第39回日本微小循環学会総会
開催にあたり

第39回日本微小循環学会総会
会 長　**中村 正彦**　北里大学薬学部臨床薬学研究・教育センター病態解析学

このたび、第39回日本微小循環学会の会長に選任いただき、会員の皆様に心より感謝申しあげます。第39回の本学会は2014年2月7日（金）と8日（土）の2日間、港区白金の北里大学薬学部コンベンションホールで開催させていただくことになりました。4年前の馬嶋正隆先生（北里大学医学部薬理学）の会と同じ会場になります。

微小循環系は、大循環系と違い、一時は黒子的な存在と考えられたこともありましたが、組織代謝、炎症、薬剤の作用点などのフィールドであることが益々明らかとなり、さらに近年注目されております組織再生、腫瘍化と微小循環系、特に血管新生の関連が様々な分野で注目されております。

そこで、今回のメインテーマは“微小循環系と幹細胞”を取り上げました。平成25年度北里大学 AKPS（All Kitasato Project Study）研究との共催のシンポジウムを初日の午後に企画しました。

基調講演は、まず福田恵一先生（慶應義塾大学循環器内科）に循環器と iPS 細胞の観点から“Clinical application of human iPS cells for cardiovascular medicine”をご講演していただくこととしました。森正樹先生（大阪大学外科）には“Cancer stem cell of digestive organs”をお願いしております。シンポジウムでは馬嶋正隆先生に基調講演をしていただき、最後に福村大先生（Massachussetts General Hospital, Cancer Center）に cancer microcirculation の観点から“Balancing angiogenic pathways in solid tumors”をお願いしております。二日目の特別講演は、長年にわたり微小循環学会の発展に貢献されました山本哲郎先生（熊本大学大学院生命科学研究部分子病理学分野）に、“Role of ribosomal protein S19 oligomer–C5a receptor system in acute inflammation resolution”をお話頂く予定でございます。また、お世話になっております土本寛二先生（北里大学薬学部）には、ライフワークとされています北里柴三郎と北里研究所についての講演をお願いしております。

さらに Luncheon seminar は、初日は高橋信一先生（杏林大学第三内科）に *Helicobacter pylori* について、二日目は、鈴木康夫先生（東邦大学医療センター佐倉病院）にお願いしました。

本学術集会の開催にあたり、特別講演、シンポジウム、Luncheon Seminar をお引き受けいただきました先生方、座長の労をおとりくださいました先生方、御協賛いただきました企業に深甚なる御礼を申し上げます。

学会の活性化および今後の展開につながるのは、一般演題の充実であります。多くの会員の方に討議に参加いただき、明日の研究、臨床につながる一助となれば幸いです。

日本微小循環学会役員一覧

（平成24年7月31日現在）

名誉会員

朝倉　均　淺野　牧茂　石川　浩一　磯貝　行秀　大塩　力　大島　宣雄　織田　正也
梶谷　文彦　鹿取　信　神谷　瞭　神原　武　佐藤　信紘　所澤　剛　関　清
関　淳二　高橋　和人　田中　健蔵　対馬　信子　中山　龍　新見　英幸　野坂洋一郎
深田　栄一　福内　靖男　南谷　晴之

（故　人）　土屋　雅春　石井　裕正　東　健彦　飯島　宗一　岡　小天　影山　圭三
神村　瑞夫　岸　好彰　佐藤　春郎　鈴木　友二　砂田　輝武　高木健太郎　竹重　順夫
長嶋　長節　西丸　和義　松田幸次郎　曲直部寿夫　松山　秀一

理事長

末松　誠

理　事

荒木　信夫　石川　眞美　大橋　俊夫　岡田　英吉　小椋祐一郎　梶村　眞弓　柴田　政廣
鈴木　則宏　鈴木　秀和　棚橋　紀夫　永田　博司　中村　正彦　西野　博一　藤村　朗
馬嶋　正隆　三浦総一郎　矢田　豊隆　山本　哲郎　吉川　敏一　吉田　晃敏

監　事

大久保千代次　寺山　靖夫

評議員

相磯　貞和　秋葉　保忠　天野　英樹　安藤　譲二　池本　卓　伊古美文隆　伊藤　和郎
伊藤　義彰　伊藤　義也　牛山　明　畝川美悠紀　大島　厚　大野　隆　岡部栄逸朗
荻原　達雄　長田　高志　河合　康明　河合　佳子　韓　晶岩　菊池　佑二　合田　亘人
沢　禎彦　澤登　公勇　芝山　雄老　鈴木　磨郎　関塚　永一　蘇原　泰則　高清水眞二
高橋　俊介　高安　正和　谷下　一夫　塚田　孝介　都築　義和　塗々木和男　冨田　裕
長岡　泰司　長坂　昌人　長野　弘　西崎　泰弘　西田　次郎　橋本　一成　花井荘太郎
船津　和夫　穂苅　量太　八月朔日秀明　本間　覚　前田　俊彦　松尾　雅斗　松原　明久
丸山　征郎　水野　嘉夫　水野　理介　南山　求　三好　千香　森下　鉄夫　柳　健一
矢吹　壮　山川　隆司　山口佳寿博　山口　三郎　吉田　憲正　和久井　信　渡辺　勳史
渡辺　嘉久

日本微小循環学会総会の開催日および会長一覧

（＊印は「微小循環研究者の集い」）

回 数	開催年月日	世話人あるいは会長	開催場所	
第1回*	1976年2月14日	浅野 牧茂（国立公衆衛生院）	東 京	国立公衆衛生院
第2回*	1977年2月20日	影山 圭三（慶應義塾大学医学部病理）	東 京	慶應義塾大学医学部
第3回*	1978年2月11日	飯島 宗一・入沢 宏（広島大学医学部病理）	広 島	広島大学医学部
第4回*	1979年2月10～11日	高木 健太郎（名古屋市立大学本部）	名古屋	愛知県労働者研修センター
第5回*	1980年2月9日	長嶋 長節（杏林大学医学部生理）	東 京	農林年金会館
第6回*	1981年4月18日	佐藤 春郎（東北大学抗酸菌病研究所）	仙 台	斎藤報恩会会館
第7回*	1982年2月6～7日	岡 小天・中山 龍・新美 英幸（国立循環器病センター）	大 阪	国立循環器病センター
第8回*	1983年2月5～6日	竹重 順夫・村上 正浩・宮崎 道雄（久留米大学医学部解剖）	久留米	石橋文化センター
第9回*	1984年2月4～5日	関 清（東邦大学医学部内科）	東 京	こまばエミナース
第10回	1985年2月16～17日	砂田 輝武（香川医科大学）	高 松	高松国際ホテル
第11回	1986年2月1～2日	林 秀男・神原 武（熊本大学医学部病理・免疫アレルギー）	熊 本	ニュースカイホテル
第12回	1987年1月30～31日	三島 好雄（東京医科歯科大学医学部外科）	東 京	東京医科歯科大学
第13回	1988年5月20～21日	松山 秀一（弘前大学医学部眼科）	弘 前	弘前市文化センター
第14回	1989年3月20～21日	高橋 和人（神奈川歯科大学口腔解剖学）	横須賀	神奈川歯科大学
第15回	1990年4月28～29日	所澤 剛（秋田大学医学部病理）	秋 田	秋田県総合保険センター
第16回	1991年4月25～26日	鹿取 信（北里大学医学部薬理）	東 京	アルカディア市ヶ谷
第17回	1992年5月21～22日	大島 宣雄（筑波大学基礎医学医工学）	つくば	筑波大学大学会館
第18回	1993年4月22～23日	磯貝 行秀（東京慈恵会医科大学内科）	東 京	全共連ビル
第19回	1994年5月26～27日	大橋 俊夫（信州大学医学部生理学）	松 本	長野県松本文化会館
第20回	1995年4月20～21日	神谷 暸（東京大学医学部医用生体工学）	東 京	東京大学山上会館
第21回	1996年2月23～24日	対馬 信子（国立循環器病センター内科）	大 阪	千里ライフサイエンスセンター
第22回	1997年2月28～3月1日	佐藤 信紘（順天堂大学医学部内科）	東 京	日本海運倶楽部
第23回	1998年2月26～27日	野坂 洋一郎（岩手医科大学歯学部口腔解剖学）	盛 岡	盛岡グランドホテル
第24回	1999年2月26～27日	福内 靖男（慶應大学医学部内科）	東 京	日本海運倶楽部
第25回	2000年2月18～19日	時岡 孝夫（明海大学歯学部解剖）	横須賀	神奈川歯科大学
第26回	2001年2月15～16日	梶谷 文彦（岡山大学／川崎医大医用工学）	倉 敷	倉敷市立美術館
第27回	2002年2月21～22日	大久保 千代次（国立公衆衛生院）	東 京	国立公衆衛生院
第28回	2003年2月13～14日	三浦 総一郎（防衛医科大学校内科）	東 京	グランドヒル市ヶ谷
第29回	2004年2月19～20日	山本 哲郎（熊本大学医学部分子病理）	熊 本	ニュースカイホテル
第30回	2005年2月23～24日	織田 正也（国際医療福祉大学内科）	東 京	東京国際フォーラム
第31回	2006年2月10～11日	末松 誠（慶應義塾大学医学部医化学）	東 京	京王プラザホテル
第32回	2007年2月23～24日	吉川 敏一（京都府立医科大学生体機能制御学）	京 都	ぱ・る・るプラザ京都
第33回	2008年2月21～22日	南谷 晴之（慶應義塾大学理工学部生体医工学）	東 京	慶應義塾大学本部
第34回	2009年2月21～22日	馬嶋 正隆（北里大学医学部薬理学）	東 京	北里大学薬学部コンベンションホール
第35回	2010年2月26～27日	棚橋 紀夫（埼玉医科大学国際医療センター神経内科）	埼 玉	大宮ソニックシティー
第36回	2011年2月11～12日	小椋 祐一郎（名古屋市立大学大学院学研究科視覚化学）	名古屋	名古屋市立病院大ホール
第37回	2012年3月16～17日	藤村 朗（岩手医科大学解剖学講座）	盛 岡	盛岡グランドホテル
第38回	2013年2月8～9日	西村 博一（東京慈恵会科大学消化器肝臓内科）	東 京	東京慈恵会医科大学
第39回	2014年2月7～8日	中村 正彦（北里大学薬学部臨床薬学研究・教育センター病態解析学）	東 京	北里大学薬学部コンベンションホール

会場への交通案内

北里大学白金キャンパス（薬学部）へのアクセス

【渋谷駅（JR･私鉄･地下鉄）】

東口下車、都営バス（田 87 系統：渋谷一田町間）田町駅行15分　北里研究所前下車

【恵比寿駅（JR･地下鉄日比谷線）】

東口下車、都営バス（田 87 系統）田町駅行7分　北里研究所前下車

【広尾駅（地下鉄日比谷線）】

天現寺方面（出口1 、2）下車、徒歩10分

【田町駅（JR）･三田駅（地下鉄浅草線･三田線）】

三田口下車、都営バス（田 87 系統）渋谷駅行15分　北里研究所前下車

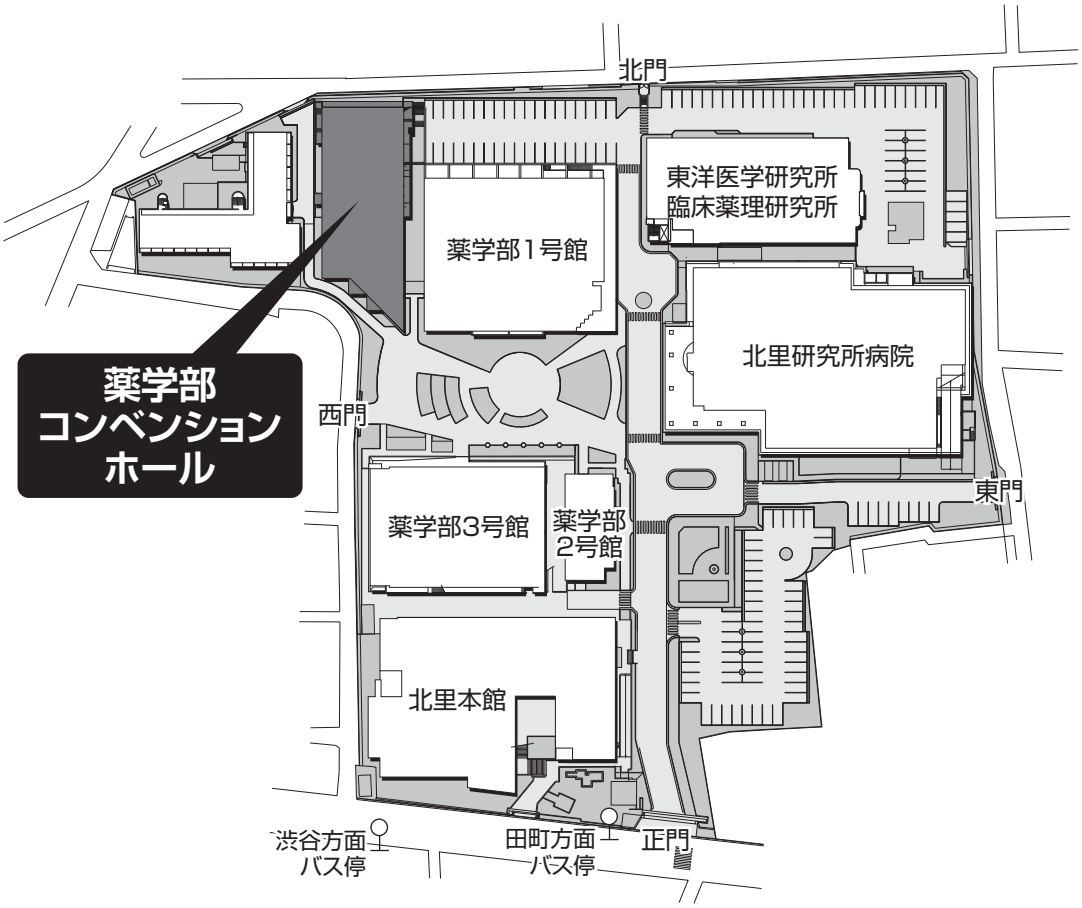
【白金高輪駅（地下鉄南北線･三田線）】

出口3番下車､徒歩約10分または都営バス（田 87 系統）渋谷駅行4分　北里研究所前下車

※白金高輪駅から徒歩でご来場の際は、都営バス（田 87 系統渋谷駅行）路線道路を渋谷方向へ直進ください。

会場案内図


←渋谷方面
↑広尾方面
天現寺
交差点
ニュー
山王ホテル
フランス
大使館
光林寺前
(バス停)
麻布十番方面→
418
広尾病院
外苑西通り
慶応義塾
幼稚舎
明治通り
天現寺
出入口
首都高速2号目黒線
北里大学
白金キャンパス
東門
西門
415
←恵比寿方面
北里研究所病院
白金北里通り
三光小学校
都営バス
北里研究所前
正門
目黒方面↓
神応小学校
朝日中学校
305
白金高輪田町方面→


