Asia-Pacific Diabetes and Obesity Study Group
APDO

Asia-Pacific Diabetes and Obesity Study Group
Joint with the 39th Annual Meeting of Japan Society for the Study of Obesity

APDO SYMPOSIUM 2018

[Dates] October 8 (mon) to 9 (tue), 2018

[Venue] Kobe Convention Center

President : Wataru Ogawa

Professor and Chair, Division of Diabetes and Endocrinology, Department of Internal Medicine
Kobe University Graduate School of Medicine




Program & Abstract Book

APDO SYMPOSIUM 2018
Program & Abstract Book

Welcome Message from the President of APDO2018

Wataru Ogawa

The president, APDO2018 and 39th annual meeting of JASSO
Professor and Chair, Division of Diabetes and Endocrinology,
Department of Internal Medicine,
Kobe University Graduate School of Medicine

I would like to extend my warmest welcome to all the participants of the 13th Symposium of Asia-Pacific Diabetes and Obesity Study Group in Kobe (APDO2018). The APDO was founded in 2004 and has met annually every year. The brainchild of Professors Masato Kasuga and David James, the APDO concept received enthusiastic support from leading diabetes and obesity researchers throughout the Asia Pacific region. The purpose of APDO is to unite basic scientists in the Asia Pacific region who have an interest in Diabetes and Obesity research to foster relationships and collaborative ventures in this key part of the world.

Ten years have passed since the APDO meeting was held in Kobe (APDO2008), which was organized by Professor Masato Kasuga. APDO2018 is held in conjunction with the 39th annual meeting of Japan Society for the Study of Obesity (JASSO). In this 2-days symposium, we invited symposium speakers from Australia, China, Hong Kong, Korea, New Zealand, Singapore, Taiwan and Japan to form the symposium as traditionally. We invited Professor David James and Professor Gregory R. Steinberg as sparkers for plenary lectures. I hope that all of you will enjoy this wonderful opportunity to keep up-to-date findings in the research field of diabetes and obesity.

Overview

Dates

October 8 (Mon) to 9 (tue), 2018

Venue

Kobe Convention Center
Kobe Portopia Hotel

President

Wataru Ogawa
Professor and Chair, Division of Diabetes and Endocrinology,
Department of Internal Medicine, Kobe University Graduate School of Medicine

Organizer

Division of Diabetes and Endocrinology
Department of Internal Medicine
Kobe University Graduate School of Medicine
7-5-1 Kusunoki-cho, Chuo-ku,Kobe, Hyogo, 650-0017,Japan

APDO registration

Place: 1F In front of “Owada” room, South building at Kobe Portpia Hotel
Date&Time:October 7 (Sun.) 8:00-18:00
October 8 (Mon.) 8:30-15:00

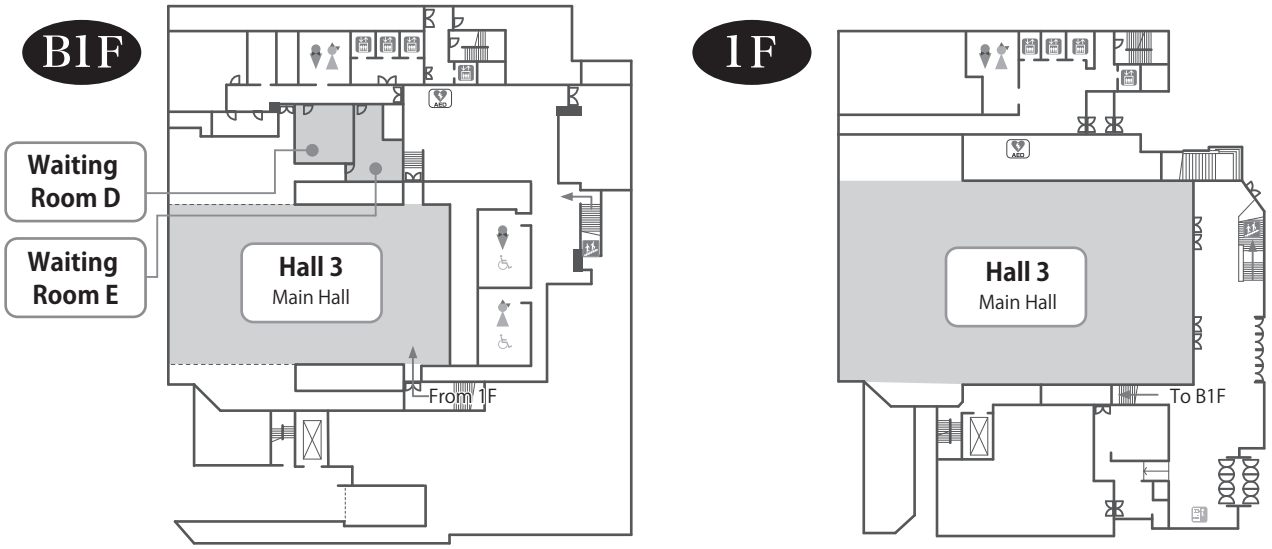
Place: 3F at Kobe Convention center
Date&Time:October 8 (Mon.) 12:30-18:00
October 9 (Tue.) 7:30-11:30

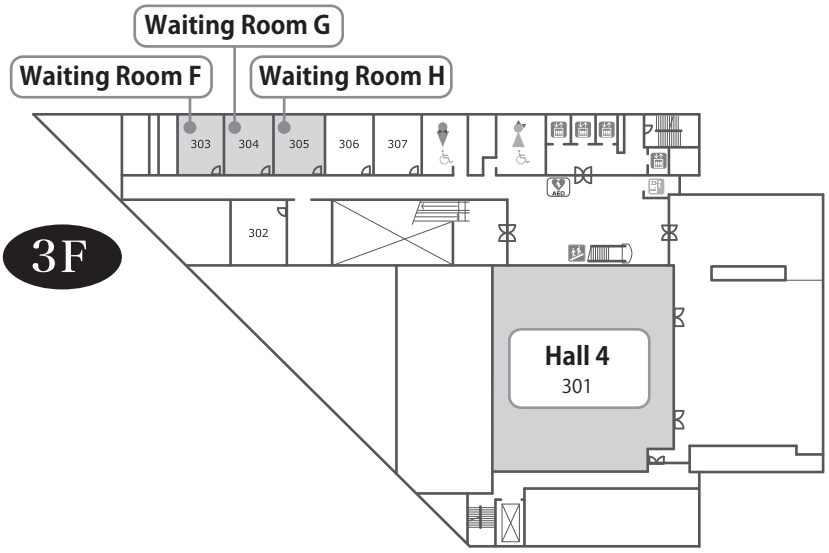
APDO Banquet

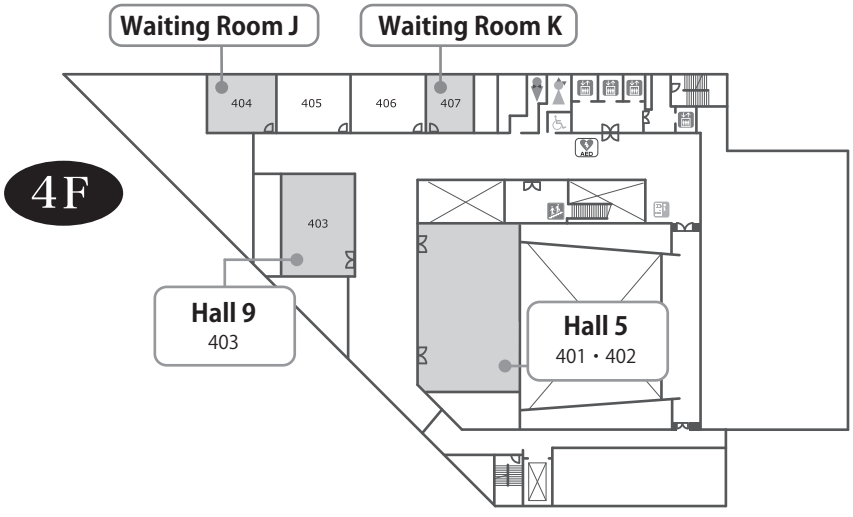
We have a banquet of APDO2018 at “Terrace Banquet Levante” at Kobe Portpia hotel from 18:40-20:40 on October 8 (Mon.).

Floor Map

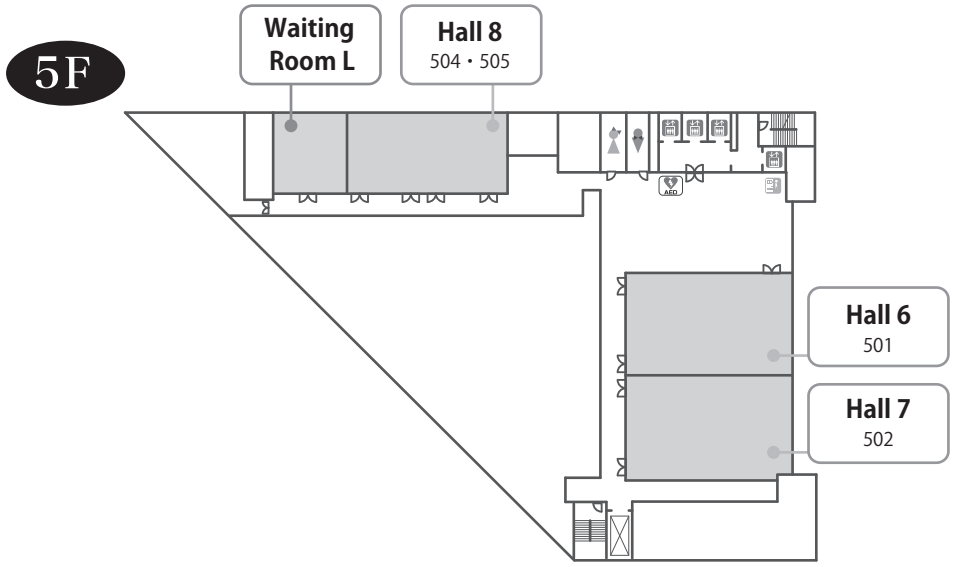
Kobe Convention Center



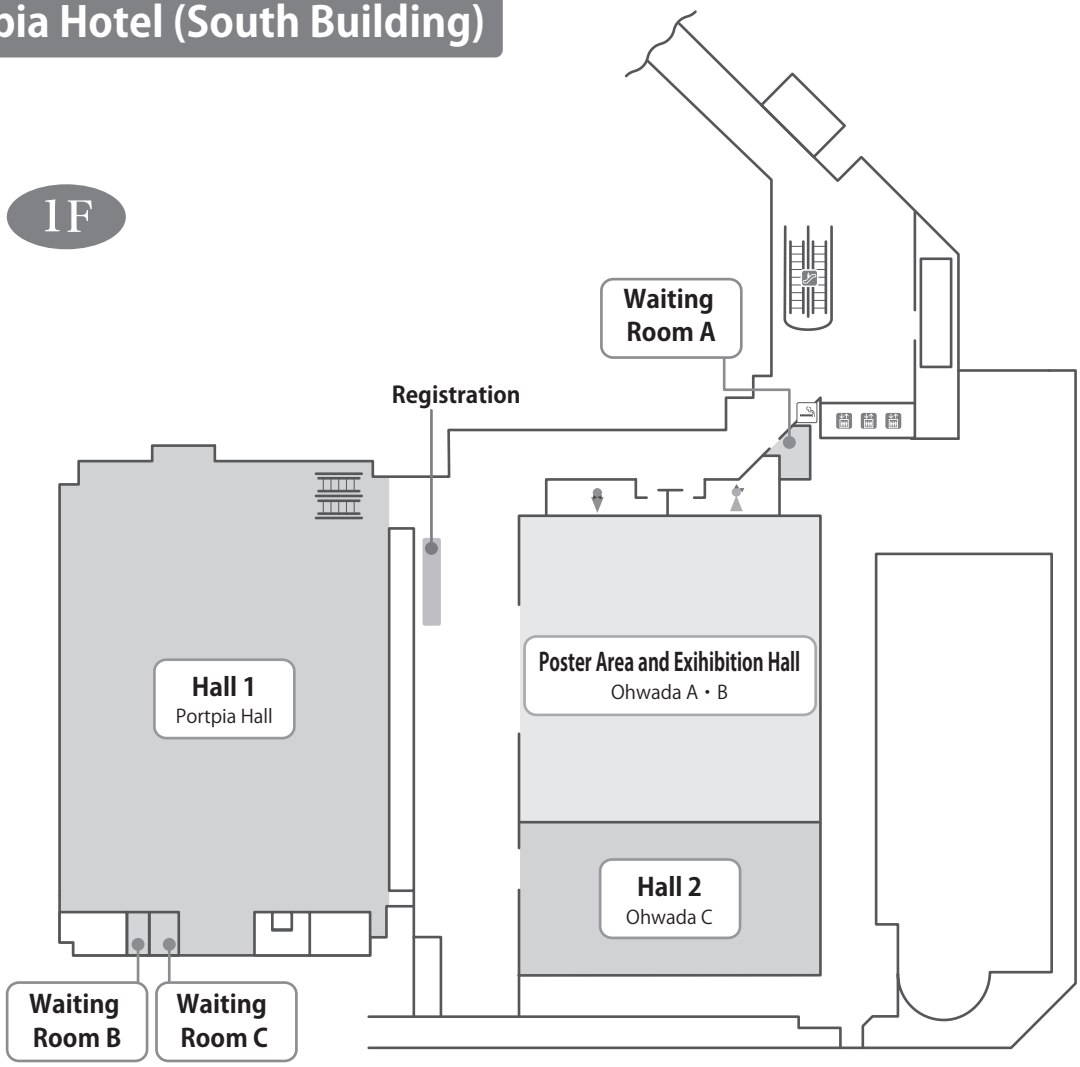




Kobe Convention Center



Portpia Hotel (South Building)



Time Table

October 7 (Sun.)

※[J]: Japanese Session

	Hall 1 Portpia Hotel (South Building) 1F Portpia Hall	Hall 2 Portpia Hotel (South Building) 1F Ohwada C	Hall 3 Kobe Convention Center 1F Main Hall	Hall 4 Kobe Convention Center 3F 301	Hall 5 Kobe Convention Center 4F 401・402
8:00					
8:30					
9:00	JASSO Opening Remarks（8:50-9:00）		JASSO Educational Lecture 1 （9:00-9:30）[J]	JASSO Joint Symposium 1 （9:00-11:15） "Sarcopenic Obesity: Commemorative Symposium in Establishment the Joint Working Group of Japan Society for the Study of Obesity (JASSO) and Japanese Society of Sarcopenia and Frailty (JSSF)"[J]	JASSO Special Program 1 （9:00-11:15） "Management of Childhood Obesity: Challenges and Prospects through childhood to adulthood"[J]
9:30	JASSO Symposium 1 （9:00-11:15） "Front lines in obese adipose tissue pathophysiology"[J]	JASSO Symposium 2 （9:00-11:15） "NASH and Hepatocellular Carcinoma as Obesity-associated Complications"[J]	JASSO Educational Lecture 2 （9:30-10:00）[J]		
10:00			JASSO Educational Lecture 3 （10:00-10:30）[J]		
10:30			JASSO Educational Lecture 4 （10:30-11:00）[J]		
11:00					
11:30	JASSO Special Program （11:30-11:55）[J]				
12:00					
12:30		JASSO Luncheon Seminar 1 （12:10-13:00）[J]	JASSO Luncheon Seminar 2 （12:10-13:00）[J]	JASSO Luncheon Seminar 3 （12:10-13:00）[J]	JASSO Luncheon Seminar 4 （12:10-13:00）[J]
13:00					
13:30	JASSO General Assembly （13:15-13:55）[J]				
14:00	JASSO Presidential Proposal （13:55-14:15）[J]				
14:30	JASSO Chairperson's Lecture （14:15-14:45）[J]				
15:00	JASSO Special Lecture 1 （14:45-15:40）[J]				
15:30					
16:00			JASSO Afternoon Seminar （16:00-16:40）[J]		
16:30					
17:00	JASSO Symposium 3 （16:55-18:55） "Strategy of Treatment for Obese Type 2 Diabetes" Chairs : Wataru Ogawa Hiroshi Maegawa Presenters : Chia-Chia Liu José Manuel Fernández-Real Lemos Christoph Wanner Vincent Woo			JASSO Educational Lecture 5 （16:55-17:25）[J]	
17:30		JASSO Symposium 4 （16:55-18:55） "Diversity of obesity disease - the measures against obesity disease - related disorders -"[J]	JASSO Symposium 5 （16:55-18:55） "Women doctors' career development as researchers and/or physicians in obesity medicine"[J]	JASSO Educational Lecture 6 （17:25-17:55）[J]	JASSO Special Program 2 （16:55-18:55） "Effects of health counselling for preventing the aggravation of lifestyle related diseases -From evidence to practice-"[J]
18:00				JASSO Educational Lecture 7 （17:55-18:25）[J]	
18:30				JASSO Educational Lecture 8 （18:25-18:55）[J]	
19:00					
19:30	JASSO Banquet （19:15-21:15） (Banquet hall Kairaku at KOBE PORTOPIA HOTEL)				
20:00					
20:30					
21:00					

Time Table

Hall 6 Kobe Convention Center 5F 501	Hall 7 Kobe Convention Center 5F 502	Hall 8 Kobe Convention Center 5F 504・505	Hall 9 Kobe Convention Center 4F 403	Poster Area and Exihibition Hall Portpia Hotel (South Building) 1F Ohwada A・B
JASSO Young Investigator Award Presentation (9:00-11:00) J	JASSO Oral Session 1 (9:00-9:54) J JASSO Oral Session 3 (9:54-10:30) J JASSO Oral Session 5 (10:30-10:57) J	JASSO Oral Session 2 (9:00-9:27) J JASSO Oral Session 4 (9:27-10:03) J JASSO Oral Session 6 (10:03-10:48) J JASSO LUNCHBOX presentation Session (10:48-11:15) J		
JASSO Luncheon Seminar 5 (12:10-13:00) J	JASSO Luncheon Seminar 6 (12:10-13:00) J			
	JASSO Oral Session 7 (16:00-16:45) J	JASSO Oral Session 8 (16:00-16:45) J	JASSO Oral Session 9 (16:00-16:45) J	JASSO Poster Session1～13 (16:00-16:40) J
JASSO Oral Session 10 (16:55-17:31) J JASSO Oral Session 14 (17:31-18:07) J JASSO Oral Session 18 (18:07-18:43) J	JASSO Oral Session 11 (16:55-17:22) J JASSO Oral Session 15 (17:22-17:58) J JASSO Oral Session 19 (17:58-18:34) J	JASSO Oral Session 12 (16:55-17:31) J JASSO Oral Session 16 (17:31-18:07) J JASSO Oral Session 20 (18:07-18:52) J	JASSO Oral Session 13 (16:55-17:49) J JASSO Oral Session 17 (17:49-18:52) J	

JASSO Banquet (19:15-21:15)
(Banquet hall Kairaku at KOBE PORTOPIA HOTEL)

8:00 8:30 9:00 9:30 10:00 10:30 11:00 11:30 12:00 12:30 13:00 13:30 14:00 14:30 15:00 15:30 16:00 16:30 17:00 17:30 18:00 18:30 19:00 19:30 20:00 20:30 21:00

Time Table

Octorber 8 (Mon.)

