocrinology, The Second affiliated Hospital of Harbin Medical University

S-6-3 Elatoside C Protects the Heart from Ischaemia/Reperfusion Injury Through the Modulation of Oxidative Stress and Intracellular Ca2+ Homeostasis

Min Wang

Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences & Peking Union Medical College

S-6-4 Ginsenoside Rb1 Protects Against Ischemia/Reperfusion-induced Myocardial Injury Via Energy Metabolism Regulation Mediated by RhoA Signaling Pathway

Yuan-Chen Cui

Department of Integration of Chinese and Western Medicine, School of Basic Medical Sciences, Peking University

S-6-5 Angiogenesis Promoted by PNS Leading to a Neuroprotective Effects in AD-like Animal Models in a Modern Formula of Traditional Chinese Medicine Tong Luo Jiu Nao

Qian Hua

Preclinical School of Medicine, Beijing University of Chinese Medicine

S-6-1

QiShenYiQi Pills, a compound in Chinese medicine, protects against pressure overload-induced cardiac hypertrophy through a multicomponent and multi-target mode

Yuan-Yuan Chen,[1,2,3,4] Quan Li,[2,3,4] Chun-Shui Pan,[2,3,4] Li Yan,[2,3,4] Jing-Yu Fan,[2,3,4] Ke He,[2,3,4] Kai Sun,[2,3,4]Yu-Ying Liu,[2,3,4] Qing-Fang Chen,[1,2,3,4] Yan Bai,[5] Chuan-She Wang,[1,2,3,4] Bing He,[6] Ai-Ping Lv,[b,6] and Jing-Yan Hana,[1,2,3,4]

Cardiac hypertrophy (CH) is initially an adaptive response to pressure or volume stress, which is characterized by increased cardiomyocyte size, re-expression of fetal genes, and activation of signaling pathways governing protein synthesis. However, persistent and severe CH becomes a maladaptive response and ultimately contributes to subsequent heart failure that is a major and growing public health concern. Currently, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β -blockers and Ca^{2+} channel blockers are the major agents for management of CH in clinic, while the mortality and morbidity of the syndrome remain unacceptably high. This might be partly due to the fact that each of these agents acts on a single signaling pathway or target. We advocated that for complex multifactorial chronic diseases, treatment regimens that contain multiple drugs directing towards multi-pathways and multi-targets would possess stronger therapeutic efficacies.

QiShenYiQi Pills (QSYQ) is a compound Chinese medicine approved by the State Food and Drug Administration of China in 2003 for treatment of cardiac dysfunction, which is composed of Astragalus membranaceus (Huangqi), Salvia miltiorrhiza (Danshen), Panax notoginseng (Sanqi), and Dalbergia odorifera (Jiangxiang, DO). The major active ingredients are astragaloside IV (ASIV, from Huanqi), 3, 4-dihydroxy-phenyl lactic acid (DLA, from Danshen), and notoginsenoside R1 (R1, from Sanqi). Our previous study demonstrated that QSYQ could attenuate pressure over-load induced CH. However, the underlying mechanism of QSYQ attenuates CH is poorly understood. Particularly, the contribution of each ingredient of QSYQ to its pharmacological activities is unknown.

In this study, after induction of CH by ascending aortic stenosis, rats were treated with QSYQ, each identified active ingredient (ASIV, DLA, R1) or DO, either alone or combinations, for 1 month. We investigated the holistic mechanisms underlying the therapeutic effect of QSYQ on CH. By comparingg the efficacies and mechanisms of QSYQ, its single ingredient (ASIV, DLA, R1, DO) and various ingredient combinations (ASIV+ DLA, ASIV+ R1, ASIV+ DO, DLA+ R1, DLA+ R1+ DO, and ASIV+ DLA+ R1) we showed the rationality of QSYQ formula design, supporting that a regime containing multiple components is more effective than individual treatment for complex diseases.

S-6-2

Regulation of Insulin Resistance by Multiple miRNAs Via Targeting the GLUT4 Signalling Pathway

Tong Zhou, Xian-Hong Meng, Hui Che, Yang Fan, Hui-Min Xian, Nan-Nan Shen, Yong Zhang, Li-Hong Wang

Department of Endocrinology, The Second affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang Province 150081, China

Aims: The purpose of this study was to test whether the multiple-target anti-miRNA antisense oligonucleotides (MTg-AMO) technology, an innovative miRNA knockdown strategy, can be used to interfere with multiple miRNAs that play critical roles in regulating IR.
Methods: An MTg-AMO carrying the antisense sequences targeting miR-106b, miR-27a and miR-30d was constructed (MTg-$AMO_{106b/27a/30d}$). Protein levels were determined by Western blot analysis, and transcript levels were detected by real-time RT-PCR (qRT-PCR). Insulin resistance was analysed with glucose consumption and glucose uptake assays.
Results: We found that the protein level of glucose transporter 4 (GLUT4), Mitogen-activated protein kinase 14 (MAPK 14), Phosphatidylinositol 3-kinase regulatory subunit beta (PI3K regulatory subunit beta) and mRNA level of Slc2a4 (encode GLUT4), Mapk14 (encode MAPK 14) and Pik3r2 (encode PI3K regulatory subunit beta) were all significantly down-regulated in the skeletal muscle of diabetic rats and in insulin-resistant L6 cells. Overexpression of miR-106b, miR-27a and miR-30d in L6 cells decreased glucose consumption and glucose uptake, and reduced the expression of GLUT4, MAPK 14 and PI3K regulatory subunit beta. Conversely, silencing of endogenous miR-106b, miR-27a and miR-30d in insulin-resistant L6 cells enhanced glucose consumption and glucose uptake, and increased the expression of GLUT4, MAPK 14 and PI3K regulatory subunit beta. MTg-$AMO_{106b/27a/30d}$ up-regulated the protein levels of GLUT4, MAPK 14 and PI3K regulatory subunit beta, enhanced glucose consumption and glucose uptake. **Conclusion:** Our data suggested that miR-106b, miR-27a and miR-30d play crucial roles in the regulation of glucose metabolism by targeting the GLUT4 signalling pathway in L6 cells. Moreover, MTg-$AMO_{106b/27a/30d}$ offers more potent effects than regular singular AMOs.

S-6-3

Elatoside C Protects the Heart from Ischaemia/Reperfusion Injury Through the Modulation of Oxidative Stress and Intracellular Ca2+ Homeostasis

Min Wang[1], Gui-Bo Sun[1]*,Jing-Yi Zhang[1], Yun-Luo[1],Ying-Li Yu[1],Xu-Dong Xu[1],Xiang-Bao Meng[1], and Xiao-Bo Sun[1]*

(1)Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, 100193, P. R. China.

Abstract

Background: We have previously shown that Elatoside C reduces cardiomyocyte apoptosis during ischemia/reperfusion (I/R). Here, we investigated whether Elatoside C improves heart function in isolated rat hearts subjected to I/R and elucidated the potential mechanisms involved in Elatoside C-induced protection.

Methods and Results: Isolated rat hearts were subjected to global ischaemia followed by reperfusion in the absence or presence of Elatoside C. We found that Elatoside C significantly attenuated cardiac dysfunction and depressed oxidative stress induced by I/R. Consistently, Elatoside C prevented I/R-induced mitochondrial dysfunction, which was evident by the inhibition of mitochondrial ROS production, mitochondrial permeability transition pore (mPTP) opening, cytochrome c release from the mitochondria and Bax translocation. Moreover, Elatoside C improved abnormal calcium handling during I/R, including increasing sarcoplasmic reticulum Ca^{2+} ATPase (SERCA2) activity, alleviating $[Ca^{2+}]_{ER}$ depletion, and reducing the expression levels of ER stress protein markers. All of these protective effects of Elatoside C were partially abolished by the PI3K/Akt inhibitor LY294002, ERK1/2 inhibitor PD98059, and JAK2/STAT3 inhibitor AG490. Further assessment in isolated cardiomyocytes showed that Elatoside C maintained the Ca^{2+}transientsand cell shortening against I/R.

Conclusions: Elatoside C protects against cardiac injury during I/R by attenuating oxidative stress and $[Ca^{2+}]_i$ over load through the activation of both the reperfusion injury salvage kinases (RISK) pathway (including PI3K/Akt and ERK1/2) and the survivor activating factor enhancement (SAFE) pathway (including JAK2/STAT3) and, subsequently, inhibiting the opening of mPTPs.

Keywords: Elatoside C; ischaemia/reperfusion; oxidative stress; calcium overload

S-6-4

Ginsenoside Rb1 Protects Against Ischemia/Reperfusion-induced Myocardial Injury Via Energy Metabolism Regulation Mediated by RhoA Signaling Pathway

Yuan-Chen Cui[1,2,3,4], Chun-Shui Pan[2,3,4], Li Yan[2,3,4], Lin Li[5], Bai-He Hu[2,3,4], Xin Chang[2,3,4], Yu-Ying Liu[2,3,4], Jing-Yu Fan[2], Kai Sun[2,3,4]，Quan-Li[2,3,4] and Jing-Yan Han[1,2,3,4]

1 Department of Integration of Chinese and Western Medicine, School of Basic Medical Sciences, Peking University, Beijing 100191, China
2 Tasly Microcirculation Research Center, Peking University Health Science Center, Beijing 100191, China
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5Department of Cardiology, Beijing China-Japan Friendship Hospital, Beijing 100029, China

Abstract

Cardiac ischemia and reperfusion (I/R) injury remains a challenge for clinicians. Ginsenoside Rb1 (Rb1) has been reported to have the ability to attenuate I/R injury, but its effect on energy metabolism during cardiac I/R and the underlying mechanism remain unknown. In this study, we detected the effect of Rb1 on rat myocardial blood flow, myocardial infarct size, cardiac function, velocity of venule red blood cell, myocardial structure and apoptosis, energy metabolism and change in RhoA signaling pathway during cardiac I/R injury. In addition, the binding affinity of RhoA to Rb1 was detected using surface plasmon resonance (SPR). Results showed that Rb1 treatment at 5 mg/kg/h protected all the cardiac injuries induced by I/R, including damaged myocardial structure, decrease in myocardial blood flow, impaired heart function and microcirculation, cardiomyocyte apoptosis, myocardial infarction and release of myocardial cTnI. Rb1 also inhibited the activation of RhoA signaling pathway and restored the production of ATP during cardiac I/R. Moreover, SPR assay showed that Rb1 was able to bind to RhoA in a dose-dependent manner. These results indicate that Rb1 may prevent I/R-induced cardiac injury by regulation of RhoA signaling pathway, and may serve as a potential regime to improve PCI outcome.

Key words: ATP synthesis, RhoA signaling pathway, myocardial injury, small GTPase

S-6-5

Angiogenesis Promoted by PNS Leading to a Neuroprotective Effects in AD-like Animal Models in a Modern Formula of Traditional Chinese Medicine Tong Luo Jiu Nao

Yan Tan, Jiao Li, Haiming Ding, Feng Wang, Yuan Liu, Yan Yan, Xu Wang, Qian Hua*

Preclinical School of Medicine, Beijing University of Chinese Medicine, 11 East Road, North 3rd Ring Road, Chaoyang District, Beijing, China 100029
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Objective: *Panax notoginseng* (Burk.) F. H. Chen, one of popular Traditional Chinese medicine, has been widely used in clinic. Its function mainly refers to hemostasis, dispersing blood stasis, and restraining new blood. Tong Luo Jiu Nao (TLJN), consisting two main bioactive ingredients Geniposide (GP) and *Panax Notoginseng* Saponins (PNS), has been proved clinically efficacious in ischemic stroke patients and also those with memory declining. Cerebral ischemia is closely associated with brain disorders, such as stroke and Alzheimer disease (AD), susceptibly leading to a damage in hippocampus. Here, we further explore whether TLJN has an efficacy on angiogenesis in AD-like animal models and evaluate the number of amyloid plaques and synaptic plasticity in hippocampus after treatments.
Method: In APP/PS1 transgenic mice, special learning and memory has been evaluated by Water Maze test (WMT) and Step-down test. Angiogenesis was evaluated by BrdU and CD105 double-staining both before and after PNS or TLJN treatments. The number of amyloid plaques and the number of dendritic spines were measured in hippocampus. Furthermore, in rat AD-like animal model, degradative enzymes of amyloid-β (Aβ), neprilysin (NEP) and insulin-degrading enzyme (IDE) were evaluated.
Result: In APP/PS1 transgenic mice, TLJN significantly reduced the latency to platform in WMT; the number of errors to electricity-shock area was reduced under the treatment of TLJN, suggesting that TLJN can improve impaired cognition in APP/PS1 transgenic mice. Then, we found PNS or TLJN promoted angiogenesis, leading to a reduced number of amyloid plaques and an increased number of dendritic spines in hippocampus, indicating that the angiogenesis mediated by PNS promoted the clearance of amyloid plaques and enhanced the synaptic plasticity. In addition, in rat AD-like animal model, we found that TLJN increased the level of NEP and IDE, two of the main degradative enzymes of Aβ.
Conclusion: TLJN improved special learning and memory in AD-like animal models. One of its main ingredient, PNS has an efficacy on angiogenesis, assisting in cleaning amyloid plaques and enhancing synaptic plasticity.
Acknowledgements: This study was supported by grant from the National Natural Science Foundation (81473546).

Symposium 7

8:00-10:00 October 30 Sunday Room 408 Yifu Building

Blood stasis and Phlegm-stasis

Chairs:

Yan Zhu

Tianjin State Key Laboratory of Modern Chinese Medicine, Tianjin University of Traditional Chinese Medicine

Yan Lei

China Academy of Chinese Medical Sciences

S-7-1 Panax Notoginseng Saponins Superior to Aspirin in Inhibiting Platelet Adhesion to Injured Endothelial Cells Through COX Pathway

Mei-Xue

Xiyuan Hospital China Academy of Chinese Medical Sciences

S-7-2 Deepure Tea Improves High Fat Diet-induced Insulin Resistance and Non-alcoholic Fatty Liver Disease

Jing-Na Deng

Tasly Microcirculation Research Center, Peking University Health Science Center

S-7-3 Coordinated Activation of VEGF/VEGFR-2 and PPARD Pathways by a Multi-component Chinese Medicine DHI Accelerated Recovery from Peripheral Arterial Disease in Type 2 Diabetic Mice

Yan Zhu

Tianjin State Key Laboratory of Modern Chinese Medicine, Tianjin University of Traditional Chinese Medicine

S-7-4 Post-treatment with Ma-Huang-Tang Ameliorates Cold-warm-cycles Induced Rat Lung Injury

Chun-Shui Pan

Tasly Microcirculation Research Center, Peking University Health Science Center

S-7-5 Protective Effect of Curcumin Against Cerebral Ischemia-reperfusion Injury in Rats

Wei Li

International Ph.D. Program in Medical Science

S-7-6 Pharmacological Assessment of the Efficacy of Traditional Chinese Medicine for Coronary Heart Disease of Phlegm-stasis Syndrome

Lei Li

Xiyuan Hospital China Academy of Chinese Medical Sciences

S-7-1

Panax Notoginseng Saponins Superior to Aspirin in Inhibiting Platelet Adhesion to Injured Endothelial Cells Through COX Pathway

Mei-Xue, Da-Zuo Shi

Objective: This study was designed to investigate the effect of Panax notoginseng saponin (PNS) on platelet adhesion to injured endothelial cells (ECs) and platelet activation induced by injured ECs, and to explore its underlying mechanisms.

Methods: Human umbilical vein endothelial cells (HUVECs) pretreated with aspirin (ASA,15 μg/mL) or PNS (160 μg/mL), or neither, were exposed to oxidized low-density lipoprotein (ox-LDL,80 mg/L) for 16 h. Platelets were then added and co-cultured with HUVECs for 5 min. Platelet adhesion to ECs, platelet CD62p expression, and HUVEC apoptosis were assessed by fluorescence activated cell sorting (FACS). Supernatant concentration of 6-keto-PGF1α and thromboxane 2 (TXB2) were measured by radioimmunoassay. Cyclooxygenase-1 (COX-1) and COX-2 protein expression were measured by western blotting.

Results: The inhibitory effect of PNS on platelet activation was similar to ASA, but the inhibitory effect of PNS on platelet adhesion to ECs was superior to ASA. PNS modulated COX-2 expression, and increased 6-keto-PGF1α concentration inHUVECs, while down-regulated COX-1 expression and decreased supernatant TXB2 concentration in platelets. Co-culturing of injured HUVECswith platelets increased HUVEC apoptosis induced by ox-LDL compared with HUVECs cultured without platelets; ASA increased HUVEC apoptosis induced by ox-LDL when cultured without platelets, while decreased the apoptosis when co-cultured with platelets.

Conclusions: EC protection by ASA is closely associated with its inhibitory effect on platelet activation. PNS is superior to ASA in protecting ECs and in inhibiting platelet adhesion to injured ECs, and the regulation of COX pathway in both ECs and platelets might be the underlying mechanisms of PNS.

S-7-2

Deepure Tea Improves High Fat Diet-induced Insulin Resistance and Non-alcoholic Fatty Liver Disease

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Abstract

This study was to explore the protective effects of deepure tea against insulin resistance and hepatic steatosis and elucidate the potential underlying molecular mechanisms. C57BL/6 mice were fed with a high fat-diet (HFD) for 8 weeks to induce the metabolic syndrome. In the deepure tea group, HFD mice were administrated with deepure tea at 160 mg/kg/day by gavage for 14 days. The mice in HFD group received water in the same way over the same period. The age-matched C57BL/6 mice fed with standard chow were used as normal control. Compared to the mice in HFD group, mice received deepure tea showed significantly reduced plasma insulin and improved insulin sensitivity. Deepure tea increased the expression of insulin receptor substrate 2 (IRS-2), which plays an important role in hepatic insulin signaling pathway. Deepure tea also led to a decrease in hepatic fatty acid synthesis and lipid accumulation, which were mediated by the downregulation of sterol regulatory element binding protein 1c (SREBP-1c), fatty acid synthesis (FAS) and acetyl-CoA carboxylase (ACC) proteins that are involved in liver lipogenesis. Deepure tea also significantly attenuated high fat diet-induced liver microcirculatory disturbance, evidenced by improved the number of perfused sinusoids in the hepatic terminal portal venule and terminal hepatic venule. These results suggest that deepure tea may be effective for protecting against insulin resistance and hepatic steatosis via modulating IRS-2 and downstream signaling SREBP-1c, FAS and ACC, and then inproved high fat diet-induced liver microcirculatory disturbance.

S-7-3

Coordinated Activation of VEGF/VEGFR-2 and PPARD Pathways by a Multi-component Chinese Medicine DHI Accelerated Recovery from Peripheral Arterial Disease in Type 2 Diabetic Mice

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Aim: Diabetic mellitus (DM) patients are at an increased risk of developing peripheral arterial disease (PAD) because of the peripheral angiopathy. Danhong injection (DHI) is a Chinese patent medicine widely used for several cardiovascular indications but the mechanism of action is not well-understood. **Methods：** We investigated the therapeutic potential of DHI on experimental PAD in mice with chemically induced as well as genetic (KKAy) type 2 DM and determined the effect of DHI on therapeutic angiogenesis and the pathways regulating glucose homeostasis. **Results**: Compared with normal wild type (WT) mice, both DM mice showed impaired perfusion recovery in a hind-limb ischemia (HLI) model. DHI treatment significantly accelerated perfusion recovery, lowered blood glucose and improved glucose tolerance in both DM mice. Bioluminescent imaging showed a continuous ischemia-induced vascular endothelial growth factor receptor 2 (VEGFR-2) gene expressions with a peak time coincident with the maximal DHI stimulation. Flow cytometry analysis demonstrated DHI-mediated increase in endothelial progenitor cell (EPC) mobilization from bone marrow to circulating peripheral blood. DHI administration upregulated the expression of vascular endothelial growth factor A (VEGF-A) and VEGFR-2 in ischemic muscle. DHI-triggered cross talk between ischemia-induced angiogenesis and glucose tolerance pathways was analyzed by Ingenuity Pathway Analysis (IPA) which suggested an interaction of VEGF-A/VEGFR-2 and peroxisome proliferator-activated receptor delta (PPARD)/peroxisome proliferator-activated receptor γ (PPARγ) genes. We confirmed that up-regulation of VEGF-A/VEGFR-2 by DHI promoted PPARD gene expression in both type 2 diabetic mice. **Conclusion:** Our findings demonstrated that a multi-component Chinese medicine DHI effectively increased blood flow recovery after tissue ischemia in diabetic mice by promoting angiogenesis and improving glucose tolerance through a concomitant activation of VEGF-A/VEGFR-2 and PPARD signaling pathways.