北門
東洋医学研究所
臨床薬理研究所
薬学部1号館
北里研究所病院
薬学部
コンベンション
ホール
西門
東門
薬学部3号館
薬学部
2号館
北里本館
渋谷方面
バス停
田町方面
バス停
正門

お知らせとお願い

1. 会　場

北里大学薬学部コンベンションホール

2. 参加登録受付

北里大学薬学部コンベンションホール前受付

一日目：8：00～18：00

二日目：8：00～14：30

3. 受付方法

当日、北里大学薬学部コンベンションホール受付にお越し下さい。

登録料

参加費（会員）　10,000円
参加費（非会員）12,000円
参加費（学生）　5,000円
懇親会費、プログラム・抄録集も含みます。

4. ネームカード

所属・氏名をご記入の上、入場の際は必ず着用ください。
ネームカードを着用されていない方の入場は、ご遠慮願います。

5. プログラム・抄録集

プログラム・抄録集は会期前に本学会会員に送付いたします。
プログラム・抄録集をお忘れの方、ご希望の方は、当日一部2,000円で頒布いたします。

6. 会場での呼び出し

会場内での呼び出しは行いません。受付周辺に伝言板を設置いたしますので、ご利用ください。

7. 会場内でのご注意

会場内での録音・写真およびビデオ撮影は、著作権法に触れますので、固くお断りいたします。
また、携帯電話はマナーモードに設定していただくか、電源をお切りください。

8. 会場内での御飲食

コンベンションホール内は飲食ならびに持ち込みも禁止しております。ご協力お願いいたします。

9. 駐車場

駐車場はございません。公共交通機関等をご利用ください。

10. 食　事

会期中、ランチョンセミナーを開催いたします。
お弁当をご用意いたしておりますが、数に限りがございますので、予めご了承ください。

11. 関連会議

理 事 会　2月6日（木）15時30分より18時まで薬学部1号館1507教室
評議員会　2月8日（土）14時30分より15時15分まで北里大学薬学部コンベンションホール
総　　会　2月8日（土）15時15分まで15時45分まで北里大学薬学部コンベンションホール
学会奨励賞審査委員会　2月7日（金）12時30分より薬学部1号館1507教室

12. 学会入会申し込み

会期中、新規入会、年会費受付デスクを設けております。
巻末綴じ込みの入会申込書・変更届けをご利用ください。
なお、年会費は、役員は年額10,000円、評議員は年額7,000円、正会員は年額3,000円です。また入会の申し込みについては、下記にお問い合わせください。

日本微小循環学会事務局
〒160-0016 東京都新宿区信濃町35 信濃町煉瓦館5階
（財）国際医学情報センター内
Tel：03-3359-0443
Fax：03-5361-7091
e-mail：js-micro@imic.or.jp

次回開催情報

第40回日本微小循環学会総会

会期：2015年9月27日（日）
※第10回世界微小循環学会（WCMic2015）期間中
（2015年9月25日（金）～27日（日））
会場：京都国際会館
会長：矢田　豊隆（川崎医科大学医用工学）

特別講演1

日　時：2月7日（金）11：15～12：15
場　所：薬学部コンベンションホール
演　題：Clinical application of human iPS cells for cardiovascular Medicine
講演者：福田 恵一（慶應義塾大学循環器内科）
座　長：鈴木 則宏（慶應義塾大学）

特別講演2

日　時：2月7日（金）13：45～14：45
場　所：薬学部コンベンションホール
演　題：Cancer stem cell of digestive organs
講演者：森 正樹（大阪大学消化器外科学）
座　長：日比 紀文（北里大学）

特別講演3

日　時：2月7日（金）17：00～18：00
場　所：薬学部コンベンションホール
演　題：Balancing angiogenic pathways in solid tumors
講演者：福村 大（Massachusetts General Hospital, Cancer Center）
座　長：末松 誠（慶應義塾大学）

特別講演4

日　時：2月8日（土）11：15～12：15
場　所：薬学部コンベンションホール
演　題：Role of ribosomal protein S19 oligomer-C5a receptor system in acute inflammation resolution
講演者：山本 哲郎（熊本大学大学院生命科学研究部分子病理学分野）
座　長：矢田 豊隆（川崎医大）

特別講演5

日　時：2月8日（土）13：45～14：35
場　所：薬学部コンベンションホール
演　題：Shibasaburou Kitasato and the Kitasato Institute
講演者：土本 寛二（北里研究所病院院長、北里大学薬学部）
座　長：三浦 総一郎（防衛医科大学）

ランチョンセミナー1

日　時：2月7日（金）12：30～13：30
場　所：薬学部一号館1202教室
演　題：ヘリコバクター・ピロリ感染胃炎診療のコツ
　　The secret to diagnose Hp-induced Gastritis
講演者：高橋 信一（杏林大学第三内科）
座　長：中村 正彦（北里大学）

ランチョンセミナー2

日　時：2月8日（土）12：30～13：30
場　所：薬学部一号館1202教室
演　題：潰瘍性大腸炎における顆粒球吸着療法 ―有効性のメカニズム―
　　Granulocyte-Monocyte adsorptive therapy in Ulcerative colitis
　　－the mechanism of the efficacy－
講演者：鈴木 康夫（東邦大学医療センター佐倉病院）
座　長：日比 紀文（北里大学）

口 演 規 定

1. データ・パソコン受付

USB フラッシュメモリ持ち込みの方は発表の60分前までに PC 受付にご持参ください。パソコンをお持ち込みの方は PC 受付後、発表の30分前までに発表会場の左手前方のオペレーター席までパソコンをご持参ください。

2. 発表時間

一般演題発表：発表12分、質疑3分　計15分
シンポジウムは、プログラム通りの進行をお願いいたします。

3. パソコン持ち込みの際の注意点

1）モニターの出力端末は D-SUB15 ピン以外の変換ケーブルが必要な機種を使用する方は変換ケーブルをご持参ください。

2）必ず電源アダプターをご持参ください。

3）動画、音声の再生が必要な方は、PC 受付で必ずお話ください。

4）発表終了後、パソコンは会場内で返却いたします。

第39回日本微小循環学会総会 事務局
北里大学薬学部臨床薬学研究・教育センター病態解析学
高橋 哲史
〒108-8641 港区白金5-9-1
TEL&FAX：03-3446-9036

日　程　表

2月 7日金

8:25〜 **開会の辞**

8:30〜9:15
学会奨励賞候補者講演 1
Y-1〜Y-3
座長：穂苅 量太

9:15〜10:00
学会奨励賞候補者講演 2
Y-4〜Y-6
座長：梶村 眞弓

10:00〜11:15
一般演題 1
F-1〜F-5（脳、神経）
座長：荒木 信夫

11:15〜12:15
特別講演 1
SL-1　福田 恵一（慶應義塾大学循環器内科）
座長：鈴木 則宏

12:30〜13:30　1202教室
ランチョンセミナー 1
ヘリコバクター・ピロリ感染胃炎診療のコツ
LS-1　高橋 信一（杏林大学第三内科）
座長：中村 正彦
共催：エーザイ株式会社

13:45〜14:45
特別講演 2
SL-2　森　正樹（大阪大学消化器外科学）
座長：日比 紀文

14:45〜16:40
日本微小循環学会、
AKPS 共催シンポジウム
座長：永田 博司
　　馬嶋 正隆

17:00〜18:00
特別講演 3
SL-3　福村　大
（Massachusetts General Hospital, Cancer Center）
座長：末松　誠

18:30〜　学生食堂
学会奨励賞・懇親会

February 7 (Fri)

8:25〜 **Opening Remarks**

8:30〜9:15 **Applicants' Presention for Young Investigators Award 1**
Y-1〜Y-3
Chair: Ryota Hokari

9:15〜10:00 **Applicants' Presention for Young Investigators Award 2**
Y-4〜Y-6
Chair: Mayumi Kajimura

10:00〜11:15
Free Paper 1
F-1〜F-5 (Brain, Nerve)
Chair: Nobuo Araki

11:15〜12:15
Special Lecture 1
SL-1　Keiichi Fukuda
Chair: Norihiro Suzuki

12:30〜13:30　Room 1202
Luncheon Seminar 1
The secret to diagnose Hp-induced gastritis
LS-1　Shinichi Takahashi
Chair: Masahiko Nakamura
Sponsored by Eisai Co Ltd

13:45〜14:45
Special Lecture 2
SL-2　Masaki Mori
Chair: Toshifumi Hibi

14:45〜16:40
Symposium
co-sponsored by JSMC and AKPS
Chair: Hiroshi Nagata
　　Masataka Majima

17:00〜18:00
Special Lecture 3
SL-3　Dai Fukumura
Chair: Makoto Suematsu

18:30〜　University Cafeteria
Award Ceremony and Reception

Program at a Glance

2月 8日(土)

8:30〜9:30
一般演題 2
F-6〜F-9（腫瘍、内皮）
座長：鈴木 秀和

9:30〜10:15
一般演題 3
F-10〜F-12（腎、糖尿病、眼）
座長：西野 博一

10:15〜11:15
一般演題 4
F-13〜F-16（心、肺）
座長：韓　晶岩

11:15〜12:15
特別講演 4
SL-4　山本 哲郎（熊本大学分子病理学分野）
座長：矢田 豊隆

12:30〜13:30　1202 教室
ランチョンセミナー 2
潰瘍性大腸炎における顆粒球吸着療法
―有効性のメカニズム―
LS-2　鈴木 康夫（東邦大学医療センター佐倉病院）
座長：日比 紀文　協賛：株式会社 JIMRO

13:45〜14:35
特別講演 5
SL-5　土本 寛二（北里研究所病院院長、北里大学薬学部）
座長：三浦 総一郎

14:40〜15:30
評議員会

15:30〜16:00
総　会

16:00〜
閉会の辞

February 8 (Sat)

8:30〜9:30
Free Paper 2
F-6〜F-9（Tumor, Endothelium）
Chair: Hidekazu Suzuki

9:30〜10:15
Free Paper 3
F-10〜F-12（Kidney, DM, Retina）
Chair: Hirokazu Nishino

10:15〜11:15
Free Paper 4
F-13〜F-16（Heart, Lung）
Chair: Jing-Yan Han

11:15〜12:15
Special Lecture 4
SL-4　Tetsuro Yamamoto
Chair: Toyotaka Yada

12:30〜13:30　Room 1202
Luncheon Seminar 2
Granulocyte-Monocyte adsorptive therapy in Ulcerative colitis −the mechanism of the efficacy−
LS-2　Yasuo Suzuki
Chair: Toshifumi Hibi　Sponsored by JIMRO Co Ltd

13:45〜14:35
Special Lecture 5
SL-5　Kanji Tsuchimoto
Chair: Soichiro Miura

14:40〜15:30
Council Meeting of JSMC

15:30〜16:00
General Assembly of JSMC

16:00〜
Closing Remarks

PROGRAM

Friday, February, 7, 2014

8：25－8：30

Opening Remarks President：Masahiko Nakamura

8：30－9：15

Applicants' Presention for Young Investigators Award 1 Chair：Ryota Hokari

Y-01 Nicotine ameliorates colonic inflammation via down-regulation of MAdCAM-1 expression on high endotherial venule like vessel.