※[J]: Japanese Session

	Hall 1 Portpia Hotel (South Building) 1F Portpia Hall	Hall 2 Portpia Hotel (South Building) 1F Ohwada C	Hall 3 Kobe Convention Center 1F Main Hall	Hall 4 Kobe Convention Center 3F 301	Hall 5 Kobe Convention Center 4F 401・402
8:00					
8:30					
9:00	**APDO Opening Remarks** (8:50-9:00)				
9:30	**JASSO・APDO Joint Symposium 1** (9:00-11:00) **"Biology of Brown and White Adipocytes"** Chairs: Takashi Kadowaki Wataru Ogawa Presenters: Hironori Waki Takeshi Inagaki Jae Bum Kim Edward T. Chouchani	JASSO Symposium 6 (9:00-11:00) "Approaches towards obesity disease in various life stages" [J]	JASSO Industrial Physician Workshop 1 (9:00-10:00) [J]	JASSO Symposium 7 (9:00-11:00) "Nutritional Insight on Obesity And Sarcopenia" [J]	JASSO Symposium 8 (9:00-11:00) "Effective instruction and counseling for behavior change of obesity diseases patients" [J]
10:00			JASSO Industrial Physician Workshop 2 (10:00-11:00) [J]		
10:30					
11:00					
11:30	Jasso Plenary Lecture 2 (11:30-11:55) Chair: Takashi Kadowaki Lecturer: Barbara Kahn				
12:00					
12:30		JASSO Luncheon Seminar 7 (12:10-13:00) "Contribution of the gut microbiome to type 2 diabetes treatment"	JASSO Luncheon Seminar 8 (12:10-13:00) "Cellular Energy Sensing and Metabolism : Implications for Obesity"		JASSO Luncheon Seminar 9 (12:10-13:00) "SGLT2 inhibitors and diabetic kidney disease: association of obesity and CKD"
13:00		Chair: Wataru Ogawa Presenter: José Manuel Fernández-Real Lemosl	Chair: Toshimasa Yamauchi Presenter: Gregory R. Steinberg		Chair: Hiroshi Ito Presenter：Christoph Wanner
13:30	JASSO Award Ceremony and Lectures (13:15-14:15) [J]			**APDO Symposium 1** (13:15-14:35) Chair: Iichiro Shimomura Weiping Han Connie Wai Hong Woo Youfei Guan Ching-Feng Cheng	
14:00					
14:30					
15:00	JASSO Symposium 9 (14:30-16:30) "Mechanism of homeostatic regulation by brain-peripheral tissues and its abnormality in obesity" [J]	JASSO Joint Symposium 2 (14:30-16:30) "Locomobiology" [J]	JASSO Open Public Lecture (14:30-16:30) [J]	**APDO Plenary Lecture 1** (14:40-15:20) Chair: Masato Kasuga Lecturer: David Ernest James	JASSO Special Program 3 (14:30-16:30) "Insight into approaches improving the metabolic syndrome and prevention of the cognitive dysfunction" [J]
15:30				**APDO Symposium 2** (15:30-16:30) Chair: Karen Lam Jacqueline Stoeckli Wanjin Hong Peter Shepherd	
16:00					
16:30	Closing Remarks (16:30-16:40)			**APDO Symposium 3** (16:30-17:50) Chair: Weiping Han Iichiro Shimomura Karen SL Lam Yi-Cheng Chang Troy Leslie Merry co-sponsored : Sanofi K.K.	
17:00					
17:30					
18:00					
18:30				**APDO Poster Session** (18:10-18:30)	
19:00	**Banquet** (18:40-20:40) (Terrace Banquet Levante at KOBE PORTOPIA HOTEL)				
19:30					
20:00					
20:30					
21:00					

Time Table

Hall 6 Kobe Convention Center 5F 501	Hall 7 Kobe Convention Center 5F 502	Hall 8 Kobe Convention Center 5F 504・505	Hall 9 Kobe Convention Center 4F 403	Poster Area and Exihibition Hall Portpia Hotel (South Building) 1F Ohwada A・B
JASSO Oral Session 21 (9:00-9:36) J	JASSO Oral Session 22 (9:00-9:27) J	JASSO Oral Session 23 (9:00-9:36) J	JASSO Oral Session 24 (9:00-9:36) J	
JASSO Oral Session 25 (9:36-10:12) J	JASSO Oral Session 26 (9:27-10:12) J	JASSO Oral Session 27 (9:36-10:21) J	JASSO Oral Session 28 (9:36-10:21) J	
JASSO Oral Session 29 (10:12-10:48) J	JASSO Oral Session 30 (10:12-10:48) J	JASSO Oral Session 31 (10:21-10:57) J	JASSO Oral Session 32 (10:21-10:57) J	
JASSO Luncheon Seminar 10 (12:10-13:00) "GLP-1 receptor agonists: battling against both T2DM and obesity" Chair：Kazuyuki Tobe Presenter：Vincent Woo	JASSO Luncheon Seminar 11 (12:10-13:00) J	JASSO Luncheon Seminar 12 (12:10-13:00) J		
JASSO Joint Symposium 3 (14:30-16:30) J	JASSO Oral Session 33 (14:30-15:15) J		JASSO Oral Session 34 (14:30-15:24) J	JASSO Poster Session14～29 (14:30-15:10) J
	JASSO Oral Session 35 (15:15-15:51) J		JASSO Oral Session 36 (15:24-16:00) J	
	JASSO Oral Session 37 (15:51-16:27) J			
Banquet (18:40-20:40) (Terrace Banquet Levante at KOBE PORTOPIA HOTEL)				

8:00 8:30 9:00 9:30 10:00 10:30 11:00 11:30 12:00 12:30 13:00 13:30 14:00 14:30 15:00 15:30 16:00 16:30 17:00 17:30 18:00 18:30 19:00 19:30 20:00 20:30 21:00

Time Table

Octorber 9 (Tue.)

Hall 4

Kobe Convention Center
3F 301

7:00

Committee Meeting (7:15-7:45)
(Waiting Room at Kobe Convention Center 3F 306)

7:30

8:00

APDO Symposium 4
(8:00-9:00)
Chair：Yasuhiko Minokoshi
Paul CH Lee, Kae Won Cho, Lihong Chen

8:30

9:00

APDO Plenary Lecture 2 (9:10-9:50)
Chair：Peter Shepherd
Lecturer：Gregory R. Steinberg

9:30

Jasso・APDO Joint Symposium 2
(9:50-10:50)
Chair: Wataru Ogawa
Co-Sponsored: Takeda Pharmaceutical Company Limited
4 presentation by Japanese young investigators

10:00

10:30

11:00

APDO Symposium 5
(11:00-12:00)
Chair：Chang Yi-Cheng
Feng Xu, Weizhen Zhang, Sharon Ladyman

11:30

12:00

APDO Symposium 6
(12:00-13:00)
Chair：Youfei Guan
John Francis O'Sullivan, Seung-Hoi Koo, Yi-Ching Lee

12:30

13:00

Closing Remarks (13:00-13:10)

13:30

14:00

14:30

15:00

15:30

16:00

16:30

17:00

17:30

18:00

18:30

19:00

19:30

20:00

Program

［Day 1］ October 8 (Mon.)

APDO Opening Remarks

Date and Time: Octorber 8 (Monday) 8:50 ～ 9:00
Session Room: Hall 1

JASSO・APDO Joint Symposium 1 "Biology of Brown and White Adipocytes"

Date and Time: Octorber 8 (Monday) 9:00 ～ 11:00
Session Room: Hall 1
Chairs: Takashi Kadowaki (Department of Prevention of Diabetes and Lifestyle-Related Diseases, Graduate School of Medicine, The University of Tokyo, Department of Metabolism and Nutrition, Teikyo University Mizonokuchi Hospital)
Wataru Ogawa (Professor and Chair, Division of Diabetes and Endocrinology, Department of Internal Medicine, Kobe University Graduate School of Medicine)

JAJS1-1 Transcriptional Regulation of Brown Adipocytes and Its Implication for Obesity in Humans

Hironori Waki
(Department of Diabetes and Metabolic Diseases
Department of Molecular Science on Diabetes
Graduate School of Medicine
The University of Tokyo)

JAJS1-2 Epigenetic Regulation of Adipocyte Characteristics by Histone Demethylase JMJD1A

Takeshi Inagaki
(Gunma University)

JAJS1-3 Dysregulation of Lipid Metabolism and Energy Balance in Obesity

Jae Bum Kim
(Center for Adipose Tissue Remodeling, Department of Biological Sciences, Institute of Molecular Biology and Genetics, Seoul National University)

JAJS1-4 A novel molecular pathway controls activation of thermogenic adipose tissue

Edward T. Chouchani
(Harvard Medical School
Dana-Farber Cancer Institute)

APDO Symposium 1

Date and Time: Octorber 8 (Monday) 13:15 ～ 14:35
Session Room: Hall 4
Chair: Iichiro Shimomura (Department of Metabolic Medicine, Graduate School of Medicine, Osaka University)

S1-1 Adaptive metabolic programming promotes liver cancer cell proliferation

Weiping Han
(Singapore Bioimaging Consortium, A*STAR Research Entities)

S1-2 A novel atheroprotective role of gut microbiota: an unconventional bridging by Toll-like Receptor

Connie Wai Hong Woo
(Department of Pharmacology and Pharmacy, LKS Faculty of Medicine, University of Hong Kong)

S1-3 Role of novel lipid droplet-associated proteins in non-alcoholic fatty liver disease

Youfei Guan
(Advanced Institute for Medical Sciences, Dalian Medical University,
Department of Physiology and Pathophysiology, School of Basic Medical Sciences,
Dalian Medical University)

S1-4 ATF3 inducers as a therapy for high-fat-diet induced obesity and metabolic syndrome

Ching-Feng Cheng
(Department of Pediatrics, Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation)

APDO Plenary Lecture 1

Date and Time: Octorber 8 (Monday) 14:40 ～ 15:20
Session Room: Hall 4
Chair: Masato Kasuga (The Institute for Adult Diseases, Asahi Life Foundation)

PL-1 New Insights into Insulin Resistance

David Ernest James
(Charles Perkins Centre, University of Sydney)

APDO Symposium 2

Date and Time: Octorber 8 (Monday) 15:30 ～ 16:30
Session Room: Hall 4
Chair: Karen SL Lam (Department of Medicine, The University of Hong Kong)

S2-1 **Novel regulator of adipocyte lipolysis**

Jacqueline Stoeckli
(Charles Perkins Centre, School of Life and Environmental Sciences, The University of Sydney)

S2-2 **SNAREs and Membrane Traffic**

Wanjin Hong
(Institute of Molecular and Cell Biology (IMCB), A*STAR)

S2-3 **Role of adherens junction proteins in regulating insulin secretion**

Peter Shepherd
(Molecular Medicine, University of Auckland)

APDO Symposium 3

Date and Time: Octorber 8 (Monday) 16:30 ～ 17:50
Session Room: Hall 4
Chair: Weiping Han (Singapore Bioimaging Consortium, A*STAR Research Entities)
Co-Sponsored: Sanofi K.K.

S3-1 **Adiponectin/T-cadherin exerts vascular protection partly through exosome biogenesis and secretion.**

Iichiro Shimomura
(Department of Metabolic Medicine, Graduate School of Medicine, Osaka University)

S3-2 **FGF21 resistance in obesity and diabetes**

Karen SL Lam
(Department of Medicine, The University of Hong Kong)

S3-3 **East Asia-specific *ALDH2* mutation promotes diet-induced obesity and fatty liver: the therapeutic effect of ALDH2 agonist**

Yi-Cheng Chang
(Department of Internal Medicine, National Taiwan University Hospital,
Graduate Institute of Medical Genomics and Proteomics, National Taiwan University,
Institute of Biomedical Science, Academia Sinica)

S3-4 **Understanding how a missense variant, rs373863828, in the CREBRF genes influences the metabolism of Polynesian people.**

Troy Leslie Merry
(Nutrition, The University of Auckland)

［Day 3］ October 9 (Tue.)

APDO symposium 4

Date and Time: Octorber 9 (Tuesday) 8:00 ～ 9:00
Session Room: Hall 4
Chair： Yasuhiko Minokoshi (Division of Endocrinology and Metabolism, National Institute for Physiological Sciences)

S4-1 **Adipocyte Fatty Acid Binding Protein and Diabetic Kidney Disease**
Paul Chi-ho Lee
(Department of Medicine, University of Hong Kong)

S4-2 **Role of Nuclear Envelope Protein Lamin A in the Obesity-induced Inflammation**
Kae Won Cho
(Soonchunhyang Institute of Medi-bio Science (SIMS), Soonchunhynag University)

S4-3 **Prostaglandins E2 and Inflammatory Cardiovascular Diseases**
Lihong Chen
(Advanced Institute for Medical Sciences, Dalian Medical University)

APDO Plenary Lecture 2

Date and Time: Octorber 9 (Tuesday) 9:10 ～ 9:50
Session Room: Hall 4
Chair: Peter Shepherd (Molecular Medicine, University of Auckland)

PL-2 **Cellular Energy Sensing and Metabolism: Implications for Treating Type 2 Diabetes**
Gregory R Steinberg
(Department of Medicine, McMaster University)

Jasso/APDO Joint Symposium 2

Date and Time: Octorber 9 (Tuesday) 9:50 ～ 10:50
Session Room: Hall 4
Chair： Wataru Ogawa (Professor and Chair, Division of Diabetes and Endocrinology, Department of Internal Medicine, Kobe University Graduate School of Medicine)
Co-Sponsored: Takeda Pharmaceutical Company Limited

JAJS2-1 **Vaccination Therapy against Semaphorin 3E Ameliorates Glucose Intolerance in Diet-induced Obese Mice**

Yohko Yoshida
(Department of Cardiovascular Biology and Medicine, Niigata University Graduate School of Medical and Dental Sciences,
Division of Molecular Aging and Cell Biology, Niigata University Graduate School of Medical and Dental Sciences)

JAJS2-2 **Control of body weight by FTO**

Daisuke Kohno
(Metabolic Signal Research Center, Institute for Molecular and Cellular Regulation, Gunma University)

JAJS2-3 **Hypothalamic neuronal circuits regulating hunger-induced taste modification**

Ken-ichiro Nakajima
(National Institute for Physiological Sciences)

JAJS2-4 **Hepatic Activin B controls glucose metabolism**

Naoki Kobayashi
(Department of Molecular Diabetic Medicine, Diabetes Research Center, NCGM National Center for Global Health and Medicine)