S-7-4

Post-treatment with Ma-Huang-Tang ameliorates cold-warm-cycles induced rat lung injury

Meng-Meng Xiao[1], Chun-Shui Pan[1], Yu-Ying Liu[1], Li-Qian Ma[1], Li Yan[1], Jing-Yu Fan[1], Chuan-She Wang[1], Rong Huang[1] and Jing-Yan Han[1,2]

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Frequent and drastic ambient temperature variation may cause respiratory diseases such as common cold and pneumonia, the mechanism for which is not fully understood, however, due to lack of appropriate animal models. Ma-Huang-Tang (MHT) is widely used in China for treatment of respiratory diseases. The present study aimed to investigate the effect of MHT on temperature alternation induced rat lung injury and explore underlying mechanisms. Male Sprague-Dawley rats were exposed to a cold environment for 1 h and then shifted to a warm environment for 30 min. This cold and warm alteration cycled 4 times. Rats were administrated with MHT (1.87 g/kg) by gavage 6 h after cold-warm-cycles. Cold-warm-cycles induced pulmonary microcirculatory disorders, decrease in the expression of tight junction proteins, increase in VE-cadherin activation, increase in the expression and activation of Caveolin-1, Src and NF-κB, and NADPH oxidase subunits $p47^{phox}$, $p40^{phox}$ and $p67^{phox}$ membrane translocation and inflammatory cytokines production. All alterations were significantly ameliorated by post-treatment with MHT. This study showed rat subjected to cold-warm-cycles may be used as an animal model to investigate ambient temperature variation induced lung injury, and suggested MHT as a potential strategy to combat lung injury induced by temperature variation.

S-7-5

Protective effect of curcumin against cerebral ischemia-reperfusion injury in rats

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Introduction: It has been well documented that the attenuation of inflammatory processes has therapeutically potential against cerebral ischemia/reperfusion (I/R) injury. Curcumin, which is a yellow pigment belonging to a family of *Curcuma Longa* Linn, is reported for its potent anti-inflammatory property against the cerebral I/R injury; however, the underlying mechanisms remain poorly understood.

Methods: In the present study, 1 hour cerebral ischemia and 24 hours reperfusion model was induced by middle cerebral artery occlusion (MCAO+CORN) with monofilament in Wistar rats. Curcumin was injected intraperitoneally at 300 mg/kg (30 min before reperfusion; MCAO+CORN). Immunohistochemistry was used for detections of biomarkers, including ICAM-1, MMP-9, caspases-3 and NF-kappa B.

Results: It was found that curcumin significantly prevented the deterioration of brain infarction size, brain edema, and neurological dysfunction. In addition, the immunohistochemistry results showed that the expressions of biomarkers, including ICAM-1, MMP-9, caspases-3 and NF-kappa B, were significantly down-regulated in MCAO+CUR when compared with MCAO+CORN group. Taken together with the Pearson's Correlation test, our investigation demonstrated that the neuro-protective effects of curcumin against cerebral I/R injury demonstrated a closed correlated ($r>0.6$) between the expressions of ICAM-1, MMP-9, caspases-3 with NF-kappa B expression.

Conclusion: Therefore, our research provided more evidences about the neuro-protective effect of curcumin against stroke, which might be a promising treatment for the acute ischemic stroke in the future.

S-7-6

Pharmacological Assessment of the Efficacy of Traditional Chinese Medicine for Coronary Heart Disease of Phlegm-stasis Syndrome

Lei Li, Chengren Lin, Jianxun Ren, Yue Shi, Yanlei Ma, Jianxun Liu*

(*Institute of Basic Medical Sciences of Xiyuan Hospital, China Academy of Chinese Medical Sciences, Beijing 100091, China*)

Objective: The purpose of this study is to describe a novel strategy for the pharmacological assessment of the efficacy of traditional Chinese medicine for coronary heart disease (CHD) of phlegm-stasis syndrome based on the mini swine model. **Method:** Chinese mini swine were randomly divided to six groups: the normal control group, the model group，the Danlou tablet group，and Tanyu Tongzhi Fang(TYTZ) groups with doses of 2.0, 1.0 and 0.5 $g \cdot kg^{-1}$，with six animals in each group. Except for the normal control group, all of other groups were fed with high-fat diet for 2 weeks. Left anterior descending coronary artery endothelium in the model group and medication groups was injured by balloon intervention technique after 2-week feeding to establish model CHD of phlegm-stasis syndrome. After the operation, they were administered with drugs for 8 weeks. The changes in body surface electrocardiograph (BS-ECG), serum lipid level, left ventricular structure and function, noninvasive hemorheological parameters, myocardial ischemia level and range were observed. Their main symptoms，accompanied symptoms，tongue manifestation and pulse manifestation of the CHD mini swine with phlegm-stasis syndrome were also observed according to the symptom-graded scoring method. **Results:** Compared with the normal control group, the model group showed significant increase in serum TC,TG,LDL-C and VLDL-C levels，whole blood viscosity under the shear rate of 5 s^{-1} and 60 s^{-1}; the degree and range of myocardial ischemia , also a decrease in CO, SV and LCW in noninvasive hemodynamic parameters; notable decrease in IVSd, LVPWs, EF and FS. Compared with the model group, TYTZ could reduce the myocardial ischemia，strengthen cardiac function，and improve the abnormal cardiac structure and function induced by ischemia; TYTZ groups revealed significant decrease in myocardial ischemia degree and range, serum TC,TG,LDL-C and VLDL-C levels and whole blood viscosity under the shear rate of 5 s^{-1} and 60 s^{-1}; TYTZ in different doses could reduce the scores of main symptoms at the 6th and 10th week, TYTZ in low dose could reduce the scores of tongue manifestation at the 6th week and the scores of accompanied symptoms and tongue and pulse manifestation at the 10th week, TYTZ in high dose could decrease all symptom scores at the 6th and 10th week. **Conclusion:** Animal model derived from clinical features and apply clinical examination methods is a novel strategy for pharmacological assessment of the efficacy of Chinese herbal medicine for CHD of phlegm-stasis syndrome.

Symposium 8

8:00-10:00 October 30 Sunday Room 402 Yifu Building

New Technique

Chairs:

Gang-Min Ning

Department of Biomedical Engineering, MOE Key Laboratory of Biomedical Engineering, Zhejiang University

Feng Han

Institute of Pharmacology and Toxicology, Zhejiang University

S-8-1 Visualization of the Inflammatory Response During Neurovascular Damage: Communication Between Microvessel and Microglia

Feng Han

Institute of Pharmacology and Toxicology, Zhejiang University

S-8-2 A Mathematical Model for the Interaction of Nitric Oxide and Oxygen in the Microcirculation Network

Ruo-Fan Wang

Department of Biomedical Engineering, MOE Key Laboratory of Biomedical Engineering, Zhejiang University

S-8-3 Tissue Viability Imaging for Reconstructive Plastic Surgery

Xia-Bing Huang

Moor Instruments

S-8-4 High-speed Atomic Force Microscopy for Nano-visualization of Living Biological Samples

Jing Li

National Center for Nanoscience and Technology

S-8-5 Generation of Human-like Small Rodent Models for Dyslipidemic and Atherosclerotic Studies: CRISPR/Cas9 Mediated Gene Targeting of Syrian Golden Hamsters

Ming-Ming Gao

Basic medical college of hebei medical university

S-8-6 Deep RNA Sequencing Elucidates MicroRNA Regulated Molecular Pathways in Ischemic Cardiomyopathy (ICM) And Non Ischemic Cardiomyopathy (NICM)

Xiang Li

National Center for Nanoscience and Technology

S-8-1

Visualization of the Inflammatory Response During Neurovascular Damage: Communication Between Microvessel and Microglia

Feng Han

Institute of Pharmacology and Toxicology, Zhejiang University, Hangzhou, Zhejiang, China

Abstract

AIM: Encephalopathy is a pivotal complication of sepsis yet the pathophysiology remains unclear. METHODS AND RESULTS: We tested the hypothesis that cerebral leukocyte-endothelial cell adhesion and microvascular leak are dependent on purinergic $P2RX_7$ signaling that engages a specific β2-integrin/adhesion molecule/chemokine cascade culiminating in cerebral microglial activation and migration, neurovascular damage and septic encephalopathy. *In vivo* two-photon laser scanning microscopy (TPLSM) tracked cerebral microvascular leukocyte adhesion and microglial activation and migration following the cecal ligation and puncture (CLP) model of septic shock. Pharmacological blockade of *$P2XR_7$* and $P2XR_7$ or β2 integrin deficient mice defined their roles in linking leukocyte activation to microglial migration and neurovascular damage *in vivo*. Time-lapse *in vivo* TPLSM of *Cx3cr1*-expressing brain cells demonstrated microglial activation and migration to sites adjacent to leukocyte adhesion on inflamed cerebral microvessels of septic mice. Sepsis transcribed a family of chemokines but CXCL1 was required to mediate Mac-1/ICAM-1 activation. Functional $P2RX_7$ cation channels were expressed on endothelial cells where they enhanced expression of ICAM-1 and the CX3CL1 chemokine during sepsis that initiated microglial cells migration. This inflammatory cascade in septic mouse brain was prevented by blockade or knockdown of P2RX7, β2-integrin, CXCL1 pathway which also doubled early survival after CLP. CONCLUSION: Septic encephalopathy is initiated by $P2RX_7$ signaling on endothelial cells that engages leukocyte attachment via Mac-1/ICAM-1 pathway through generation of specific chemokinesis including CXCL1. Thus, targeting $P2RX_7$ could be a novel strategy for prevention of neurovascular damage and septic encephalopathy.

S-8-2

A mathematical model for the interaction of nitric oxide and oxygen in the microcirculation network

Ruo-Fan Wang, Yan-Nan Chen, Gang-Mmin Ning*

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Nitric oxide (NO) and oxygen (O_2) play vital roles in maintaining the function of microcirculation. In order to investigate the interactions of nitric oxide (NO) and oxygen (O_2) in microvascular network a mathematical model was developed. The model was designed to represent the generation, transport, diffusion and consumption procedures of NO and O_2. In the model the NO is assumed to be produced from the local endothelium of each vessel segment under the stimulation of shear stress, while the O_2 is assumed to originate from the main feeding arteriole and transports along the whole network. The finite element method was applied to achieve the segmentation of the vessels and tissues. To simulate the diffusion and consumption of NO and O_2, the Fick's law of diffusion and Michaelis-Menten kinetics of consumption were implemented in the model. The model is able to provide the NO concentration and partial pressure of O_2 (P_{O2}) on arbitrary site of the vessels and tissues, and consequently the spacial distribution of the NO and O_2 in the network. The model was tested on a realistic rat mesenteric network containing 546 vessel segments and the results show that the NO and O_2 collaborate to accomplish the physiological functions in the microvascular network, and the interactions between NO and O_2 should not be ignored in the study of microcirculation.

S-8-3

Tissue Viability Imaging for Reconstructive Plastic Surgery

C To[1], KM Gooding[1], AC Shore[1], JE Rees-Lee[2,] RL Tillett[2], NH Cawrse[2], DW Oliver[2], JH Palmer[2], ADH Wilson[2], RJ Gush[3], X Huang[3]

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2, RD&E Hospital
3, Moor Instruments

Introduction: Reconstructive and Plastic surgery is on the continuous increase; a total of 47,161 procedures were carried out in UK in 2013-2014. Partial or total flap loss, due to impaired perfusion, remains one of the most serious complications in reconstructive surgery. The challenge for surgeons in reducing Post-operative complication (POC) is to assess tissue viability potential intra-operatively so that techniques to avoid POC can be implemented immediately. Laser Speckle contrast imaging (LSI) is a new, non-invasive imaging technique that is capable of providing real-time skin blood flow images. The aims of this observational study were to assess the feasibility of using the real time imaging provided by LSI to assess flap and mastectomy breast skin perfusion intra-operatively and to assess its potential clinical usefulness in mapping tissue perfusion to reduce post-operative complications.

Methods: The feasibility of performing LSI (moorFLPI-2) in 21 free-flap breast reconstructions and two immediate breast implant breast reconstructions was assessed. Prototype for LSI was developed and clinical usefulness of intra-operative LSI images was assessed in free-flap reconstructions (1) by comparing zonal blood flow at the time point of abdominal flap isolated on pedicle and (2) by comparing tissue perfusion post anastomosis and occurrence of post-operative complications.

Results: The feasibility of using LSI intra-operatively was demonstrated and on average added only 10 minutes to the overall operating time. Areas of perfusion zones (Holm's) above an arbitrary tissue viability threshold (200PU) were calculated (percentage of total zone (Z) area), these were median Z1 (81%); Z2 (67%); Z3 (51%) and Z4 (1%) (p=0.001 for Z1 vs all; Z2 vs Z3, ns; p=0.001 for Z4 vs all; Wilcoxon). Very promising results were shown for LSI images to guide selection of flap boundaries, highlighting areas of poor flap perfusion and potential to predict breast skin necrosis in the immediate setting.

Conclusions: LSI was easily used intra-operatively and allowed earlier detection of inadequate flap perfusion. These pilot data suggested that LSI has the potential to aid surgical decisions to avoid the use of poorly perfused tissue and reduce the risk of flap perfusion related post-operative complications.

S-8-4

High-speed atomic force microscopy for nano-visualization of living biological samples

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High speed atomic force microscopy (HS-AFM) is beginning to be employed to visualize the dynamic processes of biological events at single-molecule level. These improvements, in both the imaging rate and the tip force acting on the sample, have enabled the direct visualization of dynamic structural changes and dynamic interactions occurring in individual biological macromolecules, which is currently not possible with other techniques. Therefore, high-speed AFM is expected to have a revolutionary impact on biological sciences. However, the application of HS-AFM in more complex living system like cells and tissues still remains large challenges as well. Herein, based on our home-made HS-AFM device (up to 80Hz loading rate) with a large scanning area up to 100μm×100μm, *in situ* imaging of living cultured micro-vessel endothelial cells was then performed by using contact mode under different loading rates from 1Hz to 50Hz. The results show that different information of living cells may be addressed under different rates, suggesting that imaging of living architectures needs optimized loading rate from low to high to better descript living physiological processes.

S-8-5

Generation of Human-like Small Rodent Models for Dyslipidemic and Atherosclerotic Studies: CRISPR/Cas9 Mediated Gene Targeting of Syrian Golden Hamsters

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Abstract
Hamsters are widely used small rodents animal model. They are very similar to humans in lipid metabolism. They exhibit LDL priority plasma lipid profile, high levels of cholesteryl ester transport protein expression, intestinal-only ApoB editing, etc. In order to make full use of the advantages of hamsters, we first established the preparation method of genetically engineered hamster in the world. In this study, we propose to generate dyslipidemic hamster models to study lipid metabolism and atherosclerosis (As), including hypercholesterolemia (low density lipoprotein receptor, LDLR), hypertriglyceridemia (Apolipoprotein C2, ApoC2) and low HDL-C level (ATP-binding cassette transporter A1, ABCA1).

LDLR could mediate uptake and degradation of LDL, LDLR deficiency cause familiar hypercholesterolemia (FH) and As in humans. We designed gRNA target site in exon 2 of hamster LDLR gene and got 4 LDLR mutation founders. LDLR KO hamsters displayed hypercholesterolemia (Hch) under chow diet. Because the incidence of human heterozygous FH is very high (~1/500), they display Hch and aggravated As. We fed LDLR+/- hamster high fat diet (HFD), total cholesterol in LDLR+/- hamsters reached 2000mg/dL after 2 weeks feeding. They displayed As not only in aortic artery but also in coronary artery after 12 weeks HFD feeding.

ApoC2 is an obligatory activator of lipoprotein lipase (LPL), the most important lipase that hydrolyzes triglycerides (TG). ApoC2 deficiency in humans results in hypertriglyceridemia (HTG) and prone to acute pancreatitis. Because there are no ApoC2 knockout mammals, in-depth study of ApoC2 function is limited. We designed gRNA target site in exon 2 of hamster ApoC2 gene and got 2 mutation founders with 6 mutants (1nt insert, 12, 17, 68, 166 and 167nt deletion). ApoC2 KO hamsters looked pale with pink blood vessel. They had lower body weight compare with WT hamsters and finally death 3 to 9 days after birth. Seven days ApoC2 KO hamsters displayed severe chylaemia and hypoglycemia with plasma TG about 40,000mg/dL and plasma glucose only about 20mg/dL. To rescue ApoC2 KO hamsters, we injected normal hamster serum (4, 8, 12, 16, 20 days after birth) which contained normal ApoC2 protein into retrorbital sinus. About 75% ApoC2 KO hamsters survived until adulthood. Adult ApoC2 KO hamsters showed severe HTG, Hch (TG: ~8,000mg/dL; TC: ~900mg/dL) and significantly decreased HDL-C level. Plasma glucose reached 82.4% of WT hamsters.

ABCA1 can mediate phospholipids and cholesterol efflux from peripheral tissue and initiate the first process of cholesterol reverse transport. ABCA1 deficient patients suffer from Tangier disease. They have almost absence of HDL in plasma with intracellular cholesterol ester accumulation in macrophages and other peripheral tissues. We designed gRNA target site in exon 3 of hamster ABCA1 gene and only obtain 1 mutation founder with 15bp deletion. F2 homozygous hamster study showed ABCA1 KO hamsters have hardly detectable HDL-C and ApoA1 level. ABCA1 KO hamsters also displayed significantly increased TG level with fat clearance obstacle by oral fat load test.

In summary, we successfully generated 3 dyslipidemic knockout hamster models using CRISPR/Cas system. LDLR KO hamsters display hyperlipidemia and LDLR+/- hamsters show aortic and coronary artery As under HFD. ApoC2 KO hamsters display severe HTG, hypoglycemia and lactation death which could be rescued by normal serum injection. ABCA1 KO hamsters have hardly detectable HDL-C and ApoA1 level. These 3 knockout hamsters are excellent human-liked animal model for dyslipidemic and As studies. And also can be used for gene functional study.

S-8-6

Deep RNA Sequencing Elucidates MicroRNA Regulated Molecular Pathways in Ischemic Cardiomyopathy (ICM) And Non Ischemic Cardiomyopathy (NICM)

Xiang Li

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Abstract

Cardiovascular disease is a complex disease involved in a variety of factors, the morbidity and mortality increased year by year. Researchers have trying to excavate the pathogenesis of cardiovascular disease from different angles, however, the prevention and treatment, early diagnosis and effective drug intervention of the disease is still got no great breakthrough. Circulating non-coding RNA (circulating ncRNA) and competing endogenous RNA (ceRNA) play critical roles in development and pathogenesis of cardiovascular disease characterized by pathology changes in vascular structure and function. In this project, systematically dissecting molecular pathogenesis of cardiovascular disease. The expected results in this study will give advises for the etiology and pathology research, and will provide reliable theoretical basis for cardiovascular disease targeted therapy, it has potential economic value and social benefits.