Koji Maruta, Hideaki Hozumi, Ryota Hokari, Yuichi Yasutake, Hirokazu Sato, Kazuyuki Narimatsu, Chie Kurihara, Yoshikiyo Okada, Shingo Usui, Chikako Watanabe, Shunsuke Komoto, Kengo Tomita, Shigeaki Nagao, Soichiro Miura

The Second Department of Internal Medicine, National Defense Medical College, Tokorozawa, Japan

Y-02 VEGFR1 signaling facilitates diabetic skin wound healing in mice

Shin-ichiro Okizaki[1,3], Yoshiya Ito[2], Hirotoki Okubo[1,2], Ken Kojyou[1,2], Kazuhito Ohba[1,3], Shichiri Masayoshi[3], Masataka Majima[1]

Departments of 1) Pharmacology, 2) Surgery, and 3) Endocrinology, Kitasato University School of Medicine, Kanagawa, Japan

Y-03 Post-stroke administration of cilostazol changes metabolic profile in transsulfuration pathway of ischemic brain in a mouse model

Yasoo Sugiura[1,4], Mayumi Kajimura[1,2], Tsuyoshi Nakanishi[1,3], Takayuki Morikawa[1,2], Takako Hishiki[1,2], Makoto Suematsu[1,2]

1) Department of Biochemistry, School of Medicine, Keio University, Tokyo 160-8582
2) JST, ERATO, Suematsu Gas Biology Project, Tokyo 160-8582, Japan
3) MS Business Unit, Shimadzu Corporation, Kyoto 604-8511, Japan
4) Department of Pulmonary and Thoracic Surgery, Kanagawa National Hospital, Hadano 257-8585

9：15－10：00

Applicants' Presention for Young Investigators Award 2 Chair：Mayumi Kajimura

Y-04 Role of leukotriene B4 receptor 1 (BLT1) signaling in liver repair after hepatic ischemia reperfusion injury

Hirotoki Ohkubo[1,2], Yoshiya Ito[2], Ken Kojo[1], Masahiko Watanabe[2], Masataka Majima[1]

Departments of 1) Pharmacology and 2) Surgery, Kitasato University School of Medicine, Kanagawa, Japan

Y-05 3, 4-dihydroxyl-phenyl lactic acid restores NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 10 expression to ameliorate cardiac reperfusion injury

Ke He[1,2], Xiao-Yuan Yang[1,2], Na Zhao[1], Yu-Ying Liu[1], Bai-He Hu[1], Kai Sun[1], Xin Chang[1], Xiao-Hong Wei[1], Jing-Yu Fan[1], Jing-Yan Han[1,2]

1) Tasly Microcirculation Research Center, Peking University Health Science Center, Beijing 100191, China
2) Department of Integration of Traditional Chinese and Western Medicine, School of Basic Medical Sciences, Peking University, Beijing 100191, China

Y-06 Comparison of peripheral vascular resistance based on macro- and micro-circulatory responses by Poilleuille's law

Kazuhiro Yokokawa, Saki Hamashima, Masahiro Shibata

Department of Bio-Science and Engineering, Shibaura Institute of Technology

10：00－11：15

Free Paper 1

Chair：Nobuo Araki

F-01 Cilostazol inhibits leukocyte-endothelial cell interactions in murine microvessels after transient bilateral common carotid artery occlusion

Takuya Fukuoka, Takeshi Hayashi, Makiko Hirayama, Hajime Maruyama, Norio Tanahashi

Department of Neurology, Saitama Medical University International Medical Center, Saitama, Japan

F-02 Impairment of CO_2 reactivity in RBC velocity and CBF after cortical spreading depression in anesthetized mice

Miyuki Unekawa[1)], Yutaka Tomita[1)], Haruki Toriumi[1)], Takashi Osada[1,2)], Kazuto Masamoto[3,4)], Hiroshi Kawaguchi[4)], Yoshiaki Itoh[1)], Iwao Kanno[4)], Norihiro Suzuki[1)]

1) Department of Neurology, Keio University School of Medicine
2) Department of Neurology, Tachikawa Hospital
3) Center for Frontier Science and Engineering, University of Electro-Communications
4) Molecular Imaging Center, National Institute of Radiological Sciences

F-03 EXPLORE THE ANGIOGENESIS OF AUTOLOGOUS TRANSPLANTED BRAIN TISSUES IN RABBITS

Jin Xuelong

Department of Physiology, Tianjin Medical University, Tianjin, 300070, China

F-04 HO-2/CO system protects against metabolic disorders following acute cerebral ischemia

Takayuki Morikawa[1)], Mayumi Kajimura[1,2)], Tsuyoshi Nakanishi[1,3)], Yoshinori Yukutake[2)], Makoto Suematsu[1,2)]

1) Department of Biochemistry, School of Medicine, Keio University, Tokyo 160-8582
2) JST, ERATO, Suematsu Gas Biology Project, Tokyo 160-8582, Japan
3) MS Business Unit, Shimadzu Corporation, Kyoto 604-8511, Japan

F-05 The blood cell flow and the vascular responses in arterioles and capillaries after subarachnoid hemorrhage

Mami Ishikawa[1,2)], Mayumi Kajimura[1)], Takayuki Morikawa[1)], Tomomi Nakamura[1)], Yuichi Tanaka[2)], Eiju Watanabe[2)], Makoto Suematsu[1)]

1) Department of Biochemistry, School of Medicine, Keio University
2) Department of Neurosurgery, Jichi Medical University

11：15－12：15

Special Lecture 1

Chair：Norihiro Suzuki

SL-1 Clinical application of huma iPS cells for cardiovascular Medicine

Keiichi Fukuda

Department of Cardiology, Keio University School of Medicine

12：30－13：30

Sponsored by Eisai Pharmaceutical

Luncheon Seminar 1

Chair：Masahiko Nakamura

LS-1 The secret to diagnose Hp-induced Gastritis

Shinichi Takahashi

3rd Department of Internal Medicine, Kyorin University

13：45－14：45

Special Lecture 2

Chair：Norihumi Hibi

SL-2 Cancer Stem Cell of Digestive Organs

Masaki Mori

Department of Surgery, Osaka University

14：45－16：40

Symposium cosponsored by JSMS and AKPS

Chair：Hiroshi Nagata
Masataka Majima

A-01 Roles of Prostanoids in Regulation of Angiogenesis and Lymphatic Tissue Remodeling

Masataka Majima

Department of Pharmacology, Kitasato University School of Medicine, Kitasato 1-15-1, Sagamihara, Kanagawa 252-0374, Japan

A-02 New Trends in therapeutic strategies against ischemia/reperfusion injury; Postconditioning and pharmacological intervention in acute myocardial infarction

Megumi Shimada[1)], Takashi Koyama[2)], Akiyasu Baba[1)], Rie Kosugi[1)], Makoto Akaishi[1)]

1) Department of Cardiology, Kitasato Institute Hospital, Kitasato University
2) Cardiovascular center, Tachikawa Hospital

A-03 Perfusion fixation method is critical for immunoelectron microscopy and ultrastructural evaluation on changes of caveolin-1 and caveolae relates with capillarization of liver sinusoidal endothelial cells in human cirrhotic liver

Hiroaki Yokomori[1)], Jing-Yan Han[2)], Masaya Oda[3)]

1) Internal Medicine, Kitasato University Medical Center, Saitama, Japan.
2) Tasly Microcirculation Research Center, Peking University Health Science Center, Beijing, China.
3) Organized Center of Clinical Medicine, International University of Health and Welfare, Sanno Hospital, Tokyo, Japan.

A-04 Brain-derived neurotrophic factor promotes angiogenesis via oxidative stress in human vascular endothelial cells: Implication for atherogenesis?

Hideyuki Yamawaki

Laboratory of Veterinary Pharmacology, School of Veterinary Medicine, Kitasato University

17：00－18：00

Special Lecture 3

Chair：Makoto Suematsu

SL-3 Balancing angiogenic pathways in solid tumors

Dai Fukumura

Edwin L. Steele Laboratory, Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical School, Boston MA.

18：30－

Award Ceremony / Reception

at 学生食堂

8：30－9：30

Free Paper 2

President：Hidekazu Suzuki

F-06 c-Met interaction with Angiogenesis and Stem Cell in Helicobacter heilmannii-induced gastric MALT lymphoma: Interaction with VASH-2

Masahiko Nakamura[1)], Hidenori Matsui[2)], Tetsufumi Takahashi[1)], Shinichi Takahashi[3)], Toshifumi Hibi[4)], K. Tsuchimoto[1)]

1) School of Pharmaceutical Sciences, Kitasato University, Tokyo, Japan
2) Kitasato Institute for Life Sciences, Kitasato University, Tokyo, Japan
3) 3rd Department of Internal Medicine, Kyorin University School of Medicine, Mitaka, Japan
4) Kitasato Institute Hospital

F-07 Visualisation of drug delivery by using high resolution microscopic mass spectrometry

Masahiro Yasunaga[1)], Masaru Furuta[2)], Koretsugu Ogata[2)], Yoshikatsu Koga[1)], Yoshiyuki Yamamoto[1)], Misato Takigahira[1)], Yasuhiro Matsumura[1)]

1) Investigative Treatment Division, National Cancer Center Hospital East
2) Analytical & Measuring Instruments Division, Shimadzu Corporation

F-08 Salvianolic acid B binds to Src and ameliorates mesenteric venules hyperpermeability in endotoxmia rats

Chun-Shui Pan[1)], Ying-Hua Liu[1)], Yu-Ying Liu[1)], Yu Zhang[1)], Ke He[1,2)], Xiao-Yuan Yang[1,2)], Bai-He Hu[1,2)], Xin Chang[1,2)], Xiao-Hong Wei[1)], Jing-Yu Fan[1)], Jing-Yan Han[1,2)]

1) Tasly Microcirculation Research Center, Peking University Health Science Center, Beijing 100191, China.
2) Department of Integration of Traditional Chinese and Western Medicine, School of Basic Medical Sciences, Peking University, Beijing 100191, China.

F-09 RhoJ defines angiogenic endothelial cell motility by integrating VEGF and Sema3E signals

Akiyoshi Uemura[1)], Yoko Fukushima[1)], Koichi Nishiyama[2)], Yuichiro Ogura[3)], Shin-Ichi Nishikawa[4)]

1) Division of Vascular Biology, Kobe University Graduate School of Medicine
2) Department of Physiological Chemistry and Metabolism, Graduate School of Medicine, The University of Tokyo
3) Department of Ophthalmology and Visual Science, Nagoya City University Graduate School of Medical Sciences
4) Laboratory for Stem Cell Biology, RIKEN Center for Developmental Biology

9：30－10：15

Free Paper 3

Chair：Hirokazu Nishino

F-10 C-peptide Effects on Glomerular Filtration

Hiroshi Nakamoto[1)], Kazuhiko Nakayama[2)], Noriaki Emoto[2)], Toyotaka Yada[1)], Yasuo Ogasawara[1)]

1) Department of Medical Engineering and Systems Cardiology, Kawasaki Medical School, Kurashiki, Okayama, JAPAN
2) Clinical Pharmacy, Kobe Pharmaceutical University, Kobe, Hyogo, JAPAN

F-11 Measurement of blood flow velocity profiles in retinal arterioles and venules using spectral-domain doppler optical coherence tomography in healthy subjects

Taiji Nagaoka, Tomofumi Tani, Akihiro Ishibazawa, Kenji Sogawa, Seigo Nakabayashi, Tsuneaki Omae, Akitoshi Yoshida

Department of Ophthalmology, Asahikawa Medical University, Asahikawa, Japan.

F-12 Clinical characteristics of peripheral type of diabetic retinopathy diagnosed with ultra-wide field fluorescein angiography

Shuichiro Hirahara, Taneto Tomiyasu, Miho Nozaki, Munenori Yoshida, Yuichiro Ogura

Department of Ophthalmology and Visual Science, Nagoya City University Graduate School of Medical Sciences

10：15－11：15

Free Paper 4

Chair：韓 晶岩

F-13 H_2O_2-induced Vasodilatation Compensates Diabetes-induced Microvascular Endothelial Dysfunction during Acute Coronary Occlusion in Canine Coronary Native Collateral Microvessels in Vivo

Toyotaka Yada[1)], Hiroaki Shimokawa[2)], Osamu Hiramatsu[1)], Hiroshi Nakamoto[1)], Masami Goto[1)], Yasuo Ogasawara[1)], Fumihiko Kajiya[1)]

1) Department of Medical Engineering and Systems Cardiology
2) Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Japan

F-14 Nailfold microcapillary findings reveal early stage of congestion of right ventricle of the heart.