APDO Symposium 5

Date and Time: Octorber 9 (Tuesday) 11:00 ～ 12:00
Session Room: Hall 4
Chair： Chang Yi-Cheng (Department of Internal Medicine, National Taiwan University Hospital,
Graduate Institute of Medical Genomics and Proteomics,
National Taiwan University,
Institute of Biomedical Science, Academia Sinica)

S5-1 **Identification of Novel Regulators of Thermogenic Program through Epigenomic Analysis**

Feng Xu
(Institute of Molecular and Cell Biology, A*STAR)

S5-2 **X/A like cells in lipid metabolism**

Weizhen Zhang
(Department of Physiology, Peking University Health Science Center,
Department of Surgery, the University of Michigan)

S5-3 **Central and peripheral actions of prolactin promote metabolic adaptation to pregnancy**

Sharon Rachel Ladyman
(Anatomy, and Centre for Neuroendocrinology, University of Otago)

APDO Symposium 6

Date and Time: Octorber 9 (Tuesday) 12:00 ～ 13:00
Session Room: Hall 4
Chair： Youfei Guan (Advanced Institute for Medical Sciences, Dalian Medical University,
Department of Physiology and Pathophysiology,
School of Basic Medical Sciences, Dalian Medical University)

S6-1 Novel Pathways in Cardiometabolic Disease

John Francis O'Sullivan
(Cardiology, The University of Sydney / Heart Research Institute)

S6-2 Role of PRMT1 in skeletal muscle homeostasis

Seung-Hoi Koo
(Division of Life Sciences, Korea University)

S6-3 Impaired Glucose Transporter 10 Function Predisposes Mice to High-Fat Diet-Induced Type 2 Diabetes

Yi-Ching Lee
(Institute of Cellular and Organismic Biology, Academia Sinica)

Closing Remarks

Date and Time: Octorber 9 (Tuesday) 13:00 ～ 13:10
Session Room: Hall 4

Poster Session

Date and Time: Octorber 8 (Monday) 18:10 ～ 18:30
Session Room: Poster Area

P-01 **Protection Against HFD Obesity in Helz2-Deficient Mice by Enhancing Hepatic Leptin Sensitivity**

Satoshi Yoshino
(Gunma University Graduate School of Medicine, Department of Internal Medicine, Division of Endocrinology and Metabolism)

P-02 **Novel roles for SFPQ, a splicing regulator for the early differentiation of 3T3-L1 preadipocytes**

Akiko Katano-Toki
(Division of Endocrinology and Metabolism, Department of Internal Medicine,Gunma University Graduate School of Medicine)

P-03 **The Pilot study of the RJ-TOMODACHI program ; lifestyle intervention program for obesity in Russia**

Kazuyo Tsushita
(Comprehensive Health Science Center, Aichi Health Promotion Foundation)

P-04 **Intraperitoneal glucose reduces rat GLP-1 concentrations**

Haji Maidin Quddsyiah Nur 'Azimatul
(Hokkaido University Graduate School of Agriculture)

P-05 **Postprandial GLP-1 response in Wistar and Goto-Kakizaki rats during diet-induced obesity**

Jukkrapong Pinyo
(Graduate School of Agriculture, Hokkaido University)

P-06 **Effects of testosterone ointment in Japanese men with metabolic syndrome**

Hajime Ueshiba
(Toho University Health Care Center)

P-07 **Pivotal role of miR-494 in mitochondrial biogenesis and glucose metabolism during adipocytes browning**

Mengistu Lemecha
(Division of Endocrinology and Metabolism, Department of Medicine, Shiga University of Medical Science)

P-08 **Survey on hidden obesity among japanese women**

shinobu sakurai
(Juntendo University school of nursing)

P-09 **Flaxseed and extra virgin olive oils impact gut microbiota, support gut barrier and metabolic health**

Jasmine Frances Millman
(University of the Ryukyus)

P-10 **Adipose tissue-derived MFG-E8, regulates chronic inflammation and obesity-related liver disease**

Masashi Kuroda
(Department of Nutrition and Metabolism, Institute of Biomedical Sciences, Tokushima University Graduate School)

P-11 **Changes of metabolic indexes in patients with Pheochromocytoma.**

Takashi Okamura
(Gunma University Graduate School of Medicine Department of Internal Medichine Division of Endocrinology and Metabolism)

P-12 **Impact of obesity on dissociation of energy intake and total energy expenditure in diabetic patients**

Itsuko Miyazawa
(Shiga University of Medical Science)

P-13 **Obesity associated pro-fibrotic protein promotes pathologies in non-alcoholic steatohepatitis.**

Ippei Shimizu
(Department of Cardiovascular Biology and Medicine, Niigata University,
Division of Molecular Aging and Cell Biology, Niigata University)

P-14 **Dapagliflozin reduces weight and changes body composition in T2DM: a randomized, clinical trial**

Katsutaro Morino
(Department of Medicine, Shiga University of Medical Science)

P-15 **Brown adipose tissue is involved in the suppression of pathologies in heart failure**

Yohko Yoshida
(Department of Cardiovascular Biology and Medicine, Niigata University Graduate School of Medical and Dental Sciences,
Division of Molecular Aging and Cell Biology, Niigata University Graduate School of Medical and Dental Sciences)

P-16 **Transient hyperglycaemia promotes myelopoiesis and accelerates atherosclerosis**

Andrew J Murphy
(Baker Heart and Diabetes Institute)

Abstracts

PL-1 New Insights into Insulin Resistance

David Ernest James

Charles Perkins Centre, University of Sydney

Insulin resistance can be triggered by a range of perturbations including diet, obesity, inflammation or steroids. Thus, it is important to establish if there are convergent mechanisms that explain each of these modes or if insulin resistance is a multifactorial defect. Using systems biology approaches we have identified the CoenzymeQ (CoQ) biosynthesis pathway as a common thread in many insulin resistance models. Using targeted approaches, we show that the levels of CoQ in mitochondria are decreased in a range of insulin resistance models including adipose tissue from humans. Moreover, genetic or pharmacologic manipulations were used to show that mitochondrial CoQ is both necessary and sufficient to preserve a robust insulin response in adipocytes. We next showed that changes in mitochondrial CoQ lead to changes in mitochondrial oxidant production specifically at complex II of the electron transport chain. These data suggest that insulin resistance is caused by a pathological change in mitochondrial oxidant production and this can be mediated partly via changes in mitochondrial CoQ. We construct a model whereby diets high in BOTH fat and carbohydrate are likely to give rise to deleterious outcomes while preferential selection of either fats or carbohydrates may escape detrimental outcomes due to the metabolic partitioning of insulin responsive cells. This model has important implications for substrate switching in metabolic tissues and metabolic flexibility.

【Curriculum Vitae】

Professor David E James FAA

David James was awarded a PhD in 1985 from UNSW.

In 1985 he was awarded a Fogarty Fellowship and later a Juvenile Diabetes Foundation fellowship to undertake postdoctoral training at Boston University and subsequently at Washington University in St Louis. During this period he identified the insulin responsive glucose transporter GLUT4, work that was published in a series of *Nature* papers in the late 80s. This landmark work is now a prominent feature of most modern textbooks of cell biology and biochemistry.

In 1989 he established his own independent career as Assist/Professor at Washington University in St Louis where he continued his work on GLUT4.

In 1993 he returned to Australia on a prestigious Wellcome Trust Senior Research Fellowship taking up a position at the IMB in Brisbane.

In 2002 he moved to Sydney to head up the Diabetes and Obesity Research Program at the Garvan Institute as an NHMRC Senior Principal Research Fellow where he remained until February 2014.

He currently holds the Leonard P Ullmann Chair in Molecular Systems Biology and he is the Domain Leader for Biology at the Charles Perkins Centre, University of Sydney.

Since returning to Australia he has won several awards including the Glaxo Wellcome Medal for Medical Research and the Kellion medal for outstanding contributions to Diabetes research. In 2007 he was elected as a fellow of the Australian Academy of Science. He was awarded the NSW Premier Prize in Excellence in Medical Biological Sciences in 2016. He is on the editorial board of a number of prestigious journals and he is regularly invited to speak at key international meetings on diabetes and metabolism.

PL-2 Cellular Energy Sensing and Metabolism: Implications for Treating Type 2 Diabetes

Gregory R Steinberg

Department of Medicine, McMaster University

The survival of all cells is dependent on the constant challenge to match energetic demands with nutrient availability, a task which is mediated through a highly conserved network of metabolic fuel sensors that orchestrate both cellular and whole organism energy balance. A mismatch between cellular energy demand and nutrient availability is a key factor contributing to the development of type 2 diabetes, thus understanding the fundamental mechanisms by which cells sense nutrient availability and demand may lead to the development of new treatments. Glucose lowering therapies such as caloric restriction, exercise, metformin and cold all induce an energetic challenge that results in the activation of the cellular energy sensor AMP-activated protein kinase (AMPK). Activation of AMPK in turn suppresses lipid synthesis and inflammation while increasing glucose uptake, fatty acid oxidation and mitochondrial function. In contrast, high levels of nutrient availability, suppress AMPK activity while also increasing the production of peripheral serotonin, a gut-derived endocrine factor which suppresses beta-adrenergic-induced activation of brown adipose tissue. Identifying new ways to manipulate these two ancient fuel gauges, by activating AMPK and inhibiting peripheral serotonin, may lead to the development of new therapies for treating type 2 diabetes.

【Curriculum Vitae】

Education:

- BSc, Human Kinetics, University of Guelph (1998)
- PhD, Human Biology & Nutritional Sciences, University of Guelph (2002)
- Postdoctoral Fellowship, St. Vincent's Institute of Medical Research, University of Melbourne (2007)

Current Appointments:

- Professor, Faculty of Health Sciences, Division of Endocrinology and Metabolism, Department of Medicine and Biochemistry and Biomedical Sciences, McMaster University
- Co-Director of Metabolism And Childhood (MAC) Obesity Research Program
- Canada Research Chair in Metabolism and Obesity, McMaster University,
- J Bruce Duncan Endowed Chair in Metabolic Diseases, McMaster University
- Principal Research Associate, St. Vincent's Institute of Medical Research, Australia

Honours and Awards:

- Department of Medicine, McMaster University, Graduate Teaching Award (2013)
- Bayer 150th Year Celebration, Canadian Scientist of the Year in Aspirin, Inflammation and Pain Relief (2013)
- Fellow of the Royal Society of Canada College of New Scholars and Scientists (2014)
- Distinguished University Scholar, McMaster University (2015)
- Canadian Institutes of Health Research Gold Leaf Prize for Outstanding Achievements by an Early Career Investigator (2017)
- American Diabetes Association Outstanding Scientific Achievement Award (2017)
- Diabetes Canada Young Scientist Award (2017)
- Endocrine Society Richard E. Weitzman Outstanding Early Career Investigator Award (2017)

S1-1 Adaptive metabolic programming promotes liver cancer cell proliferation

Weiping Han

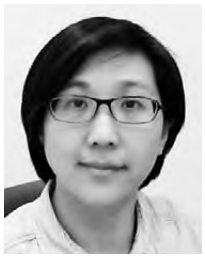
Singapore Bioimaging Consortium, A*STAR Research Entities

Although liver cancer is a leading cause of cancer-related death worldwide, there is very limited treatment option available. Most of the liver cancer is hepatocellular carcinoma, or HCC. In recent years, accumulating evidence from a renewed interest of onco-metabolism supports metabolic reprogramming as a signature of many cancers including HCC. As such, the cancer phenotype is now viewed as a complex interplay of genetic mutations, epigenetic deregulation, and metabolic reprogramming. It is hoped that understanding the functional integration of the signaling pathways relevant to liver cancer with the altered metabolic network will reveal novel approaches to cancer therapy. Considering that tumors display profound and highly adaptive changes in cellular metabolism, we used a comprehensive 'multi-omics' approach across multiple rodent models of HCC, and studied metabolic pathways and enzymes that may be directed in potential therapeutic development. Here I will provide the latest update on this study.

【Curriculum Vitae】

Biography: Weiping Han obtained his Ph.D. from Cornell University and did his postdoctoral work at the University of Pittsburgh and HHMI/UT Southwestern Medical Center in Dallas. In 2003, he was promoted to Research Assistant Professor in the Center for Basic Neuroscience at UT Southwestern Medical Center, where he studied molecular mechanisms of hormone secretion and signaling. In 2005, he moved to Singapore to set up a research program in the Laboratory of Metabolic Medicine (LMM) at Singapore Bioimaging Consortium (SBIC), A*STAR Research Entities. Currently he is Deputy Director of SBIC with concurrent appointment as Head of LMM. He is also Research Director at Institute of Molecular and Cell Biology, A*RE, and Professor at National University of Singapore (NUS) and Duke-NUS Medical School.

S1-2 A novel atheroprotective role of gut microbiota: an unconventional bridging by Toll-like Receptor



Connie Wai Hong Woo

Department of Pharmacology and Pharmacy, LKS Faculty of Medicine, University of Hong Kong

Gut microbiota play both beneficial and detrimental roles in chronic diseases, depending on the alteration of certain strains of bacteria. Our previous (Li J et al. Circulation 2016) and other (Yoshida N et al. Circulation 2018) studies have shown that certain strains of gut bacteria, including *Akkermansia muciniphila, Bacteroides Vulgatus and Bacteroides Dorei* can exert protective role against atherosclerosis through ameliorating endotoxemia. On the other hand, a human study has shown that change in gut microbiota is association with variation of HDL but not LDL or total cholesterol in blood (Fu J et al. Circulation Research 2015). Whether and how gut microbiota affect atherosclerosis through alteration of lipoprotein metabolism remain unknown. In this study, we discovered another type of gut bacteria that display another type of atheroprotective property, namely the manipulation of apolipoprotein-A1 and HDL production, instead of suppression of LPS leakage. Such protection is mediated by the classic toll-like receptor pathway. The mechanism of how these types of bacteria affect apolipoprotein-A1 and HDL production will be discussed in my talk.

【Curriculum Vitae】

Short CV for Connie Wai Hong Woo

BSc Pharmacy (The Ohio State University, USA, 1996); MPhil Pharmacology (The University of Hong Kong, 2003); PhD Physiology (University of Manitoba, Canada, 2007)

Assistant Professor, Department of Pharmacology and Pharmacy, HKU (2/2015-present); Research Assistant Professor, Department of Pharmacology and Pharmacy, HKU (11/2013-1/2015); Post-doctoral Fellow, Department of Medicine, Columbia University, USA (12/2007-12/2011)

My research interests: Local and systemic inflammation is commonly found in many chronic diseases, and metabolic stress appears to be the trigger of these kinds of non-infectious inflammation. Toll like receptor family (TLR) is a group of sensors detecting different kinds of microbes and their products including endotoxin and flagellin, resulting in stimulation of immune response. Many studies have reported the significant roles of different TLRs in these chronic diseases. In spite of their immune-originality, TLRs are present in non-immune cells; however, the functions of TLR signaling pathway in these cells are not clear. We are particularly interested in the nonconventional TLR functions in non-immune cells such as hepatocytes during cardiovascular and metabolic diseases. Our study also extends to the area of gut microbiota which are the sources of various TLR ligands to as us host.

S1-3 Role of novel lipid droplet-associated proteins in non-alcoholic fatty liver disease

Bing Wang[1,2], Wen Su[3], Xiaoyan Zhang[1,2], Youfei Guan[1,2]

Advanced Institute for Medical Sciences, Dalian Medical University[1],
Department of Physiology and Pathophysiology, School of Basic Medical Sciences, Dalian Medical University[2],
Shenzhen University Diabetes Center, Shenzhen University Health Science Center[3]

17β-hydroxysteroid dehydrogenases (17β-HSDs) comprise a large family of 14 members that are mainly involved in sex hormone metabolism. Some 17β-HSD enzymes also play key roles in cholesterol and fatty acid metabolism. Recent study showed that 17β-HSD13, an enzyme with unknown biological function, is a novel liver-specific lipid droplet-associated protein in mouse and humans. 17β-HSD13 expression is markedly upregulated in patients and mice with non-alcoholic fatty liver disease (NAFLD). Hepatic overexpression of 17β-HSD13 promotes lipid accumulation in the liver. Expression level and activity of 17β-HSD13 in the liver is closely associated with the development and outcome of chronic liver diseases in human. We summarize recent progress regarding the role of 17β-HSD13 in the regulation of hepatic lipid homeostasis and discuss genetic, genomic and proteomic evidence supporting the pathogenic role of 17β-HSD13 in NAFLD. We also emphasize its potential as a biomarker of advanced liver disease, such as NASH and liver cancer.

Keywords 17β-HSD13, NAFLD, lipid droplets, genome-wide association study, proteomics

【Curriculum Vitae】

Professor and Vice President of Dalian Medical University and Dean of Advanced Institute for Medical Science (AIMS). He was a recipient of the Outstanding Young Investigator Award from the National Natural Science Foundation of China in 2007 and has been a Changjiang Professor at Peking University selected by the Ministry of Education since 2005. He has become the Chief Scientist leading the "973" program sponsored by the Ministry of Science and Technology. His pioneering studies have resulted in over 160 papers in high-level internationally peer-reviewed journals, including Nature Medicine, Journal of Clinical Investigation, Diabetes, PNAS, Hepatology, JASN, Kidney Int, and American Journal of Physiology and has contributed more than 20 invited reviews and editorial commentaries. He has been invited to serve as either an associate editor or as an editorial board member for many journals and also served as an invited reviewer for many peer-review journals. His research focuses on the role of the metabolic nuclear receptor family and prostaglandin system in metabolic diseases, especially in the pathogenesis and treatment of diabetes, fatty liver disease, hyperlipidemia and hypertension.