Free Oral Presentation 1

8:00-10:00 October 29 Saturday Room 408 Yifu Building

Chairs:

Bao-Liang Sun
Key Lab of Cerebral Microcirculation in Universities of Shandong, Taishan Medical University

Yue-Hong Zheng
Department of vascular surgery, Peking Union Medical College Hospital

O-1-1 Screening and Functional Study of miRNAs in Arteriosclerosis Obliterans
Xiang-Yu Zhou
Department of Vascular and Thyroid Surgery, the Affiliated Hospital of SouthWest Medical University

O-1-2 The Involvement of Beta-catenin in AGE-induced Endothelial Hyperpermeability
Xiao-Hua Guo
Department of Pathophysiology, Key Laboratory for Shock and Microcirculation Research of Guangdong Province, Southern Medical University

O-1-3 Effects of FOXO1 Mediated Regulation of Mitochondrial Function in Diabetic Wound Healing
Lu Tie
State Key Laboratory of Natural & Biomimetic Drugs, Department of Pharmacology, School of Basic Medical Sciences, and Institute of System Biomedicine, Peking University

O-1-4 Sulfur Dioxide Protects against Pulmonary Artery Collagen Accumulation in Association with Downregulating TGF-β/Smad Pathway in Pulmonary Hypertensive Rats
Wen Yu
Department of Pediatrics, Peking University First Hospital

O-1-5 The Amelioration Effects of Berberine on Mesareic Vascular Damage in STZ - induced Diabetic Rats
Ding Zhao
School of Pharmacy & Institute of Integrated Traditional and Western Medicine, Hebei Medical University

O-1-6 GLP-1 Inhibits the Receptor for Advanced Glycation Endproducts to Prevent Podocyte Apoptosis Induced by Advanced Oxidative Protein Products
Shuang-Shuang Zhang
Department of Pathophysiology, Key Laboratory for Shock and Microcirculation Research of Guangdong Province, Southern Medical University

O-1-7 Aquaporin-3 Deficiency Slows Renal Cystogenesis via Regulation of AMPK/ERK/mTOR Signaling
Wei-Ling Wang
Department of Pharmacology, School of Basic Medical Sciences, Peking University, and State Key Laboratory of Natural and Biomimetic Drugs, Key Laboratory of Molecular Cardiovascular Sciences, Ministry of Education

O-1-8 Effect of Low-dose Simvastatin on Therapeutic Efficacy of Mesenchymal Stem Cells (MSCs) Transplantation in Diabetic Wound Healing
Sukpat Supakanda
Faculty of Medicine, Chulalongkorn University

O-1-9 Enhanced Therapeutic Potential of Nano-curcumin Against Subarachnoid Hemorrhage-induced Blood-brain Barrier Disruption Through Inhibition of Inflammatory Response and Oxidative Stress
Zong-Yong Zhang
Key Lab of Cerebral Microcirculation in Universities of Shandong, Taishan Medical University

O-1-10 Estrogen Treatment Improves Lymphatic Contractility in Rats Following Hemorrhagic Shock
Li-Min Zhang
Institute of Microcirculation, Hebei North University

O-1-1

Screening and Functional Study of miRNAs in Arteriosclerosis Obliterans

Xiang-Yu Zhou[1], Xue-Mei He[2]
1, Department of Vascular and Thyroid Surgery, the Affiliated Hospital of SouthWest Medical University,
2, Medical Research Center, the Affiliated Hospital of SouthWest Medical University,

Aim: Arteriosclerosis obliterans (ASO) of the lower extremities is a major reason of adult limb loss worldwide. Lacking of palpable symptoms results in the delay of therapy. Previous studies reveal that micorRNAs (miRNAs) participate in atherosclerosis, and it is easy to be detected. Therefore, the aim of current study is to screen a cluster of miRNAs that can be used as biomarker for ASO in the earlier stages. And we further study the function of such miRNAs in vitro.
Methods: Plasma from 3 patients with ASO and 3 healthy controls was profiled to screen aberrantly expressed miRNAs, and real time PCR was used to further identify in 55 patients and 54 age and sex matched controls as well as in 24 sclerotic and normal intimas. We also analyzed the correlation of miRNAs expression with Fontaine stages and T2DM which is a common complication with ASO. The function of identified miRNAs was investigated in HUVEC and HASMC.
Results: miRNA array result showed that 24 miRNAs were altered with change more than 2 fold (P<0.05), in which 4 miRNAs were up-regulated while 20 miRNAs were down-regulated. Real time PCR verified that the level of miR-4284 was significantly increased, while level of miR-4463, miR-4306 and miR-221-3p was significantly decreased in the plasma and sclerotic samples compared with the controls. Interestingly, we revealed that the four miRNAs were associated with Fontaine stages, as shown that expression of miR-4284 increased at the stage I of ASO and maintained the tendency to stage IV while miR-4463 expression decreased at every stage of ASO. miR-4306 and miR-221-3p did not change in Fontaine I, but decreased in Fontaine III and Fontaine IV. In addition, the expression of miR-4284 increased in the plasma of ASO and T2DM patients but showed no difference in ASO combined with T2DM patients. What's more, miR-4463 level showed opposite changes in ASO patients with or without T2DM. In vitro, HUVEC and HASMC were incubated in 1%O_2 (hypoxia) without FBS to mimic ischemia-induced tissue starvation, and in 25 mmol/L D-glucose (HG) to mimic hyperglycemia. The expression of miR-4463 was significantly increased in HUVEC but decreased in HASMC under hypoxia for 1h, 2h, 4h, 6h or HG 24h, 48h, 72h conditions. CCK 8 assay revealed that miR-4463 did not affect the proliferation of HUVEC and HASMC. However, miR-4463 mimic up-regulated the apoptosis of HUVEC under normal condition, which could be reversed by miR-4463 inhibitor. Meanwhile, miR-4463 inhibitor down-regulated the apoptosis of HUVEC at different degrees after HG 24h, hypoxia 4h and HG 24h combined with hypoxia 4h treatment, and miR-4463 mimic slightly increase the apoptosis but without significant difference. Moreover, Western blot result showed that, compared to NC group, the HUVEC transfected with miR-4463 inhibitor exhibited lower Cleaved-Caspase 3 and higher Bcl-2、XIAP, which further supported that miR-4463 inhibitor inhibits the apoptosis. As to HASMC cell, miR-4463 showed no effect on its apoptosis, but miR-4463 mimic promoted the migration by scratch and transwell assay. Conversely, miR-4463 inhibitor depressed the migration.
Conclusions: Our findings indicate that altered expressions of miR-4284 and miR-4463 are novel characteristics and may serve as potential biomarkers for the early diagnosis of ASO. miR-4463 plays different roles in HUVEC and HASMC. Down-regulation of miR-4463 could help HUVEC escape apoptosis induced by HG and hypoxia. Up-regulation of miR-4463 promotes the migration of HASMC which could be reversed by down-regulation of miR-4463.
Key words: Arteriosclerosis obliterans; miRNA; miR-4463

O-1-2

The Involvement of Beta-catenin in AGE-induced Endothelial Hyperpermeability

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Objective: To study the role of beta-catenin and its association with Src in endothelial hyperpermeability induced by advanced glycation end products (AGEs).

Methods: Beta-catenin siRNA, overexpression plasmid, dominant active mutant and negative mutant were applied to examine the role of beta-catenin in increased vascular hyperpermeability by measuring dextran transendothelial flux and transendothelial electric resistance (TER). Western blotting was performed to study Y654 and Y142 phosphorylation of beta-catenin. PP2, Src siRNA, Src overexpression plasmid, Src dominant active mutant and negative mutant were applied to testify the role of Src in AGE-induced beta-catenin Y654 phosphorylation.

Results: We verified that AGEs induced the phosphorylation of beta-catenin, accompanying with increased monolayer permeability in endothelial cells (ECs). Over-expression of beta-catenin in ECs displayed higher permeability after AGEs treatment. Activation of beta-catenin with dominant active mutant alone duplicated these effects, while inhibition of beta-catenin via siRNA and dominant negative mutant abolished AGE-induced ECs dysfunction. Overexpression of Src displayed more phosphorylation of beta-catenin, while inhibiton of Src abolished this effect.

Conclusions: Our studies demonstrated that beta-catenin is responsible for AGEs induced endothelial hyperpermeability through Src activation.

O-1-3

Effects of FOXO1 Mediated Regulation of Mitochondrial Function in Diabetic Wound Healing

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Aims/hypothesis Refractory wounds in diabetic patients constitute a serious complication that often leads to amputation with limited treatment regimens. Recent studies have shown that the imbalance of mitochondrial dynamics was associated with the increased reactive oxygen species (ROS) production in endothelial cells, which is a significant contributor to the microvascular complications of diabetes. The present study was designed to determine the involvement of transcription factor FOXO1 in diabetic wound healing and investigate underlying mechanisms.

Methods&Results Impaired mitochondrial networks and increased phosphorylation of dynaminrelated protein-1 (Drp1) at ser616, a protein required for mitochondrial fission, were observed in human umbilical vein endothelial cells (HUVECs) 24 h after exposure to high concentrations of glucose. Inhibition of FOXO1 by siRNA or by FOXO1 selective inhibitor AS1842856 abrogated high glucose–induced alterations in mitochondrial networks and phosphorylation of Drp1. Treatment with AS1842856 or siRNA of FOXO1 could significantly increase the mitochondrial membrane potential and suppress the overproduction of ROS induced by high glucose. Addition of AS1842856 inhibited glucose-induced apoptosis, ameliorated capillary tube formation in HUVECs. In vivo, AS1842856 dose-dependently rescued the delay of wound closure in diabetic mice, and 5 mg/kg of AS1842856 treatment significantly increased the mean perfusion rate.

Conclusion These findings suggested that FOXO1 is critical to preserve mitochondrial quantity and function in endothelial cells, inhibition of FOXO1 rescued the delayed wound healing and improved wound angiogenesis in diabetic mice.

O-1-4

Sulfur Dioxide Protects against Pulmonary Artery Collagen Accumulation in Association with Downregulating TGF-β/Smad Pathway in Pulmonary Hypertensive Rats

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Objective: We aimed to explore the role of endogenous sulfur dioxide (SO_2) in pulmonary vascular collagen remodeling induced by monocrotaline (MCT) and its mechanisms.

Methods and Results: A rat model of MCT-induced pulmonary vascular collagen remodeling was developed and administered with L-aspartate-β-hydroxamate (HDX) or SO_2 donor. The morphology of small pulmonary arteries and collagen metabolism were examined. Transforming growth factor-β1 (TGF-β1)-stimulated cultured pulmonary arterial fibroblasts (PAFs) were used to explore the mechanism. The results showed that in MCT-treated rats, mean pulmonary artery pressure (mPAP) increased markedly, small pulmonary arterial remodeling developed, and collagen deposition in lung tissue and pulmonary arteries increased significantly in association with elevated SO_2 content, glutamate-oxaloacetate transaminase (GOT) activity and expression of GOT1, compared to control rats. Interestingly, HDX, an inhibitor of SO_2 generation, further aggravated pulmonary vascular collagen remodeling in MCT-treated rats and inhibition of SO_2 in pulmonary artery smooth muscle cells activated collagen accumulation in PAFs. SO_2 donor, however, alleviated pulmonary vascular collagen remodeling with an inhibited collagen synthesis, augmented collagen degradation, and decreased TGF-β1 expression of pulmonary arteries. Mechanistically, overexpression of GOT1, a key enzyme of SO_2 production, prevented the activation of TGF-β/type I TGF-β receptor (TβRI) /Smad2/3 signaling pathway as well as abnormal collagen synthesis in PAFs. In contrast, knockdown of GOT1 exacerbated Smad2/3 phosphorylation and collagen type I and III deposition in TGF-β1-treated PAFs.

Conclusion: Endogenous SO_2 plays a protective role in pulmonary artery collagen accumulation induced by MCT via inhibiting the TGF-β/TβRI/Smad2/3 pathway.

O-1-5

The Amelioration Effects of Berberine on Mesareic Vascular Damage in STZ - induced Diabetic Rats

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Objective: To investigate the mechanism of berberine (BBR) for ameliorating mesareic vascular damage in early diabetic rats.

Methods: Streptozotocin (STZ, 55 $mg \cdot kg^{-1}$) was intraperitoneally injected to induce the diabetic rats model. After 2 weeks of diabetes success, BBR (200 $mg \cdot kg^{-1}$) was administered by gavage once a day for another 2 weeks. Histomorphologic changes were observed in mesareic vascular using the HE staining; neurogenic reactions were investigated using organ bath and electric field stimulation induced constrictions on superior mesenteric artery and common iliac artery.

Results:

1. In the early STZ-induced diabetic rats, different grades of mesentery vessels and fatty tissues around blood vessels had different extent of pathological changes, and that were related to inflammation. BBR ameliorated the pathological damage, and reduced the number of leukocyte on vessels and fat tissues in diabetic rats, especially on small vassels.
2. In the early STZ-induced diabetic rats, the nitrergic nerve of superior mesenteric artery was damaged, the release of NO was decreased; the adrenergic nerve excitation of common iliac artery was increased. BBR ameliorated the nitrergic nerve function significantly, but had little effect on adrenergic nerve in diabetic rats.

Conclusion: BBR has protected effects on the mesareic vascular by anti-inflammation and improving the nitrergic nerve function in STZ - induced diabetic rats.

O-1-6

GLP-1 Inhibits the Receptor for Advanced Glycation Endproducts to Prevent Podocyte Apoptosis Induced by Advanced Oxidative Protein Products

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Objective: Advanced oxidative protein products (AOPPs) play a central role in the pathogenesis of diabetic nephropathy by mediating the apoptosis of podocytes via the receptor for advanced glycation endproducts (RAGE). Glucagon-like peptide-1 (GLP-1) has been shown to down-regulate RAGE and exert anti-apoptotic effects in various cell types. The objective of this study was to investigate whether and how GLP-1 can protect podocytes from AOPP-induced apoptosis.

Methods*:* Murine podocytes were stimulated with 200 □g/ml AOPP for 48 h in the presence or absence of GLP-1. Cell viability was assessed using the cell counting kit-8 assay. Podocyte apoptosis was detected by flow cytometry and Hoechst 33258 staining. O_2^- production was assayed using lucigenin-enhanced chemiluminescence, and Western blotting was used to measure expression of RAGE, NADPH oxidase subunits $p47^{phox}$ and $gp91^{phox}$, as well as apoptosis-associated proteins p53, Bax, Bcl-2 and caspase-3.

Results: Incubating podocytes with AOPPs reduced cell viability, triggered changes in cell morphology and promoted apoptosis. GLP-1 partially inhibited AOPP-induced apoptosis and O_2^- overproduction. The AOPP-induced expression of RAGE was also attenuated by GLP-1 treatment. The expression of $p47^{phox}$ and $gp91^{phox}$ were inhibited by GLP-1 in AOPP-treated podocytes. While AOPP-induced expression of p53, Bax and cleaved caspase-3 were attenuated by GLP-1, the expression of Bcl-2 was recovered by GLP-1 treatment.

Conclusion: GLP-1 partially inhibits AOPP-induced apoptosis in podocytes, perhaps by interfering with the AOPP-RAGE axis, decreasing oxidative stress and inhibiting the downstream p53/Bax/caspase-3 apoptotic pathway. GLP-1 may be a useful anti-apoptotic agent for early intervention in diabetic nephropathy.

O-1-7

Aquaporin-3 Deficiency Slows Renal Cystogenesis via Regulation of AMPK/ERK/mTOR Signaling

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Objective: Human autosomal dominant polycystic kidney disease (ADPKD) is characterized by numerous bilateral renal cysts that lead to a decline in renal function over time. ADPKD is a disease that described as “neoplasia in disguise”. The process of cyst generation requires proliferative expansion of the epithelial lining of the collecting duct or renal tubules. Previous studies reported aquaporin-3 (AQP3) expression in cysts derived from collecting ducts in ADPKD. Here, we investigated the effects of AQP3 on the renal cyst development.

Methods: We used *Pkd1* kidney specific knockout mice and *Pkd1* inducible knockout mice to study the role of AQP3 deficiency on neonatal cystogenesis and indolent adult forms. *In vitro* AQP3 overexpressed MDCK cell line was established and matrix-grown MDCK cyst model was used to study the role of AQP3 overexpression on cyst growth. To investigate the mechanism of AQP3-dependent cyst development, we detected AMPK/ERK/mTOR signaling pathways. The intracellular ATP, glucose, glycerol and lactate were also detected in MDCK and AQP3 over-expression MDCK cells.

Results: Kidney size and cyst number were ~30% smaller in AQP3 null PKD mice than in AQP3-expressing PKD mice, with the difference due mainly to smaller collecting ducts cysts. In matrix culture with forskolin treatment, AQP3 transfection promoted cyst enlargement in MDCK cyst model. The diameter of AQP3-MDCK cysts was ~38% larger than in control MDCK cells. It was found that the AMPK/ERK/mTOR signaling, as well as intracellular ATP, were down-regulated after AQP3 depletion. In addition, the AMPK/ERK/mTOR signaling and intracellular ATP synthesis was up-regulated in AQP3 overexpressed MDCK cells. Thereby epithelial secretion and proliferation were increased in AQP3 overexpressed MDCK cells.

Conclusion: Our study demonstrates that AQP3 deficiency retards cyst development in PKD mice and MDCK cyst models. The mechanism that underlies this phenomenon seems to be involved in lower energy metabolism and activation of AMPK, resulting in inhibition of ERK/mTOR. These results reveal a previously unrecognized role of AQP3 in ADPKD and energy metabolism and hence may provide a novel therapeutic target.

O-1-8

Effect of Low-dose Simvastatin on Therapeutic Efficacy of Mesenchymal Stem Cells (MSCs) Transplantation in Diabetic Wound Healing

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Introduction Non-healing diabetic ulcer were causes the patient at much higher risk for amputation. Several studies suggest that simvastatin and mesenchymal stem cells (MSCs) could increase angiogenic factors and improve wound healing. Therefore, the objective of this study was to evaluate the effect of pre-treatment of low-dose simvastatin supplementation and MSCs transplantation on angiogenesis and wound healing in a diabetic mouse.

Methods Balb/c nude mice were divided into five groups including control (CON), diabetic (DM, streptozotocin 45 mg/kg i.p. daily for 5 days), diabetic pre-treated with low-dose simvastatin (DM+SIM), diabetic implanted MSCs (DM+MSCs) and diabetic pre-treated with low-dose simvastatin and implanted MSCs (DM+MSCs+SIM) groups. Seven days before wound-induction, DM+SIM and DM+MSCs+SIM were started on oral simvastatin (0.25mg/kg/day). Eleven weeks after the diabetic induction, all mice were created bilateral full-thickness excisional skin wounds on the back (0.6x0.6 cm^2) and received fibrin gel or $1x10^6$ MSCs into wound bed. On day 14 post-wound, the percentage of wound closure (%WC), the percentage of capillary vascularity (%CV), the neutrophil infiltrations and stromal cell-derived factor 1 (SDF-1) were determined by using Image Pro-Plus, confocal fluorescence microscopy, haematoxylin and eosin staining and immunohistochemically staining respectively. Tissue vascular endothelial growth factor (VEGF) was detected by ELISA at day 7 and 14 post-wound.

Results On day14, the %WC and %CV in all groups were increased than DM. The %WC and %CV of DM+SIM+MSCs group were higher than DM+MSCs group. The number of neutrophil infiltration in all groups were lower than DM group. The expression of SDF-1 in the all groups seems to be increased than in DM group. The VEGF levels in all groups were higher than DM on day 7 without difference on Day 14.