Ichiro Miura[1)], Masato Matsuo[2)], Tsuyoshi Konta[3)], Katsuya Nagayama[4)], Masami Miyazaki[5)]

1) Dept. human pathol. Juntendo university
2) Dept. Oral Anatomy, Kanagawa Dental College
3) Ogawa iin
4) Dept.Mechanical information and Technology Kyushu institute of technology
5) School of human science Waseda univ

F-15 Ma-Xing-Shi-Gan-Tang, a traditional Chinese medicine, attenuates lipopolysaccharide-induced pulmonary microcirculatory disturbance and lung edema in rats

Li-Qian Ma[1,2)], Kai Sun[1)], Chun-Shui Pan[1)], Yu-Ying Liu[1)], Li Yan[1)], Jing-Yu Fan[1)], Jing-Yan Han[1,2)]

1) Tasly Microcirculation Research Center, Peking University Health Science Center, Beijing 100191, China
2) Department of Integration of Chinese and Western Medicine, School of Basic Medical Sciences, Peking University, Beijing 100191, China

F-16 The protective effects of rapamycin on intestinal ischemia/reperfusion induced remote lung injury in mice

Takaya Iida[1)], Yuji Naito[1)], Tomohisa Takagi[1)], Kazuhiro Katada[1)], Katsura Mizushima[1)], Kazuhiro Kamada[1)], Kazuhiko Uchiyama[1)], Osamu Handa[1)], Nobuaki Yagi[1)], Yoshito Ito[1)], Toshikazu Yoshikawa[2)]

1) Department of Molecular Gastroenterology and Hepatology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine
2) Kyoto Prefectural University of Medicine

11：15－12:15

Special Lecture 4

Chair：Toyotaka Yada

SL-4 Role of ribosomal protein S19 oligomer-C5a receptor system in acute inflammation resolution

Tetsuro Yamamoto

Department of Molecular Pathology, Faculty of Life Science, Kumamoto University

12：30－13：30

Sponsored by JIMRO

Luncheon Seminar 2

Chair：Toshifumi Hibi

LS-2 Granulocyte-Monocyte adsorptive therapy in Ulcerative colitis －the mechanism of the efficacy－

Yasuo Suzuki

Toho University Sakura Medical Center

13 : 45 – 14:35

Special Lecture 5

Chair : Soichiro Miura

SL-5 **Sibasaburou Kitasato and the Kitasato Institute**

Kanji Tsuchimoto

Kitasato University Kitasato Institute Hospital Department of Clinical Medicine (Pathophysiology), School of Pharmacy, Kitasato University

14 : 40 – 15 : 30

Council Meeting of JSMC

15 : 30 – 16 : 00

General Assenbly of JSMC

16 : 00 –

Closing Remarks

Abstracts

Clinical application of huma iPS cells for cardiovascular Medicine

Keiichi Fukuda

Department of Cardiology, Keio University School of Medicine

Although heart transplantation can drastically improve the survival, shortage of the donor heart is a serious problem. The regenerative medicine of the failing heart had been long awaited. To address this question, we had developed novel methods to induce human iPS cells from circulating human T lymphocytes using Sendai virus containing Yamanaka 4 factors. We had screened the factor that were expressed in future heart forming area of the early mouse embryo, found several growth factors and cytokines that can induce cardiomyocytes differentiation and proliferation, and applied them to human iPS cells. We performed transcriptome of the metabolic enzymes and fluxome analysis using ^{13}glucose and ^{13}lactic acid on ES/iPS cells and cardiomyocytes, and found that their metabolic pathways were completely different. Based on these findings, we purified cardiomyocytes using glucose-free lactate-supplemented medium. Purity of the cardiomyocytes was > 99%, and they did not make teratoma formation. The transplanted cardiomyocytes using our technique can survive in the heart with more than 90%, and can show physiological growth after transplantation. We expect the combination of these techniques can achieve future heart regeneration. We also developed human disease model cardiomyocytes using human iPS cells from the patients with long QT syndrome and other hereditary heart disease. These disease model cardiomyocytes represented the phenotype of the disease, and might be helpful for drug screening and pathophysiological analysis.

Cancer Stem Cell of Digestive Organs

Masaki Mori
Department of Surgery, Osaka University

Recent studies supported the notion that a small population, which mimics norm al adult stem cells in the dormant phase of the cell cycle, plays a role in th e biological behaviors of tumors. Indeed such distinct cells, i.e., cancer ste m cells are resistant to toxic injuries and chemoradiation therapy in vitro an d in vivo. After possible involvement was indicated in leukemia, we were able to report cancer stem cells in gastrointestinal tumors. Our exploration of new screening for surface markers were supposed to be beneficial to identify gast rointestinal cancer stem cells, followed by characterization of chemoresistanc e and tumorigenicity, indicating that several cell surface markers including CD13/APN play a role in biological function of cancer stem cells. Furthermore, we examined the possible effects of cellular reprogramming by induction or inh ibition of cancer-related genes and immature status-related genes including th at of induced pluripotent stem (iPS) cell genes, whose alterations have been r eported in gastrointestinal cancer cells. Introduction of iPS cell genes but a lso several microRNAs, including miR302 was necessary for inducing the express ion of immature status-related proteins and the possible expression of morphol ogical patterns and showed slow proliferation and were sensitized to different iation-inducing treatment, and in vivo tumorigenesis was reduced in nonobese d iabetic mice with severe combined immunodeficiency. Taken together the present study indicates that the combination of traditional therapies with targeted c ancer stem cell-specific agents may target the whole tumors and may offer a pr omising strategy for lasting treatment and even cure.

Balancing angiogenic pathways in solid tumors

Dai Fukumura

Edwin L. Steele Laboratory, Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical School, Boston MA.

Intravital microscopy techniques have provided unprecedented insight into tumor angiogenesis, microcirculation and microenvironment. Tumor microvasculature has an abnormal organization, structure, and function. Tumor vessels are leaky. Blood flow is heterogeneous and often compromised. Lymphatic vessels are either defective or not functional inside tumors and together with leaky blood vessels elevate interstitial fluid pressure in solid tumors. All of these abnormalities hinder the delivery of therapeutic agents to tumors and also induce a hostile microenvironment characterized by hypoxia and acidosis. The abnormal microenvironment fuels malignancies of tumors and further lowers the effectiveness of anti-tumor treatments such as radiation therapy, chemotherapy and novel molecularly targeting therapies.

However, one can also exploit aberrant microenvironment in tumors for selective treatment of tumors. Enhanced permeability and retention effect of relatively large size particles in tumors is the major basis of nanomedicine. It not only increases therapeutic index but also allows delivering toxic agents and hydrophobic drugs to tumors otherwise prohibited for clinical use due to normal tissue toxicity. Unfortunately, crucial drawback of this approach is diffusion hindrance of the large nanoparticles. These nanotherapeutics cannot advance into tumor tissues after the extravasation from tumor vessels. To solve this dichotomy we proposed a multistage nanoparticle delivery system. We have developed a relatively large nanoparticle that can release small size nanoparticles upon exposure to enzymes uniquely present in tumor tissues and demonstrated superior intratumoral diffusion of these multistage nanoparticles.

Alternatively, one may try to tame abnormal tumor microenvironment. For example, host-tumor interactions regulate expression of pro- and anti-angiogenic factors. Imbalance of these factors results in above-mentioned pathophysiological features in the tumor. In a physiological setting, angiogenic vessels eventually become mature and stable vessels that represent long-lasting functional units. Restoring tissue balance of these factors in tumors may “normalize” tumor vasculature and thus, improve its function. Administration of cytotoxic therapy during the vascular normalization can enhance its efficacy. We have demonstrated a number of approaches to normalize tumor vasculature and microenvironment that improve a variety of anti-tumor therapies.

Role of ribosomal protein S19 oligomer-C5a receptor system in acute inflammation resolution

Tetsuro Yamamoto

Department of Molecular Pathology, Faculty of Life Science, Kumamoto University

Ribosomal protein S19 (RP S19) is a component of the small ribosome subunit and essential for ribosome biogenesis. RP S19 is also present in blood plasma, forming a complex with prothrombin. Cellular RP S19 is inter-molecularly cross-linked by an intracellular transglutaminase during apoptosis, and plasma RP S19 is similarly cross-linked by activated coagulation factor XIII during blood coagulation, forming an isopeptide bond between Lys122 and Gln137 in both cases. The cross-linked RP S19 oligomers thus formed gain a ligand capacity to the C5a receptor and express various kinds of extra-ribosomal functions.

The cells undergoing apoptosis *de novo* synthesize the C5a receptor. The RP S19 oligomers liberated by the apoptotic cells hasten the apoptosis execution on one hand and recruit phagocytic macrophages on the other, completing the prompt clearance of the apoptotic cells. Isolated neutrophils spontaneously undergo apoptosis and generate the RP S19 oligomers. The RP S19 oligomers do not elicit chemotactic response of neutrophils but rather speed up the apoptotic process of the cells, while these molecules induce chemotactic migration of monocytes/macrophages. We currently made a hypothesis that this would be a crucial mechanism in resolution of acute inflammation. This hypothesis has been experimentally supported. For instance, when the RP S19 oligomers were immunologically neutralized in a carrageenan-induced mouse pleurisy model, neutrophil number in the pleural exudate greatly increased and the inflammation spread to lung parenchyma. Similar phenomena were observed in the carrageenan pleurisy induced in Gln137Glu-RP S19 knock-in mice without the neutralization.

Regarding the discrimination by the RP S19 oligomers but not by complement C5a between neutrophils and monocytes/macrophages, we made a hypothesis that a molecule(s) that disconnects the RP S19 oligomer/C5a receptor complex but not the C5a/C5a receptor complex from the intracellular signal transduction pathway is present near C5a receptor in neutrophils but not in monocytes/macrophages. To examine the hypothesis and identify the disconnecter molecule(s), we prepared a recombinant C5a/RP S19 chimeric protein which reproduces the functions of RP S19 oligomers as a monomeric protein. Delta-lactoferrin (δ-Lf) was co-separated with C5a receptor when ligated by C5a/RP S19 but not by C5a in neutrophils. δ-Lf is an intracellular protein, and it is not synthesized by monocytes/macrophages. When δ-Lf mRNA translation was blocked, HL-60-derived neutrophil-like phenotypes changed to chemotactically respond to C5a/RPS19. δ-Lf seems to be the disconnecter molecule.

Sibasaburou Kitasato and the Kitasato Institute

Kanji Tsuchimoto

Kitasato University Kitasato Institute Hospital
Department of Clinical Medicine (Pathophysiology), School of Pharmacy,
Kitasato University

Dr.Shibasaburo Kitasato officially established the Kitasato Institute in 1914, but the long history exists before then.

Shibasaburo Kitasato was born in 1853 in Kumamoto Prefecture. He received strict home discipline and instruction from Constant George van Mansveldt at Kumamoto Medical School. After graduating from the University of Tokyo in 1883, he went to Robert Koch's laboratory in 1886 and achieved in the field of preventive medicine, especially immunology, where he successfully grew a pure culture of tetanus bacilli, followed by his discovery of the serotherapy used to treat that disease. After returning from Germany in 1892, he established Japan's first private medical research facility for infectious diseases supported by Yukichi Fukuzawa, the founder of Keio University and others both materially and spiritually. This institute made great progress and was placed under the control of the Japan Hygiene Society in 1899. In 1914, as the government transferred the Institute under the University of Tokyo, Kitasato and his followers resigned and started the Kitasato Institute.

The Spirit of Kitasato, which he developed over a life time - to investigate with a pioneering spirit, be appreciative in your dealings with people, possess wisdom and be a person of practical science, as well as to persist with an unwavering spirit - has been continuously handed down from generation to generation at the Kitasato Institute・Kitasato University and Keio University.

Now approaching our centennial of the founding of the Institute, a landmark moment, we take the Spirit to heart once more and I am sure　the Institute will evolve eternally.

The secret to diagnose Hp-induced Gastritis

Shinichi Takahashi

3rd Department of Internal Medicine, Kyorin University

Granulocyte-Monocyte adsorptive therapy in Ulcerative colitis —the mechanism of the efficacy—

Yasuo Suzuki

Toho University Sakura Medical Center

Y-01

Nicotine ameliorates colonic inflammation via down-regulation of MAdCAM-1 expression on high endotherial venule like vessel.

Koji Maruta, Hideaki Hozumi, Ryota Hokari, Yuichi Yasutake, Hirokazu Sato, Kazuyuki Narimatsu, Chie Kurihara, Yoshikiyo Okada, Shingo Usui, Chikako Watanabe, Shunsuke Komoto, Kengo Tomita, Shigeaki Nagao, Soichiro Miura

The Second Department of Internal Medicine, National Defense Medical College, Tokorozawa, Japan

Background: Ulcerative colitis (UC) is an intractable colonic disease. Lymphocytes migration to colonic mucosa through endotherial venule like vessel is considered to be involved in pathophysiology of this disease. Anti-adhesion molecule therapy targeting MAdCAM-1 on high endotherial venule like vessel is one of the promising therapy. Smoking has been reported to have a beneficial effect on UC. Nevertheless, pathophysiology of nicotine on activity of UC is still to be elucidated. This time, we investigated the involvement of nicotine in the colonic inflammation using murine colitis model.

Method: In murine study, tissue samples were obtained from colon of C57BL/6J mouse provided with drinking water containing dextran sulfate sodium (DSS). Degree of mRNA expression of TNF-α and MAdCAM-1 was determined by using quantitative RT-PCR. The inhibitory effects of nicotine on activity of colitis and mRNA expression were determined. To induce high endothelial venules in vitro, bEnd3 cell line was treated with TNF-alpha. Effect of nicotine on MAdCAM-1 expression on high endothelial venule (HEV) like vessel was also measured by using quantitative RT-PCR.

Results: In murine colitis model, administration of nicotine ameliorated DSS colitis. Administration of nicotine also significantly decreased degree of expression of MAdCAM-1 mRNA on HEV-like vessel.

Conclusion: Nicotine ameliorates DSS colitis possibly via down regulation of MAdCAM-1 expression on HEV-like vessel, and accordingly, inhibition of aberrant lymphocyte migration in colonic mucosa.