S1-4 ATF3 inducers as a therapy for high-fat-diet induced obesity and metabolic syndrome

Ching-Feng Cheng

Department of Pediatrics, Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation

Heart failure and obesity are severe and complicated health issue related dietary modifications, and are highly associated with cardio-metabolic disorders. Activating transcription factor 3 (ATF3) is a member of the ATF/cAMPresponse element-binding protein family of transcriptional factors. The cellular mechanism of ATF3 in both cardiomyocytes and adipocytes and their physiological regulation in vivo are not clear. We have previously revealed that ATF3 can protect against pressure overload-induced heart failure by using ATF3 KO mice and the selective ATF3 inducer. For research on obesity and metabolic syndrome, we give high-fat-diet (HFD) to ATF3 KO for 16 weeks, and body weights significantly increased in the KO. We further investigate the role of ATF3 in 3T3L1 adipocytes. ATF3-overexpressing adipocytes exhibited less lipid accumulation with diminished expression of adipogenic/ lipogenic markers. Mechanistically, we found that expression of ATF3 repressed the ChREBP signaling and promoted white adipocytes trans-differentiation and activate browning. Furthermore, a new ATF3 inducer, derived from Chinese herbs, increased adipose browning, reduced lipogenesis, and increased lipolysis in HFD-fed obese mice. This new ATF3 induce can exert its anti-obesity effect either through intraperitoneal delivery as well as oral ingestion. Oral administration showed anti-obesity efficacy similar to the clinical drug orlistat. In summary, our work identifies ATF3 as an important metabolic regulator and suggest that ATF3 inducer has promising therapeutic potential for treating obesity and related metabolic disorders.

References:

Lin H, et al. Activating Transcription Factor 3 Protects against Pressure-Overload Heart Failure via the Autophagy Molecule Beclin-1 Pathway. Molecular Pharmacology. 2014, 85: 682-91.

Cheng CF, et al. ATF3 regulates high fat diet induced adipocytes hypertrophy and obesity in mice via repression of ChREBP signaling pathway. European Heart Journal. 2015, 36, 355

【Curriculum Vitae】

Dr. Ching-Feng Cheng, received his M.D. degree from Taipei Medical University in 1989, and trained in Taiwan National University Hospital for his Clinical Pediatric Residency and Pediatric Cardiology Fellowship from 1989-1995. Then, he went to Hualien Tzu Chi General Hospital as a Pediatric Attending Physician. On 1999, he received Physician Scientist Award from National Health Research Institute (NHRI) and join the Molecular Medicine Program and mentored by Professor Kenneth R. Chien in UCSD for his Post-Doctoral Fellowship from 1999 to 2001. He received a number of awards, including AHA Young Investigator Award in 2001, Medical Contribution Award on NHRI Tenth Anniversary Symposium (2005), Raising Foundation Sixth Children Health Medical Contribution Award (2015), and Excellence Research Award for 5 Years Periods (2011-2015) by Hualien Tzu Chi Medical Center on 2016. He has published nearly 50 research papers as first author in Cell (2001), Trends in Molecular Medicine (2003), Molecular Pharmacology (2013 and 2014) and others. His works focus on using in vivo disease mouse models for integrative physiologic research, including cardiac oxidative stress and iron overload induced remodeling and therapy, KCHIP2 and cardiac arrhythmias, ASIC3 and cardiac pain, ATF3 and its regulation on kidney, heart, obesity, and metabolic diseases. Currently, he is the Director and Professor of Pediatric Department in Tzu Chi University in Hualien; the Vice-superintendent in Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, and Joint-appoint Associate Research Fellow in Institute of Biomedical Sciences, Academia Sinica, Taipei. In 2018, he is appointed the Convenor in grant review program on Pediatric and OBS/GYN Section in Ministry of Science and Technology (MOST) in Taiwan.

S2-1 Novel regulator of adipocyte lipolysis

Jacqueline Stoeckli

Charles Perkins Centre, School of Life and Environmental Sciences,
The University of Sydney

Adipose tissue lipolysis is upregulated during fasting via catecholamines and is suppressed in response to insulin. Dysregulated lipolysis, as occurs in insulin resistance, results in deleterious lipid deposition in other tissues as well as liver insulin resistance and non-alcoholic fatty liver disease (NAFLD). Catecholamines stimulate lipolysis via elevation of cAMP that activates of the protein kinase PKA that in turn phosphorylates a number of lipid droplet proteins to induce lipolysis. Insulin was thought to suppress this process via Akt-dependent phosphorylation of the phosphodiesterase PDE3B, thus lowering cAMP levels and inhibiting PKA. However, recent studies indicate that this explanation is incomplete. While PDE3B is essential for the anti-lipolytic effects of insulin, the role of its cAMP hydrolytic activity and its Akt-dependent phosphorylation in anti-lipolysis is unclear. We have identified a PDE3B-interacting protein, ABHD15 that is phosphorylated by Akt in response to insulin. Knock down or knock out of ABHD15 in adipocytes results in a defect in insulin regulated lipolysis and concomitant loss of expression of the PDE3B protein. Importantly, insu-lin-mediated suppression of lipolysis, as assessed by a reduction in serum FFA levels, is almost completely blocked in ABHD15 knock out mice *in vivo*. In summary we have discovered a novel regulator of lipolysis that could at least in part explain the controversy about insulin regulation of lipolysis.

【Curriculum Vitae】

Jacqueline Stoeckli obtained her PhD from the University of Basel in Switzerland where she studied intracellular protein trafficking and trafficking signals. She then joined Prof David James' group when he was at the Garvan Institute in Sydney and she initially focused on insulin regulated protein trafficking with a particular interest in GLUT4 and vesicle trafficking proteins, such as Rabs and RabGAPs. In the James Lab she learned about Insulin Signalling, Glucose Metabolism and Mouse Physiology. She is currently a Senior Research Fellow at the Charles Perkins Centre and the School of Life and Environmental Sciences at the University of Sydney. Her group "Molecular Cell Biology" focuses on the insulin regulation of lipolysis.

S2-2 SNAREs and Membrane Traffic

Wanjin Hong

Institute of Molecular and Cell Biology (IMCB), A*STAR

Intracellular membrane trafficking and regulated secretion such as insulin secretion of beta cells, pancreatic acinar secretion and synaptic transmission of neuron is mediated by shuttling vesicles that bud from donor compartment and fuse with a target compartment. After tethering of vesicles with a target compartment, the SNARE proteins will catalyse the fusion of the vesicles with the target compartment. SNARE family proteins are distributed throughout the secretory and endocytic pathways. I will summarize our works on the identification of SNARE proteins, defining of SNARE complexes mediating various fusion events as well as revealing a role of endobrevin/VAMP8 in regulated secretion.

【Curriculum Vitae】

Biography:

Prof Wanjin HONG graduated from Xiamen University in 1982 and was one of a few hundred Chinese students chosen for further graduate training in the United States via the CUSBEA (China–United States Biochemistry Examination and Application) program. He received his PhD from the State University of New York (SUNY Buffalo), and was a postdoctoral fellow there before he joined the Institute of Molecular and Cell Biology (IMCB) in Singapore as a PI in 1989. He became the Executive Director of IMCB at A*STAR (Agency for Science, Technology and Research) in 2011. He was the recipient of Singapore's National Science Award (now President's Science Award) in 1999. He also received Singapore's government Public Administration Medal (Silver) in 2014. He serves as the Editor-in-Chief of Bioscience Reports, Associate Editor of Cell & Bioscience, and is on the editorial board of TRAFFIC.

S2-3 Role of adherens junction proteins in regulating insulin secretion

Peter Shepherd

Molecular Medicine, University of Auckland

The mechanisms regulating the secretion of insulin are only partially understood but are known to require adherens junctions. We have reported that the adherens junction protein beta-catenin plays an important role in regulating the levels of insulin secretion with reduced levels of beta-catenin resulting in reductions in maximum achieveable levels of glucose stuimulated insulin secretion (GSIS) and this was associated with changes in actin fibres. In addition we find levels of beta-catenin change rapidly with changes in metabolic status of the cells thus providing a mechanism for modulating overall levels of insulin secretion. Recently we have gone on to show that reducing levels of the beta-catenin binding partner alpha-catenin results in a surprising increase in levels of GSIS in beta-cells. This was associated with corresponding regulation of changes in pottasium induced calcium flux. Together this indicates that alpha and beta-catenin are part of a novel mechanism for regulating overall levels of GSIS most likely involving regulation of the actin cytoskeleton at the plasma membrane.

【Curriculum Vitae】

Professor Peter Shepherd graduated from Massey University (New Zealand) and did his postdoctoral training at Harvard (U.S.A.) and Cambridge (U.K.). He was appointed as a staff member at University College London (U.K.) thereafter and promoted to full professor in 2003. During that period he became involved in biotechnology development and was named "London Young Biotechnology Entrepreneur of the year" in 2002. Since moving back to Auckland (New Zealand) in 2004 he has continued to focus on research of the signal transduction pathways in the cell and how defects in these lead to the development of cancer and diabetes. He founded biotechnology company Symansis to develop novel tools for drug discovery. He was a co-founder of drug development company Pathway Therapeutics which developed a PI 3-kinase inhibitor through to phase-1 clinical trial. He is currently deputy director of the Maurice Wilkins Centre which is one of New Zealand's national centre's of research excellence and he heads the centre's programme investigating genetic risk factors linked to obesity and type-2 diabetes in the idigenous Maori people of New Zealand.

S3-1 Adiponectin/T-cadherin exerts vascular protection partly through exosome biogenesis and secretion.

Yoshinari Obata, Fukuda Shiro, Shunbun Kita, Yuya Fujisima, Hitoshi Nishizawa, Norikazu Maeda, Iichiro Shimomura

Department of Metabolic Medicine, Graduate School of Medicine, Osaka University

Our group discovered adiponectin from human adipose tissues. Uniquely, circulating adiponectin concentration ranges 1-30 mg/mL, which is around 10^3~10^6-fold higher than ordinary hormones and cytokines. Decreased adiponectin concentration in obesity associates with many metabolic disorders and chronic organ diseases, especially diabetes and atherosclerosis. Higher adiponectin concentration in blood, experimentally and clinically, has been shown to be protective against diabetes and atherosclerosis.

We demonstrated adiponectin's adherence to vascular component cells. Adiponectin required T-cadherin (T-cad), a glycosylphosphatidylinositol (GPI)-anchored cadherin on membrane, to accumulate on the cells. In T-cadherin (Tcad)/ApoE-double knockout (DKO) mice, there was no adiopnectin protein in vasculature, accompanying severer atherosclerosis.

We recently found the relationship between adiponectin and exosome biogenesis. High-molecular multimer adiponectin and T-cadherin, dose-dependently and synergistically, stimulate exosome biogenesis, and affect systemic plasma exosome level. The adiponectin effect to enhance exosome biogenesis was dependent on T-cadherin, not on AdipoRs. These enhancements accompanied the reduction of cellular ceramide and enhanced ceramide-release to exosome. Adiponectin/T-cadherin system physiologically activates exosome biogenesis and secretion, regulates cellular ceramide levels, and exerts beneficial effect on metabolism and organ protection. Therapeutic maneuver to enhance this system should be considered for the protection and prevention of organ damages.

【Curriculum Vitae】

Iichiro Shimomura, M.D., Ph.D.

Dr. Shimomura is currently Professor and Chairman, Department of Internal Medicine and Metabolic Medicine, Graduate School of Medicine, Osaka University. His group has been working on mechanism how visceral fat obesity associates with many clinical complications. He demonstrated the adipose tissue as endocrine organ and conceptualized such adipose derived factors as adipocytokines. He showed the significance of PAI-1 in visceral fat obesity and leptin in lipoatrophic diabetes. He and colleagues discovered adiponectin from human fat cDNA in 1996 and have shown the importance of hypoadiponectinemia in metabolic syndrome and chronic organ diseases. As upstream factors to disregulated adipocytekines, he showed the significance of Fat ROS (reactive oxidative stress) and Fat Hypoxia in obese adipose tissue. Recently, his group has revealed unique feature of adiponectin as a very abundant plasma defense protein, from the aspect of its adherence to cardiovascular cells and inducing exosome production in body, via T-cadherin.

1989:	Faculty of Medicine, Osaka University (M.D.)
1993:	Osaka University Graduate School of Medicine (Ph.D.) (Dr. Yuji Matsuzawa)
1995-2001:	University of Texas, Southwestern Medical Center at Dallas (Drs.Joseph L Goldstein and Michael S Brown). 1995-1997: Postdoctoral fellow, 1997-1999: Instructor, 1999-2001: Assistant Professor
2002-2004:	Professor, Department of Medicine and Pathophysiology, Graduate School of Medicine, Graduate School of Frontier Bioscience, Osaka University.
2004-present:	Professor and Chairman, Department of Internal Medicine and Metabolic Medicine, Graduate School of Medicine, Osaka University.

S3-2 FGF21 resistance in obesity and diabetes

Karen SL Lam

Department of Medicine, The University of Hong Kong

FGF21, fibroblastic growth factor 21, a hormone produced from the liver, adipose tissue, pancreas and muscles, has been shown to regulate glucose, lipid and energy metabolism, via beneficial effects in multiple target organs. Paradoxically, circulating levels are elevated in obesity and its related cardiometabolic disorders, including type 2 diabetes and its cardio-renal complications, suggesting the presence of FGF21 resistance or a compensatory response to the underlying metabolic disturbance or tissue injury. Indeed high serum levels of FGF21 have been shown to be a good biomarker for predicting the development of type 2 diabetes, coronary artery disease and diabetic nephropathy. Impaired FGF21 signaling has been demonstrated in the adipose tissue of obese mice and humans, and pancreatic islet of obese diabetic mice. Mechanistically, this likely results from decreased expression of FGFR1 and/or its co-receptor protein, β-klopho, consequent to adipose tissue inflammation, activated expression of inflammatory cytokines and microRNAs, or hyperglycemia induced reduction in PPAR-γ activity. Thus, in addition to insulin and leptin, FGF21 represents another metabolic hormone to which resistance is present in obesity. As FGF21 regulates adiponectin expression and secretion, FGF21 resistance likely contributes to insulin resistance in obesity, via hypoadiponectinemia.

【Curriculum Vitae】

Professor Karen Lam is Chair Professor in Medicine, Faculty Board Chairman of the Li Ka Shing Faculty of Medicine, Clinical Director of the State Key Lab of Pharmaceutical & Biotechnology, Chairman of the Clinical Trial Centre and Director of Clinical Operations, HKU Health System, at the University of Hong Kong.

Professor Lam was the Founding President of Diabetes Hongkong (Honorary President since 2014), a past President of the Hong Kong Society of Endocrine, Metabolism and Reproduction, and past Chairman of two specialty boards of the HK College of Physicians – Advanced Internal Medicine and Endocrinology, Diabetes & Metabolism, Chairman of Working Party on Diabetes Care, Hospital Authority and Visiting Professor of Sun Yat Sun University of Medical Sciences and Shantou University Medical College. She is currently the associate editor/editorial board member of several international peer-reviewed journals in diabetes and endocrinology.

Professor Lam has published over 400 peer-reviewed international publications on clinical, basic and translational research in diabetes and endocrinology. Her current research focuses on the role of adipocyte derived hormones in diabetes and other obesity-related cardiometabolic disorders. Her team has established two large cohorts, the CRISPS and HKW Diabetes Registry, for prospective studies on genetic and environmental determinants of diabetes and related medical problems. More recently she spearheaded the establishment of the HKU Phase 1 Clinical Trial Centre at the Queen Mary Hospital.

S3-3 East Asia-specific *ALDH2* mutation promotes diet-induced obesity and fatty liver: the therapeutic effect of ALDH2 agonist

Yi-Cheng Chang[1,2,3], Wenjin Yang[4], Che-Hong Chen[5], Daria Mochly-Rosen[5], Lee-Ming Chuang[1,6,7]

Department of Internal Medicine, National Taiwan University Hospital[1],
Graduate Institute of Medical Genomics and Proteomics, National Taiwan University[2],
Institute of Biomedical Science, Academia Sinica[3],
Foresee Pharmaceuticals, Co, Ltd[4],
Department of Chemical and Systems Biology, Stanford University School of Medicine, Stanford[5],
Graduate Institute of Molecular Medicine, National Taiwan University[6],
Graduate Institute of Epidemiology and Preventive Medicine, National Taiwan University[7]

ALDH2 (acetaldehyde dehydrogenase 2, mitochondria) is the key metabolizing enzyme of acetaldehyde. After alcohol ingestion, ethanol is first metabolized to acetaldehyde, which is further converted to non-toxic acetic acid by ALDH2. In addition to exogenous ethanol ingestion, acetaldehyde is also generated from intermediate metabolism, food-derived peroxidized fatty acid, fermented food, gut microbes, smoking, and thermal degradation of plastics. Other toxic bioactive aldehydes such as 4-hydroxynonenal (4-HNE) which plays important roles in the pathogenesis of myocardial ischemia and esophageal cancer are also metabolized by ALDH2. A mis-sense mutation (Glu487Lys) of ALDH2 is highly prevalent in East Asia with a ~36 % of population (~540 million) carrying this mutation.