Conclusion The present study demonstrated that the pre-treatment of low-dose simvastatin supplementation and MSCs transplantation can increase angiogenesis and improve wound healing in diabetic mice model.

O-1-9

Enhanced Therapeutic Potential of Nano-curcumin Against Subarachnoid Hemorrhage-induced Blood-brain Barrier Disruption through Inhibition of Inflammatory Response and Oxidative Stress

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Objectives: Curcumin and nano-curcumin both exhibit neuroprotective effects in early brain injury (EBI) after experimental subarachnoid hemorrhage (SAH). However, the mechanism that whether curcumin and its nanoparticles affect blood-brain barrier (BBB) following SAH remains unclearly. This study investigated the effect of curcumin and the poly (lactideco-glycolide) (PLGA) encapsulated curcumin nanoparticles (Cur-NPs) on BBB disruption and evaluated the possible mechanism underlying BBB dysfunction in EBI using the endovascular perforation rats SAH model.

Methods: The animals were divided randomly into six groups: sham-operated group (n = 24), vehicle-treated SAH group (n = 24), curcumin-treated SAH group (150 mg/kg, n = 24; 300 mg/kg, n = 24); Cur-NPs-treated SAH group (10 mg/kg, n = 30; 10 mg/kg, n = 30). Eighteen rats of each group were for measuring mortality rates analysis (at 24 and 48 h), neurological assessment (at 24 h), glutamate concentration in CSF (at 48 h), LDH activity and release of cyochrome c (at 48 h). Six rats of each group were for detecting brain water content and BBB permeability at 24 h. Six rats of Cur-NPs-treated SAH group were for molecular biological and biochemical experiments at 24 h. Three rats of Cur-NPs-treated SAH group were for immunohistological staining at 24 h.

Results: Cur-NPs showed enhanced therapeutic effects than that of curcumin in improving neurological function, reducing brain water content and Evans blue dye extravasation after SAH. Mechanically, Cur-NPs attenuated BBB dysfunction after SAH by preventing the disruption of tight junction protein (ZO-1, Occludin and Claudin-5). Cur-NPs also up-regulated glutamate transporter-1 and attenuated glutamate concentration of cerebrospinal fluid following SAH. Moreover, inhibition of inflammatory response and microglia activation both contributed to Cur-NPs's protective effects. Additionally, Cur-NPs markedly suppressed SAH-mediated oxidative stress and eventually reversed SAH-induced cells apoptosis in rats.

Conclusions: Cur-NPs against SAH-induced BBB disruption may involve the prevention of glutamate-induced neurotoxicity, inflammatory responses, oxidative stress and cell apoptosis in the endovascular perforation rat SAH model.

O-1-10

Estrogen Treatment Improves Lymphatic Contractility in Rats Following Hemorrhagic Shock

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Abstract

The lymphatic contractility dysfunction and hypo-reactivity play important role in the development of hemorrhagic shock leading to organ injury. Previous investigations have shown that estrogen treatment could attenuate hemorrhagic shock-induced organ injury. However, it remains unclear whether estrogen treatment improves lymphatic contractility following hemorrhagic shock. Therefore, the aim of this study was to investigate the effect of estrogen treatment on the lymphatic contractility in rats following hemorrhagic shock. Wistar male rats were divided into the sham, shock, and shock+17β-estradiol (E2) groups. The rats were subjected to hemorrhage (40±2 mmHg for 90 min) and resuscitation with subcutaneous injection of E2 (2 mg/kg) or not. Three hours after resuscitation, the lymphatic contractility *in vivo* was observed using dynamic visualization microvascular observation system. Furthermore, the isolated mesenteric micro-lymphatic rings of were prepared for the observations of lymphatic contractility and [Ca^{2+}] change using an vascular tension and ion concentration measurement system (IonOptix BioIOn1.33) at a transmural pressure of 3 cmH_2O. Finally, the intestinal morphology was observed. The current results showed that E2 administration significantly enhanced the contraction frequency (CF), fractional contraction contractile index (Index I), total contractile activity index (Index Ⅱ), and lymphatic dynamics index (LD-Index) of lymphatics *in vivo*, increased the CF and fractional pump flow (FPF) of isolated lymphatics *in vitro*, following hemorrhagic shock. The results also indicated that hemorrhagic shock-induced lymphatic contractility dysfunction was related to the difference in intra and exta cellular [Ca^{2+}] of lymphatic smooth muscle cells, which was abolished by E2 treatment. In addition, E2 treatment also reversed hemorrhagic shock-induced intestinal edema. In conclusion, our findings suggested that estrogen treatment improved lymphatic contractility in rats following hemorrhagic shock, which was favorable to attenuate intestinal edema through increasing lymph transport function. This work was supported by the Natural Science Foundation of China (81670446).

Free Oral Presentation 2

8:00-10:00 October 30 Sunday Room 409 Yifu Building

Chairs:

Zi-Gang Zhao

Institute of Microcirculation, Hebei North University

Qing-Fu Zhang

The first hospital of Hebei Medical University

O-2-1 In Vivo Morphological Observation of Cortical Vessel in Cerebral Hypoperfusion Mice

Di Nan

Department of Neurology, People's Hospital, Peking University

O-2-2 Cardioprotective Effects of Gypenoside XVII on Endoplasmic Reticulum Stress–Mitochondrial Damage Crosstalk after Ischemia–reperfusion Injury through PI3K/AKT and P38 Signalling Pathways

Ying−li Yu

Institute of Medicinal Plant Development, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing

O-2-3 Staphylococcal SSL5-induced Platelet Microparticles Provoke Proinflammatory Responses Via the CD40/TRAF6/NFκB Signaling Pathway in Monocytes

Hou-Yuan Hu

Department of Cardiology, Southwest Hospital

O-2-4 Role of Vimentin in the Inhibitory Effects of Low-Molecular-Weight Heparin on PC-3M Cell Adhesion to, and Migration through, Endothelium

Yan Pan

Department of Pharmacology, School of Basic Medical, Peking University Health Science Center

O-2-5 AQP3 protects against Renal Ischemia/Reperfusion Injury by promoting MAPK Signaling

Lei Lei，Bao-Xue Yang

Department of Pharmacology, School of Basic Medical Sciences, Peking University

O-2-6 Density and Kinetics of Ito、IK1、IKs and IKr in Guinea Pig ventricular Myocytes: Implications for Arrhythmogenesis in Humans

Yong-Xia Wang

The first affiliated hospital of Henan University of traditional Chinese medicine

O-2-7 Cardioprotective Effects of Rosa Rugosa Flavoniods on Myocardial Ischemia Reperfusion Injury in Mice

Xue-Hui Zhang

Pharmacy school, Shihezi University

O-2-8 Endogenous sulfur dioxide alleviates collagen remodeling via inhibiting TGF-β/Smad pathway in vascular smooth muscle cells

Ya-Qian Huang

Department of Pediatrics, Peking University First Hospital

O-2-9 H_2S regulates endothelial nitric oxide synthase protein stability by promotingmicroRNA-455-3p expression

Wen-Long Xue

Shanghai Key Laboratory of Bioactive Small Molecules, Department of Physiology and Pathophysiology, Shanghai Medical College, Fudan University

O-2-10 The effect and mechanism of XST capsule inhibiting THP-HUVECs adhesion under different flow conditions

Shu-Xian Han

Institute of Chinese Materia Medica China Academy of Chinese Medical Science

O-2-1

In Vivo Morphological Observation of Cortical Vessel in Cerebral Hypoperfusion Mice

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Abstract:

Objective: To dynamically observe the morphological changes of cortical vessel in cerebral hypoperfusion mice through cranial window. **Methods:** The operation of left common carotid artery ligation and transient right common carotid artery ligation was applied to 7 Tie2-GFP transgenic mice. The cortical vessels were observed using confocol microscopy through cranial window before the brain ischemia (D0) and 7 days after the brain ischemia (D7). The diameter and density of capillary, along with the diameter and morphological change of arterioles and venules were analyzed. **Results:** (1) The diameter of capillary before and 7 days after the brain ischemia were (6.62±0.75) μm and (12.50±3.29) μm, which increased significantly after brain ischemia (P<0.001); (2) The capillary density before and 7 days after the brain ischemia were (11.67±1.72) segments per ROI and (11.08±2.06) segments per ROI. The difference was not significant (P=0.0583); (3) The diameter of precapillary arteriole, post capillary venule, true capillary and thoroughfare channel before and 7 days after the brain ischemia were (6.33±0.94) μm vs (12.36±3.20) μm, (6.87±1.10) μm vs (12.37±2.78) μm, (6.37±0.52) μm vs (11.41±3.10) μm and (6.35±0.92) μm vs (13.91±6.17) μm, respectively, all increased significantly after brain ischemia (P<0.01, <0.01, <0.01, and <0.05, respectively). The most significant dilation was observed in thoroughfare channel; (4) The diameter of venules on D0 and D7 were (9.59±8.74) μm and (24.81±6.25) μm, which increased signigicantly after brain ischemia (P=0.0054). However, the diameter of arterioles on D0 and D7 were (12.71±2.10) μm and (13.20±3.09) μm, the difference was not significant (P=0.2947); (5) Capillary remodeling, and tortuosity and new anastomosis between venules were observed after brain ischemia. **Conclusion:** The dilation of capillary, dilation of venules, and remodeling of cortical vessel were observed after brain ischemia. These changes may contribute to the regulation of cerebral blood flow after cerebral hypoperfusion.

Keywords: Cerebral hypoperfusion; Confocol microscopy; Capillary; Arterioles; Venules

O-2-2

Cardioprotective Effects of Gypenoside XVII on Endoplasmic Reticulum Stress–Mitochondrial Damage Crosstalk after Ischemia–reperfusion Injury through PI3K/AKT and P38 Signalling Pathways

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Aim: Effective strategies have been developed to prevent or improve recovery from myocardial ischemia and reperfusion (I/R) injury. Direct interactions between mitochondria and endoplasmic reticulum (ER) during heart diseases progression have been extensively investigated. This study aims to explore the cardioprotective effects of gypenoside XVII (GP-17) against I/R injury and illustrate the roles of ER stress, mitochondrial damage and their crosstalk within the progression of I/R injury and in GP-17-induced cardioprotection.

Methods: Isolated rat hearts were subjected to global ischemia followed by reperfusion in the absence or presence of GP-17. Cardiac contractility function was monitored in the Langendoff-perfused rat hearts. Simultaneously, H9c2 cardiomyocytes subjected to hypoxia/reoxygenation was used to minic in vitro I/R. The effects of GP-17 on mitochondrial functions, particularly opening of the mitochondrial permeability transition pore (mPTP), respiratory function and reactive oxygen species (ROS) production, were determined. Myocardium apoptosis was determined by TUNEL staining. The biomarkers related to myocardial ischemia injury were examined.

Results: We find that GP-17 reduces cardiac dysfunction, inhibits myocardial apoptosis and improves contractile recovery after I/R in both isolated rat hearts and H9c2 cardiomyocytes. I/R-induced apoptosis is predominantly regulated by ER stress as well as mitochondrial damage. The cardioprotective effects of GP-17 are controlled by phosphoinositide 3-kinase/protein kinase b (PI3K/AKT) and p38 signalling pathways, which were illustrated by the treatment with the inhibitor of PI3K, namely, LY294002, or the p38/ MAPK inhibitor SB203580. The inhibition of oxidative stress is also involved in the cardioprotective effects of GP-17.

Conclusion: GP-17 ameliorates I/R-induced mitochondrial damage and delays the onset of ER stress through PI3K/AKT and p38 signalling pathways.

Key words: ischemia/reperfusion; gypenoside XVII; endoplasmic reticulum stress; mitochondria; oxidative stress; apoptosis.

O-2-3

Staphylococcal SSL5-induced Platelet Microparticles Provoke Proinflammatory Responses via the CD40/TRAF6/NFκB Signaling Pathway in Monocytes

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Objective: Pathogens-induced platelet activation contributes to inflammation in cardiovascular diseases, but underlying mechanisms remain elusive. Staphylococcal superantigen-like protein 5 (SSL5) is a known activator of platelets. Here we examined whether SSL5 is implicated in Staphylococcus aureus (*S. aureus*)-induced inflammation and potential mechanisms involved.

Methods: As expected, we show that SSL5 activates human platelets and induces generation of platelet microparticles (PMPs). Flow cytometry and scanning electron microscopy studies demonstrate that SSL5-induced PMPs (SSL5-PMPs) bind to monocytes, causing aggregate formation.

Results: SSL5-PMPs provoke monocyte expression and release of inflammatory mediators, including interleukin-1β (IL-1β), tumor necrosis factor-α (TNFα), monocyte chemoattractant protein-1 (MCP-1) and matrix metalloproteinase-9 (MMP-9) in a dose- and time-dependent manner. SSL5-PMPs also enhance MCP-1-induced monocyte migration. Blockade of CD40 and CD40 ligand (CD40L) interactions with neutralizing antibodies significantly reduce monocyte release of inflammatory mediators and migration induced by SSL5-PMPs. SiRNA-mediated silencing of CD40 or TNF receptor (TNFR)-associated factor 6 (TRAF6) gene largely abrogates phosphorylation and nuclear translocation of NFκB (p65).

Conclusions: SSL5 provokes the release of inflammatory mediators in monocytes, at least in part, via PMPs-mediated activation of the CD40/TRAF6/NFκB signaling pathway, though it normally inhibits leukocyte function. Our findings thus reveal a novel mechanism by which *S. aureus* induces inflammation.

O-2-4

Role of Vimentin in the Inhibitory Effects of Low-Molecular-Weight Heparin on PC-3M Cell Adhesion to, and Migration through, Endothelium

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Metastasis is the main obstacle of cancer treatment. Metastasis prevention would be the key factor in cancer prognosis. Cancer patients who had been treated with low molecular weight heparin (LMWH) for their thrombosis had a significantly improved 3 to 6 month survival. Experimental studies showed that LMWH had anti-metastasis effect. There were reports that LMWH could protect endothelial cells (EC) from being activated and inhibit the expression of cell adhesion molecules when it was used as an anticoagulant in patients with coronary artery disease. But by far, there are still no definite report concerning the mechanisms of LMWH on tumor and metastasis. In the present study, human umbilical vein endothelial cells (HUVECs) were treated with LMWH for 24 h. We found that the resulting HUVECs could significantly inhibit the highly metastatic human prostate cancer cell line (PC-3M) in terms of its adhesion to the endothelium and migration across the endothelium, according to scanning electron microscopy. We also determined the elevated levels of endothelial intercellular Ca^{2+} concentration after the adhesion of PC-3M cells to HUVECs was greatly reduced by incubation with LMWH. Using proteomics, we surveyed the global protein changes in HUVECs after LMWH treatment and identified four down-regulated proteins that were possible isoforms of cytoskeletal vimentin intermediate filaments, cartilage-derived C type lectin, and serine/threonine protein phosphatase 1 (PP-1B). LMWH affected the morphology of vimentin and the expression levels of αv integrin and PP-1B in HUVECs bound to PC-3M cells. Vimentin assists in the adhesion of PC-3M cells, which was confirmed by short interfering RNA experiments. Furthermore, the direct binding of purified vimentin protein with LMWH was detected with surface plasmon resonance methods. However, when we used fluorescence-labeled heparin for 24 h to identify whether this binding occurred within cells, heparin was distributed principally around endothelial cells. Taken together, these findings suggest that the monoincubation of LMWH with HUVECs could inhibit PC-3M cell adhesion to, and migration through, endothelium. LMWH's regulation of vimentin plays a role in the antimetastatic action.

Keywords:
Low molecular weight heparin, Human umbilical cord vascular endothelial cells, Adhesion, Transendothelial migration, Proteomics, Vimentin

O-2-5

AQP3 protects against Renal Ischemia/Reperfusion Injury by promoting MAPK Signaling

Lei Lei，Bao-Xue Yang
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Objective: Ischemia/reperfusion injury (IRI) is a significant cause of acute kidney injury (AKI) in such clinical conditions as transplanted kidneys. IR injury is characterized by subsequent deteriorated renal function and particularly related to delayed graft function and chronic graft survival. Integrity of the renal collecting duct (CD) is rarely mentioned as an important limiting factor in the recovery from IRI. Recent studies have shown that AQP3 expression was down-regulated in renal collecting duct after ischemia reperfusion (IR). AQP3 can facilitate hydrogen peroxide (H_2O_2) passage across the plasma membrane, which indicates that AQP3 might have antioxidant effect via mediated membrane H_2O_2 permeability. Furthermore, AQP3-facilitated water transport might be involved in migration of bulge cells, accelerating injury repair. The target of our study was to evaluate whether AQP3 could relieve renal IRI by promoting CD integrity and study the mechanisms in which AQP3 protected from IRI.
Methods: Male mice were subjected to right renal ischemia for 25 min and reperfusion for 24 h, or to a sham operation with left kidney removed. Kidneys after reperfusion for 24 h were harvested to measure the MPO, SOD and MDA levels, and fixed for hematoxylin and eosin staining and TUNEL assay. Blood samples were collected for determination of urea, creatinine, and LDH. Related molecules of the MAPK pathways and apoptosis were determined. MDCK cells and AQP3 stably transfected MDCK cells were cultured for chemical hypoxia and physical hypoxia. Cells after 600 μM cobalt chloride ($CoCl_2$) for 18 h or in a hypoxic atmosphere under the 1.0% O_2 at 37 °C for 18 h were harvested for related molecules of the MAPK pathways and apoptosis detection.
Results: Kidneys of wild type undergone IR showed no characteristic morphological changes, such as tubular dilatation, and brush border loss. However, AQP3 knockdown significantly aggravated the renal dysfunction and the abnormal levels of MPO, MDA and SOD induced by IR. AQP3 knockdown also inhibited the activation of MAPK pathways, which consequently resulted in a significant increase in the ratios of Bax/Bcl-2 and cleaved caspase-3/caspase-3, and phosphorylation of p53 induced by IR. Overexpression of AQP3 promoted cell proliferation and migration. AQP3 alleviated $CoCl_2$ and hypoxia-reoxygenation induced cell viability loss in MDCK renal collecting tube epithelial cells, which proved by the increased level of Bcl-2 and decreased levels of Bax、p-p53 and cleaved caspase 3 compared with the MDCK. Otherwise, AQP3 inhibited $CoCl_2$ and hypoxia-reoxygenation activated p38, ERK1/2 compared with MDCK cells, indicating that AQP3 might result in an inhibition of the apoptosis pathway through strengthening activity of MAPK pathways.
Conclusions: Our *in vivo* studies show that AQP3 knockdown aggravates renal IRI *via* inhibiting MAPK signaling pathways and overexpression of AQP3 *in vitro* ameliorates IR *via* promoting MAPK signaling pathways. The data provides evidence that AQP3 may serve as a potential therapeutic agent for acute renal IRI.

O-2-6

Density and Kinetics of Ito、IK1、IKs and IKr in Guinea Pig ventricular Myocytes: Implications for Arrhythmogenesis in Humans

Yong-Xia Wang, Zuo-Ying Xing, Ming-Jun Zhu

The first affiliated hospital of Henan University of traditional Chinese medicine

Objective: The purpose of this experiment was to observe the pharmacological effects of each component of the cassia twig liquorice decoction drug-containing serum（GZGC）on a single guinea pig ventricular myocyte, to the ion channel Ito, IK1 and IKs channel current and its kinetic parameters, and the character of IKr channels expressed in HEK293 cells, discuss the influence of GZGC anti-arrhythmic pharmacological mechanism.