Y-02

VEGFR1 signaling facilitates diabetic skin wound healing in mice

Shin-ichiro Okizaki[1,3], Yoshiya Ito[2], Hirotoki Okubo[1,2], Ken Kojyou[1,2], Kazuhito Ohba[1,3], Shichiri Masayoshi[3], Masataka Majima[1]

Departments of 1) Pharmacology, 2) Surgery, and 3) Endocrinology, Kitasato University School of Medicine, Kanagawa, Japan

Aims: Signaling of vascular endothelial growth factor receptor 1 (VEGFR1) is suggested to involve in angiogenesis and lymphangiogenesis. The objective of the present study was to examine the role of VEGFR1 signaling in angiogenesis/lymphangiogenesis during diabetic skin wound healing.

Methods: VEGFR1-tyrosine kinase knockout mice (KO) or their wild counterparts (WT) were treated with streptozotosin (STZ) or vehicle (Veh). Full-thickness skin wounds were created on the backs of mice.

Results: Compared with non-diabetic mice (Veh/WT), wound healing and angiogenesis were suppressed in diabetic mice (STZ/WT) and non-diabetic KO mice (Veh/KO), with reduced expression of VEGF-A and CD31 in wound granulation tissues. Formation of lymphatic vessels was inhibited with reduced expression of VEGF-C, VEGF-D and VEGFR3. Accumulated VEGFR1-positive macrophages with VEGF-C or VEGF-D-expressing cells in granulation tissues were decreased. This was associated with attenuated expression of mannose receptor (MR) and transforming growth factor-beta (TGFβ). Diabetic KO (STZ/KO) showed further delayed wound healing and wound-induced angiogenesis/lymphangiogenesis. Exaggerated reduction in recruitment of VEGFR1-positive macrophages and in expression of MR and TGFβ was also demonstrated.

Conclusions: These results indicate that VEGFR1 signaling plays a role in angiogenesis/lymphangiogenesis through recruitment of VEGFR1-positive macrophages during diabetic wound healing.

Y-03

Post-stroke administration of cilostazol changes metabolic profile in transsulfuration pathway of ischemic brain in a mouse model

Yasoo Sugiura[1,4], Mayumi Kajimura[1,2], Tsuyoshi Nakanishi[1,3], Takayuki Morikawa[1,2], Takako Hishiki[1,2], Makoto Suematsu[1,2]

1) Department of Biochemistry, School of Medicine, Keio University, Tokyo 160-8582
2) JST, ERATO, Suematsu Gas Biology Project, Tokyo 160-8582, Japan
3) MS Business Unit, Shimadzu Corporation, Kyoto 604-8511, Japan
4) Department of Pulmonary and Thoracic Surgery, Kanagawa National Hospital, Hadano 257-8585

Cilostazol, an inhibitor of phosphodiesterase3 (PDE3), has been suggested to minimize post-stroke cognitive impairment. However, mechanisms underlining these beneficial effects remain elusive. We, therefore, examined effects of cilostazol on biochemical characteristics of cerebral metabolism using mouse cerebral ischemia model *in vivo*. To decipher multifold mechanisms whereby cilostazol changes metabolic dynamics in different regions of the brain, we conducted metabolome analysis to target metabolic pathways responding to the cilostazol treatment. To this end, focal ischemia was induced by a left middle cerebral artery occlusion. Right after the induction of ischemia, either the cilostazol (30 mg/kg or 100 mg/kg) or vehicle was administered orally. At 60 min after the occlusion, metabolic processes were rapidly suspended by the *in situ* freezing to minimize autolytic changes. Metabolites were extracted and measured with high-throughput capillary electrophoresis mass spectrometry. We then conducted cluster analysis to compare and contrast changes in 90 metabolites extracted from contralateral (CL) and ipsilateral (IL) hemispheric brains. In both CL and IL, the cilostazol treatment tended to increase cystathionine, taurine, cysteine, and the reduced form of glutathione, suggesting that the treatment alters sulfur amino acid metabolism and the transsulfuration pathway. Such an observation led us to hypothesize that cilostazol controls the activity of cystathionine β-synthase (CBS) which catalyzes the first committed step of the transsulfuration pathway. When primary cultured astrocytes which endogenously express CBS were treated with cilostazol, CBS expression increased as judged by Western blot analysis. These results indicate that cilostazol treatment could achieve neuroprotection via controlling CBS activity. Alteration of metabolites in the transsulfulation pathway induced by cilostazol oral administration may lead to beneficial therapeutic stratagem in cerebrovascular diseases.

Y-04

Role of leukotriene B4 receptor 1 (BLT1) signaling in liver repair after hepatic ischemia reperfusion injury

Hirotoki Ohkubo[1,2], Yoshiya Ito[2], Ken Kojo[1], Masahiko Watanabe[2], Masataka Majima[1]

Departments of 1) Pharmacology and 2) Surgery, Kitasato University School of Medicine, Kanagawa, Japan

Aims: Leukotriene B4 (LTB4) is a potent chemoattractant for macrophages, and recruited macrophages play a critical role in liver repair and recovery from acute liver injury. The objective of the present study was to examine the role of LTB4 receptor 1 (BLT1) signaling in liver repair after hepatic ischemia/reperfusion (I/R) injury.

Methods: BLT1knockout mice (BLT1-/-) and wild-type mice (WT) were subjected to 60 min of partial (70%) hepatic warm ischemia followed by reperfusion. The process of liver repair after hepatic I/R was determined.

Results: In WT, ALT levels peaked at 6h, and then declined to controls at 96h. In BLT1-/-, ALT levels also peaked at 6h, but those at 48 and 96h (recovery phase) were 2-fold higher than WT. The necrotic area in WT peaked at 24h, and reduced gradually, while that in BLT1-/- was remained high until 96 h. In BLT1-/-, the expression of proliferating cell nuclear antigen (PCNA) was delayed, which was associated with reduced levels of hepatic mRNA expression of epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), and VEGF receptor 1 (VEGFR1). Recruitment of VEGFR1-positive macrophages expressing EGF in injured liver from BLT1-/- was attenuated. Treatment of WT mice with an EGF-neutralizing antibody delayed liver repair and reduced macrophage recruitment, compared with control immunoglobulin G (IgG). BLT1 signaling enhanced the expression of VEGF, VEGFR1, and EGF in isolated peritoneal macrophages *in vitro*.

Conclusions: BLT1 signaling plays an important role in liver repair after hepatic I/R through enhanced EGF expression in recruited macrophages.

Y-05

3, 4-dihydroxyl-phenyl lactic acid restores NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 10 expression to ameliorate cardiac reperfusion injury

Ke He[1,2], Xiao-Yuan Yang[1,2], Na Zhao[1], Yu-Ying Liu[1], Bai-He Hu[1], Kai Sun[1], Xin Chang[1], Xiao-Hong Wei[1], Jing-Yu Fan[1], Jing-Yan Han[1,2]

1) Tasly Microcirculation Research Center, Peking University Health Science Center, Beijing 100191, China
2) Department of Integration of Traditional Chinese and Western Medicine, School of Basic Medical Sciences, Peking University, Beijing 100191, China

Background: Protection of ischemia/reperfusion (I/R) induced myocardial injury remains a challenge for clinician. 3, 4-dihydroxyl-phenyl lactic acid (DLA) is a major ingredient of cardiotonic pills®, a undergoing phase Ⅲ clinical trials drug for treatment of cardiovascular diseases in FDA in USA. However whether DLA exerts protective role against I/R and the intracellular target for DLA action remains unclear.

Methods and Results: Male Spragu-Dawley (SD) rats were subjected to left descending artery occlusion for 30 min, followed by reperfusion with or without DLA administration for 90 min. Results showed DLA reduced infarct size, diminished myocardial apoptosis and ameliorated impaired cardiac function and myocardial blood flow (MBF) after I/R. The results of 2-D fluorescence difference gel electrophoresis and activity assay kit revealed that DLA prevented from decrease in NADH dehydrogenase [ubiquinone] 1 alpha subcomplex, 10 (NDUFA10) expression, one of the subunits of Complex Ⅰ, blunted the impairment of Complex Ⅰ activity and mitochondrial function. To find the target of DLA, the binding affinity of Sirtuin 1 (SIRT1) to DLA and DLA derivatives with replaced two phenolic hydroxyls were detected using surface plasmon resonance and bilayer interferometry. The observed results demonstrated DLA was able to bind to SIRT1, depending on phenolic hydroxyl.

Conclusions: The present study demonstrated the capability of DLA to bind to and activate SIRT1, which plays an essential role in the cadioprotective effects of DLA. Preserved SIRT1 activity by DLA is responsible for the restored NDUFA10 protein and improved mitochondrial function, eventually leading to repressed infarct size and apoptosis, preserved cardiac function and MBF after I/R.

Y-06

Comparison of peripheral vascular resistance based on macro- and micro-circulatory responses by Poilleuille's law

Kazuhiro Yokokawa, Saki Hamashima, Masahiro Shibata

Department of Bio-Science and Engineering, Shibaura Institute of Technology

The total peripheral vascular resistance (TPR) is essential index in the cardiovascular system, since both the systemic blood pressure and blood flow could be determined by the changes of TPR. Such important index, the TPR cannot be measured directly, so Darcy's law would be applied to determine TPR. On the other hand, vascular flow resistance would be mainly controlled by the contraction or dilation of small arteries and arterioles, existing at the upstream of capillaries. Regarding the single small artery and the arteriole, the vascular flow resistance (R) could be represented as $R=8\mu L/\pi r^4$, called Poilleuille's law (μ : viscosity, r: vessel radius L: vessel length=constant). In addition, the major contribution of these vascular resistances would be caused by the resistance vessels in the skeletal muscle, since the blood flow in skeletal muscle dramatically changes from resting to excise, approximately 20 times increases. These facts suggest the TPR would be determined by the levels of contraction and dilation in skeletal muscle arterioles. In the present study, we tried to investigate in macro- and microcirculation whether the TPR can be estimated from the diameter changes of single arteriole in the skeletal muscle using Dalcy and Poilleuille's laws. Wister rats (180 - 400g b.w.) were anesthetized, and carotid artery and vein were canulated for the blood pressure measurement and administration of L-NAME, inhibiter of NOS production, respectively. The observation of microcirculation was carried out in the cremaster muscle by intravitalmicroscopy. The TPR was calculated by the changes in the blood pressure during L-NAME caused vasoconstriction based on the Dalcy's law, while the R was calculated by the changes in the arteriolar diameter based on the Poillleulle's law. The TPR and R were increased 23.9±7.7% and 23.5±8.7% from control to L-NAME caused vasocontraction, respectively. These results suggest the Poilleulle's law can apply to estimate the TPR in vivo microcirculation. Furthermore, it has been confirmed the TPR would be regulated mainly by the contraction and dilation of the skeletal muscle arterioles.

A-01

Roles of Prostanoids in Regulation of Angiogenesis and Lymphatic Tissue Remodeling

Masataka Majima

Department of Pharmacology, Kitasato University School of Medicine, Kitasato 1-15-1, Sagamihara, Kanagawa 252-0374, Japan

Inflammation influences the pathogenesis of cancers by induction of genome damage, proliferation in stromal cells, and generation of inflammatory mediators. Angiogenesis is also a critical step for development and metastasis of cancers. Proinflammatory mediators, such as prostaglandins (PGs) may have cell-autonomous effects on tumor cells in autocrine fashion, however, our results from tumor implantation models in knockout mice which lack the host receptor signaling clarified that host stromal signaling of a G-protein coupled PGE receptor, EP3 has a crucial role in tumor-associated angiogenesis through the induction of proaniogenic growth factors, and exhibited the landscaping effects on tumor cells. An EP3 antagonist inhibited tumor-associated angiogenesis in wild type mice, but not in EP3 knockout mice, suggesting that the blockade of host EP3 receptor signaling is important in prevention of tumor-associated angiogenesis. Further, bone marrow transplantation experiment revealed that recruitment of bone marrow cells which express EP3 is critical for angiogenesis in vivo. Our recent results also suggested that lymphangiogenesis observed in chronic inflammation and wound healing was regulated by an inducible cyclooxygenase, COX-2 and EP signaling. Further, we recently clarified that lymph node metastasis is enhanced by COX-2 and EP signaling via tissue remodeling of the regional lymph nodes to form premetastatic niche in the subcapsular regions. Thus, control of EP signaling as well as COX-2 in the tumor microenvironment is likely to be a therapeutic approach against cancers.

A-02

New Trends in therapeutic strategies against ischemia/reperfusion injury; Postconditioning and pharmacological intervention in acute myocardial infarction

Megumi Shimada[1)], Takashi Koyama[2)], Akiyasu Baba[1)], Rie Kosugi[1)], Makoto Akaishi[1)]

1) Department of Cardiology, Kitasato Institute Hospital, Kitasato University
2) Cardiovascular center, Tachikawa Hospital

Despite better outcomes with early coronary artery reperfusion for the treatment of acute myocardial infarction (AMI), morbidity and mortality from AMI remain significant, and myocardial reperfusion injury is a critical contributor to the final infarct size. In the past decade, several pharmacological treatments applied at early reperfusion have been tested in experimental models and in the clinical setting. Unfortunately, efforts at reducing reperfusion injury by several studies have largely been unsuccessful. There is a need to provide better cardioprotective therapy that reduces the amount of necrosis that may be coupled with better clinical outcomes.