We here reported that *Aldh2* knockin mice carrying this mutation developed diet-induced obesity, insulin resistance, fatty liver, and adipocyte hypertrophy on high-fat high sucrose diet (HFHSD) as compared to controls. A small-moleculeALDH2 agonist, which is water-soluble, safe, and has high oral bio-availability effectively reduced diet-induced obesity in both *Aldh2* wild-type and knockin mice with improved insulin sensitivity. These results indicate a substantial role of toxic aldehyde in the pathogenesis of obesity, fatty liver, and insulin resistance.

【Curriculum Vitae】

Education

1994-2001 MD, College of Medicine, National Taiwan University (NTU)
2010-2013 PhD, Program of Translational Medicine, NTU & Academia Sinica

Appointment

2016- Attending physician, Division of Endocrinology and Metabolism, Department of Internal Medicine, NTUH
2015- Assistant professor, Graduate Institute of Medical Genomics and Proteomics, NTU
2015- Joint appointment assistant fellow, Academia Sinica, Taiwan

S3-4 Understanding how a missense variant, rs373863828, in the CREBRF genes influences the metabolism of Polynesian people.

Troy Leslie Merry

Nutrition, The University of Auckland

The minor allele of the Māori and Pacific (Polynesian) specific missense variant in the CREBRF gene, rs373863828 (p.Arg457Gln), is associated with body mass index (BMI) but lower risk of type 2 diabetes (T2D). To investigate the mechanism of T2D risk reduction, young (18-40 y) Polynesian males without diabetes and positive (n=21) or negative (n=59) for the p.Arg457Gln CREBRF variant were matched for BMI, and underwent detailed metabolic phenotyping. Preliminary evidence suggests that despite similar resting metabolic rates and body composition, Gln457-positive individuals have lower fasted blood glucose (5.0 ± 0.1 vs 5.4 ± 0.1, p=0.02) and trend for reduced blood glucose response to a mixed meal (p=0.12) challenge. These findings indicate that the Gln457 allele improves glucose homeostasis and does not promote disproportionally greater fat, lean or bone mass. Since CREBRF is not currently recognised as being a metabolic regulator, understanding how rs373863828 enhances blood glucose regulation is likely to provide novel insights into mechanisms underpinning the development of T2D.

【Curriculum Vitae】

Merry-Biography

Troy Merry is a Rutherford Discovery Research Fellow and Senior Lecturer in the Discipline of Nutrition, The University of Auckland. He gained his PhD from the University of Melbourne in 2010 by investigating the molecular regulators of skeletal muscle glucose uptake during exercise. His post-doctoral research at Monash University and ETH Zurich showed that reactive oxygen species can act as signaling molecules to improve metabolic function, even under conditions of metabolic stress, and provided early evidence that hyperinsulinemia is central to the pathogenesis of metabolic disease. Dr. Merry has authored >23 publications, some of which are in top-tier journal such as Nature communications, Cell and Cell Metabolism. Since starting his laboratory in 2016 he has continued his research into understanding the molecular mechanisms of metabolic disease, and how regular exercise improves metabolic health, for which he has funding from the Health and Research Council New Zealand, The Marsden Fund, and the Auckland Medical Research Fund.

S4-1 Adipocyte Fatty Acid Binding Protein and Diabetic Kidney Disease

Paul Chi-ho Lee

Department of Medicine, University of Hong Kong

Diabetic kidney disease is a global threat, and is a major cause of morbidity and mortality in subjects with type 2 diabetes. Over the past decade, the classical paradigm of microalbuminuria always preceding nephropathy progression has been challenged, suggesting the need of novel sensitive renal biomarkers for early risk stratification. Adipocyte fatty acid binding protein, on the other hand, is an adipokine with its circulating levels highly associated with various cardiometabolic diseases. In addition to its function as a lipid chaperone mediating intracellular fatty acid trafficking, adipocyte fatty acid binding protein also modulates inflammatory responses due to its high expression in macrophages. In recent years, the role of inflammation in diabetic kidney disease has been increasingly recognized. Therefore, in this short talk, the role of adipocyte fatty acid binding protein in diabetic kidney disease will be discussed, and its potential to be employed as a useful candidate marker of diabetic kidney disease will also be presented.

【Curriculum Vitae】

Academic / Professional Qualifications

2006	M.B.B.S. (H.K.)	The University of Hong Kong
2009	M.R.C.P. (U.K.)	Royal Colleges of Physicians, United Kingdom
2013	F.H.K.C.P. (ENDO)	The Hong Kong College of Physicians
2013	F.H.K.A.M. (Med)	The Hong Kong Academy of Medicine
2014	F.H.K.C.P. (AIM)	The Hong Kong College of Physicians

Previous and present positions

2015 – Present **Clinical Assistant Professor**
Department of Medicine, The University of Hong Kong

Honours and Post-graduate Awards

2017 Croucher Foundation Fellowship 2016/2017 for overseas training at the Garvan Institute of Medical Research, Sydney, Australia
University of Hong Kong / China Medical Board Grants 2016/2017 for overseas training at the Garvan Institute of Medical Research, Sydney, Australia

S4-2 Role of Nuclear Envelope Protein Lamin A in the Obesity-induced Inflammation

Kae Won Cho

Soonchunhyang Institute of Medi-bio Science (SIMS), Soonchunhynag University

Obesity as a low-grade chronic inflammation leads to dynamic changes in a range of adipose tissue leukocytes that contribute to inflammation and systemic insulin resistance. Over the past few years, it has been established that adipose tissue macrophages (ATMs) play an important role in obesity-induced inflammation and insulin resistance. However, it has been unresolved how ATMs are activated and sustained as pro-inflammatory state in obesity. Recent studies suggest that alteration of the nuclear lamina is associated with age-associated chronic inflammation in humans and fly. Here, we show that nuclear envelope protein lamin A/C mediates inflammation in macrophages. In addition, the gene and protein expression levels of lamin A/C are significantly increased in ATMs from mice with obesity. Furthermore, ectopic overexpression of lamin A/C in macrophages in vitro spontaneously increases the expression of pro-inflammatory genes, while deletion of lamin A/C in macrophages reduces LPS-induced upregulation of inflammatory genes. Importantly, we find that the myeloid cell specific Lmna deficiency ameliorates obesity-induced insulin resistance and adipose tissue inflammation. These results suggest that lamin A/C mediates ATM proinflammatory changes in adipose tissue during obesity. In this presentation, I will discuss novel mechanisms responsible for ATM activations during the development of obesity-induced inflammation and insulin resistance.

【Curriculum Vitae】

EDUCATION

Ph.D 2001~2006 Purdue University (Interdepartmental Nutrition Program)
M.S. 1997~1999 Korea University (Biotechnology)
B.S. 1993~1997 Korea University (Animal Science)

PROFESSIONAL EXPERIENCE

2018~Present Associate Professor, Soonchunghyng Institute of Medi-bio Science (SIMS), SoonChunHyang University
2014~2018 Assistant Professor, Soonchunhyang Institute of Medi-bio Science (SIMS), Soon Chun Hyang University
2011~2014 Research Fellow/Staff Scientist, Department of Pediatrics and Communicable Diseases, University of Michigan
2006~2011 Postdoctoral Fellow, Department of Molecular and Integrative Physiology, University of Michigan

S4-3 Prostaglandins E2 and Inflammatory Cardiovascular Diseases

Lihong Chen

Advanced Institute for Medical Sciences, Dalian Medical University

The cardiovascular side effects of cyclooxygenase-2 (COX-2) inhibitors have prompted scientists to try to find new ways to inhibit the production of pro-inflammatory prostaglandins (PGs), such as PGE_2. Blockade of the inducible PGE_2 terminal synthase, mPGES-1 (membrane-associated PGE_2 synthase-1), is one such approach. Although some data reflected a comparatively benign cardiovascular profile for global mPGES-1 inhibition, we and others showed that the dominant PG products formed and the biological consequences of mPGES-1 inhibition varies between cell types. For example, prostacyclin (PGI_2) is the dominant rediversion product in vascular cells, while thromboxane (Tx)A_2 predominates in macrophages. Thus, inhibition of mPGES-1 might have contrasting phenotypic impacts when achieved in macrophages vs. vascular cells. By generating mice lacking mPGES-1 selectively in myeloid cells, vascular smooth muscle cells or endothelial cells, we found that deletion of mPGES-1 in myeloid cells attenuates the vascular proliferative response to injury and slows atherogenesis; while in vascular smooth muscle cells and endothelial cells enzyme deletion promotes the proliferative response but does not affect atherogenesis. Furthermore, deletion of mPGES-1 in myeloid cells has favorable effects on post-MI survival. These results suggest that compared to global mPGES-1 inhibition, selectively targeting macrophage mPGES-1 may be a strategy further to refine the cardiovascular efficacy while limiting the adverse effects attributable to enzyme inhibition on other tissues. Therefore, macrophage mPGES-1 might serve as a novel and preferable drug target for inflammatory diseases.

【Curriculum Vitae】

EDUCATION

1999.9 - 2004.7 MD
Department of Clinical Medicine, Shanxi Medical University, Shanxi, China, 030001

2004.9 – 2009.7 PhD
Department of Physiology and Pathophysiology, Peking University Health Science Center, Beijing, China, 100191

WORK EXPERIENCE

2009.7 – 2014.6 Postdoctoral Researcher

2014.7 – 2016.4 Research Associate
Institute for Translational Medicine and Therapeutics, Department of Pharmacology, University of Pennsylvania School of Medicine, Philadelphia, PA19104

2016.4 – now Professor
Advanced Institute for Medical Sciences, Dalian Medical University, Dalian, Liaoning, CHINA, 116044

AWARDS

Certificate of Research Excellence, 2015, American Heart Association
Travel Award, 2013, 13th International Bioactive Lipids Conference in Cancer, Inflammation and Related Diseases
Young Investigator Award, 2012, 14th International Winter Eicosanoid Conference
PGFI Summer Undergraduate Student Mentorship Award, 2012, University of Pennsylvania

S5-1 Identification of Novel Regulators of Thermogenic Program through Epigenomic Analysis

Reinhard Brunmeir, Xu Peng, Raymond Ng, Qiongyi Zhang, Feng Xu

Institute of Molecular and Cell Biology, A*STAR

Increasing energy expenditure through thermogenic adipocyte recruitment is a promising approach to combat obesity. To gain molecular insights into the epigenetic regulation of this process, we performed a comprehensive profiling of the epigenome and transcriptome throughout the lineage commitment and differentiation of murine multipotent mesenchymal stem cells into brown adipocytes. Through direct comparison to datasets from differentiating white adipocytes, we systematically identified stage- and lineage-specific coding genes, lncRNAs and microRNAs. Utilizing chromatin state maps, we also define stage- and lineage-specific enhancers, including super-enhancers, and their associated transcription factor binding motifs and genes. Through these analyses, we identify Sox13 as part of a p38 MAPK dependent transcriptional response mediating early brown cell lineage commitment. We also identify and subsequently validate Pim1, Six1 and Rreb1 as novel regulators promoting brown adipogenesis. In addition, we identified miR-32 as a BAT-specific super-enhancer associated miRNA which is highly expressed in BAT and further upregulated during cold exposure. Inhibiting miR-32 *in vivo* during cold exposure led to impaired cold tolerance and reduced emergence of beige adipocytes in inguinal white fat as a result of lower serum FGF21 levels. Further examination showed that miR-32 directly represses its target gene *Tob1* thereby activating p38 MAPK signaling to drive FGF21 expression and secretion from BAT. Increased serum FGF21 promotes BAT thermogenesis and trans-activation of inguinal white fat browning and thermogenesis.

【Curriculum Vitae】

Dr. Feng Xu has been a principal investigator at the Agency for Science, Technology and Research (A*STAR), Singapore since 2009. Now he works in the Institute of Molecular and Cell Biology (IMCB). He was trained as a chromatin biologist at the University of California, Los Angeles before establishing his independent career in Singapore. His current research interest centers on the epigenetic regulation of energy balance and metabolic homeostasis. This topic includes the study of microRNAs, post-translational modifications on histones and non-histone metabolic regulators in the maintenance of metabolic homeostasis. His lab utilizes both advanced genomic tools as well as classical biochemistry and molecular biology techniques to tackle the scientific questions of interest. In addition, he is also interested in developing novel therapeutic approaches for the treatment of metabolic disorders such as obesity and diabetes. His research was published extensively in leading scientific journals including *Cell, Nature, Molecular Cell, Cell Metabolism, Cell Reports* and *PLoS Biology*.

S5-2 X/A like cells in lipid metabolism

Weizhen Zhang

Department of Physiology, Peking University Health Science Center,
Department of Surgery, the University of Michigan

Gastric mechanistic target of rapamycin (mTOR) signaling is inversely associated with the expression and secretion of ghrelin, a 28-aa peptide hormone produced by gastric X/A-like cells. Ghrelin contributes to obesity and hepatic steatosis. We hypothesized that gastric mTOR signaling in X/A like cells controls global lipid metabolism. To test this hypothesis, we established a *ghrl-cre* transgene in which the cre enzyme is expressed in X/A-like cells under the control of the ghrelin-promoter. $mTOR^{flox/flox}$ and $TSC^{1flox/flox}$ mice were separately bred with *ghrl-cre* mice to generate *mTOR-ghrl-cre* (mG) or *TSC1-ghrl-cre* (TG) mice, within which mTOR signaling was suppressed or activated respectively. Lipid metabolism in liver and adipose depots was analyzed. Under the control of the ghrelin-promoter, cre enzyme is exclusively expressed in stomach X/A-like cells in adult animals. Knockout of mTOR in X/A-like cells increased circulating acyl-ghrelin and promoted hepatic lipogenesis with effects on adipose depots. Activation of mTOR signaling by deletion of its upstream inhibitor, tuberous sclerosis 1 (TSC1), decreased ghrelin expression and secretion, altering lipid metabolism as evidenced by resistance to high fat diet-induced obesity and hepatic steatosis. Both ghrelin administration and rapamycin, an inhibitor of mTOR, altered the phenotypes of TG mice. Our observations indicate that Gastric mTOR signaling in X/A-like cells contributes to organism lipid homeostasis by regulating hepatic and adipose lipid metabolism. Gastric mTOR signaling may provide an alternative strategy for intervention in lipid disorders.

【Curriculum Vitae】

Weizhen Zhang is a professor at the Department of Physiology at Peking University Health Science Center and an adjunct research professor at the University of Michigan. Dr. Zhang has published over 120 peer-reviewed papers including 7 invited reviews and one editorial in journals such as PNAS, Ebiomedicine, Diabetes, Diabetologia, Endocrinology and Molecular Endocrinology. Collectively this work has been cited more than 17,00 times and Dr. Zhang has a Scopus h-index of 24. Other recognitions include 12 book chapters, 21 professorships, 35 invited presentations, Ad hoc reviewer for over 30 peer-reviewed journals such as Gut, Nat Commun, Endocrinology and Int J Obs, editorial board members of 6 peer-reviewed journals, and standing members of grant review committees such as NSFC, ADA, Diabetes UK, BBSRC. Dr. Zhang's research focuses on defining the mechanisms that underlie fuel sensing in the gastrointestinal tract and how the fuel sensor in GI tract coordinates the whole body energy status to control glucose and lipid metabolism.

S5-3 Central and peripheral actions of prolactin promote metabolic adaptation to pregnancy

Sharon Rachel Ladyman

Anatomy, and Centre for Neuroendocrinology, University of Otago

Pregnancy is a highly metabolically challenging state. The mother's body undergoes many adaptations to the systems regulating energy and glucose homeostasis, both to meet the metabolic requirements of the growing conceptus and to accumulate fat mass in preparation for the demands of lactation. Our hypothesis is that increased activation of the prolactin receptor (Prlr) plays a key role in driving these adaptations during pregnancy. In virgin rodents, chronic prolactin treatment is associated with increased food intake, body weight gain and beta-cell expansion, similar to what is observed during pregnancy. To investigate the contribution of Prlr in these pregnancy-induced adaptations we have generated mice with either forebrain-specific or pancreas-specific deletion of Prlr: $Prlr^{lox/lox}$/Ckc-cre and $Prlr^{lox/lox}$/Pdx-cre respectively. In these mouse lines, we monitored food intake, body weight, physical activity and aspects of glucose regulation during pregnancy. $Prlr^{lox/lox}$/Ckc-cre mice show mild attenuation of weight gain during pregnancy, likely driven by increased levels of running wheel activity, but no suppression of pregnancy- induced hyperphagia. During pregnancy, $Prlr^{lox/lox}$/Pdx-cre mice have impaired glucose tolerance, impaired beta-cell expansion and attenuated glucose-stimulated insulin secretion. Overall, our data indicate a multifaceted role for prolactin in the maternal metabolic adaptations during pregnancy. There is a key involvement of forebrain Prlr in regulating physical activity during pregnancy, and a requirement of Prlr in the pancreas for inducing adaptations in glucose homeostasis.