Methods: The guinea pig ventricular muscle cells were isolated in acute, the cells was divided into control group, Glycyrrhiza, Cassia twig, Glycyrrhiza & cassia twig and Cassia twig licorice decoction randomly, separately joined the corresponding drug serum with the concentration of 10% and 15%, cells with myocardial culture medium placed at 37℃, 5% CO2 incubation box for patch clamp experiments after incubation for 24 hours.

Results: Every drug all inhibit the ventricular myocyte transient outward potassium current (Ito) in different degrees, but has no effect on inactivation curve and recovery curve. The liquorice group 15% concentration has statistical difference compared with the control group.Cassia twig licorice soup group 10% and 15% concentration and the liquorice group 15% concentration all inhibit the ventricular myocyte of ventricular muscle cells inward rectifier potassium current (IK1) and have significant difference compared with control group, all else have no statistical difference. Drugs inhibit IKs steady peak current, the influence of licorice, cassia twig and liquorice and cassia twig group 15% concentration have significant difference compared with control group, all else have no statistical difference. Each drug components of cassia twig liquorice decoction did not significantly affect time dependence recovery curve of IKs-tail. Cassia twig liquorice 15% concentration inhibit IKr current compared with control group, statistically significant, the rest of the group to IKr current is not obvious. Each drug components make quick activation of delayed rectifier potassium current (IKr-tail) tail current steady-state activation curve move to the left, the deactivation curves and recovery curves are not significantly influence.

Conclutions: Cassia twig liquorice decoction has the action of adjusted a variety of potassium channels, the mutual coordination between various ion current may be the basis of fewer side effects besides anti-arrhythmic.

O-2-7

Cardioprotective Effects of Rosa Rugosa Flavoniods on Myocardial Ischemia Reperfusion Injury in Mice

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Aim: To investigate the cardioprotective effects of rosa rugosa flavoniods (RRF) on myocardial ischemia reperfusion injury (MIRI) in mice and its related mechanisms.

Methods: After intragastric administration of Fufangdanshen Dropping Pill (FFDS, 166 mg/kg d-1, positive drug control) or RRF (600 mg/kg d-1) for 7 days, mice received 45 min of ischemia by complete ligation of the left ascending descending (LAD) artery coronary, and were then reperfused for 3 h. The infarct size, myocardial morphology, the activity of myocardial enzymes as well as mRNA expression levels of the genes associated with inflammation and apoptosis were evaluated after 3 h of reperfusion.

Result: Compared to the MIIR model group, both FFDS and RRF significantly reduced the infarct size from 49.01± 8.84% to 33.56 ± 7.75% ($p<0.05$) and 36.75±4.84% ($P<0.01$), respectively; myocardial fibers were more uniform in the cross-sectional area of the heart tissues from the above two groups. Pre-treatment of the mice with either FFDS or RRF significantly reduced the activity of lactate dehydrogenase (LDH) and creatine kinase (CK), increased the activity of superoxide dismutase (SOD) in plasma, significantly downregulated the mRNA expression levels of IL-1β, IL-6, TGF-β, caspase-3 and Bax and upregulated the mRNA expression level of Bcl-2 in the infarcted myocardia of the mice.

Conclusion: The results suggest that RRF has comparatively cardioprotective effects with FFDS on MIRI and its mechanisms may be related to attenuation of oxidative stress, inflammation and apoptosis.

Key words: RRF, MIRI, oxidative stress, inflammation, apoptosis

O-2-8

Endogenous sulfur dioxide alleviates collagen remodeling via inhibiting TGF-β/Smad pathway in vascular smooth muscle cells

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The study was designed to investigate the role of endogenous sulfur dioxide (SO_2) in collagen remodeling and its mechanisms in vascular smooth muscle cells (VSMCs). Overexpression of endogenous SO_2 synthase aspartate aminotransferase (AAT) 1 or 2 increased SO_2 levels and inhibited collagen I and III expressions induced by transforming growth factor (TGF)-β1 in VSMCs. In contrast, AAT1 or AAT2 knockdown induced a severe collagen deposition in TGF-β1-treated VSMCs. Furthermore, AAT1 or AAT2 overexpression suppressed procollagen I and III mRNA, upregulated matrix metalloproteinase (MMP)-13 expression, downregulated tissue inhibitors of MMP-1 level, and vice versa. Mechanistically, AAT1 or AAT2 overexpression inhibited phosphorylation of type I TGF-β receptor (TβRI) and Smad2/3 in TGF-β1-stimulated VSMCs. Whereas SB431542, an inhibitor of TGF-β1/Smad signaling pathway, attenuated excessive collagen deposition induced by AAT knockdown. Most importantly, ectopically expressing AAT or exogenous addition of 100 μM SO_2 blocked AAT deficiency-aggravated collagen accumulation in TGF-β1-stimulatd VSMCs, while no inhibition was observed at 100 μM ethyl pyruvate. These findings indicated that endogenous SO_2 alleviated collagen remodeling by controlling TGF-β1/TβRI/Smad2/3-mediated modulation of collagen synthesis and degradation.

Keywords: sulfur dioxide; collagen remodeling; vascular smooth muscle cells; transforming growth factor-β1

O-2-9

H2S regulates endothelial nitric oxide synthase protein stability by promotingmicroRNA-455-3p expression

Xing-Hui Li[1,†], Wen-Long Xue[1,†], Ming-Jie Wang[1,†], Yu Zhou[1], Cai-Cai Zhang[1,2], Chen Sun[1], Lei Zhu[3], Kun Liang[3], Bo Yu[3], and Yi-Chun Zhu[1,*]

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Aims: The aims of the present study are to determine whether Hydrogen sulfide (H_2S) is involved in the expression of endothelial nitric oxide synthase (eNOS) and nitric oxide (NO) production both *in vivo* and *in vitro*, and to identify the role of microRNA-455-3p (miR-455-3p) during those processes.

Methods and Results:

In cultured Human umbilical vein endothelial cells (HUVECs), the expression of miR-455-3p, eNOS protein and the NO production was detected after administration with 50 μM NaHS. The results indicated that H_2S could augment the expression of miR-455-3p and eNOS protein, leading to the increase of NO level. We also found that overexpression of miR-455-3p in HUVECs increased the protein levels of eNOS and promoted cell migration, whereas inhibition of miR-455-3p decreased them. Moreover, H_2S and miR-455-3p could no longer increase the protein level of eNOS in the presence of proteasome inhibitor, MG-132. *In vivo*, miR-455-3p and eNOS expression were considerably increased in C57BL/6 mouse aorta, muscle and heart after administration with 50 μmol/kg/day NaHS for 7 days. Human atherosclerosis plaque and artery were collected from patients to further confirm the relationship among H_2S, miR-455-3p and eNOS. We identified that H_2S levels and miR-455-3p expression increased in human atherosclerosis plaque while H_2S plasma levels decreased in atherosclerosis patients.

Conclusions: Our data suggest that the expression of miR-455-3p is upregulated after H_2S administration. The stability of eNOS protein and the NO production is found to be regulated by H_2S through miR-455-3p. In addition, miR-455-3p may contributes to angiogenesis process by regulating endothelial cell migration.

O-2-10

The effect and mechanism of XST capsule inhibiting THP-HUVECs adhesion under different flow conditions

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Objective: This study was designed to investigate the effect and the possible mechanism of flow shear stress combined with XST capsule on the THP-HUVECs adhesion.

Methods: The biomechanopharmacology method was used to simulate the flow state *in vivo*. Human umbilical vein endothelial cells (HUVEC) were pretreated with XST capsule (0.3 $mg \cdot mL^{-1}$) or aspirin (ASA, 1 mM) under different flow shear stress (1,9 $dyn \cdot cm^{-2}$) for 12h.TNF-α (20 $ng \cdot mL^{-1}$) was used to model THP-HUVECs adhesion under controlled shear stress of 0.5 $dyn \cdot cm^{-2}$ (2 h) by Bioflux1000 assays. Effects of XST capsule were dynamically monitored by microscopic time-lapse photography. The effects of flow shear stress and XST capsule on the expression of inflammatory proteins in HUVECs were analyzed by western blot and immunofluorescence.

Results: Under different flow shear stress, XST capsule could significantly reduce the number of THP-1 adhered to TNF-α activated HUVECs monolayer. Compared with pathological low flow shear stress (1 $dyn \cdot cm^{-2}$), under physiological flow conditions (9 $dyn \cdot cm^{-2}$), the effect of XST capsule inhibiting THP-HUVECs adhesion was stronger (82.92% vs 77.27%).Western blot and immunofluorescence results showed that XST capsule could affect the expression of inflammatory proteins in HUVECs. Under pathological low flow shear stress, XST capsule could significantly decrease the expression of VCAM-1 in HUVECs; however, under physiological flow conditions, the effect of XST capsule on the expression of VCAM-1 was not obvious, but it could significantly reduce the expression of VE-cadherin and Cx43.

Conclusion: Under different flow conditions, XST capsule played a protective effect on HUVECs. It could inhibit THP-HUVECs adhesion by suppressing the expression of adhesion molecule VCAM-1 and VE-cadherin and gap junction molecule Cx43 in HUVECs. Physiological flow conditions might be more favorable for the XST capsule anti-monocyte adhesion effect.

Poster 1　Heart and Brain

Chair: Shuang-Yan Zhang
The Fourth Affiliated Hospital of Harbin Medical University

13:00-13:10　P-1-1
Effects of exercise training on microvascular degeneration and oxidative stress in aging rat brain
Channipa Chanpakdee
Inter-Department of Physiology, Graduate School, Chulalongkorn University

13:10-13:20　P-1-2
Diagnostic potential of lncRNA H19 in ischemic stroke and modulation of HDAC-dependent microglial activation
Jue Wang
Cerebrovascular Diseases Research Institute, Xuanwu Hospital of Capital Medical University

13:20-13:30　P-1-3
Ruscogenin Attenuates Cerebral Ischemia-Induced Blood-Brain Barrier Dysfunction by Suppressing TXNIP/NLRP3 Inflammasome Activation and the MAPK Pathway
Guo-Sheng Cao
Jiangsu Key Laboratory of Traditional Chinese Medicine Evaluation and Translational Research, Department of Complex Prescription of Traditional Chinese Medicine, China Pharmaceutical University

13:30-13:40　P-1-4
Kindlin-2 complexes with α-actinin-2 and β1 integrin to maintain the integrity of Z-disc in cardiac muscles
Li-Hua Qi
Department of Human Anatomy, Histology and Embryology, Peking University Health Science Center

13:40-13:50　P-1-5
Calcium homeostasis and endoplasmic reticulum stress are involved in Salvianolic acid B-offered protection against cardiac toxicity of arsenic trioxide
Jing-Yi Zhang
Institute of Medicinal Plant Development, Peking Union Medical College and Chinese Academy of Medical Sciences

13:50-14:00　P-1-6

P-1-1

Effects of exercise training on microvascular degeneration and oxidative stress in aging rat brain

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Introduction The number of elderly progressively rises comparing to the past. Several evidence shown that aging induced oxidative stress in the vascular system. Nrf2, a redox-sensitive transcription factor nuclear factor-E2-related factor 2, is a key role in maintained a healthy blood vessel by regulating transcription of antioxidant enzyme genes. Importantly, several studies demonstrated that aging could dysregulation of Nrf2 by downregulated protein and mRNA expression of Nrf2 Moreover, it has been reported that exercise training could improve Nrf2 nuclear levels along with its target antioxidants in the aging heart to protect against age associated oxidative stress. However, there are not any researchers studied the effect of exercise training on Nrf2 in the aging brain. Thus, the present study aims to examine the effect of exercise training on cerebral microvascular alterations and oxidative stress in aging rats.
Methods Male Wistar rats were divided into 3 groups: Sedentary-young (SE-young, 4-6 months), sedentary-aged (SE-age, 20-22 months), and exercise trained-aged (EX-age, 20-22 months). The EX-age swam 1 hour/day 5 days/week for 8 weeks. Brain capillary vascularity (% CV) was assessed by using Image Pro-Plus, confocal fluorescence microscopy. Vascular growth factor (VEGF) and malondialdehyde (MDA) levels in the brain were measured by immunoassay.
Results The study suggested that when compared to the young group, aged rats' physiological characteristics, including resting mean arterial blood pressure, tended to reduced. However, EX-age rats showed significant improvement in cerebral vasculature and reduced resting mean arterial blood pressure. Moreover, this study also showed that exercise could upregulate VEGF level in EX-age. Furthermore, tissue MDA in EX-age rats was reduced that indicated the decrease in oxidative damage. . It can be implied that exercise training could protect age-induced cerebral microvascular degeneration.
Conclusion These findings suggested that exercise training could improve cerebral degeneration associated to oxidative stress in aging rat.

P-1-2

Diagnostic potential of lncRNA H19 in ischemic stroke and modulation of HDAC-dependent microglial activation

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BACKGROUND AND PURPOSE: Long non-coding RNA (lncRNA) H19, selectively expressed during embryogenesis, is induced by hypoxia. Here, we investigated the diagnostic potential of lncRNA H19 in ischemic stroke and its emerging modulatory role in neuroinflammation.

METHODS: We measured the expression of circulating lncRNA H19 in ischemic stroke patients and healthy controls as well as plasma, white blood cells and brain tissue of a C57BL/6 mouse model of transient middle cerebral artery occlusion using real-time PCR. ELISA was applied to determine the TNF-α level. We analyzed correlations between lncRNA H19 and clinical indices. We examined the immunomodulatory effect of lncRNA H19 on an oxygen glucose deprivation model of BV2 cells via western blot and immunofluorescence analyses.

RESULTS: Levels of lncRNA H19 were upregulated in plasma, neutrophils and lymphocytes of stroke patients. ROC analysis revealed strong diagnostic value. In experimental stroke, lncRNA H19 levels in plasma, white blood cells, and brain tissue were upregulated. Moreover, lncRNA H19 levels were positively associated with the NIHSS score and plasma TNF-α level. *In vitro*, OGD induced conversion of BV2 microglial cells to M1 phenotype and lncRNA H19 siRNA promoted M1 to M2 transformation. OGD promoted upregulation of HDAC1 and suppressed acetyl histone levels, while lncRNA H19 siRNA inhibited HDAC1, HDAC3, HDAC4 and augmented acetyl-histone 3 and 4 expression. Immunofluorescence experiments revealed co-localization of acetyl-histone 3 and an M2 marker CD206.

CONCLUSIONS: LncRNA H19 is a potentially effective diagnostic and prognostic biomarker for ischemic stroke and its inhibition promotes M2 microglial transformation, possibly via downregulating HDAC.

P-1-3

Ruscogenin Attenuates Cerebral Ischemia-Induced Blood-Brain Barrier Dysfunction by Suppressing TXNIP/NLRP3 Inflammasome Activation and the MAPK Pathway

Guo-Sheng Cao, Nan Jiang, Yang Hu, Yuanyuan Zhang, Guangyun Wang, Mingzhu Yin, Xiaonan Ma, Kecheng Zhou, Jin Qi, Boyang Yu*, Junping Kou*

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Abstract: Ruscogenin, an important steroid sapogenin derived from *Ophiopogon japonicus*, has been shown to inhibit cerebral ischemic injury. However, its potential molecular action on blood-brain barrier (BBB) dysfunction after stroke remains unclear. This study aimed to investigate the effects of ruscogenin on BBB dysfunction and the underlying mechanisms in middle cerebral artery occlusion/reperfusion (MCAO/R)-injured mice and oxygen–glucose deprivation/reoxygenation (OGD/R)-injured mouse brain microvascular endothelial cells (bEnd.3). The results demonstrated that administration of ruscogenin (10 mg/kg) decreased the brain infarction and edema, improved neurological deficits, increased cerebral brain flow (CBF), ameliorated histopathological damage, reduced evans blue (EB) leakage and upregulated the expression of tight junctions (TJs) in MCAO/R-injured mice. Meanwhile, ruscogenin (0.1–10 μM) treatment increased cell viability and trans-endothelial electrical resistance (TEER) value, decreased sodium fluorescein leakage, and modulated the TJs expression in OGD/R-induced bEnd.3 cells. Moreover, ruscogenin also inhibited the expression of interleukin-1β (IL-1β) and caspase-1, and markedly suppressed the expression of Nucleotide-binding domain (NOD)-like receptor family, pyrin domain containing 3 (NLRP3) and thiredoxin-interactive protein (TXNIP) in vivo and in vitro. Furthermore, ruscogenin decreased reactive oxygen species (ROS) generation and inhibited the mitogen-activated protein kinase (MAPK) pathway in OGD/R-induced bEnd.3 cells. Our findings provide some new insights into its potential application for the prevention and treatment of ischemic stroke.

P-1-4

Kindlin-2 complexes with α-actinin-2 and β1 integrin to maintain the integrity of Z-disc in cardiac muscles

Lihua Qi, Yu Yu, Xiaochun Chi, Danyu Lu, Yao Song, Youyi Zhang and Hongquan Zhang*

Department of Human Anatomy, Histology and Embryology, Peking University Health Science Center, Beijing 100191, China;

Objective：Kindlin-2, as an integrin-interacting protein, was known to be essential for the structure formation of the vertebrate heart. However, the role of Kindlin-2 in cardiac muscle of postnatal mice remains unclear. In this paper, we want to explore the role of Kindlin-2 in postnatal mice.

Methods and Results: Immunofluorescent and immunohistochemical assays were carried out in cardiac muscle of postnatal mice, we found that Kindlin-2 is localized at the Z-disc and colocalized with Z-disc specific protein α-actinin-2. Using co-immunoprecipitation (Co-IP) assay, we found that Kindlin-2 forms a tripartite complex with α-actinin-2 and β1 integrin to enhance the association of β1 integrin and α-actinin-2.To determine whether Kindlin-2 deficiency alters the structure of cardiac muscle, we performed an *in vivo* gene knockdown by injecting small interfering RNA (siRNA) specific to murine Kindlin-2. Interestingly, depletion of Kindlin-2 in mice damaged the structure of Z-disc and induced cardiac myocyte hypertrophy and increased the weight of the heart. Furthermore, decreased expression of Kindlin-2 led to cardiac dysfunction and also markedly impairs systolic function.

Conclusion: Our data indicated that Kindlin-2 is not only a new α-actinin-2-interacting protein, but also is required for cardiac function

P-1-5

Calcium homeostasis and endoplasmic reticulum stress are involved in Salvianolic acid B-offered protection against cardiac toxicity of arsenic trioxide

Jing-Yi Zhang, Gui-Bo Sun*, Xiao-Bo Sun*

Institute of Medicinal Plant Development, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing, 100193, China

Background and Purpose: Arsenic trioxide (ATO) is a potent anticancer agent for acute promyelocytic leukemia. However, the severe cardiotoxicity of ATO limits its widespread clinical use. Our previous studies have demonstrated that 1) ATO can aggravate Ca^{2+} overload and promotes endoplasmic reticulum (ER) stress; and 2) salvianolic acid B exerts cardioprotective effects against ATO toxicity by suppressing oxidative stress in vivo and also enhances its anticancer activity in vitro. The present study was performed to determine whether Sal B's protective effect is related to the maintenance of calcium homeostasis and the inhibition of ER stress.

Methods and Results: For in vivo experiments, male BALB/c mice were injected with ATO (1 mg/kg ATO) or ATO and Sal B (2 mg/kg Sal B 1 h before ATO administration) via the tail vein for 2 weeks. For an in vitro study using ARVMs, we detected the direct effect of Sal B in real time by an IonOptix MyoCam system. Sal B therapeutic treatment showed significant inhibitory effects on ATO-induced abnormal cardiac contraction and the intracellular imbalance of calcium homeostasis in vitro. Sal B therapeutic treatment increased SERCA activity; this increased activity prevents the imbalance of calcium homeostasis and the ER stress in vivo and vitro by regulating the expression of Ca^{2+} handling proteins; decreasing the protein expression of ER stress-responsive proteins GRP78, P-PERK, ATF6, and IRE; and inhibiting the expression of proapoptosis proteins CHOP and Caspase-12.