Postconditioning: Ischemic postconditioning, defined as brief periods of ischemia immediately after the onset of reperfusion, has been recently shown to be one of the novel strategies of cardioprotection against reperfusion injury. However, recent clinical trials have not elucidated the protective effects of postconditioning. The protective effect of postconditioning is thought to result from delayed recovery from intracellular acidosis during the reperfusion period. It is generally accepted that lactate accumulation is responsible for intracellular acidosis during ischemia. As a higher extracellular lactate concentration impedes lactate transport from inside the cells, reperfusion with lactate-enriched blood should protect myocardial cell against reperfusion injury through prolonged intracellular acidification. We therefore modified the original postconditioning protocol by using lactated Ringer's solution to achieve controlled reperfusion with tissue oxygenation and minimal lactate washout from the cells. Ischemic postconditioning with lactate-enriched blood consistently suppressed the various detrimental effects of reperfusion and preserved myocardial viability well. Given the excellent microcirculation recovery consistently observed in this series, the modified ischemic postconditioning protocol might be a promising approach to effectively suppress myocardial reperfusion injury.

Pharmacological intervention: Recent clinical trials of cardiovascular disease have demonstrated that carperitide, a synthetic alpha-human atrial natriuretic peptide (ANP), improve survival in patients with acute myocardial infarction due to their cardioprotective effects. On the other hand, Rho kinase (ROCK) activation plays a major role as a mediator of irreversible injury in reperfused myocardium. We hypothesized that ROCK is activated specifically after ischemia-reperfusion (I-R) and that suppression of ROCK activity during I-R by ANP limits infarct size. A rat model of myocardial I-R injury was investigated by ligating the left descending coronary artery for 30 min and then reperfusing for 180 min. Continuous infusion of ANP (0.1 ug/kg/min) was started 5 min after the ligation and lasting for 175 min. Phosphorylation of the ROCK substrate protein myosin phosphatase targeting subunit (MYPT)-1 assessed by western blotting was used as a marker of ROCK activation. The myocardial infarct size and the area at risk of ischemia were measured by staining with triphenyltetrazolium chloride (TTC). The results showed that I-R injury induced ROCK activation significantly, and ANP reduced infarct size compared to control (9.4 $\pm$ 4.3 vs. 35.9 $\pm$ 3.5%, ANP vs. control, mean$\pm$SD, $p < 0.05$). Interestingly, the cardioprotective effect of ANP was abolished by 5-Hydroxydecanoate (5-HD), a putative mitochondrial KATP (mKATP) channel inhibitor (32.6$\pm$2.9% infarction). In Western blot analysis, attenuation of ROCK activation by ANP was reversed by 5HD, L-NAME, but not wortmannin, an inhibitor of phosphatidylinositol-3-kinase/Akt signaling. In conclusion, inhibition of ROCK activation by ANP limits infarct size via an opening of mKATP/NO-dependent mechanism.

A-03

Perfusion fixation method is critical for immunoelectron microscopy and ultrastructural evaluation on changes of caveolin-1 and caveolae relates with capillarization of liver sinusoidal endothelial cells in human cirrhotic liver

Hiroaki Yokomori[1], Jing-Yan Han[2], Masaya Oda[3]

1) Internal Medicine, Kitasato University Medical Center, Saitama, Japan.
2) Tasly Microcirculation Research Center, Peking University Health Science Center, Beijing, China.
3) Organized Center of Clinical Medicine, International University of Health and Welfare, Sanno Hospital, Tokyo, Japan.

Backgrounds and aims: Most vascular endothelial cells are continuously exposed to shear stress in vivo. Caveolae, omega-shaped membrane invaginations on endothelial cell (EC), also are plasmalemmal domain enriched in cholesterol, caveolins, and signaling molecules. Previous studies have proposed a role for caveolin(CAV)-1 in the regulation of angiogenesis and sinusoidal differentiation. This study was designed to elucidate the ultrastructural localization and change in CAV-1 expression on human liver sinusoidal endothelial cells (LSECs) during the progression of cirrhosis, using sections prepared by perfusion fixation method.

Methods: Normal control and Child-Pugh A and C cirrhotic liver specimens by surgical procedure were studied. CAV-1 protein and gene expression was examined by immunohistochemistry, Western blotting, laser-capture microdissection (LCM)-PCR. For immunoelectron microscopy, CAV-1 expressions in sinusoid was examined by perfusion fixed liver tissue.

Results: In control liver tissue, CAV-1 was localized on caveolae mainly in arterial and portal endothelial cells of the portal tract, and was also found on vesicles and some fenestrae in LSECs around the central vein. In cirrhotic liver tissue, aberrant CAV-1 expression was observed on caveolae-like structures and a few vesicles in LSECs. Significant overexpressions of CAV-1 at protein and mRNA level in cirrhotic liver was demonstrated by Western blotting and LCM-PCR ($p<0.01$ Child-Pugh A and C vs control, $p<0.01$ Child-Pugh A versus C).

Conclusion: CAV-1 was strongly expressed on caveolae-like structures and vesicles on LSECs in the sinusoids of cirrhotic liver, suggesting an association of CAV-1 with angiogenesis and differentiation of LSECs in cirrhosis

A-04

Brain-derived neurotrophic factor promotes angiogenesis via oxidative stress in human vascular endothelial cells: Implication for atherogenesis?

Hideyuki Yamawaki

Laboratory of Veterinary Pharmacology, School of Veterinary Medicine, Kitasato University

Aim: Brain-derived neurotrophic factor (BDNF), a major type of neurotrophins, promotes synaptic plasticity and neuronal cell survival, which contribute to the maintenance of structure and function of neuronal cells. Recent studies also indicate a possible involvement of BDNF in the atherogenesis. However, the detailed mechanisms for this remain to be fully clarified. We hypothesized that BDNF may at least partly play a role in the atherosclerotic plaque development through the promotion of angiogenesis. To gain mechanistic insights, we examined whether BDNF causes angiogenesis and underlying mechanisms with focusing on reactive oxygen species (ROS) and related intracellular signals in human cultured vascular endothelial cells (ECs).

Methods and results: In vascular ECs, BDNF increased ROS generation as measured fluorometrically using 2' 7'-dichlorofluorescein diacetate as well as NADPH oxidase (NOX) activity as determined by a chemiluminescent measurement. BDNF-increased ROS generation and NOX activity were inhibited by K252a, an inhibitor of tropomyosin-related kinase B (TrkB) receptor. BDNF caused phosphorylation of p47 phox, a regulatory component of NOX, which was inhibited by K252a as determined by Western blotting. In matrigel, BDNF caused angiogenic tube formation of ECs, which was inhibited by K252a or gp91ds-tat, a specific inhibitor of NOX. BDNF induced phosphorylation of Akt but not ERK in ECs, which was inhibited by K252a or gp91ds-tat. It was further confirmed that small interfering RNA (siRNA) against TrkB inhibited BDNF-induced ROS generation and tube formation.

Conclusion: The present results for the first time showed that BDNF promotes angiogenesis through NOX-derived ROS generation via the activation of p47 phox in a TrkB receptor-dependent manner.

F-01

Cilostazol inhibits leukocyte-endothelial cell interactions in murine microvessels after transient bilateral common carotid artery occlusion

Takuya Fukuoka, Takeshi Hayashi, Makiko Hirayama, Hajime Maruyama, Norio Tanahashi

Department of Neurology, Saitama Medical University International Medical Center, Saitama, Japan

Leukocyte behavior in the cerebral microvasculature following vessel occlusion has not been fully elucidated. The purpose of this study was to investigate the effects of cilostazol on leukocyte behavior (rolling and adhesion) in murine cerebral microvessels following transient bilateral carotid artery occlusion using intravital fluorescence microscopy. Four groups of mice were assigned: a sham group (n=16); an ischemia (induced by 15-min occlusion of bilateral common carotid arteries) and reperfusion (I/R) group (n=13); I/R+cilostazol (I/R+CZ3mg/kg) group (I/R after oral administration of cilostazol at 3mg/kg) (n=8) and I/R+cilostazol (I/R+CZ30mg/kg) group (I/R after oral administration of cilostazol at 30mg/kg) (n=12). Leukocytes labeled with 0.05% acridine orange were administered intravenously and their behavior was investigated at 3 and 6 h after reperfusion. Numbers of rolling or adherent leukocytes were expressed as the count per square millimeter per 30s. Numbers of rolling and adherent leukocytes at 3 and 6h after reperfusion were significantly higher in the I/R group than in the sham or I/R+CZ30mg/kg groups in both pial veins (P<0.05) and pial arteries (P<0.05). Cilostazol (30mg/kg) inhibited leukocyte-endothelial interactions following cerebral ischemia and reperfusion.

F-02

Impairment of CO_2 reactivity in RBC velocity and CBF after cortical spreading depression in anesthetized mice

Miyuki Unekawa[1)], Yutaka Tomita[1)], Haruki Toriumi[1)], Takashi Osada[1,2)], Kazuto Masamoto[3,4)], Hiroshi Kawaguchi[4)], Yoshiaki Itoh[1)], Iwao Kanno[4)], Norihiro Suzuki[1)]

1) Department of Neurology, Keio University School of Medicine
2) Department of Neurology, Tachikawa Hospital
3) Center for Frontier Science and Engineering, University of Electro-Communications
4) Molecular Imaging Center, National Institute of Radiological Sciences

Background: We previously reported that cortical spreading depression (CSD) drastically suppresses red blood cell (RBC) velocity and alters cerebral blood flow (CBF) and vessel diameter in cortical arteriole. It has been reported that CSD induces disruption of neurovascular and neurometabolic coupling.

Objective: To further understand mechanisms involved in the disturbance of microcirculation, reactivity to carbon dioxide (CO_2) in RBC velocity flowing in intraparenchymal capillaries and CBF was measured before and after CSD passage.

Methods: To visualize blood vessels, we used Tie2-GFP transgenic mice (N=10), in which specifically vascular endothelial cells emit fluorescence. Under urethane anesthesia and artificial ventilation, RBC velocity was measured using a confocal laser-scanning microscope with high-speed camera (125 fps) and an original image analyzing system of KEIO-IS2 working on MATLAB through a cranial window installed on the temporo-parietal region of the cerebral cortex, along with CBF by laser Doppler flowmeter. CO_2 reactivity was measured with 5% CO_2 inhalation for 1min. CSD was induced by microapplication of 1M KCl through a tiny cranial hole posterior to the cranial window.

Results: RBC velocity was measured in 4 to 21 capillaries in each mouse. CO_2 inhalation increased partial pressure of arterial CO_2 by 14.1±3.9mmHg. During hypercapnia, CBF and RBC velocity averaged in each mouse increased by 14.1±11.3% and 17.7±19.0% with significant correlation between the increases (r=0.79, n=8). After CSD passage, increase in CBF and RBC velocity were reduced to 7.3±21.8% and 11.6±22.9%, respectively, and the correlation was lost (r= -0.15, n=11).

Conclusion: CSD attenuated CO_2 reactivity in CBF and RBC velocity by different mechanism, probably due to impairment of neurovascular and neurometabolic coupling.

F-03

EXPLORE THE ANGIOGENESIS OF AUTOLOGOUS TRANSPLANTED BRAIN TISSUES IN RABBITS

Jin Xuelong

Department of Physiology, Tianjin Medical University, Tianjin, 300070, China

Objective: This study intends to discuss about the methodology of rabbit's brain tissue transplantation, including the way of operation and the law of microcirculatory formation.

Methods: 20 male Japanese white rabbits (1.2～1.3 kg) were chosen for an intracerebral transplantation test, which were anaesthetized by 3% pentobarbital sodium in vein before receiving an intracerebral transplantation operation. A window was opened on their parietal bone and the cortical brain tissues on the symmetrical areas on the left and right side of the rabbits' parietal cortex areas were exchanged and transplanted. Gentamycin sulfate was injected each day to resist infection. Ten and twenty days later, an observation was made as to the survival of the transplanted area and host brain tissue. A microcirculation color camera system was used to analyze the pictures of angiogenesis. With regard to the survival of transplanted brain tissues, their changes in micromorphology were observed. Besides, pathological sections were also prepared to determine their surviving conditions on a cell level.

Result:

(1) Surgical operation has contributed to a satisfactory morphological anastomosis between transplanted brain tissues and host brain tissues.
(2) Analysis of the pathological sections of the transplanted brain tissues showed traces of surviving neural cell.

Conclusions: Under the given conditions, transplanted brain tissues can maintain neuron's survival, and can be nourished by angiogenesis and characteristic microcirculation connections with host brain tissues.