【Curriculum Vitae】

Dr Sharon Ladyman received her Ph.D. from the University of Otago in 2005 and her thesis was entitled 'Characterization of leptin resistance during pregnancy in the rat'. Following this Dr Ladyman moved to the Vollum Institute at Oregon Health and Science University in Portland, USA, for a one year postdoctoral position investigating the interactions of Neuromedin U and the melanocortin system in the regulation of food intake. Dr Ladyman then went to work with Dr Barbara Woodside at Concordia University in Montreal, Canada where she was awarded a Fonds de la recherche en sante Quebec Postdoctoral Fellowship to study the contributions of NPY and kisspeptin in lactational infertility and the hyperphagia of lactation. Dr Ladyman returned to New Zealand in 2009 to take up a position as a Research Fellow working with Prof. David Grattan to further understand how the maternal brain adapts to deal with the increased metabolic demands of pregnancy and lactation. Dr Ladyman has published over 25 papers in this area including a number of invited reviews. Her current work focuses on using transgenic mouse models and metabolic phenotyping cages to understand the role of the pregnancy hormone prolactin in the metabolic changes, including changes in glucose homeostasis, during pregnancy and lactation.

S6-1 Novel Pathways in Cardiometabolic Disease

John Francis O'Sullivan

Cardiology, The University of Sydney / Heart Research Institute

Objective: Poor glycaemic response to type 2 diabetes (T2D) therapy is common. We aimed to identify biomarkers of insulin resistance in obesity to guide treatment in the clinical setting.

Research Design and Methods: Metabolomics and lipidomics were combined with a specialized machine-learning algorithm to identify plasma biomarkers that characterize muscle and liver insulin resistance (IR) in a cohort of 62 individuals with obesity (BMI range 31-48 kg/m^2) phenotyped using the gold-standard 2-step hyperinsulinaemic-euglycaemic clamp with deuterated glucose to evaluate glucose regulation in muscle and liver.

Results: Comprehensive metabolomic and lipidomic profiling by LC/MS revealed that a total of fourteen circulating metabolites and lipids were closely correlated with muscle insulin resistance (Spearman *rho* > 0.2, $p < 0.05$) while nineteen were associated with hepatic insulin resistance (Spearman *rho* > 0.3, $p < 0.05$). A hybrid learning model that combines clustering-based prototype selection and random forest-based feature analysis identified two triacylglycerols (TAGs) and a phosphatidylcholine (PC) in plasma as the best classifiers differentiating between the liver and muscle insulin resistance phenotypes, followed by select metabolites, clinical features, and biochemical parameters. The three lipids identified by the hybrid learning model far out-performed standard clinical measures, including fasting plasma glucose, 2-h plasma glucose post 75 g oral glucose load, glycosylated haemoglobin (HbA1c), and homeostatic model assessment of insulin resistance (HOMA-IR), classifying 61 of 62 subjects correctly.

Conclusions: We provide a simple novel tool based on circulating lipids and metabolites to guide physicians to the most effective insulin-sensitising treatment in individuals with obesity. Future studies are necessary to validate these findings and compare the efficacy of the biomarker-guided therapy with the traditional treatment.

【Curriculum Vitae】

Dr John O'Sullivan is a Clinical-Academic Cardiologist at the Royal Prince Alfred Hospital and Group Leader in Cardiometabolic Disease at the Heart Research Institute and Charles Perkins Centre of the University of Sydney. John undertook his internal medicine, cardiology, and PhD training in Ireland, and then spent 4 years at Massachusetts General Hospital and Harvard Medical School. John studies the cardiovascular consequences of obesity and related diseases such as diabetes. He is particularly interested in applying unbiased non-targeted metabolomic profiling to discover novel disease insight. In carefully-designed patient cohorts, he leverages metabolomic and genomic data to determine novel markers, effectors, and predictors of disease; he then interrogates their functional roles in model systems.

In this presentation, John will talk about his recent work identifying novel insight into cardiometabolic disease by leveraging large datasets, genomics, metabolomics, genome editing, and bioinformatics.

S6-2 Role of PRMT1 in skeletal muscle homeostasis

Seung-Hoi Koo[1], Seri Choi[1], Hyeon-Ju Jeong[2], Hyebeen Kim[2], Dahee Choi[1], JongSun Kang[2,3]

Division of Life Sciences, Korea University[1],
Department of Molecular Cell Biology, Single Cell Network Research Center, Sungkyunkwan University School of Medicine[2],
Samsung Biomedical Research Institute, Suwon, Gyeonggi-do[3]

Protein arginine methyltransferases (PRMTs) are regarded as important regulators of skeletal muscle metabolism and regeneration. However, the direct roles of the various PRMTs during skeletal muscle remodeling remain elusive to date. Here, we examined the function and downstream targets of PRMT1 in muscle homeostasis by using skeletal muscle-specific PRMT1 knockout mice. We found that muscle-specific depletion of PRMT1 in mice leads to muscle atrophy. PRMT1-deficient muscles exhibit enhanced levels of FoxO3a and muscle- specific ubiquitin ligases, MuRF1 and Atrogin1. Interestingly, PRMT1 deficiency enhances PRMT6 levels, leading to the increased methylation and activation of FoxO3a, which is abrogated by PRMT6 depletion. Taken together, we propose that PRMT1 is a key regulator for PRMT6/FoxO3a axis in the control of skeletal muscle maintenance.

【Curriculum Vitae】

Education

2000 Biochemistry, Ph.D., Department of Biochemistry, Molecular Biology and Biophysics, University of Minnesota, Minneapolis, MN, USA
1995 Biochemistry, M.S., Department of Chemistry, Seoul National University, Seoul, Korea
1992 Chemistry, B.S., Department of Chemistry, Seoul National University, Seoul, Korea

Professional Experience

2013-present Professor, Division of Life Sciences, College of Life Sciences & Biotechnology, Korea University, Seoul, Korea
2009-2013 Associate Professor, Department of Molecular Cell Biology, School of Medicine, Sungkyunkwan University, Suwon, Korea
2005-2009 Assistant Professor, Department of Molecular Cell Biology, School of Medicine, Sungkyunkwan University, Suwon, Korea
2002-2005 Research Associate, Peptide Biology Laboratories Salk Institute for Biological Studies, La Jolla, CA, USA
2001-2002 Postdoctoral Fellow, Department of Molecular Pharmacology, Stanford University, Stanford, CA, USA

S6-3 Impaired Glucose Transporter 10 Function Predisposes Mice to High-Fat Diet-Induced Type 2 Diabetes

Yi-Ching Lee

Institute of Cellular and Organismic Biology, Academia Sinica

In the context of rapid transitions in dietary pattern, increased prevalence of obesity contributes to accelerating the spread of the type 2 diabetes (T2D) epidemic. However, little is known about the interactions between diet and genes that influence T2D. Human *SLC2A10* gene encoded glucose transporter 10 (GLUT10) has been shown to be associated with T2D in family studies. Loss-of-function mutations of GLUT10 cause a rare autosomal recessive connective tissue disorder, arterial tortuosity syndrome (ATS). GLUT10 has a function as an intracellular dehydroascorbic acid (DHA) transporter and is important in maintaining intracellular ascorbic acid (AA) levels. We have generated a $Glut10^{G128E}$ mouse model with comprised Glut10 function. The mice have milder clinical and pathological features compared with these of ATS patients. The mice are suitable for studying the polymorphisms in the *SLC2A10* gene with compromised GLUT10 function might contribute to the pathogenesis of vascular diseases and T2D. Here, we found that although the mutant mice are metabolic normal under normal diet condition (CD), they have impaired adipogenesis, compromised white adipose tissue (WAT) development, and altered adipokine profiles.
Surprisingly, under high-fat-diet (HFD) feeding, $Glut10^{G128E}$ mice gain more weight, increased macrophage infiltration and adipose fibrosis in WAT, further augmented adipokines dysregulation, ectopic fatty acid accumulated in brown adipose tissues and liver, and susceptible to develop insulin resistance and T2D. Our results suggest that GUT10 plays unexpected roles in adipose development and maintaining adipose function, metabolic homeostasis, especially under HFD feeding.

【Curriculum Vitae】

Education/ Scientific Positions:

2013-present Assistant Research Fellow,
Institute of Cellular and Organismic Biology, Academia Sinica, Taipei, Taiwan
2011- 2013 Assistant Professor,
Institute of Molecular Medicine, National Tsing Hua University, Hsinchu, Taiwan
2009-2011 Adjunct Assistant Professor,
Institute of Integrated Medicine, China Medial University, Taichung, Taiwan
2006- 2011 Group leader,
National Center for Genome Medicine, Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan
2003-2006 Visiting Fellow,
National Institute of Child Health& Human Development (NICHD), National Institutes of Health (NIH), Bethesda, MD.
2003 Ph. D.
Institute of Molecular Biology, Academia Sincia and Institute of Life Science, National Defense University, Taipei, Taiwan.

JAJS1-1 Transcriptional Regulation of Brown Adipocytes and Its Implication for Obesity in Humans

Hironori Waki

Department of Diabetes and Metabolic Diseases
Department of Molecular Science on Diabetes
Graduate School of Medicine
The University of Tokyo

The development of high-throughput sequencing technology lets us investigate the epigenome in a global and comprehensive manner, and provides previously unrecognized findings and insights. We identified nuclear factor I-A (NFIA) as a transcriptional regulator of brown fat by a genome-wide open chromatin analysis of murine brown and white fat followed by motif analysis of brown-fat-specific open chromatin regions. NFIA and the master transcriptional regulator of adipogenesis, PPARγ, co-localize at the brown-fat-specific enhancers. Moreover, the binding of NFIA precedes and facilitates the binding of PPAR, leading to increased chromatin accessibility and active transcription. Knockdown and knockout experiments as well as human studies indicate that NFIA is a physiological regulator that controls the brown-fat-specific gene program. I will also introduce a result of a clinical study in which we investigated supraclavicular brown fat density by using near-infrared time-resolved spectroscopy and discuss a potential role of brown fat for obesity in humans.

【Curriculum Vitae】

Education

Mar 2003 Ph.D. Graduate School of Medicine, The University of Tokyo, Japan
Mar 1997 M.D. Faculty of Medicine, The University of Tokyo, Japan

Professional Appointments:

2016-present Project Associate Professor, Department of Molecular Science on Diabetes, Graduate School of Medicine, The University of Tokyo
2011-2016 Project Associate Professor, Functional Regulation of Adipocytes, Graduate School of Medicine, The University of Tokyo
2008- 2011 Project Assistant Professor, Laboratory of molecular physiology on Energy Metabolism, Graduate School of Medicine, The University of Tokyo
2007- 2008 Project Assistant Professor, Department of Integrated Molecular Science on Metabolic Diseases, Graduate School of Medicine, The University of Tokyo
2004- 2007 Research Associate, Howard Hughes Medical Institute, Department of Pathology and Laboratory Medicine, University of California, Los Angeles, Supervisor: Peter Tontonoz MD, PhD
2003- 2004 Postdoctoral Fellow, University of California, Los Angeles, Department of Pathology and Laboratory Medicine, Supervisor: Peter Tontonoz MD, PhD

Professional Activities:

Apr 2015 Keystone Symposia: Asian Advisory Committee
Apr 2015 IDF-WPR & AASD 2016: Scientific Program Committee
Feb 2015 The 7th AASD Scientific Programme Committee
Dec 2011 PLoS One Editorial Board, Academic Editor

Honors and Fellowships:

Oct 2017 Young Investigator Award, The Japan Society of Diabetic Complication
Sep 2017 Research Encouragement Research Award, The Japan Society of Constitutional Medicine
Sep 2015 Medical Research Encouragement Prize of The Japan Medical Association, The Japan Medical Association
Jul 2015 William Cullen Award, Japan Association for Diabetes Education and Care
Oct 2013 Encouragement Prize for Obesity Research, Japan Society for the Study of Obesity
Dec 2012 Banyu Foundation Research Grant Award, Banyu Life Science Foundation International (BANFI)
Oct 2008 Young Investigator Award, Japan Society for the Study of Obesity

Selected publications:

1. Hiraike Y, et al. Nature cell biology. 19(9):1081-1092 (Sep 2017)
2. Take K, et al. Scientific reports. 7(1):7326 (Aug 2017)
3. Wang J et al. The Journal of clinical investigation. 127(3):987-1004 (Mar 2017)
4. Waki H, et al. PLoS genetics. 7:e1002311 (Oct 2011)
5. Villanueva CJ, et al. Cell metabolism. 13:413-427 (Apr 2011)
6. Waki H, et al. Cell metabolism. 5:357-370 (May 2007)

JAJS1-2 Epigenetic Regulation of Adipocyte Characteristics by Histone Demethylase JMJD1A

Takeshi Inagaki[1], Juro Sakai[2,3]

Gunma University[1], The University of Tokyo[2], Tohoku University[3]

Adipose tissue harbors plasticity to adapt to environmental changes. White adipocyte stores energy in the form of triglycerides, while brown and beige (or brite) adipocyte produce heat by dissipating energy. A beige adipocyte is an inducible form of a thermogenic cell which emerges in the white adipose tissue depots in response to extracellular stimuli such as prolonged coldness. It is considered that such adaptability of adipocytes is regulated by epigenetic mechanisms. Among them, histone methylation is a chemically stable post-translational modification, which is an appropriate epigenetic mark for mediating cellular memory to induce and maintain the beige adipocyte characteristics. JMJD1A, a histone demethylase of H3K9, contributes to thermogenesis in both brown and beige adipocytes. In detail, cold stress induces β-adrenergic receptor stimulation and subsequent activation of PKA, which phosphorylates JMJD1A at S265. In brown adipocyte, phosphorylated JMJD1A forms a complex with chromatin remodeler SWI/SNF and nuclear receptor PPARγ, which, in turn, remodels the chromatin structure to bring the enhancer regions of thermogenic genes close to its promoter region to induce quick gene expression. This enzyme activity-independent mechanism is appropriate for producing heat acutely in brown adipose tissue in which chromatin conformation around the thermogenic genes is relatively "open". On the other hand, genomic regions of beige-selective genes in white adipose tissue are abundant in methylated H3K9, a "closed" chromatin mark. During beige adipogenesis, phosphorylated JMJD1A is recruited to beige-selective genes by forming a complex with PRDM16, PGC1α, and PPARγ, and subsequently demethylates H3K9 to facilitate gene expression. Collectively, JMJD1A mediates both acute and chronic thermogenesis in brown and beige adipose tissues, respectively. Considering that Jmjd1a-null mice show the phenotypes of hyperlipidemia, insulin insensitivity, and obesity, JMJD1A would be a potential therapeutic target for the metabolic syndrome.

【Curriculum Vitae】

EDUCATION

Ph.D.
Shinshu University Graduate School of Medicine

M.D.
Shinshu University School of Medicine

PROFESISONAL RESEARCH EXPERIENCE

2016-present **Professor**
Laboratory of Epigenetics and Metabolism
Institute for Molecular and Cellular Regulation
Gunma University

2010-2016 **Associate Professor**
Division of Metabolic Medicine (Dr. Juro Sakai)
Research Center for Advanced Science and Technology
The University of Tokyo

2008-2010 **Assistant Professor**
Division of Metabolic Medicine (Dr. Juro Sakai)
Research Center for Advanced Science and Technology
The University of Tokyo

2007-2008 **Instructor**
Department of Molecular Biology (Drs. Steven Kliewer and David Mangelsdorf)
University of Texas Southwestern Medical Center at Dallas

2002-2007 **Research Fellow**
Departments of Molecular Biology and Pharmacology (Drs. Steven Kliewer and David Mangelsdorf)
University of Texas Southwestern Medical Center at Dallas

AWARDS AND HONORS

2018 Lilly Award, the Japan Diabetes Society
2016 Japan Endocrine Society Research Award
2012 Okamoto Research Award, Japan Vascular Disease Research Foundation
2007 Japan Endocrine Society Young Investigator Award

JAJS1-3 Dysregulation of Lipid Metabolism and Energy Balance in Obesity

Jeehyung Sohn, Yun Kyung Lee, Jiseul Han, Yong Geun Jeon, Jong-In Kim, Sung Sik Choe, Jae Bum Kim

Center for Adipose Tissue Remodeling, Department of Biological Sciences, Institute of Molecular Biology and Genetics, Seoul National University

Adipose tissues are actively engaged in the regulation of energy homeostasis to respond to dynamic changes in obesity and cold acclimation. In mammals, adipose tissues have been traditionally classified into white adipose tissue and brown adipose tissue. These two types of adipose tissues differ in various aspects, including anatomical locations, cellular morphologies, and metabolic characteristics. Obesity is characterized by chronic and low grade inflammation accompanied with macrophage accumulation in adipose tissue, eventually leading to metabolic disorders including insulin resistance and type 2 diabetes. Adipose tissue macrophages (ATMs) are key players to affect adipose tissue inflammatory responses in obesity. In lean animals, the large number of ATMs is composed of alternatively activated (M2-like) macrophages which express high levels of interleukin (IL)-10 and arginase (ARG) 1 to maintain insulin sensitivity. On the contrary, in obese animals, the population of classically activated (M1-like) macrophages is rapidly increased in adipose tissue. M1-like ATMs secret numerous pro-inflammatory cytokines such as tumor necrosis factor alpha (TNFa), IL-6, and IL-1b, which aggravates adipose tissue inflammation and insulin resistance in obesity. In obese adipose tissue, pro-inflammatory cytokines secreted from M1-like ATMs induce adipokine dysregulation and impair insulin action to confer systemic insulin resistance. Thus, the imbalance between M1- and M2-like ATMs appears to be crucial to provoke proinflammatory responses in obese adipose tissue.