Conclusion: The study demonstrated the protective effect of Sal B against ATO-induced cardiotoxicity. The effect of Sal B was also correlated with the modulation of SERCA, maintenance of calcium homeostasis, and inhibition of ER stress.

P-1-6

Poster 2 Kidney

Chair: Bao-Xue Yang
Department of Pharmacology, School of Basic Medical Sciences, Peking University

13:00-13:10 P-2-1

Repulsive Guidance Molecule b Inhibits Renal Cyst Development Through the Bone Morphogenetic Protein Signaling Pathway

Jiang-Feng Liu
Department of Pharmacology, School of Basic Medical Sciences, Peking University

13:10-13:20 P-2-2

Low Molecular Weight Fucoidan Protects Renal Tubular Cells From Injury Induced by Albumin Overload

Ying-Li Jia
Department of Pharmacology, School of Basic Medical Sciences, Peking University

13:20-13:30 P-2-3

Generation and Phenotypic Analysis of Mice Lacking all Urea Transporters

Ying-Jie Li
Department of Pharmacology, School of Basic Medical Sciences, Peking University

13:30-13:40 P-2-4

The Knockout of Urea Transporter-B Improves the Hemorheological Properties of Erythrocyte

Xiao-Qiang Geng
Department of Pharmacology, School of Basic Medical Sciences, Peking University Health Science Center

13:40-13:50 P-2-5

Ganoderma Triterpenes Inhibit Renal Cysts Development by Down-regulating Ras/MAPK Signal Pathway

Li-Min Su
Department of Pharmacology, School of Basic Medical Sciences, Peking University Health Science Center

13:50-14:00 P-2-6

Ganoderma Lucidum Polysaccharide Peptide Prevents Renal Ischemia Reperfusion Injury via Reducing Oxidative Stress

Dan-Dan Zhong
Department of Pharmacology, School of Basic Medical Sciences, Peking University

P-2-1

Repulsive Guidance Molecule b Inhibits Renal Cyst Development Through the Bone Morphogenetic Protein Signaling Pathway

Jiang-Feng Liu, Wei-Ling Wang, Hong Zhou, Yin Xia, Bao-Xue Yang

Department of Pharmacology, School of Basic Medical Sciences, Peking University, Beijing, 100191, China

OBJECTIVE: Autosomal dominant polycystic kidney disease (ADPKD) is an inherited disease characterized by massive enlargement of fluid-filled cysts in bilateral kidneys. It commonly causes end-stage renal failure and affects approximately 1/1000~1/400 of individuals. It is known that *Pkd1* and *Pkd2* gene mutations contribute to 85% and 15% of ADPKD respectively. Repulsive guidance molecule b (RGMb), a co-receptor for bone morphogenetic proteins (BMPs) and a ligand for neogenin, is expressed in renal tubular epithelial cells. The present study was designed to explore the effects of RGMb in ADPKD development.

METHODS: Realtime PCR was used to detect RGMb expression in the kidney of wild-type and PKD (*Pkd1*$^{flox/flox}$*;Ksp-Cre*) mice. Then, we analyzed phenotype of RGMb knockout mice to get general knowledge of RGMb. To estimate the role of RGMb in ADPKD, embryonic kidney cyst model, embryonic kidney wholemount DBA staining and histology analysis of postnatal kidneys were used with wild-type and RGMb knockout mice. *In vitro* study, pcDNA3.1 or Flag-RGMb plasmids were transfected into MDCK cells. MDCK cyst model, MDCK tubulogenesis model and applied CCK-8 proliferation assay, transient transfection, immunofluorenscence, Co-IP, Western blot, sirus red staining were used for further mechanism analysis. Based on the acquired results, drug interfering special signaling pathway was used to confirm the effect of RGMb on ADPKD and the downstream mechanism.

RESULTS: We found that expression of RGMb in kidney was less in PKD mice than wild-type mice. With stimulation of 8-bromo-cAMP, RGMb-null embryonic kidneys had greater cyst index, though their ureteric bud branched less than wild-type mice at E13.5. Postnatal RGMb-null kidneys showed interstitial hyperplasia and decreased tubular structures, especially in the boundary area of renal cortex and medulla. RGMb overexpression dramatically inhibited cyst development and promoted tubulogenesis in MDCK cells grown in 3D collagen gels. Biochemical analysis showed increased p-Smad1/5/8 and decreased p-ERK in RGMb-overexpressing MDCK cells, suggesting modulated BMP signaling. Specific inhibition of p-Smad1/5/8 by LDN193189 reversed the suppression of RGMb on MDCK cyst model.

CONCLUSION: Our results reveal RGMb as a novel inhibitor for ADPKD by promoting renal tubule branching and regulating BMP signaling pathway. Elevating RGMb and enhancing p-Smad1/5/8 are promising new strategies to treat ADPKD.

P-2-2

Low Molecular Weight Fucoidan Protects Renal Tubular Cells from Injury Induced by Albumin Overload

Ying-Li Jia Hong Zhou Bao-Xue Yang

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Objective: Chronic kidney disease has become a public health issue. The global prevalence of chronic kidney disease is 8~16%. It has been considered as an important independent risk factor for cardiovascular diseases and greatly increases risk and mortality of cardiovascular diseases. Albuminuria is a common feature of chronic kidney disease and often associates with glomerular dysfunction, tubular lesion and interstitial injury. Albuminuria is not only a marker of renal injury, but also a causative or aggravating factor for progressive renal damage. However, the pathogenic mechanisms of albuminuria contributing to tubular injury and progression of renal disease remain unclear. In addition, it is necessary to develop novel approaches to prevent and treat chronic kidney disease. Low molecular weight fucoidan has multiple biological activities including anti-coagulant, anti-cancer, anti-inflammation, and anti-oxidation. The aim of this study was to determine if low molecular weight fucoidan could protect kidney function and tubule epithelial cells from albumin overload induced injury. **Methods:** Male 129S2/Sv mice were randomly divided into three groups: control group, albumin treated group, albumin and LMWF treated group. For albumin treatment, the mice were injected with normal saline for 1 week before albumin treatment and received injection of low endotoxin albumin for the next three weeks. The dosage of albumin was 2 mg/g body weight on the first day and was increased gradually to 10 mg/g body weight, 5 days later. For LMWF treatment, the mice were intraperitoneally injected twice daily with 100 mg/kg/day LMWF for 1 week and then received administration of LMWF for the next three weeks, when mice also received intraperitoneal injection of albumin twice daily in the same manner as albumin group. For control group, the mice received intraperitoneal injection of normal saline. For *in vitro* experiment, rat renal proximal tubule epithelial (NRK-52E) cells were treated with different concentrations of albumin, LMWF or ERK inhibitor PD98059 for various periods of time as scheduled. **Results:** Daily intraperitoneal injection of 10 mg/g bovine serum albumin for 3 weeks caused renal dysfunction, morphological changes, and overexpression of inflammation and fibrosis associated proteins in 129S2/Sv mice. LMWF (100 mg/kg) protected against kidney injury and renal dysfunction with decreased blood creatinine by 34% and urea nitrogen by 25%, increased creatinine clearance by 48%, and decreased significantly urinary albumin concentration. In vitro proximal tubule epithelial cell (NRK-52E) model showed that LMWF dose-dependently inhibited overexpression of proinflammatory and profibrotic factors, oxidative stress and apoptosis caused by albumin overload. These experimental results indicate that LMWF protects against albumin overload caused renal injury by inhibiting inflammation, fibrosis, oxidative stress and apoptosis, which suggests that LMWF could be a promising candidate drug for preventing CKD. **Conclusion:** Our data indicate that LMWF protected from albumin overload induced renal injury by decreasing proteinuria and inhibiting inflammation, fibrosis and apoptosis. The results suggest that LMWF could be a promising candidate for preventing and treating CKD.

P-2-3

Generation and Phenotypic Analysis of Mice Lacking all Urea Transporters

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Aim: The purposes of our study are to determine whether there were severe physiological disorders without any urea transporters (UTs) in the body.

Methods: The all-UT-knockout mouse model was established by deleting an 87 kb of DNA fragment containing most parts of UT-A and UT-B genes. Western blot analysis and immunofluorescence were used to detect the expression of UTs. Morphology of the kidney and testis was observed by HE staining. The role of individual UT in urine concentrating mechanism was simulated based on the data from wild-type and available UT knockout mouse models.

Results: Western blot analysis and immunofluorescence revealed that UT-A1 and UT-A3 in the renal inner medulla, UT-A2 in the renal outer medulla, and UT-B in the brain, testis, erythrocyte and kidney of the wild-type mice, but not in the all-UT-knockout mice. The all-UT-knockout mice were severely polyuric, excreting almost 3-fold more fluid than litter-matched wild-type mice. The average urine osmolality in all-UT-knockout mice was markedly lower than that in wild-type mice. There was no significant difference in the gross morphology of the kidneys of the two genotypes and histological examination showed dilatation of collecting ducts in the inner medulla in all-UT-knockout mice resulting from polyuria. UT inhibitor PU-48 treatment produced no obvious change in urine output, urinary osmolality and urinary urea concentration in all-UT-knockout mice while significantly increased in wild-type mice, indicating that PU-48 inhibited UTs specifically and did not affect other transporters.

Conclusion: We first generated the mice without any UT in the body. The experimental results revealed that functional deficiency of all UTs caused urea selective urine concentrating defect with little physiological abnormality in extrarenal organs. We demonstrated the contribution of each UT to the urine concentration mechanism by mathematical model. All-UT-knockout mouse also could be used to detect the specificity of novel UT inhibitors.

P-2-4

The Knockout of Urea Transporter-B Improves the Hemorheological Properties of Erythrocyte

Xiao-Qiang Geng[1], Tian-Luo Lei[1], Hong Zhou[1], Wei-Juan Yao[2*], and Bao-Xue Yang[1*]

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BACKGROUND AND OBJECTIVE: Urea transporter-B (UT-B), an integral membrane protein, was originally isolated from erythrocyte and highly expressed in erythrocyte, conferring specific permeability to urea, urea analogues and water. The rapid urea transport across the erythrocyte membrane facilitated by UT-B is conventionally considered to ensure structural stability of erythrocyte. The purpose of this study was to determine the hemorheological properties of UT-B null erythrocyte using a series of biophysical techniques. **METHODS:** UT-B knockout mice were generated by targeted gene disruption. The venous blood samples were collected from wild-type mice and UT-B null mice by orbital puncture and the hemorheological parameters were immediately measured. The UT-B inhibitor, PU-14, was used to treat the erythrocyte of wild-type mice in vitro and the deformability of the treated erythrocyte was analyzed. **RESULTS**: UT-B knockout increased erythrocyte deformation index (DI), small deformation index $(DI)_d$, and orientation index $(DI)_{or}$. Data showed that DI of UT-B null erythrocyte was significantly higher than that in the wild-type at low shear rate (50~100 s^{-1}), suggesting a higher erythrocyte deformability in UT-B null erythrocyte. The data suggest that the erythrocyte membrane lipid fluidity increased greatly after UT-B knockout. The results showed that DI in wild-type erythrocyte treated by UT-B inhibitor PU-14 *in vitro* was significantly higher than that in wild-type ones at low shear rate (50~100s^{-1}). However, DI in UT-B null erythrocyte treated by PU-14 did not change. The results indicated that erythrocyte deformability was concerned with the UT-B deletion and the UT-B inhibition lead to improved deformability. In the osmotic fragility measurement, we unexpectedly found that, at 0.6% NaCl, hemolysis occurred in wild-type erythrocyte but not in UT-B null erythrocyte. The data for the absorbance measurements at 540 nm showed that the hemolysis rates of UT-B null erythrocyte were significantly lower than wild-type erythrocyte at 0.6%, 0.5%, and 0.45% NaCl. The electrophoretic mobility of UT-B null erythrocytes significantly increased as compared with wide-type ones. The whole blood viscosity in UT-B null mice showed reduction trend as compared to wild-type mice at shear rates from 50 to 200 s^{-1}, which may resulted from the better deformability and higher electrophoresis rate in UT-B null mice. **CONCLUSION:** In this study, we found that UT-B knockout and functional inhibition could improve the erythrocyte deformability, membrane rigidity and increase the surface charge density. All data indicate that UT-B functional inhibition may reverse the defected hemorheological properties and UT-B could be a potential therapeutic target to reverse the deteriorated hemorheological properties in hereditary erythrocyte diseases.

P-2-5

Ganoderma Triterpenes Inhibit Renal Cysts Development by Down-regulating Ras/MAPK Signal Pathway

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OBJECTIVE: Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common human inherited diseases characterized by massive enlargement of fluid-filled cysts. It will eventually cause end-stage renal failure in most of the patients. There is no currently effective treatment for ADPKD. The purpose of this study is to investigate the effects of Ganoderma Triterpenes (GT) on renal cyst development and the related mechanisms.

METHODS: We used different *in vitro* and *in vivo* models to identify the cyst inhibitory effect of Ganodema Triterpenes.

RESULTS: We found 25μg/ml GT significantly inhibited cyst formation without destroying MDCK cells, it also inhibited cyst enlargement in a dose-dependent manner and this inhibition was reversible. MDCK tubule model proved GT significantly induced formation of tubules in MDCK cysts and MDCK colonies in a dose-dependent manner indicating that GT promoted cell differentiation. In murine embryonic kidney cyst model, GT also significantly inhibited cyst development in a dose-dependent and reversible manner. Western blot analysis proved GT dramatically down-regulated H-ras, B-raf, p-MEK, p-ERK, Egr-1 and c-fos, up-regulated Raf-1, the overall result down-regulated Ras/MAPK signal pathway thereby inhibited cell proliferation. In a *Pkd1/AQP2-Cre* mouse model of ADPKD, we found in wild type mice, 50mg/kg GT did not significantly affect mice body weight, liver weight, kidney weight and kidney morphology. But in PKD mice, GT significantly reduced kidney index, HE staining and WGA immunofluorescent staining showed less and smaller cysts in kidney after GT treatment.

CONCLUSION: Our study proved that Ganoderma Triterpenes inhibited renal cysts development both *in vitro* and *in vivo* by down-regulating Ras/MAPK signal pathway, inhibiting proliferation and promoting differentiation. This study suggests that Ganoderma Tripenes may be a potential drug for treatment of ADPKD.

P-2-6

Ganoderma Lucidum Polysaccharide Peptide Prevents Renal Ischemia Reperfusion Injury via Reducing Oxidative Stress

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Background: Ischemia reperfusion injury (IRI) is a leading cause of acute kidney injury (AKI) in both native and transplanted kidneys. *Ganoderma lucidum* polysaccharide peptide (GLPP) exerts activities of anti-oxidant and scavenging oxygen free radicals which are implicated importance in the pathogenesis of renal ischemia reperfusion injury (RIRI). The objective of the present study was to evaluate whether GLPP could attenuate renal IRI in an animal model and *in vitro* cell models and study the mechanisms in which GLPP protected from IRI.
Methods: An *in vivo* mouse renal IR injury model and *in vitro* hypoxia/reoxygenation model were utilized to explore the protective effect of GLPP. Tunicamycin stimulated NRK-52E cell were used to explore the alleviation of GLPP on ER stress. The mechanisms in which GLPP protected against RIRI were studied using a series of physiological and molecular biological methods. Renal function, oxidative stress, cell apoptosis, mitochondrial function and ER stress were detected for evaluating the protection of GLPP against RIRI.
Results: Our data showed that GLPP pretreatment attenuated renal IR induced renal dysfunction, as demonstrated by decreased BUN and creatinine levels. Proximal tubular damage including tubular brush border loss and dilatation and outer medulla injury including intertubular haemorrhage and congestion were obvious in IR group while theses morphological damages were alleviated in GLPP treated group. Besides, GLPP significantly increased the activity of antioxidases, including superoxide dismutase (SOD), catalase (CAT), glutathione (GSH) and glutathione peroxydase (GSH-Px) in renal homogenates. The level of malondialdehyde (MDA) and the activity of myeloperoxidase (MPO) were significantly decreased in GLPP treated mice. It was found that IR significantly decreased the expression of Mn-SOD while GLPP increased its expression. Also, IR stimulated the expression and translocation of p47phox to the membrane while GLPP inhibited its translocation. *In vitro*, GLPP treatment decreased the production of ROS and modified the imbalance of antioxidase/oxidases caused by H/R, which were in accordance with the results *in vivo*. These data suggested that the beneficial effect of GLPP may be partially attributed to modifying renal oxidative stress and lipid peroxidation thus alleviating renal IR injury. Apoptotic cells were reduced in mice treated with GLPP by 21.75% due to attenuated activation of caspase-3 and decreased phosphorylation of p53 and its pretreatment dramatically reduced H/R induced expression of apoptotic related proteins. In addition, GLPP alleviated H/R induced cell viability loss by 20.12 % and $\Delta\Psi m$ dissipation by 27.3 % *in vitro*, and attenuated H/R and tunicamycin induced mitochondrial and ER stress. Furthermore, we found the activation of JNK in IR group, which was significantly inhibited by GLPP.
Conclusions: The present study firstly demonstrated GLPP ameliorates renal IRI *in vivo* and *in vitro*. The data provide evidence that GLPP may serve as a potential therapeutic agent for acute renal IRI, and mitochondrial and ER stress might be an appealing target for AKI.

Poster 3 Shock

Chair: Zi-Gang Zhao
Institute of Microcirculation, Hebei North University

13:00-13:10 P-3-1

Resveratrol enhances vascular reactivity in mice following lipopolysaccharide challenge through RhoA-ROCK-MLCP pathway

Yu-Ping Zhang
Institute of Microcirculation, Hebei North University

13:10-13:20 P-3-2

Post-hemorrhagic shock mesenteric lymph induces splenic dendritic cells dysfunction

Li-Na Jiang
Institute of Microcirculation, Hebei North University

13:20-13:30 P-3-3

Post-hemorrhagic shock mesenteric lymph enhances permeability of thoracic aorta vascular endothelial cells

Ya-Xiong Guo
Institute of Microcirculation, Hebei North University

13:30-13:40 P-3-4

Estrogen treatment enhances the vascular hypo-reactivity in mice following hemorrhagic shock

Li-Min Zhang
Institute of Microcirculation, Hebei North University

13:40-13:50 P-3-5

Resveratrol improves blood rheological properties in LPS-challenged rats

Niu-Niu Feng
Institute of Microcirculation, Hebei North University

13:50-14:00 P-3-6

ω-3PUFAs alleviates hemorrhagic shock-induced acute lung injury through inhibiting autophagy in rats

Chen Zhao
Institute of Microcirculation, Hebei North University

P-3-1

Resveratrol enhances vascular reactivity in mice following lipopolysaccharide challenge through RhoA-ROCK-MLCP pathway

Xu-Qing Wang, Yu-Ping Zhang, Li-Min Zhang, Ming-Zhu Zhang, Zi-Gang Zhao*, Chun-Yu Niu*

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OBJECTIVE—Sepsis-induced vascular hyporeactivity is associated with microcirculation disturbance and multiple organ injuries. This study assessed the contributions of resveratrol (Res) treatment to lipopolysaccharide (LPS) challenge mediated vascular hyporeactivity.

METHODS—The effects of Res treatment (30 mg/kg, i.m) at 1 h following LPS stimulation (5 mg/kg, i.v) on the survival time, mean arterial pressure (MAP), maximal difference of MAP (ΔMAP) to norepinephrine (NE, 4.2 μg/kg) in mice were observed. The reactivity to gradient NE of mesenteric arterioles and the relationship with RhoA-ROCK-MLCP pathway were investigated using the wire myograph system ex vivo.