F-04

HO-2/CO system protects against metabolic disorders following acute cerebral ischemia

Takayuki Morikawa[1)], Mayumi Kajimura[1,2)], Tsuyoshi Nakanishi[1,3)], Yoshinori Yukutake[2)], Makoto Suematsu[1,2)]

1) Department of Biochemistry, School of Medicine, Keio University, Tokyo 160-8582
2) JST, ERATO, Suematsu Gas Biology Project, Tokyo 160-8582, Japan
3) MS Business Unit, Shimadzu Corporation, Kyoto 604-8511, Japan

Although it has been known that brain generates carbon monoxide (CO) via heme oxygenase (HO) catalyzed reactions, physiologic roles of CO in the central nervous system remain elusive. Previous study showed that HO-2 generates CO in an O_2-dependent manner. By acting as an acute O_2 sensor within the neurovascular unit, HO-2 contributes to the maintenance of cerebral ATP levels against acute global hypoxia (Morikawa *et al.,* PNAS, 109, 1293-1298). In this study, we examined if the deletion of HO-2 exacerbates cerebral metabolism upon acute focal brain ischemia. We compared contents of 87 metabolites extracted from contralateral- and ipsilateral hemispheres after a left middle cerebral artery occlusion (MCAO) between wild-type- and HO-2-null mice. With hierarchical clustering analysis, we found that, in ipsilateral hemispheres, there was no obvious difference in patterns of metabolic alteration between wild-type- and HO-2-null mice. On the other hand, in the contralateral hemispheres, we found the clusters showed striking difference in patterns of metabolic alteration between two groups during MCAO. Such a cluster included high energy phosphonucleotides; e.g., ATP, UTP and CTP. These data indicate that nucleotide degradation after MCAO is more severe in the HO-2-null mice than that in wild-type mice. Furthermore, our results indicate that HO-2 contributes to the improvement of metabolic disorders during cerebral ischemia in contralateral hemisphere rather than in ipsilateral hemisphere. This is the first report showing the potency of HO-2/CO system to diminish the remote metabolic insults of acute focal cerebral ischemia.

F-05

The blood cell flow and the vascular responses in arterioles and capillaries after subarachnoid hemorrhage

Mami Ishikawa[1,2], Mayumi Kajimura[1], Takayuki Morikawa[1], Tomomi Nakamura[1], Yuichi Tanaka[2], Eiju Watanabe[2], Makoto Suematsu[1]

1) Department of Biochemistry, School of Medicine, Keio University
2) Department of Neurosurgery, Jichi Medical University

Purpose: Immediately after subarachnoid hemorrhage (SAH), brain injury begins and determines the acute phase mortality and the long-term prognosis, but its mechanism is not well understood. When SAH at the skull base induces platelet-leukocyte-endothelial cell interactions in venules, the cerebral blood flow is kept well at the cerebral surface[1]. We investigated cerebral microcirculation through a mouse cranial window using two-photon laser scanning microscopy at a depth of about 100 μm[2,3], after SAH was induced at the skull base.

Methods: Tracheotomy was performed and femoral artery was cannulated in mice (FVB/N-Tg (GFAP GFP) 14Mes/j) . Q-dot 655 nanocrystal (Q21021MP; Invitrogen) or rhodamine-6G was injected from the cannulated femoral vein, after a craniotomy at the parietal bone without cutting dura matter. SAH was induced at a prone position by using the endovascular perforation model[4]. Immediately and one hour after SAH, blood cell velocities were measured with a line scan method in precapillary and capillary using two-photon laser scanning microscopy.

Results: A penetrating arteriole branched into a precapillary arteriole at the depth of 85.9 +/- 21.0 μm (n=7). Arterioles dilated immediately after SAH and then gradually constricted (n=5/7) and the blood flow disappeared immediately after SAH in the others (n=2/7). The blood cell velocity of the precapillary arteriole decreased from 10.7 +/- 3.0 mm/s before SAH to 0.9 +/- 0.4 mm/s after SAH. The capillary-velocities of blood cells (red blood cells, platelets and leukocytes) also decreased, and rolling and adherent leukocytes prevented blood cells from flowing in capillaries.

Conclusion: The cerebral blood flow decreases in arterioles and capillaries, when the SAH is induced.

References

1) Ishikawa M et al. Neurosurgery 64:546-554, 2009.
2) Nakamura T et al. Acta Physiol 203:187-196, 2010.
3) Morikawa T et al. Proc Natl Acad Sci USA 109:1293-1298, 2012.
4) Ishikawa M et al. Stroke 30:1679-1686,1999.

F-06

c-Met interaction with Angiogenesis and Stem Cell in Helicobacter heilmannii-induced gastric MALT lymphoma: Interaction with VASH-2

Masahiko Nakamura[1], Hidenori Matsui[2], Tetsufumi Takahashi[1], Shinichi Takahashi[3], Toshifumi Hibi[4], K. Tsuchimoto[1]

1) School of Pharmaceutical Sciences, Kitasato University, Tokyo, Japan
2) Kitasato Institute for Life Sciences, Kitasato University, Tokyo, Japan
3) 3rd Department of Internal Medicine, Kyorin University School of Medicine, Mitaka, Japan
4) Kitasato Institute Hospital

We established a low-grade MALT lymphoma model in C57BL/6 mouse infection of *Helicobacter heilmannii* obtained from cynomolgus monkey (Infect. Immun. 75 (3): 1214-1222, 2007). After long-term infection, we found the MALT lymphoma formation in the liver and lung in addition to gastric MALT lymphoma. Recently, c-MET, the tyrosine kinase receptor for hepatocyte growth factor (HGF) has attracted attention as one of the key players in survival and proliferation of B-cell malignancies.

Thus, we have planned to clarify the difference of c-MET, HGF and HGF activator (HGFA) expression as well as VEGF and its receptors, Flt-1, Flk-1 and vasohibin-2 (VASH2) in gastric, hepatic and pulmonary lesions in the MALT lymphoma by immunohistochemistry. The effect of c-MET antibodies or inhibitor, PHA-665752 (10 mg/kg b.w.) on the formation of liver and lung lesion was also investigated.

As a result, Nine months after the infection, small lymphocyte aggregates mostly composed of B cells were observed in the portal area of the liver and the peribronchial area of the lung as well as the gastric MALT lymphoma in approximately 50% of the infected mice. These lymphocytes were mostly centrocyte-like cells, and lymphoepithelial lesions characteristic of MALT lymphoma were also recognized. PCR and *in situ* hybridization analysis showed the existence of Helicobacter heilmannii not only in the fundic mucosa but in the lung and liver. Twelve and eighteen months after the infection, approximately 100% of infected mice had hepatic and pulmonary lesions. c-MET immunoreactivity was found in the lymphocytes composing the MALT lymphoma, and HGF immunoreactivity was recognized mostly in the endothelial cells and macrophages. HGFA was localized on mesenchymal cells other than the lymphocytes. The administration of antibodies against c-MET or a c-Met inhibitor to the infected mice induced the significant suppression of hepatic and pulmonary lesions as well as the gastric MALT lymphoma, while VASH2 immunoreactivity rather increased within the tumor.

In conclusion, HGF and c-MET pathway were suggested to contribute to the lymphomagenesis and the VASH2 has a compensatory effect in the liver and lung after *Helicobacter heilmannii* infection.

F-07

Visualisation of drug delivery by using high resolution microscopic mass spectrometry

Masahiro Yasunaga[1)], Masaru Furuta[2)], Koretsugu Ogata[2)], Yoshikatsu Koga[1)], Yoshiyuki Yamamoto[1)], Misato Takigahira[1)], Yasuhiro Matsumura[1)]

1) Investigative Treatment Division, National Cancer Center Hospital East
2) Analytical & Measuring Instruments Division, Shimadzu Corporation

Background: Pharmacokinetic (PK) and pharmacodynamic (PD) studies are important to evaluate the efficacy and toxicity of the drugs. In these analyses, tissue homogenates are generally used for the quantification by high-performance liquid chromatography (HPLC) or liquid chromatography mass spectrometry (LC-MS). However, they lack the drug distribution in a specific anatomical area. The precise information about the distribution allows the researchers to optimize the drug design enabling more efficient targeted delivery.

Purpose: We studied the tissue distribution of paclitaxel (PTX) and its micellar formulation (NK105) using a microscopic mass spectroscopy (MMS).

Method: A MMS in which a microscope is coupled with an atmospheric pressure matrix-assisted laser desorption/ionization (MALDI) and quadruple ion trap time-of-flight (TOF) analyser was used. The matrix-coated drug sample is ionised and then separated on the basis of its mass-to-charge ratio (m/z). Images were acquired from imaging mass spectrometry (IMS) or tandem mass spectrometry (MS/MS) data.

Result: (1) We established the drug imaging system with enhanced resolution and sensitivity. In the analysis, MS and MS/MS were used for quantification and validation, respectively. (2) NK105 showed much stronger antitumor effects on a human pancreatic cancer BxPC3 xenograft than PTX. In the drug imaging, we demonstrated that NK105 delivered more PTX to the whole tumor tissue (including the center lesion). In the mouse model, PTX caused the peripheral neurotoxicity but NK105 did not. Multiple high drug-signal areas surrounding and inside the caudal nerve were observed in the case of PTX, whereas the signals after NK105 injection were significantly low.

Conclusion: We succeeded in corroborating the EPR effect using MMS. The data obtained by the drug imaging may be useful for facilitating DDS-drug design.

F-08

Salvianolic acid B binds to Src and ameliorates mesenteric venules hyperpermeability in endotoxmia rats

Chun-Shui Pan[1)], Ying-Hua Liu[1)], Yu-Ying Liu[1)], Yu Zhang[1)], Ke He[1,2)], Xiao-Yuan Yang[1,2)], Bai-He Hu[1,2)], Xin Chang[1,2)], Xiao-Hong Wei[1)], Jing-Yu Fan[1)], Jing-Yan Han[1,2)]

1) Tasly Microcirculation Research Center, Peking University Health Science Center, Beijing 100191, China.
2) Department of Integration of Traditional Chinese and Western Medicine, School of Basic Medical Sciences, Peking University, Beijing 100191, China.

Background: Microvascular hyperpermeability is a crucial contributor to the gastrointestinal injury, for which the current clinical therapy remains unsatisfied. Src regulates the hyperpermeability-related proteins, such as caveolin-1, VE-cadherin and ZO-1. This study aimed to evaluate whether salvianolic acid B (SalB) binds to Src to regulate caveolin-1, VE-cadherin and ZO-1, to ameliorate mesenteric venules hyperpermeability in endotoxmia rats.

Methods: The male Wistar rats were challenged by infusion of LPS (2mg/kg/h) for 90 min, with or without SalB (5mg/kg/h). Human umbilical vein endothelial cells (HUVECs) were incubated with LPS or/and SalB. Microcirculation was assessed by intravital microscopy, caveolae in microvascular endothelial cells by electron microscopy, endothelial cell junctional proteins, caveolin-1 and Src by Western blot and confocal microscopy, and the interaction of Src and SalB by Surface Plasmon Resonance (SPR) and BioLayer Interferometry (BLI).

Results: SPR and BLI demonstrated that SalB was able to bind to Src in a dose-dependent manner, further to inhibit the phosphorylation of Src, caveolin-1 and vascular endothelial cadherin increased in human umbilical vein endothelial cells, to restore the distribution of Zonula occluden-1 and VE-cadherin degradated in cells exposed to LPS. Furthermore, SalB alleviated the inclement of caveolae in microvascular venules, and the evoked albumin leakage from venules in endotoxmia rat mesentery.

Conclusions: SalB prevents endothelial barrier dysfunction and hyperpermeability via binding to Src to inhibit the activity of Src. These findings identify SalB as a promising approach to permeability, and indicate Src as novel target for hyperpermeability treatment.

F-09

RhoJ defines angiogenic endothelial cell motility by integrating VEGF and Sema3E signals

Akiyoshi Uemura[1)], Yoko Fukushima[1)],
Koichi Nishiyama[2)], Yuichiro Ogura[3)],
Shin-Ichi Nishikawa[4)]

1) Division of Vascular Biology, Kobe University Graduate School of Medicine
2) Department of Physiological Chemistry and Metabolism, Graduate School of Medicine, The University of Tokyo
3) Department of Ophthalmology and Visual Science, Nagoya City University Graduate School of Medical Sciences
4) Laboratory for Stem Cell Biology, RIKEN Center for Developmental Biology

During tissue morphogenesis, cells migrate in response to diverse extrinsic cues. For angiogenic endothelial cells (ECs), vascular endothelial growth factor (VEGF) and semaphorin 3E (Sema3E) are a pivotal attractant and repellent, respectively. However, it is still unclear how individual ECs integrate these opposite signals to determine their migratory behaviors. Here, we show that the small GTPase RhoJ is an EC-intrinsic integrator of VEGF and Sema3E signals. In its GTP-bound state, RhoJ bound to the cytoplasmic domain of PlexinD1. Upon Sema3E stimulation, RhoJ was released from PlexinD1 and directly induced cell contraction. Upon VEGF stimulation, RhoJ facilitated VEGFR2-PlexinD1 association, thereby preventing VEGFR2 degradation, prolonging downstream signal transduction events, and promoting directional EC movements. Consequently, RhoJ deficiency, even in a single allele, led to variable morphogenetic defects in retinal vascular patterning. Our results indicate that RhoJ may be a novel therapeutic target to manipulate EC motility in disease or tissue regeneration.

F-10

C-peptide Effects on Glomerular Filtration

Hiroshi Nakamoto[1)], Kazuhiko Nakayama[2)],
Noriaki Emoto[2)], Toyotaka Yada[1)], Yasuo Ogasawara[1)]

1) Department of Medical Engineering and Systems Cardiology, Kawasaki Medical School, Kurashiki, Okayama, JAPAN
2) Clinical Pharmacy, Kobe Pharmaceutical University, Kobe, Hyogo, JAPAN

In our previous visualisation study, we reported that there is a leakage of proteins at the level of glomeruli on the early stage of diabetes when proteinuria was not present and that C-peptide ameliorated this leakage. C-peptide, a byproduct of insulin secretion was once considered biologically inactive. Since as early as the 1980s, studies have provided direct evidence that C-peptide is a biologically active endogenous peptide hormone. It is now known that administration of physiologically relevant doses of C-peptide reduces diabetes-induced glomerular hyperfiltration, decreases albuminuria, and reduces renal hypertrophy. We hypothesised that C-peptide might work on the structure of glomerular filtration barrier to show its effects.