【Curriculum Vitae】

1984~1988	BS, Seoul National University
1988~1990	MS, Seoul National University
1991~1996	Ph. D., Harvard University (Advisor: Dr. Bruce M. Spiegelman)
1997~1999	Postdoctoral Fellow, Center for Cancer Research, MIT (Advisor: Dr. Phillip A. Sharp)
2000~2003	Assistant Professor, Seoul National University
2004~2008	Associate Professor, Seoul National University
2009~present	Professor, Seoul National University
2004~2009	PI, National Research Laboratory
2011~present:	Director, Center for Adipose Tissue Remodeling, Creative Research Initiatives
2013~2014	Member of Presidential Advisory Council on Science & Technology
2014~2016	Editorial Board Member of Diabetes
2015~2020	Editorial Board Member of Journal of Biological Chemistry
2015~present	Member of The Korean Academy of Science and Technology

Research Interests
1. Molecular Understanding of Adipose Tissue Biology
2. Gene Expression Regulation of Lipid and Glucose Metabolism
3. Molecular Pathogenesis for Obesity and its Related Metabolic Diseases

JAJS1-4 A novel molecular pathway controls activation of thermogenic adipose tissue

Edward T. Chouchani

Harvard Medical School
Dana-Farber Cancer Institute

Thermogenesis by brown and beige adipose tissue, which requires activation by external stimuli, can counter metabolic disease. Thermogenic respiration is initiated by adipocyte lipolysis through cyclic AMP–protein kinase A signalling; this pathway has been subject to longstanding clinical investigation. Here we apply a comparative metabolomics approach and identify an independent metabolic pathway that controls acute activation of adipose tissue thermogenesis in vivo. We show that substantial and selective accumulation of the tricarboxylic acid cycle intermediate succinate is a metabolic signature of adipose tissue thermogenesis. Succinate accumulation occurs independently of adrenergic signalling, and is sufficient to elevate thermogenic respiration in brown adipocytes. Selective accumulation of succinate may be driven by a capacity of brown adipocytes to sequester elevated circulating succinate. Furthermore, brown adipose tissue thermogenesis can be initiated by systemic administration of succinate in mice. Succinate from the extracellular milieu is rapidly metabolized by brown adipocytes, and its oxidation by succinate dehydrogenase is required for activation of thermogenesis. We identify a mechanism whereby succinate dehydrogenase-mediated oxidation of succinate initiates production of reactive oxygen species (ROS), and drives thermogenic respiration, whereas inhibition of succinate dehydrogenase suppresses thermogenesis. Finally, we show that pharmacological elevation of circulating succinate drives ROS production and UCP1-dependent thermogenesis by brown adipose tissue in vivo, which stimulates robust protection against diet-induced obesity and improves glucose tolerance. These findings reveal an unexpected mechanism for control of thermogenesis, using succinate as a systemically-derived thermogenic molecule.

【Curriculum Vitae】

Bio: Edward Chouchani joined the faculty of Harvard Medical School as an Assistant Professor of Cell Biology in 2017. He received his Ph.D. in Biological Sciences at the University of Cambridge and MRC Mitochondrial Biology Unit. He then performed postdoctoral research at the Dana-Farber Cancer Institute and Harvard Medical School. His research focuses on deciphering molecular mechanisms that drive metabolic disease, and using this information to develop targeted therapeutic strategies. Mitochondria are critical hubs for metabolic signalling, and their dysfunction is key in the pathology of metabolic disease. Edward's lab combines combine mass spectrometry and targeted pharmacological approaches in vivo to understand how mitochondrial redox metabolism controls physiology in clinically informative mouse models of obesity and diabetes.

JAJS2-1 Vaccination Therapy against Semaphorin 3E Ameliorates Glucose Intolerance in Diet-induced Obese Mice

Yohko Yoshida[1,2], Ippei Shimizu[1,2], Hironori Nakagami[3], Tohru Minamino[1]

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Obesity and diabetes are one of the major health problems for many societies in the modern world. We previously demonstrated a pathological role of class 3 semaphorin E (Sema3E) in adipose tissue inflammation and insulin resistance. Expression of Sema3E and its receptor plexinD1 was up-regulated in adipose tissue of a murine dietary obesity model. Sema3E-plexinD1 axis induced adipose tissue inflammation and glucose intolerance through its chemoattractant effects for macrophages. Here we show that peptide vaccine against Sema3E improves glucose intolerance and adipose tissue inflammation in obesity. Immunization with the Sema3E peptide vaccine significantly improved glucose intolerance in obese mice fed a high fat diet. The expression level of plexinD1 and inflammatory cell markers were decreased in the Sema3E vaccine group, suggesting the suppression of Sema3E-induced adipose tissue inflammation by Sema3E vaccine. These results indicate that the vaccination against Sema3E may become a novel therapy for lifestyle-related diseases.

JAJS2-2 Hypothalamic neuronal circuits regulating hunger-induced taste modification

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Central neural circuits for feeding behavior are highly complex and regulated by many factors such as internal state and palatability of food. The gustatory system plays a critical role in sensing appetitive and aversive taste stimuli for the evaluation of food quality. Although taste sensitivity and food preference are known to change depending on internal states, such as hunger, the mechanistic insight remains unclear. Here we examine the neuronal mechanisms regulating hunger-induced taste modification in the mouse brain.

Starved mice exhibit an increased sensitivity for sweet taste and tolerance for aversive taste. This hunger-induced taste modification is recapitulated by selective activation of orexigenic Agouti-related peptide (AgRP)-expressing neurons in the hypothalamus projecting to the lateral hypothalamus, but not to other brain regions. Glutamatergic neurons in the lateral hypothalamus function as downstream neurons of AgRP neurons. Importantly, these neurons are sufficient and necessary to modulate sensitivities for both appetitive and aversive tastes by using two distinct pathways projecting to the lateral septum or the lateral habenula, respectively. Our results suggest that these hypothalamic circuits for taste modification would be important for optimizing feeding behavior under energy deficit conditions.

Since increased appetite and change in taste sensitivities are often observed in genetic mouse models of obesity and type 2 diabetes, such as db/db mice, drugs able to regulate the hypothalamic neuronal circuits for taste modification may become useful for reversing the biased food preference and taste sensitivities.

JAJS2-3 Hepatic Activin B controls glucose metabolism

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Activins, members of transforming growth factor β (TGFβ) superfamily proteins, are known to play pivotal roles in the reproductive and developmental processes, and their variety of functions have recently been discovered in many cell types, while their significance in glucose metabolism is poorly understood. Here we show that administration or overexpression of Activin B, which is endogenously produced in liver, markedly reduces blood glucose levels in both obese diabetic mice and insulin deficient diabetic mice. Activin B exerts glucose-lowering effects through multiple mechanisms, including induction of FGF21 through the canonical pathway, suppressing gluconeogenesis and increasing insulin secretion through the non-canonical pathway. While the expression of Activin B is not altered by obesity, the expression of FSTL3, known as an inhibitory molecule for TGFβ superfamily proteins, in adipocytes is highly increased in obese model mice, and strongly correlates with body mass index and insulin resistance in humans. Indeed, metabolically beneficial effects of Activin B are completely canceled by co-administration of FSTL3, while suppression of FSTL3 ameliorates glucose intolerance in obese mice. Thus, Activin B produced by liver improves glucose tolerance and insulin sensitivity in obesity, while obesity induces functional suppression of Activin B via increased FSTL3 and thereby leads to dysregulation of glucose homeostasis.

JAJS2-4 Control of body weight by FTO

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N^6-methyladenosine (m^6A) is a common form of mRNA methyl modification, and plays roles in a wide variety of biological processes through the control of protein synthesis. FTO protein is an m^6A demethylase. Knockout and overexpression studies in mice suggested that FTO contributes to body weight control. We focused on the roles of FTO in the hypothalamic feeding center. AgRP neuron-specific FTO deletion mice had lower body weight and food intake. M^6A-immunoprecipitation followed by NGS analysis (m^6A-seq) revealed that FTO demethylates m^6A on RNAs related to neural development. In addition, RNA-seq suggested that the axonal growth-signaling pathway is the most associated. Histological analysis of FTO deletion mice showed that, from 3 weeks of age, AgRP neurite density was decreased. These results indicate that FTO in AgRP neurons promotes neurite growth via m^6A demethylation, thereby positively controlling energy balance.

Poster Session

P-01 Protection Against HFD Obesity in Helz2-Deficient Mice by Enhancing Hepatic Leptin Sensitivity

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Obesity arises from impairment of energy homeostasis, which is centrally coordinated by activating the long form of leptin receptor (Leprb). Obesity causes central leptin resistance; however, whether enhanced peripheral leptin sensitivity overcomes central leptin resistance remains unclear. A peripheral metabolic organ targeted is the liver with low *Leprb* expression. Weshow that mice fed a high-fat diet (HD) and patients with hepatosteatosis exhibit upexpression of hepatic *Helz2*, which functions as a transcriptional coregulator for nuclear receptors including PPARγ *in vitro*. To explore physiological importance of Helz2, we generated *Helz2*-deficient mice and analyzed their metabolic phenotypes. *Helz2*-deficient mice showing hyperleptinemia associated with central leptin resistance are protected against HD-induced obesity and significantly upregulates hepatic Leprb expression. *Helz2*-deficiency and adenovirus-mediated liver-specific Leprb overexpression in wild-type mice significantly stimulated hepatic AMPK on HD, whereas *Helz2*-deficient *db/db* mice lacking functional Leprb did not. The enhanced hepatic AMPK energy-sensing pathway ameliorates hyperlipidemia, hepatosteatosis and insulin resistance. The activity of murine *Lepr* gene promoter was cooperatively stimulated by Sp1 and GATA4, and HELZ2 could suppress its transcription by squelching GATA4 from promoter-bound Sp1 in cultured hepatocytes. These findings together demonstrate that *Helz2*-deficiency ameliorates HD-induced metabolic abnormalities by stimulating endogenous hepatic Leprb expression, despite central leptin resistance. Hepatic HELZ2 might be a novel target molecule for the treatment of obesity with leptin resistance.

P-02 Novel roles for SFPQ, a splicing regulator for the early differentiation of 3T3-L1 preadipocytes

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Identification of new molecules involved in adipogenesis would be useful to develop novel approaches to obesity therapy. We previously isolated helicase with zinc finger 2 (HELZ2) as a co-activator of peroxisome proliferator-activated receptorγ. Since HELZ2 was reported to be tyrosine-phosphorylated, we performed co-immunoprecipitation coupled with mass spectrometry analyses to isolate factors interacting with HELZ2 in the presence of a tyrosine phosphatase inhibitor. We herein identified splicing factor, proline and glutamine-rich (SFPQ) as a protein associating with the tyrosine-phosphorylated HELZ2. Knockdown of *Sfpq* in 3T3-L1 cells significantly attenuated adipocyte differentiation. This appeared to be due to decreased expression of transcription factors including *Cebpβ* and *δ*, and *Krox20* as well as aberrant alternative mRNA splicing of silencing mediator of retinoid and thyroid hormone receptors during the early differentiation process. The present findings identified novel roles of SFPQ for promoting the differentiation of 3T3-L1 cells by modulating transcription and alternative splicing.

P-03 The Pilot study of the RJ-TOMODACHI program ; lifestyle intervention program for obesity in Russia

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Backgrounds In Russia, there has been a significant increasing in the prevalence of obesity in last decades. Early detection of persons with risk factors of NCDs and providing them with preventive care is one of the effective ways of dealing with this important health issues. Japanese team and National Research Center for Preventive Medicine (NRCPM, Moscow, Russia) collaborate to develop lifestyle intervention program (RJ-TOMODACHI program:Russia − Japan Tackle Obesity and Metabolic syndrome Outcome by Diet, Activities and Checking BW Intervention Program) for overweight and obesity patients in Russia.

Design of the pilot study Obesity patients aged from 25 to 60 yo., with the inclusion criteria (BMI 27-35 and/or abdominal obesity) are recruited by NRCPM. Face-to-face guidance are given on initial visit using newly developed education materials. Measurements using devices (pedometers, BP monitor and body weight scale) are carried out and recorded by subjects. Continuous support are conducted via phone calls, interviews, or e-mail on a regular basis for three months. Feasibility assessment and evaluation of effectiveness are performed.

Results Ten Patients were recruited (7 women and 3 Men) and no patients were dropped out. Average age; 37.9 ± 7.9 years old, BMI: 32.1 ± 2.4, Abdominal circumference(AC) 100.2 ± 11.0. BW change during 3 months; -4.5 ± 3.5 kg , BMI change -1.5 ± 1,1, AC change; -6.6 ± 3.8 cm. We will show other metabolic parameters in the session.

Conclusion RJ-TOMODACHI program is shown to be feasible and effective for Russian obesity people in the pilot study. We will launch RCT for 200 patients in September 2018 after finalizing of the study protocol, including improvement of the program and training for educators.

P-04 Intraperitoneal glucose reduces rat GLP-1 concentrations

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Background & Objectives: An incretin hormone secreted by intestinal L-cells, Glucagon-like peptide-1 (GLP-1) promotes pancreatic insulin release to regulate plasma glucose. Among luminal nutrients, glucose is a known secretagogue of GLP-1. However, we've observed a decrease in peripheral GLP-1 concentration following oral glucose administration in rats. Therefore, we designed an in situ study to determine whether GLP-1 secretion is suppressed by glucose.

Material & Methods: After an overnight fast, Sprague Dawley rats were placed under anaesthesia and administered glucose (1g/Kg BW) either via luminal infusion or intraperitoneal administration. Catheters were surgically inserted into the portal and jugular vein, and blood samples were drawn within 60 minutes in order to compare GLP-1 concentrations upon secretion and within the peripheral blood.

Results & Conclusion: We confirmed an increase in GLP-1 secretion by luminal glucose, but we also observed a tendency for GLP-1 concentration to reduce following intraperitoneal glucose in the jugular vein. These results suggest that glucose in circulation is involved in GLP-1 clearance.

P-05 Postprandial GLP-1 response in Wistar and Goto-Kakizaki rats during diet-induced obesity

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Background & Objective: Glucagon-like peptide-1 (GLP-1) is an incretin hormone that regulates glycemic response through augmentation of insulin secretion. To date, existing data on GLP-1 response in obesity and diabetes are still controversial. Hence, the present study was designed to investigate GLP-1 secretion in response to meal ingestion during long-term diet-induced obesity in both nondiabetic and diabetic rat models.

Methods: Nondiabetic Wistar and diabetic Goto-Kakizaki (GK) rats (5 weeks old) were fed a control and a high fat/high sucrose (HFS, 30% fat and 40% sucrose) diet for 26 weeks. Meal tolerance tests (MTTs) were conducted to determine postprandial glucose and GLP-1 responses to a liquid diet administration during the experimental period.

Results and Conclusions: Postprandial glycemic responses in Wistar rats fed the HFS diet (WH) were similar to Wistar rats fed the control diet (WC) in the early period, and were then higher than WC group after 12 weeks of feeding period. GK rats fed the HFS diet (GH) had higher glycemic response compared to GK rats fed the control diet (GC) throughout the experimental period. Postprandial GLP-1 responses in WH group significantly or tended to be higher than WC group. In contrast to Wistar rats, GH and GC groups showed similar GLP-1 response. The results suggest that the increment of postprandial GLP-1 in nondiabetic rats played a role in the prevention of glucose intolerance development, while the protective adaptation has been lost in diabetic state.

P-06 Effects of testosterone ointment in Japanese men with metabolic syndrome

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The metabolic syndrome involves a cluster of clinical features including visceral obesity, insulin resistance, hypertension, glucose intolerance, and dyslipidemia. Recent studies have shown that low testosterone levels are significantly associated with metabolic syndrome and type 2 diabetes.