RESULTS—Res treatment prolonged the survival time of mice subjected to LPS challenge, but did not prevent the LPS-induced hypotension and increase in ΔMAP. Res treatment and RhoA agonist U-46619 incubation prevented the LPS-induced vascular hyporeactivity of arterioles ex vivo, which were abolished by ROCK inhibitor Y-27632. The decreasing role of LPS on vascular reactivity was not affected by the MLCP inhibitor OA incubation, but was further down-regulated by the co-incubation of OA and Y-27632. In addition, the inhibiting effect of Y-27632 on Res treatment was suppressed by the U-46619 incubation. Moreover, RhoA inhibitor C3 transferase did not significantly inhibit the enhancing role of Res treatment, which was further increased by U-46619 plus C3 transferase co-incubation.

CONCLUSION—These findings suggested that post-treatment with Res significantly ameliorated LPS-induced vascular hyporeactivity, which was related to the RhoA-ROCK-MLCP pathway.

P-3-2

Post-hemorrhagic shock mesenteric lymph induces splenic dendritic cells dysfunction

Hua Liu, Jian-Feng Li, Li-Min Zhang, Huai-Huai Wang, Gui-Qing Liu, Xu-Qing Wang, Zi-Gang Zhao*, Chun-Yu Niu

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Abstract

Previous studies demonstrated that immune cell dysfunction contributed to the development of immunosuppression, which is associated with organ injury and mortality induced by hemorrhagic shock. Dendritic cells (DCs) are the key antigenpresenting cells for the initiation of T-cell dependent immune response, and previous investigations have shown that hemorrhagic shock suppresses splenic DCs maturation and antigen presentation capacity. Meanwhile, our studies indicated the post-hemorrhagic shock mesenteric lymph (PHSML) return promotes the development of hemorrhagic shock-induced systemic inflammatory response syndrome and organ injury. However, it remains unclear whether PHSML modulates splenic DCs functions. Therefore, the aim of this study was to investigate the role of PHSML on splenic DCs ability to produce inflammatory cytokines in mice. Firstly, we established a hemorrhagic shock model (40±2 mmHg for 60 min), followed by fluid resuscitation with the shed blood and equal Ringer' solution, and drained the PHSML after resuscitation in the shock+drainage group. At 3 h after resuscitation, we harvested the splenic tissue, and isolated splenic DCs using anti-CD11c immunomagnetic beads. After cultivation with DMEM for 24 h, we detected the TNFα, IL-10, and IL-12 levels in the culture supernatants of CD11c-positive cells obtained form mice of the sham, shock, and shock+drainage groups, respectively. However, we have not found the obvious differences in these indices among there groups. After incubation with LPS (10 μg/mL, 10 μL) for 24 h, the TNFα and IL-12 in the sham group, the TNFα and IL-10 in the shock group, and the TNFα, IL-10, and IL-12 in the shock+drainage group were obviously increased compared to the same group without incubation with LPS, respectively. Meanwhile, after incubation with LPS, the TNFα and IL-12 in the shock group were significantly decreased, and IL-10 was increased than that of the sham group, which was reversed in shock+drainage group. Secondly, we drained the PHSML during hypotension (PHSML-H) and PHSML after resuscitation from 0 to 3 h (PHSML-R) from mice with hemorrhagic shock, respectively. Meanwhile, we drained normal mesenteric lymph (NML) from normal mice, as a control. Then, we isolated splenic DCs from normal mice. Subsequently, the normal DCs were cultured with PHSML-H, PHSML-R and NML at a concentration of 4% (V/V) *in vitro* for 3, 6, 12 and 24 h, respectively, along with DMEM as a negative control, LPS as a positive control. The results showed the contents of TNF-α and IL-10 in supernatant increased at several time points after treatment with PHSML-H or PHSML-R, the content of IL-12 has no significant change, but the contents of TNF-α and IL-10 decreased significantly compared with that of LPS control. Lastly, after incubation with mesenteric lymph or control in different time, the DCs were incubated with LPS for 24 h *in vitro*, again. The results showed that the ability of TNF-α, IL-10 and IL-12 production increased after treatment by PHSML-H or PHSML-R at some extent, but still decreased compared with LPS control, especially treated by PHSML-R. In summary, the current investigation demonstrated that PHSML leads to the dysfunction of cytokines secretion of spleen DCs, which is one of major contributors to immune suppression during the episode of hemorrhagic shock. However, the role of DCs on PHSML-induced immunosuppression should be further research. This work was supported by the Key Research Program of Education Department in Hebei Province (ZH2012004).

P-3-3

Post-hemorrhagic shock mesenteric lymph enhances permeability of thoracic aorta vascular endothelial cells

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Abstract

Vascular hyperpermeability is an important reason of refractory hypotension following severe hemorrhagic shock. Post-hemorrhagic shock mesenteric lymph (PHSML) return plays an important role during hemorrhagic shock. Therefore, we investigated the role of PHSML on permeability of thoracic aorta vascular endothelial cells (TAVECs) *in vitro*. Firstly, a hemorrhagic shock model (40±2 mmHg for 90 min, followed by fluid resuscitation) in rats was established. After resuscitation, the mesenteric lymph duct was cannulated and PHSML was drained up to 6 hours, and divided into PHSML 0-3 h and PHSML 3-6 h. Secondly, the primary culture of TAVECs from normal rats was performed, and the expression of CD31, a marker of endothelial cells, was observed. Subsequently, the TAVECs were treated with different factors, as follows: DMEM (dulbecco modified eagle medium), DMEM+FBS (DMEM and 10% (v/v) fetal bovine serum), LPS (DMEM and 10 μg/ml LPS), 4% PHMSL 0-3 h (DMEM and 4% (V/V) PHMSL 0-3 h), 10% PHMSL 0-3 h (DMEM and 10% (V/V) PHMSL 0-3 h), 4% PHMSL 3-6 h (DMEM and 4% (V/V) PHMSL 3-6 h), and 10% PHMSL 3-6 h (DMEM and 10% (V/V) PHMSL 3~6 h) groups. After 6 h of treatment, these indices were observed, including cellular morphology with scanning electron microscope, cellular viability with MTT method, cellular trans-endothelial electrical resistance (TEER) and permeability to FITC-Albumin with costar transwell system, the cellular expressions of F-actin, a cytoskeletal protein, with fluorescent cytochemistry staining. The results showed that the current study successfully established the primary culture of TAVECs, which has the positive expression of CD 31. In addition, the present results showed that there were no obvious differences in morphology, viability, TEER, permeability to FITC-Albumin, and F-actin expression between the DMEM and FBS+DMEM groups. The 4% and 10% PHMSL of 0~3 h, 4% and 10% PHMSL of 3~6 h, and LPS all induced the damage of TAVECs, decreased the viability, TEER, and F-actin expression of TAVECs, and increased the permeability of TAVECs. In summary, these results indicated that the PHSML in vitro could increase the cellular permeability of TAVECs, and its mechanism was related to decreasing the expressions of F-actin. This work was supported by the Program of Innovative Talents in Hebei Province (BR2-105).

P-3-4

Estrogen treatment enhances the vascular hypo-reactivity in mice following hemorrhagic shock

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The vascular hypo-reactivity plays an important role in hemorrhagic shock leading to organ injury, which is related to RhoA-Rho kinase-MLCP pathway. In the present study, we observed the effects of 17β-estradiol (E2) treatment on vascular reactivity *in vitro* following hemorrhagic shock. C57BL/6 healthy female mice randomly received the ovariectomized (OVX) or ovary intact sham operation (OVI). After a week, the 12 mice in the OVX group received subcutaneous injection of E2 (140 μg/kg) once a day for a week, along with same amount of vehicle injection in the other mice. After E2 administration for a week, the mice were subjected to hemorrhagic shock (40±2 mmHg for 1 h, followed by resuscitation) or sham operation, respectively. The results showed that OVX decreased the level of E2 in the plasma, which was elevated by E2 treatment significantly. Meanwhile, hemorrhagic shock reduced the microvascular reactivity to NE significantly; OVX reduced the microvascular reactivity to NE following hemorrhagic shock, which was reversed by E2 treatment. In addition, U-46619 (RhoA agonist) incubation increased the microvascular reactivity of the sham mice, C3 transferase (RhoA inhibitor) or Y-27632 (ROCK inhibitor) incubation inhibited the microvascular reactivity, respectively. U-46619 increased microvascular reactivity in the Shock+OVI+vehicle and Shock+OVX+vehicle groups significantly, which was abolished by Y-27632 incubation. OA (MLCP inhibitor) has no effect on the microvascular reactivity in the Shock+OVI+vehicle and Shock+OVX+Vehicle groups, however, the combination of OA and Y-27632 reduced significantly reactivity. In the Shock+OVX+E2 group, Y-27632 inhibited microvascular reactivity, which was abolished by the U-46619 incubation; C3 transferase has no obvious effect, but significantly improved microvascular reactivity after joint application with U-46619. Lastly, hemorrhagic shock remarkably decreased the blood flow volume of intestinal loop, which was observably enhanced by the E2 treatment. These results demonstrated that estrogen therapy significantly improved the microvascular reactivity in mice following hemorrhagic shock, and its mechanism might be related to RhoA-ROCK-MLCP signaling pathway.

P-3-5

Resveratrol improves blood rheological properties in LPS-challenged rats

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BACKGROUND: Abnormal rheological properties induce negative effects during sepsis. This study aims to observe the effects of resveratrol (Res) on blood rheological properties in rats following a lipopolysaccharide (LPS) challenge.

MATERIALS AND METHODS: The rats were randomly divided into sham, sham+Res, LPS, and LPS+Res groups (n=6). The LPS and LPS+Res groups underwent intraperitoneal injection of LPS (8 mg/kg). The LPS+Res and sham+Res groups received Res treatment (30 mg/kg) after 1 h of LPS or control injections. After 6 h of LPS injection, the mean arterial pressure (MAP), regional blood flow, erythrocyte parameters, and blood viscosity were observed and analyzed with ANOVA and SNK test.

RESULTS: The LPS administration reduced the MAP, whole blood viscosity at low and medium shear rates, and the blood flow in the spleen and kidney, but it did not show obvious effects on the erythrocyte parameters and plasma viscosity. Res treatment decreased the red blood cell distribution width-CV; whole blood viscosity at high, medium, and low shear rates; whole blood relative viscosity at high shear rate; and the blood flow in the stomach. The Res treatment also increased the mean corpuscular hemoglobin of the erythrocytes but did not show a significant effect on the MAP.

CONCLUSION: The Res treatment partly reduced the whole blood viscosity and regional blood flow following the LPS challenge. This result is favorable for expanding the quasi-sympathetic effects of LPS at early stages.

P-3-6

ω-3PUFAs alleviates hemorrhagic shock-induced acute lung injury through inhibiting autophagy in rats

Xue-Rong Lin, Li-Min Zhang, Li-Na Jiang, Ya-Xiong Guo, Jing Zhang, Yu-Ping Zhang, Fu-Long Li, Zi-Gang Zhao*, Chun-Yu Niu*

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Abstract

Hemorrhagic shock-induced acute lung injury (ALI) is one of the most serious complications and an important part of multiple organ failure. ω-3 polyunsaturated fatty acids (ω-3PUFAs) is a parenteral nutrition drug with a wide range of biological role in clinical treatment. In this study, we investigated the role of autophagy in ω-3PUFAs alleviating hemorrhagic shock-induced ALI. We established the hemorrhagic shock model by bleeding and fluid resuscitation with ω-3PUFAs (0.2 g/kg), rapamycin (RAPA, autophagy activator/mammalian target of rapamycin (mTOR) inhibitor, 10 mg/kg), 3-methyladenine (3-MA, autophagy inhibitor, 30 mg/kg), or not. We observed the effect of ω-3PuFAs on the survival time, then, we collected the pulmonary tissue for the detections of wet/dry ratio (W/D), morphology, the expressions of light chain 3II (LC3-II), phosphatidylinositol 3-kinase (PI3K), serine/threonine kinase (AKt), and mTOR. The present results showed that ω-3PuFAs treatment significantly prolonged survival time of rats following hemorrhagic shock, decreased the pulmonary W/D, histological scores, LC3-II protein levels and mTOR expression; 3-MA treatment significantly decreased the pulmonary W/D, histological scores, LC3-II and PI3K expressions; RAPA treatment has no obvious effects on these indices, but significantly increased the pulmonary W/D, histological scores, LC3-II and mTOR expressions of shocked rats treated with ω-3PUFAs. In summary, the present results revealed that ω-3PUFAs treatment alleviated hemorrhagic shock-induced autophagy in lung tissue via the signaling pathway of PI3K-AKt-mTOR. Therefore, ω-3PUFAs have therapeutic potential for ALI induced by hemorrhagic shock.

Poster 4 Traditional Medicine

Chair: Fei Ye
Institute of Materia Medica, Chinese Academy of Medical Sciences & Peking Union Medical College

13:00-13:10 P-4-1
Establishment and Evaluation of Qi Deficiency Syndrome Model in Mice
Jun-Guo Ren
Institute of Basic Medical Sciences of Xiyuan Hospital, Key Laboratory of Pharmacology of Chinese Materia in Beijing

13:10-13:20 P-4-2
The establishment and evaluation of a rat model with syndrome of dampness retention due to spleen deficiency
Cui Ning
College of Basic Medical Sciences, Shandong University of Traditional Chinese Medicine

13:20-13:30 P-4-3
The anti-tumor and anti-angiogenesis effects of crude extract of Acanthus ebracteatus Vahl on HPV16-induced cervical cancer in nude mice xenograft model
Liao T
Center of Excellence for Microcirculation, Department of Physiology, Faculty of Medicine, Chulalongkorn University

13:30-13:40 P-4-4
Catalpol Protects the desruction of BMECs tight junctions induced by LPS based on Rho / ROCK pathway
Li Zou
College of Pharmaceutical Sciences & Chinese Medicine, Southwest University

13:40-13:50 P-4-5
Study on the effect and mechanism of JTD on Diabetic Nephropathy
Jin-Ni Hong
Integrated laboratory of Traditional Chinese Medicine and Western Medicine, Peking University First Hospital

13:50-14:00 P-4-6
Glucocorticoid-like effect found in geniposide but accompanied with a selective function
Qi Zhang
Preclinical School of Medicine, Beijing University of Chinese Medicine

P-4-1

Establishment and Evaluation of Qi Deficiency Syndrome Model in Mice

Jia-Kuan Gan, Jun-Guo Ren, Jian-Xun Liu

Institute of Basic Medical Sciences of Xiyuan Hospital, Key Laboratory of Pharmacology of Chinese Materia in Beijing, Beijing 100091, China

Objective: To study the establishment and evaluation of Qi deficiency Syndrome model in mice by comparing the 3 methods of sleep deprivation, exhausted swimming and combination of sleep deprivation and exhaustive swimming.

Methods: The mice were randomly divided into normal control group, sleep deprivation group, exhausted swimming group, sleep deprivation and exhaustive swimming group (combined group), 12 rats in each group. Multi platform water environment was used with 10 hours a day in sleep deprivation group; loading swimming with 10% of the body weight was used with once a day in exhaustive swimming group; combination of two methods was used in combined group for 28 days. At the end of the experiment, the behavior and body weight were observed, Grab force meter used to measure holding force, Small animal noninvasive monitor used to detect the pulse signal (heart rate, respiratory rate, respiratory rate, pulse amplitude), digital camera used to photo tongue image, T cell subsets (CD3 +, CD4 +, CD8 +) and B cell (CD19 +) in spleen was detected by flow cytometry

Results: Compared with the normal control group, the activity was reduced and showing fatigue characteristics, the body weight and holding force decreased significantly ($P < 0.05$-0.01) in three groups; the mice tongue were seen in different degrees of white, with a significant difference only in the combined group($P < 0.05$); heart rate, respiratory rate, pulse rate and respiratory rate were significantly decreased ($P < 0.05$-0.01) in sleep deprivation group and the combined group; the CD3 +, CD4 +, CD8 + T cell subsets increased significantly ($P < 0.01$) in three groups , CD19 + B cells decreased significantly ($P < 0.01$) in sleep deprivation group.

Conclusion: The three methods can successfully prepare Qi deficiency Syndrome model in mice.

Key words : Qi deficiency model; mice; sleep deprivation; exhausted swimming

P-4-2

The establishment and evaluation of a rat model with syndrome of dampness retention due to spleen deficiency

Cui Ning [1],Zhao Wen-xiao[2],Han Bing-bing[1],Ji Xu-ming[1],Gao Jie[1],Han Xu[1],Wang Shi-jun[1△]

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2. *College of Nursing, Shandong University of Traditional Chinese Medicine, Jinan* 250355,*China*

Abstract

Objective: To explore establishment and evaluation of the rat model with syndrome of dampness retention due to spleen deficiency.

Methods: Rat models with syndrome of dampness retention due to spleen deficiency were induced by complex factors of high fat and low protein diet, loading swimming for six weeks. And then，ordinary situation, autonomy activities, gastric emptying rate, water loading index, etc., were tested. All the data were collected and evaluated with partial least square analysis (PLS).

Results: After 6 weeks, rats in model group had specific syndromes of dampness retention due to spleen deficiency. Compared to rats in the control group, rats in model group had significant increase in general status score (t = −6.708, P = 0.000), decrease in body weight (t = 4.932, P = 0.000), and reduced locomotor activity (t = 3.737, P = 0.002). Compared to the control group, rats in model group had lower gastric emptying (t = 2.864, P = 0.022), propulsion rate of small intestine (t = 2.349, P= 0.034), D-xylose excretory rate in urine (t = 2.456, P = 0.028), and serum gastrin (t = 8.372, P = 0.000). Moreover, rats in model group had lower level of serum total protein (t = 2.260, P = 0.040), albumin (t = 2.808, P = 0.014), and HDL-C (t = 2.463, P = 0.027), and higher level of total cholesterol (t = −4.692, P = 0.000) and LDL-C (t = −6.141, P = 0.000). Rats in model group had also significantly higher water load index (t = −2.398，P = 0.040) and less urine volume (t = 2.778，P = 0.026), indicating prolonged retention of water and dysfunction of water transportation and transformation in rats of model group. The comprehensive evaluation function of syndrome of dampness retention due to spleen deficiency based on PLS showed that the fitting effect of the model was perfect with 91.6% of the prediction rate and 93.4% of interpretation rate. And the variables that had great importance in the prediction of model of dampness retention due to spleen deficiency included X_4 (gas), X_{14} (LDL-C), X_8 (water load index), X_1 (general status score), X_{12} (total cholesterol), X_3 (body weight) and X_2 (locomotor activity).

Conclusion: Rat models with syndrome of dampness retention due to spleen deficiency were successfully induced by complex factors of high fat and low protein diet, loading swimming for six weeks. Rat models with syndrome of dampness retention due to spleen deficiency were successfully evaluated by PLS, which was a suitable method capable of being used in evaluation of traditional Chinese medicine syndrome models.