We used streptozotocin-induced rats as diabetic animal models (50mg/kg). Part of both control and diabetic rats were given C-peptide continuously one hour prior to sacrifice (50pmol/kg/min). Extracted kidney samples were examined by fluorescence antibody technique and electron microscopy. Of glomerular slit membrane components, podocin, nephrin and CD2AP were stained and glomerular section images were binalised. The distribution of slit membrane proteins were analysed by area ratio (ratio for coexisting area of two component proteins). Inter-footprocess spaces were measured as podocytic structural change.

There was a loose negative correlation between the diabetic duration and the area ratio of either two out of three protein components ($r=-0.24$ to -0.59). There was not a significant change in area ratio after C-peptide administration in both control and diabetic rats. The inter-footprocess spaces were significantly different ($p<0.01$), 8.17 ± 0.44nm, 9.72 ± 0.44nm for control and diabetic rats respectively. C-peptide administration widened the spaces to 10.39 ± 0.65nm ($p<0.01$) and to 15.45 ± 0.96nm ($p<0.01$) for control and diabetic rats respectively.

C-peptide did not change the structure of glomerular slit membranes but widened the inter-footprocess spaces. C-peptide effects on ameliorating glomerular leakage of protein was considered to be due to other effects than causing structural changes to glomerular filtration barrier.

F-11

Measurement of blood flow velocity profiles in retinal arterioles and venules using spectral-domain doppler optical coherence tomography in healthy subjects

Taiji Nagaoka, Tomofumi Tani, Akihiro Ishibazawa, Kenji Sogawa, Seigo Nakabayashi, Tsuneaki Omae, Akitoshi Yoshida

Department of Ophthalmology, Asahikawa Medical University, Asahikawa, Japan.

Purpose: To evaluate the reproducibility of retinal blood flow (RBF) velocity profiles using Doppler optical coherence tomography (OCT) in healthy young volunteers.

Methods: RBF velocity profiles were measured over one cardiac cycle using Doppler OCT in six healthy volunteers. The measured vessels were chosen at the straight portion 1 to 2 disc diameters from the optic disc. Two-dimensional velocity profiles in the venules and arterioles were extracted, and the maximal (V_{max}) and average (Vave) velocities were calculated automatically. The ratio of V_{max} and V_{ave} was set to characterize the flow conditions in the vessels.

Results: The ratios of V_{max} to V_{ave} were about 1.6 to 1.8 for the arterioles and venules in most cases. The ratio in the arterioles was unchanged during the cardiac cycle. In addition, this ratio has constant for one cardiac cycle at the straight portion.

Conclusions: The current study showed that Doppler OCT enables accurate and reproducible measurements of the blood velocity profiles in the entire lumen of the retinal arterioles and venules in healthy young volunteers.

F-12

Clinical characteristics of peripheral type of diabetic retinopathy diagnosed with ultra-wide field fluorescein angiography

Shuichiro Hirahara, Taneto Tomiyasu, Miho Nozaki, Munenori Yoshida, Yuichiro Ogura

Department of Ophthalmology and Visual Science, Nagoya City University Graduate School of Medical Sciences

Purpose: Fluorescein angiography with Optos® 200Tx is useful to visualize the microcirculations of peripheral retina. The purpose of this study is to evaluate the feature of the patients with peripheral type of diabetic retinopathy (DR) diagnosed by using Ultra-wide field FA (UWFA) with Optos® 200Tx.

Methods: The UWFA was performed on 154 eyes of 77 patients with DR (62 male, 15 female, average age : 60.2 years). Fifteen eyes (9.7%) were found to have the capillary non-perfusion area only in the far-periphery without any evidences of non-perfusion in the posterior pole and the mid-periphery. Eight eyes of 6 patients were non-treated cases with peripheral type of DR (4 male, 12 female, average age : 66.3 years). We evaluated the FA findings, HbA1c and disease duration of these patients with peripheral type of DR.

Results: All of the non-treated patients with peripheral type of DR have been having diabetes for more than 20 years (average of 26.2 years). The control of blood sugar was poor (HbA1c 6.7~10.1%, average 8.1%). One of these cases, whose blood sugar was good (HbA1c 6.7%), had diabetes for as long as 40 years. It was reported that most cases of peripheral type of DR progress slowly. However, we experienced a case that represented vitreous hemorrhage caused by retinal neovascularization existed in only periphery.

Conclusions: Peripheral type of DR was considered to progress slowly. Most of them were found in elder patients. It is not rare to see the cases in which peripheral capillary occlusion exist even though posterior pole is intact, especially in the patients with long history of diabetes.

F-13

H_2O_2-induced Vasodilatation Compensates Diabetes-induced Microvascular Endothelial Dysfunction during Acute Coronary Occlusion in Canine Coronary Native Collateral Microvessels in Vivo

Toyotaka Yada[1], Hiroaki Shimokawa[2], Osamu Hiramatsu[1], Hiroshi Nakamoto[1], Masami Goto[1], Yasuo Ogasawara[1], Fumihiko Kajiya[1]

1) Department of Medical Engineering and Systems Cardiology
2) Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Japan

Background: It has been previously demonstrated that endothelial Cu, Zn-SOD and caveolin-1 play crucial roles of hydrogen peroxide (H_2O_2) production as an endothelium-derived hyperpolarizing factor (EDHF) in mouse mesenteric arteries. We thus examined whether this mechanism is involved in the EDHF-mediated responses in diabetes mellitus (DM) during acute coronary occlusion.

Methods: Canine subepicardial coronary collateral small arteries (CSA>100μm) and arterioles (CA <100μm) were visually traced by an intravital microscope between left anterior descending artery (LAD) and left circumflex coronary artery (LCX) with an injection of indocyanine green. We examined bradykinin-induced vasodilatation of native coronary collaterals before and after myocardial ischemia by proximal LAD occlusion (90min) under the following conditions (n=6 each); (i) control and (ii) DM (alloxan, 1 week prior to study, IV) with cyclooxygenase blockade (ibuprofen, 12.5 mg/kg, IV) before the onset of the ischemia. Myocardial levels of Cu,Zn-SOD, caveolin-1 and H_2O_2 (Amplex Red) and plasma levels of 8-OHdG, as a marker of oxidative stress and tetrahydrobiopterin in the coronary sinus were measured by ELISA and high-performance liquid chromatography.

Results: Although the levels of Cu, Zn-SOD, tetrahydrobiopterin and caveolin-1 in the LAD area were comparable between the control and DM groups, caveolin-1 levels were greater in coronary microvessels than in coronary conduit arteries in the control group. Nitric oxide (NO)-mediated coronary vasodilatation of CSA by bradykinin significantly decreased in DM compared with control, and was restored by compensation of EDHF/H_2O_2 in CA with H_2O_2 production for the loss of NO. Oxidative stress (8-OHdG) was significantly increased in DM compared with control.

Conclusions: NO-mediated, endothelium-dependent vasodilatations of CSA during acute coronary occlusion are impaired in DM and are compensated by EDHF/H_2O_2 in dogs in vivo.

F-14

Nailfold microcapillary findings reveal early stage of congestion of right ventricle of the heart.

Ichiro Miura[1], Masato Matsuo[2], Tsuyoshi Konta[3], Katsuya Nagayama[4], Masami Miyazaki[5]

1) Dept. human pathol. Juntendo university
2) Dept. Oral Anatomy, Kanagawa Dental College
3) Ogawa iin
4) Dept.Mechanical information and Technology Kyushu institute of technology
5) School of human science Waseda univ

Back groud and aims: Nailfold capillaroscopy is usefull for determine the state of peripheral microvessels in various disease, especially rheumatic disease. While capillary loss is well known in essential hypertension as findings of the cardiovascular disease, clinical significance of horizontal capillaries is not well known. We have examined the relationship between serum concentration of brain natriuretic peptide (BNP) and horizontal vessels in nailfold capillary microscopy.

Method: The study examined 78 patients 60 years of age or older. Serum BNP concentration was measured for all cases, and we examined the statistical significant difference of the cases with and without findings of transverse blood vessels by the nailfold capillary microscopy.

Result: Serum BNP concentration increased in many cases with a horizontal vessels and significant difference was observed statistically. BNP concentration was enough to slightly more than normal values.

Discussion: Using the nailfold capillary microscopy, deformation of the vessel in the vertical direction is most notable. On the other hand, the meaning of the transverse blood vessels has received less attention. Evaluated the observation of blood flow of many finger tips, it was considered that the blood flow in the horizontal direction is venous blood flow. We estimated that horizontal blood flow means the decrease of venous return, namely expresses the early state of congestion of the right ventricle of the heart. Since the BNP rise and this finding had a significant difference statistically, we considered nailfold microcapillary findings can reveal early stage of congestion of right ventricle of the heart.

F-15

Ma-Xing-Shi-Gan-Tang, a traditional Chinese medicine, attenuates lipopolysaccharide-induced pulmonary microcirculatory disturbance and lung edema in rats

Li-Qian Ma[1,2], Kai Sun[1], Chun-Shui Pan[1], Yu-Ying Liu[1], Li Yan[1], Jing-Yu Fan[1], Jing-Yan Han[1,2]

1) Tasly Microcirculation Research Center, Peking University Health Science Center, Beijing 100191, China
2) Department of Integration of Chinese and Western Medicine, School of Basic Medical Sciences, Peking University, Beijing 100191, China

Background: Ma-Xing-Shi-Gan-Tang (MXSGT) is a compound traditional Chinese medicine which has been widely used in clinic for treatment of acute upper respiratory tract infection in China. However, whether MXSGT could improve LPS-induced pulmonary microcirculatory disturbance and lung edema is still not clear.

Objective: The aim of this study is to investigate the ameliorating effect and potential mechanism of MXSGT on the LPS-induced pulmonary microcirculatory disturbance and lung edema.

Method: Male Sprague-Dawley rats (weight in 200±20g) were injected with LPS (7mg/kg) intraperitoneally to induce lung microcirculatory disturbance and lung edema. MXSGT (2.6075g/kg) was given by gavage 6 hours after LPS exposure. Examinations were undertaken at 6 and 12 hours after LPS exposure, respectively.

Result: The number of leukocytes adhering to pulmonary venules and the expression of ICAM-1 in lung tissue were increased at 6 hours and 12 hours after LPS exposure. In addition, LPS increased pulmonary tissue W/D ratio and decreased the expression of junctional adhesion molecule-1 and claudin-5 in lung tissue. Post-treatment with MXSGT significantly suppressed these changes induced by LPS exposure.

Conclusion: This study demonstrated that MXSGT ameliorated rat pulmonary microcirculation disturbance and lung edema induced by LPS, the underlying mechanism may involve protection of leukocytes from adhering to pulmonary venule and up -regulation of junctional adhesion molecule-1 and claudin-5 in lung tissue.

F-16

The protective effects of rapamycin on intestinal ischemia/reperfusion induced remote lung injury in mice

Takaya Iida[1], Yuji Naito[1], Tomohisa Takagi[1], Kazuhiro Katada[1], Katsura Mizushima[1], Kazuhiro Kamada[1], Kazuhiko Uchiyama[1], Osamu Handa[1], Nobuaki Yagi[1], Yoshito Ito[1], Toshikazu Yoshikawa[2]

1) Department of Molecular Gastroenterology and Hepatology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine
2) Kyoto Prefectural University of Medicine

Introduction: The intestinal ischemia/reperfusion (I/R) injury occurs in various clinical settings, such as mesenteric artery occlusion, trauma, and intestinal transplantation. Intestinal I/R injury elicits inflammatory responses within the intestine, including mucosal epithelial cell damage, loss of barrier function, proinflammatory cytokine production, and increased microvascular permeability. These changes develop multiple organ failure, and become fatal. However, the cure is not fully established. The mammalian target of rapamycin (mTOR) plays an important role in cellular proliferation and survival. It has been shown to be focused on a therapeutic target for various diseases such as cancer and inflammation. Herein, this study was designed to determine whether the mTOR inhibitor, rapamycin, had protective effects on intestinal I/R injury in mice.

Methods: The small intestine of C57BL/6 mice was challenged with ischemia by occluding superior mesenteric artery for 1h. Rapamycin was administered intraperitoneally 1h before the induction of ischemia. In mice following intestinal I/R, the survival rate, inflammatory responses and adhesion molecules in the small intestine and lung were assessed. Bacterial cultures were performed using the homogenate samples from lungs. Phagocytic capacity in the alveolar macrophages and the activation of NF-κB in the lung were also assessed.

Results: Treatment with rapamycin significantly improved survival rate after intestinal I/R. Inflammatory markers (TNF-alpha and MPO activity) in the intestinal tissue of rapamycin-treated mice were unchanged but these assays in the lung were attenuated in rapamycin-treated mice along with decreased bacterial culture and increased phagocytic capacity. The activation of NF-κB and downstream expression of adhesion molecules in the lung of rapamycin-treated mice were downregulated.

Conclusion: Treatment with rapamycin improved survival rate via attenuation of intestinal I/R-induced remote lung injury.