We examined the change in insulin resistanceafter testosterone treatment in 18 Japanese men with metabolic syndrome and low free testosterone levels. Testosterone supplements were administered by testosterone ointment (Glowmin,Daito Pharmaceutrical, Tokyo, Japan) for 3 to 6 months. Glowmin contains 10mg of testosterone per 1g of matrix. A 2-cm line of Glowmin was applied to the submandibular skin and contained a dosage of 3mg of testosterone and this was given twice a day in the morning and evening.

Fasting plasma glucose (FPG), fasting serum insulin (F-IRI), HbA1c, total cholesterol(TCHO), triglyceride(TG), HDL-C, LDL-C, free testosterone, LH, FSH, BMI and waist circumference were measured. We used homeostasis model assessment (HOMA-R) as an index of insulin resistance and investigated the change in insulin resistance and lipid profiles after testosterone treatment.

After treatment, F-IRI, HOMA-R, TCHO and LDL-C were significantly decreased from 17.8 ± 6.9μIU/ml to 11.9 ± 3.6μIU/ml, 4.81 ± 2.06 to 3.13 ± 1.01, 250 ± 25mg/dl to 216 ± 20mg/dl and 172 ± 27mg/dl to 139 ± 24mg/dl, respectively. Free testosterone was significantly increased from 5.9 ± 0.8pg/ml to 9.0 ± 1.6pg/ml. Other parameters were not changed significantly.

In conclusion, these results suggest that testosterone replacement therapy by testosterone ointment improves insulin resistance and LDL-C in Japanese men with metabolic syndrome and low free testosterone levels.

P-07 Pivotal role of miR-494 in mitochondrial biogenesis and glucose metabolism during adipocytes browning

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Mitochondria play an essential role in energy homeostasis. Their functionsare regulated in response to external stimuli such as cold exposure and beta-3 adrenergic receptor (β_3-AR) agonist. Previously, we have reported that miR-494 regulates mitochondrial biogenesis in the skeletal muscle. However, this remains unknown in adipocytes and glucose metabolism. The expressions of miR-494 were decreased in inguinal adipocytes by cold exposure, and in beige cells by adrenergic stimulation. Overexpression of miR-494 substantially reduced the protein expression of peroxisome proliferator activated receptor gamma coactivator 1-alpha (PGC-1α), mitochondrial proteins including mitochondrial transcription factor A (TFAM), and uncoupling protein 1 (Ucp1) in inguinal beige adipocytes. Using luciferase assay, we found that 3`UTR region of PGC1-α is a direct target of miR-494. Preliminary results in the miR-494 null mice generated by CRIPR/cas9 exhibited higher rectal temperature and lower glucose levels during acute cold exposure compared to wild-type mice. In conclusion, mitochondrial biogenesis regulated by miR-494 through PGC1-α may be a potential mechanism of browning.

P-08 Survey on hidden obesity among japanese women

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Background&Object:Recently,BMI of woman in Japan is very low compared with Europe and America. However, some Japanese women have "Hidden Obesity “that means low BMI but high body fat percentage. We aimed to clarify the realities of "Hidden obesity" by using Bioelectrical impedance analysis(BIA) for adult women in this survey. Method:The study conducted for 638 subjects (122men 516 women) with agreement from 2016 to 2017. The measurement are height, weight, abdominal circumference, blood pressure, blood test(HbA1c,Cholestelo, FBS and others),visceral fat, body composition measurement, grip power, bone densitometry, and lifestyle questioner. Bioelectrical impedance analysis(BIA) for the body composition measurement “inbody" was used to identify “Hidden Obesity”. This study obtains approval in Juntendo University IRB. The statistical analysis was performed to identify the differences in proportions using chi-square test, T test and one-way analysis of variance. All P values of <0.05 was considered statistically significant. Result&conclusion:We analyzed 211 (38 men and 173 woman) evaluated "Hidden obesity (The man:BMI<22, body fat ≧20, and woman:BMI<22 and body fat ≧28)" and "Propriety" (The man:BMI 18.5-25 and body fat15-20 and woman:BMI18.5-25 and body fat 23-28). Hidden obesity was recognized 30.3% in women and 23.7% in men. "Hidden obesity" was lower than “Propriety” in the woman on grip (R,L), the body moisture, the protein, the mineral, the skeletal muscle mass, the muscle bulk with significant difference(P<0.05)

P-09 Flaxseed and extra virgin olive oils impact gut microbiota, support gut barrier and metabolic health

APDO travel grant award

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University of the Ryukyus

Flaxseed oil (FO) and Extra Virgin Olive Oil (EVOO) oil are recognized to have an overall beneficial impact on host metabolic health. However, little is known about the impact of these oils on gut microbiota and barrier function. We aimed to assess the impact of FO and EVOO on mouse gut microbiota, barrier function and metabolism. C57BL/6J, male (6wk old) mice were exposed to either a low fat (LF), high fat lard (HF), high fat FO (FO) or high fat EVOO (EVOO) diet for 10 weeks. Composition of gut microbiota was examined by 16S-rRNA sequencing. mRNA levels of cytokines and intestinal barrier markers in the proximal colon as well as lipopolysaccharide binding protein (LBP) in liver was measured by qPCR. Mice fed FO or EVOO were able to prevent excessive body weight gain and had a reduced Firmicutes to Bacteroidetes ratio. mRNA abundance of LBP in the liver was significantly reduced in mice fed FO and EVOO. mRNA levels of Claudin-1, Zonulin-1 and Occludin were increased in mice fed EVOO in comparison to all other groups. Mice fed EVOO showed significantly increased levels of FOXP3 and IL-10 mRNA in comparison to mice fed HF diet. FO fed mice showed a significant increase in Reg3γ in comparison to mice fed HF and an increase in IL-22 mRNA. Our data demonstrate that mice fed either FO or EVOO were protected from excessive body weight gain, exhibited metabolically-beneficial changes in gut microbiota and had enhanced gut barrier function. Currently, we are in the process of conducting experiments to functionally assess intestinal permeability. We envisage these results will reflect an enhanced gut barrier function in mice fed either FO or EVOO.

P-10 Adipose tissue-derived MFG-E8, regulates chronic inflammation and obesity-related liver disease

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[Introduction] Cell death is closely linked to inflammation and metabolic disorders associated with obesity. With DNA microarray, we have found that MFG-E8 (Milk-fat globule EGF 8), secreted protein which promotes apoptotic cell clearance by liking the dead cells to phagocytes, is increased specifically in white adipose tissue (WAT) from obese mice. We hypothesized that WAT-derived MFG-E8 might regulate "dead cell-macrophage" interaction, and contribute to inflammation and obesity-related complications. [Methods and Results] Although MFG-E8 deficiency did not affect body weight gain and adiposity on high-fat diet, KO mice showed improved insulin sensitivity and decreased pro-inflammatory cytokine in epididymal WAT (eWAT). We next determined the ratio of M1/M2 polarity of macrophages within eWAT. Inflammatory M1 macrophages were increased upon high fat feeding in wild type (WT) mice, whereas, in KO mice, the M1 polarization was attenuated. TUNEL staining of eWAT section showed apoptotic adipocytes were increased in KO obese mice. We finally investigated the role of MFG-E8 on obesity-related liver disease, non-alcoholic steatohepatitis (NASH). The NAFLD activity score, histological scoring system, of liver section from STAM™-NASH model of KO was significantly lower than in WT mice. qPCR analysis revealed that both pro-inflammatory cytokine and type I collagen expression were suppressed in KO mice, whereas no difference was found in the degree of steatosis. [Discussion] These results indicate that WAT derived MFG-E8 might be involved in local inflammation and insulin resistance. In addition, this secreted protein might regulate inflammatory status in remote organ and contribute to the progression of NASH.

P-11 Changes of metabolic indexes in patients with Pheochromocytoma.

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Excess secretion of catecholamine induces not only hypertension but also glucose intolerance and dyslipidemia. Our objective was to investigate changes of metabolic factors including visceral and subcutaneous fat areas in patients with pheochromocytoma(Pheo). This was a cross-sectional and longitudinal follow-up study of cases collected from Gunma University Hospital. Forty-two patients with Pheo and 23 with non-functioning adrenal adenoma (NFA) were analyzed before and after adrenalectomy. Multivariate logistic-regression analysis adjusted by age and gender revealed that abdominal visceral fat area (VFA) and subcutaneous fat area (SFA) were significantly lower in patients with Pheo than in those with NFA (80.2 ± 38.7 v.s. 124.3 ± 61.8 cm2, $p<0.05$;114.6 ± 58.9 v.s. 164.3 ± 40cm2, $p<0.05$, respectively). Glucose intolerance was more common in patients with Pheo than in patients with NFA (21/42, 51% vs. 4/23, 17.3%, $p<0.05$). Significant correlations were observed between fractionated urine normetanephrine level and tumor size ($r=0.57$, $p<0.01$), urine noradrenaline level and serum HDL-cholesterol level ($r=0.36$, $p<0.05$) in Pheo. Furthermore, both VFA and SFA, body weight, and BMI were significantly increased, and serum HbA1c as well as HDL levels were decreased after adrenalectomy in Pheo. These findings suggest that catecholamine might regulate the serum HDL-cholesterol level and both abdominal visceral and subcutaneous fat mass in men.

P-12 Impact of obesity on dissociation of energy intake and total energy expenditure in diabetic patients

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Background:The issue of energy intake (EI) underreporting has been discussed in only a few studies in diabetic patients. Objective: To investigate the impact of obesity on the dissociation between energy intake from dietary records and total energy expenditure in diabetic patients. Material and Method(s): Fifty-two patients with type 2 diabetes aged 60 to 79 years old were enrolled for the CLEVER-DM study at a single university hospital. Total energy expenditure (TEE) was measured over 14 days by doubly labeled water (DLW) method. EI was calculated by 3-day dietary records assessed by a dietitian. Results: Mean difference between TEE and EI was 238 ± 412 kcal/day. Both EI and TEE resulted in no significant difference between obese (BMI>=25) and non-obese (BMI<25) groups. EI/TEE ratio showed a negative correlation to BMI (R=-0.437, P=0.033) in women, but no correlation in men (R=-0.174, P=0.377). EI/TEE ratio between obese and non-obese showed a significant difference in women (0.85 ± 0.15 vs 1.01 ± 0.21, P=0.045), but no difference in men (0.85 ± 0.20 vs 0.87 ± 0.17, P=0.79). Conclusions: EI calculated by 3-day dietary records may underestimate the habitual intake which is assumed to be equal to TEE measured by DLW. Caution is necessary especially in diabetic men and obese diabetic women.

P-13 Obesity associated pro-fibrotic protein promotes pathologies in non-alcoholic steatohepatitis.

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Brown adipose tissue (BAT) is initially identified as an organ critically involved in thermogenesis, and accumulating evidence indicates that it also has critical roles for the maintenance of metabolic homeostasis. Recently we found that BAT has a potential to secrete adipokines. Among them, we found that metabolic stress up-regulates the production of obesity associated pro-fibrotic protein (OAFP) in BAT of dietary obese mice. Non-alcoholic steatohepatitis (NASH), is the extreme form of non-alcoholic fatty liver disease (NAFLD). It is characterized with sterile inflammation and fibrosis in the liver, however, molecular mechanisms of fibrosis in NASH are yet to be defined. Here we show that OAFP promotes liver fibrosis in obese NASH model. We generated a murine obese-NASH model by imposing a high fat diet (HFD) to C57BL/6NCr mice for totally 8-10 months since 4 weeks of age. Obese-NASH model developed significant liver fibrosis, and this associated with high circulating OAFP level. Injection of a plasmid encoding OAFP into skeletal muscle promoted fibrosis in the liver, in contrast, liver fibrosis was suppressed in the OAFP systemic knockout mice. Peptide vaccine therapy targeting OAFP also ameliorated liver fibrosis. We found a significant increase in OAFP level in the serum from NASH patients compared to control groups . Interestingly, OAFP was predominantly produced by BAT in the murine obese-NASH model, suggesting the causal role of this brown adipokine in promoting pathologies in NASH. Our studies from humans and rodents suggest the pathological role of OAFP in promoting fibrotic responses in liver upon metabolic stress. Suppression of OAFP would become next generation therapy for NASH.

P-14 Dapagliflozin reduces weight and changes body composition in T2DM: a randomized, clinical trial

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Background and aims: SGLT2 inhibitors are expected to reduce body weight (BW) because of a negative energy balance. However, the efficacy of an SGLT2 inhibitor on BW and body composition in Japanese patients in the clinical setting remains unclear. We hypothesize that Japanese who are petite compared with Caucasians achieve a greater percentage change of body weight loss and may have reduced muscle mass when a comparable BW reduction is achieved.

Materials and methods: The study was an open-label, randomized, controlled trial. Fifty-two overweight patients (BMI > 23 kg/m^2) who had inadequate glycemic control with oral anti-diabetic agents were randomly assigned to dapagliflozin (Dapa) or standard treatment (Con) and followed for 24 weeks. The primary endpoint was a change in BW from baseline to week 24 between the two groups. The secondary endpoint was body composition, which was assessed by the bioelectrical impedance method to evaluate fat and muscle mass of the arms, lower limbs, and trunk.

Results: The change in BW was significantly larger in the Dapa group than the Con group. The mean difference between two groups was -1.72 kg (95%CI: -2.85, -0.59, p = 0.004) which was comparable with the previous studies of Caucasians. Total fat mass was reduced in the Dapa group compared with the Con group, mainly due to lower limb and trunk fat. Total muscle mass was maintained after 24 weeks of intervention. Trunk muscle mass was maintained, but lower limb muscle tended to be reduced in the Dapa group.

Conclusion: Dapa treatment for 24 weeks results in reduction of BW, which was comparable with that of Caucasians, mainly due to fat mass at the lower limbs and trunk. The tendency for reduction in muscle mass at the lower limbs may be due to an anti-gravity effect.

P-15 Brown adipose tissue is involved in the suppression of pathologies in heart failure

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Prognosis of severe heart failure is unacceptably high, and it is our urgent task to find therapies for this critical condition. It has been reported that low body temperature predicts poor clinical outcomes in patients with heart failure, however, underlying mechanisms and pathological implications are largely unknown. Brown adipose tissue (BAT) was initially characterized as a heat generating organ, and studies suggest that BAT has crucial roles for the maintenance of systemic metabolic health. Here we show that BAT dysfunction develops in a murine thoracic aortic constriction (TAC) model, and has a causal role for promoting pathologies in failing heart. TAC operation led to a significant reduction both in intraperitoneal and subcutaneous temperature. TUNEL-positive cells significantly increased in BAT during left ventricular (LV)-pressure overload, and in-vitro studies with differentiated brown adipocytes suggested that the chronic activation of adrenergic signaling promotes apoptosis in these cells. Gain of BAT function model, generated with BAT implantation into peritoneal cavity, improved thermogenesis and ameliorated cardiac dysfunction in TAC. In contrast, genetic model of BAT dysfunction promoted cardiac dysfunction. Metabolomic analyses showed that BAT dysfunction led to an increase of oxidized choline that promoted metabolic dysfunction in the failing heart. We found that dilated cardiomyopathy patients have lower body temperature, and confirmed by metabolomic study that both choline and oxidized choline are increased in circulation. Maintenance of BAT homeostasis and suppression of oxidized choline would become a novel therapeutic target for heart failure.

P-16 Transient hyperglycaemia promotes myelopoiesis and accelerates atherosclerosis

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Transient postprandial hyperglycaemia is an independent risk factor for cardiovascular disease. We have previously shown that chronic hyperglycaemia in diabetic mice increases myelopoiesis and atherosclerosis. Using a model mimicking transient intermittent hyperglycaemia (TIH) observed in adults with impaired glucose tolerance, we found that TIH increases myelopoiesis in the bone marrow within 24 hours, which translated to increased blood monocyte levels, particularly the inflammatory Ly6-C^{hi}subset, and neutrophils at 7 days post-TIH.Weekly recurrence of TIH also results in accelerated atherogenesis, comparable to lesion formation in diabetic mice which experience chronic hyperglycaemia. Haematopoietic deletion of S100a9$^{-/-}$, S100a8$^{-/-}$or its cognate receptor RAGE, affords protection against TIH-induced myelopoiesis, monocytosis and neutrophilia. Increased glycolytic rate in neutrophils via GLUT-1-dependent glucose uptake appears to promote the release of S100A8/A9, and deletion of this transporter in the myeloid lineage protects from TIH-induced myelopoiesis. Moreover, inhibiting S100A8/A9 using the small molecular inhibitor, ABR-215757, reduces myelopoiesis in mice subjected to TIH, resulting in decreased circulating monocytes and neutrophils and smaller atherosclerotic lesions, with lower lipid and macrophage content. Together, these data suggest that TIH accelerates atherogenesis by stimulating S100A8/A9 signaling through RAGE to promote myelopoiesis and generate monocytosis and neutrophilia, and this axis represents a potential target for vasculoprotective therapy.

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