Key words: syndrome of dampness retention due to spleen deficiency; PLS; evaluation

P-4-3

The anti-tumor and anti-angiogenesis effects of crude extract of Acanthus ebracteatus Vahl on HPV16-induced cervical cancer in nude mice xenograft model

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Purpose: The aim of this study was to examine the anti-tumor and anti-angiogenesis effect of different dosages of the crude extract of Acanthus ebracteatus Vahl (AE) on cervical cancer by using a tumor model in which nude mice being implanted with cervical cancer cells containing human papillomavirus 16 DNA (HPV-16 DNA).
Materials and Methods: The anti-tumor and anti-angiogenesis effect of crude extract of AE are investigated in HPV-16-induced nude mice xenograft model of cervical carcinoma. To conduct the studies in vivo, female BALB/c nude mice (aged 6-7 weeks, weight 20-22g) are used. A cervical cancer-derived CaSki cell line integrated with HPV-16 DNA was injected subcutaneously (1×10^6 cells/200μl) in the middle dorsum of each animal (HPV group). After the cervical cancer xenograft model had been established successfully, mice were given AE crude extract 30, 300, 3,000 mg/kg/day for 7 days and 14 days (HPV-AE groups). Tumor volumes are measured everyday by caliper. And tumor microvasculature and capillary vascularity will be determined using laser scanning confocal microscopy. SPSS and Image-Pro are used to do the analysis in the study.
Results: The time-response and dose-response curves of AE and the anti-tumor and anti-angiogenesis effect of AE on cervical cancer will be determined. A microvascular network is observed around the tumor area in the HPV groups. The minimum effective dose and ED50 were read from the dose-effective curve.
Conclusion: We found that AE crude extract could reduce tumor volume and inhibit tumor angiogenesis in an effective dosage range in CaSki-cell transplanted model in mice. This effect is also related to the treatment period. Minimum effective dose and ED50 were found out. Dose-response and time-response relationship have been found out. This will provide more information for the further preclinical research of Acanthus ebracteatus Vahl..
Key Words: Acanthus ebracteatus, Cervical Cancer, HPV-16, CaSki.

P-4-4

Catalpol Protects the desruction of BMECs tight junctions induced by LPS based on Rho / ROCK pathway

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Objective To observe the protect effect of Catalpol on the destruction of rat primary brain microvascular endothelial cells (BMECs) tight junctions induced by LPS.

Methods Construct the damaging BMECs model with LPS, and then evaluate the Catalpol protects on survival by MTT and LDH. In addition, the permeability improved by Catalpol was investigated by transendothelial electrical resistance and sodium fluorescein permeability. Immunofluorescence was applied to observe the influence of Catalpol on the expression of tight junctions protein Claudin-5, ZO-1 and Factin.

Results LPS-induced BMECs injury model, and Catalpol could enhance the survival rate of BMECs in a dose-dependent manner of (0.3-30) μM. What's more, the BMECs TEER value and the permeability of sodium fluorescein were improved by Catalpol. Mean while, Immunofluorescence showed that the model group was significantly reduced on lattice-like structure of Claudin-5, ZO-1 expression, besides with polymerizated and shrinked Factin cytoskeleton, and pyknosis of nucleolus. Catalpol improved the expression of protein Claudin-5, ZO-1 for BMECs in a dose-dependent manner of (0.3-30) μM. And the ROCK inhibitor fasudil was observed positive protection in the above experiments.

Conclusion Catalpol protects the destruction of tight junctions induced by LPS in BMECs, and its protection mechanisms are may closely related to Rho / ROCK pathway.

P-4-5

Study on the effect and mechanism of JTD on Diabetic Nephropathy

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Objective: To explore the effect and mechanism of Jiangtang Decoction (JTD) on diabetic nephropathy (DN) in type 2 diabetic model KK-Ay mice. Methods: 50 KK-Ay mice were divided into 5 groups randomly: the model group, metformin group, low-dose of JTD ethanol extract group, medium-dose of JTD ethanol extract group and high-dose of JTD ethanol extract group, with 10 C57BL/6J as the normal group. All groups are orally administrated with equal distilled water, metformin hydrochloride (25 0mg ŀkg^{-1}), low concentration of JTD ethanol extract (2g ŀkg^{-1}), medium concentration of JTD ethanol extract (4g ŀkg^{-1}), high concentration of JTD ethanol extract (8g ŀkg^{-1}), equal distilled water respectively. The oral administration were given every day and lasted for 12 weeks. During the experiments, cholesterol (TC), triglyceride (TG), fasting blood glucose (FBG), postprandial blood sugar (PPBS), oral glucose tolerance test (OGTT), insulin tolerance test (ITT), serum creatinine (CREA), blood urea nitrogen (BUN) and alanine aminotransferase (ALT) in blood were detected. Mice were put into metabolic cages for 24 hours once every 4 weeks, with food-intake, urine volume calculated and urine collected. After that, creatinine, nitrogen and protein in urine were detected. After 12 weeks' oral administration, mice were executed, and electron microscope and immunohistochemistry were used to check the effect of JTD on kidney. Results: JTD hardly did harm to the liver and kidney. Ethanol extract of JTD had positive effects on FBG, PPBS, OGTT, ITT and kidney, and the mechanism may be related to the inflammation, to be more specific, the regulation of IL-6, TNF-α, NF-κB, AGEs, RAGE and so on.

Conclusion: The mechanism of JTD on Diabetic Nephropathy may be related to the inflammation and microcirculation.

Key words: JTD;diabetic nephropathy; inflammation; microcirculation.

P-4-6

Glucocorticoid-like effect found in geniposide but accompanied with a selective function

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Objective: The aim of this study is utilizing affinity chromatography technology and bioinformatics methods to screen the specific binding protein of geniposide and laying the foundation for investigating the interactions between geniposide and target proteins.
Methods: First, geniposide was used as a small molecular probe to search potential target proteins from drug target database. Second, geniposide was coupled with epoxy activated Sepharose CL-6B to screen the binding proteins, and then HPLC was put into use to verify the efficiency of immobilization. Third, the drug uptake and pGMGRE-Luc transfection were performed to detect the interaction between geniposide and target proteins.
Results: Virtual screening from drug-target database predicted that glucocorticoid receptor may one of the binding protein of geniposide. SDS-PAGE indicated that bands were comprised by glucocorticoid receptor (GR), heat shock protein 70, heat shock protein 90, etc. Flow cytometry showed that the mean fluorescence intense of dexamethasone significantly decreased after addition of the geniposide and in dose dependent manner. But, the Luc activity did no significant change after treatment with the increase of geniposide concentration.
Conclusions: Molecular docking predicted that GR may be the binding proteins of geniposide. We successfully established the geniposide-epoxy activated affinity resin and screened out some binding proteins, including GR. Drug uptake assay manifested that geniposide could competitively bind to GR with dexamethasone, however, there was no significant effect on transcriptional activation of GR.
Acknowledgements: This study was supported by grant from the National Natural Science Foundation (81473546).

Poster 5 Other

Chair: Lu Tie

State Key Laboratory of Natural & Biomimetic Drugs, Department of Pharmacology, School of Basic Medical Sciences, and Institute of System Biomedicine, Peking University

13:00-13:10 P-5-1

Silibinin capsules improve high fat diet-induced nonalcoholic fatty liver disease through hepatic de novo lipogenesis and fatty acid oxidation pathways in hamsters

Chun-Xue Cui

Tasly Microcirculation Research Center, Peking University Health Science Center

13:10-13:20 P-5-2

The association of diabetic kidney disease and diabetic cardiovascular autonomic neuropathy of type 2 diabetic patients

Fang-Fang Zeng

Department of endocrinology of North Huashan Hospital

13:20-13:30 P-5-3

Nordihydroguaiaretic acid impairs prostate cancer cell migration and tumor metastasis by suppressing neuropilin 1

Xin Li

Department of Pharmacology, School of Basic Medical Sciences, Peking University

13:30-13:40 P-5-4

An *in vivo* study of the biodistribution of gold nanoparticles after intervaginal spaces injection in the tarsal tunnel

Xiao-Li Shi

CAS Center of Excellence in Nanoscience, National Center for Nanoscience and Technology

13:40-13:50 P-5-5

H&K Quantum Chip, a brand new Microcirculation enhancement device
Open a new Era for Microcirculation Biotherapy

Tien-Fung Wu

Chinese International MicroCirculation Association Taipei

13:50-14:00

P-5-1

Silibinin capsules improve high fat diet-induced nonalcoholic fatty liver disease through hepatic de novo lipogenesis and fatty acid oxidation pathways in hamsters

Chun-Xue Cui [1,2,4,5], Jing-Na Deng [1,4,5], Ying-Hong Wang [3], Li Yan [1,4,5], Yu-Ying Liu [1,4,5], Jing-Yu Fan [1,4,5], Hong-Na Mu [1,2,4,5], Hao-Yu Sun [1,2,4,5], Jing-Yan Han [1,2,4,5*]

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Objective: The present study was conducted to investigate whether silibinin capsules, the silybin-phospholipid complex, could ameliorate non-alcoholic fatty liver disease in high fat diet raised hamsters and possible mechanisms of its action.
Methods: Male hamsters were randomly allocated to two groups: the normal diet group and the high fat diet (HFD) group, which fed with HFD for 10 weeks. After 2 weeks, silibinin capsules were given by administration for 8 weeks at 50 mg/kg/day or 100 mg/kg/day. We used enzyme-linked immunosorbent assay and enzymatic method to measure plasma biochemical parameters. Proton nuclear magnetic resonance spectroscopy was conducted to detect low molecular lipid and amino acid metabolic of hamsters. Hematoxylin and Eosin staining and immunofluorescence staining were used for hepatic histological analysis. Porteins related to lipogenesis, fatty acid oxidation, fatty acid uptake and triglyceride lipolysis in liver tissues were determined by western blotting.
Results: Silibinin capsules decreased plasma ALT, AST and insulin, inhibited low molecular lipid and amino acid metabolic disturbance in HFD hamsters. It markedly decreased hepatic TG accumulation caused by HFD. Silibinin capsules down-regulated peroxisome proliferator-activated receptors γ, acetyl-CoA carboxylase and fatty acid synthase and up-regulation of carnitine palmitoyltransferase-1A. In addition, silibinin capsules decreased the expression of adenosine monophosphate activated protein kinase.
Conclusions: silibinin capsules attenuate histopathological appearance of the liver and decrease intrahepatic TG levels in NAFLD hamsters, which were related to affecting hepatic de novo lipogenesis pathway and hepatic fatty acid oxidation pathway.

P-5-2

The association of diabetic kidney disease and diabetic cardiovascular autonomic neuropathy of type 2 diabetic patients

Fangfang Zeng *, Wei Gong *, Dihe Cheng, Linuo Zhou

Department of endocrinology of North Huashan Hospital, Shanghai

Objective: Diabetic kidney disease (DKD) and diabetic cardiovascular autonomic neuropathy (DCAN) are important components of diabetic microvascular complications and share many common pathogenic mechanisms. In our study, the correlations were analyzed by short-term (5 min) heart rate variability.
Methods: A retrospective analysis of patients with type 2 diabetes, ranging from 36-75 years old, in department of endocrinology of North Huashan Hospital was taken from Oct. 2014 to Oct. 2015. Information of clinical data, physical examination, biochemical blood tests, urine albumin/creatinine (ACR) and was measured and short-term (5 min) heart rate variability was collected, excluding the influential factors of micro-albuminuria and cardiovascular autonomic function. Clinical albuminuria was defined as ACR≥300 mg/g*Cr, and 30-299 mg/g*Cr as micro-albuminuria, so <30mg/g*Cr as negative. There are six indicators of domain analysis of short-term (5 min) heart rate variability, such as TP, LF, LF nu, HF, HF nu and LF / HF. At least two abnormalities of the above six indicators is diagnosed as DCAN. Statistical analysis was performed using SPSS 21.0, and non-normal distribution data was natural logarithm transformed.
Results: A total of 88 cases (male to female ratio of 1: 1) were enrolled in this study. 23 cases (26.1%) were grouped as micro-albuminuria, marked as the ACR elevated group, and 65 cases (73.9%) as ACR normal group (albuminuria negative). There were 14 DCAN cases (60.9%) in the ACR elevated group and 21 DACN cases (32.3%) of the ACR normal group, indicating a correlation between ACR elevation and DACN ($p = 0.016$). Comparing with the ACR normal group, the indices of TP, LF and HF were decreased in the ACR elevated group ($p < 0.05$), and the indices of TP, LF and HF were negatively correlated with ACR ($p < 0.05$).
Discussions: Urinary albumin/creatinine and heart rate variability are early damage markers, suggesting the existence of DKD and DCAN. On the one hand, DKD and DCAN, as chronic complications of diabetes microvascular disease, may have common pathogenesis. On the other hand, DACN may aggravate DKD due to the increased micro-albuminuria filtration by abnormal autonomic regulation of blood pressure and dysregulation of glomerular arterioles. The present study reminds us that the screening of cardiovascular autonomic dysfunction should be taken as the elevation of urine albumin is found in type 2 diabetic patients. Intensive treatment should be performed as DKD and DCAN are diagnosed.
* co-author

P-5-3

Nordihydroguaiaretic acid impairs prostate cancer cell migration and tumor metastasis by suppressing neuropilin 1

Xin Li, Xuejun Li

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Tumor metastasis is a major cause for the deaths of cancer patients. The metastatic cascade is a multistep and complex biological process, dynamically modulated by tumor cells, tumor microenvironment and the interactions between them. For decades, great efforts have been made to understand the mechanisms underlying metastasis and a series of potential therapeutic targets have been identified. However, there are still very few drugs that are developed directly targeting tumor metastasis in clinical therapies.

Natural products have been an important source for drug discovery and development for centuries. Nordihydroguaiaretic acid (NDGA), a phenolic compound extracted from creosote bush Larrea tridentata, is proved to have versatile effects on multiple signaling pathways and potentials in therapeutic applications in a series of diseases. In various cancer models, NDGA has been demonstrated to promote apoptosis and inhibit proliferation by suppressing the activities of lipoxygenase (LOX), insulin-like growth factor receptor (IGF-1R) and human epidermal growth factor receptor 2 (HER2/neu). However, in contrast to the much better understood anti-proliferation activities, the effects of NDGA on cell migration and tumor metastasis were rarely studied.

Neuropilin 1 (NRP1) is a single-pass transmembrane protein playing important roles in development, angiogenesis, immunity and cancer. In many types of cancer NRP1 can be found overexpressed and the abnormal expression pattern usually correlates with tumor aggressiveness, metastasis and poor prognosis. It has been demonstrated that NRP1 regulates multiple cellular processes involved in tumor progression by binding with various cancer-associated growth factors and enhancing activities of the respective receptor tyrosine kinases. In addition to its co-receptor functions mentioned above, recent studies show that NRP1 is able to modulate tumor microenvironment by interacting with integrins and remodeling extracellular matrix (ECM).

Methods: Transwell assay, wound healing assay, LC-MS/MS based proteomic assay, networks construction and analysis, generation of NRP1 knockout cell line using CRISPR/Cas9 system, cell adhesion, intravenous injection model.

Conclusion: In this study, we elevated the inhibitory effect of NDGA on PC3 cell migration using in silico, in vitro and in vivo studies. We demonstrated that NDGA suppresses NRP1 expression and consequently impairs cell motility and cell adhesion to ECM in cancer cells and attenuates tumor metastasis in nude mice model. Our findings reveal a novel mechanism underlying the anti-metastasis function of NDGA and indicate the potential value of NDGA in NRP1 targeting therapy for selected subtypes of cancer.

P-5-4

An *in vivo* study of the biodistribution of gold nanoparticles after intervaginal spaces injection in the tarsal tunnel

Xiao-Li Shi, Dong Han

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Purpose: The biodistribution of gold nanoparticles (AuNPs) is closely related to toxicological effects and of great concern because of the particles' potential application in diverse biomedicine areas. However, with the discovery of other novel anatomic and histological structures for fluid transport, the mechanism underlying the AuNPs' *in vivo* transport and biodistribution requires further in-depth understanding. Herein, we investigated the biodistribution and transport of 10-nm AuNPs in rats after intervaginal space injection in the tarsal tunnel (ISI), where a focal point of tendons, vessels, and nerve fibers may better connect to other remote connective tissues.

Method: To further determine whether the NPs could be transported by loose connective tissues, we chose AuNPs as model substrate to investigate the biodistribution of AuNPs after intervaginal space injection in the ISI. Rats injected a suspension containing 10-nm diameter AuNPs via ISI were compared to rats that had received the suspension via intravascular injection into the femoral vein (IVI, control group). The blood and organs were collected after 5, 15, and 30 min and 1, 4, 12, and 24 h for quantitative Au determination with inductively coupled plasma mass spectrometry (ICP-MS).

Results：IVI and ISI yielded significantly different results: the AuNP content in blood after ISI was much lower than that after IVI, but was similar in lungs, heart, and intestines, and higher in the skin and muscle. This finding was confirmed by the ratio of the AuNP content and the relative organ AuNP distribution proportion.

Conclusions: Our results show the existence of a clearly different transport and biodistribution pathway of AuNPs between the ISI and IVI route at the time points measured herein. The distribution proportion of AuNPs to skin, muscle, the heart, intestines, and lungs at the early time points measured was higher after ISI than after IVI. Therefore, we postulate that the distribution of AuNPs to some of the organs is mediated not via the systemic circulation but via loose connective tissues, which exist in almost every part of the living body and which form a complex network system. Our study provides novel evidence for the existence of an alternative transport mechanism for NPs, contributes to the deeper understanding of the physiological and pathological processes involved therein, and may facilitate the application and development of nanoscale drug delivery to several organism species.

[1] Xiaoli Shi, Dong Han et al. An in vivo study of the biodistribution of gold Nanoparticles after intervaginal spaces injection in the tarsal tunnel. ***Nano research.*** 2016, 9(7), 2097-2109.

P-5-5

H&K Quantum Chip, a brand new Microcirculation enhancement device
Open a new Era for Microcirculation Biotherapy

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**Vein & Vascular Surgery, Shu-Tien Clinic Taipei, Taiwan

Purpose:

H&K Quantum Chip is an unique micro circuit providing continuous specific low Radiofrequency(RF) wave to human body. This RF shift into bioelectronic energy in vivo enhance microcirculation and relieve the relevant hypoxia. To verify this microcirculation changes, a study of the effect of H&K Quantum Chips on myocardial ischemia was conducted.

Method:

The Cardiac Quantum Spectrum (CQSD) (NOVONT Cardio Inc., USA) is a convenient outpatient basis device to diagnose myocardial ischemia. This noninvasive cardiac Quantum Spectrum (CQS) Technology detect myocardial ischemia is published by Ke Li in Mde. Sci. Monit, 2016;22:2235-2242. The clinical testing was conducted by Dr. Fang's group in 2013, March to September LA USA. Total 35 cases were enrolled, age 31-81. Only 27 complete the study. The clinical testing was conducted using (CQSD) (NOVONT Cardio Inc., USA). Resting status was record first. A 12 lead ECG was recorded over a 90 second periods with supine position. The collected signals were processed to derive the cardiac quantum power spectrum, and a biocybernetic analysis was performed (using V5 as the input signal and lead II as the output signal) to obtain the phase shift, impulse response, cross correlation and coherence. 3D localization of ischemic area was undertaken, obvious abnormalities in three or more lead indicating myocardial ischemia or insufficient perfusion in of myocardium. Cardiac risk was determined by combining the CQS analysis with ECG findings and traditional risk factor for heart disease. The CQS evaluative scores were rated a scale of 1 to 10, 1-3 : normal, 4-6 : borderline, 7-10: abnormal.

All testing candidate received 2-8 pieces of H&K quantum chips application over the pericardial area for 15 minutes then CQS procedure followed.

Result :

Myocardial Ischemia was found in all 27 patients. After application of H&K quantum chip, 80% of 27 myocardial ischemia patients show improvement 2-3 degree by CQS score scale.

Conclusion :

The CQS score scale 2-3 improvement in CQS study after H&K quantum chip regiment in myocardial ischemia victims is an important evidence to support the hypothesis H&K quantum chip enhance the microcirculation relive the relevant Hypoxia. This will open a new era of microcirculation biotherapy. The limitation of this study is the case number is low and the specificity for CQS study is also low. The myocardial ischemia with scar tissue might lead to misinterpreted. Further study is warranted

P-5-6