The 12th Asia Pacific Diabetes & Obesity Study Group Symposium

The University of Hong Kong

21-22 October, 2017

Exhibition Area, Seminar Room 1-3, G/F, Laboratory Block,
Li Ka Shing Faculty of Medicine, The University of Hong Kong,
21 Sassoon Road, Pokfulam, Hong Kong

Jointly organized by:

Contents

Asia Pacific Diabetes and Obesity Study Group

The Asia Pacific Diabetes Obesity Study group or APDO was founded in 2004 and has met annually every year but one since that time. 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.

The concept of APDO was timely in view of the rapid spread of diabetes and obesity throughout many countries in the Asia Pacific region. By sharing knowledge, experience and ideas we hope to reach synergistic outcomes in our common pursuit – to halt and reverse the spread of obesity and diabetes, two of the most crippling conditions facing the developed world. As shown by the network map, APDO has spawned important scientific collaborations between numerous groups throughout AP and this alone indicates the success of this non-for profit venture.

The major forum of APDO is an annual scientific meeting held in different countries throughout the region. APDO was established and reached maturity by virtue of generous support from the Japanese pharmaceutical company Takeda. Takeda fully supported our annual meetings for five years during which time the meetings were held at different locations throughout Japan with the exception of the third meeting, which was held just outside Shanghai. APDO then evolved into a more independent entity in 2010 when the first meeting outside Japan was held in Singapore. Since then, annual APDO meetings have been held in Korea and Japan and future meetings are planned for China, Taiwan and Australia. Aside from these countries, each year we welcome delegates from New Zealand and Hong Kong.

APDO has been host to outstanding international speakers including Harvey Lodish, Vamsi Mootha, Domenico Accili, Bernard Thorens, Daniel Zeve, Steve Shoelson, Michael Czech, Noboru Mizushima, Patrick Seale and Randy Seeley. As the problems of diabetes and obesity continue to plague countries throughout the world, there remains a strong justification for organisations such as APDO that have no political nor financial links but exist purely to facilitate basic scientific efforts in the Asia Pacific region in this crucial research endeavor. We welcome new delegates and hope that APDO will inspire many more scientific linkages and collaborations that it already has.

Masato Kasuga and David James (November, 2014)

Welcome Message from the Chairmen of Organizing Committee

On behalf of the local organizing committee of the 12th Asia Pacific Diabetes Obesity Study Group (APDO) Symposium, we would like to extend our warmest welcome to all the speakers and participants of this exciting event.

In this 2-day symposium, we have invited prominent speakers from various countries/regions (USA, United Kingdom, Singapore, Japan, Korea, Australia, New Zealand, Taiwan, Mainland China and Hong Kong), who are at the forefront of diabetes and obesity research, to discuss the hot topics in these fields including immunometabolism, insulin signaling and regulation of glucose metabolism, lipid metabolism, adipose tissue inflammation, adipokine biology and physiology, regulation of energy homeostasis, as well as new treatment approaches and biomarkers for diabetes. We hope to facilitate fruitful discussions among our speakers and participants and help to promote collaborative research activities.

We hope that you will enjoy this golden opportunity to keep abreast with the latest discoveries and technological advances in diabetes and obesity.

Aimin Xu
Director, the State Key Laboratory of Pharmaceutical Biotechnology
Professor, Li Ka Shing Faculty of Medicine
The University of Hong Kong

Karen Lam
Rosie TT Young Professor in Endocrinology and Metabolism
Chair Professor in Medicine
Faculty Board Chairman, Li Ka Shing Faculty of Medicine
The University of Hong Kong

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THE UNIVERSITY OF HONG KONG

生物醫藥技術國家重點實驗室
THE STATE KEY LABORATORY OF PHARMACEUTICAL BIOTECHNOLOGY

Honorary Guest

Professor Andy Tzi Sum Hor
Vice-President and Pro-Vice-Chancellor (Research), the University of Hong Kong
Director, Knowledge Exchange Office
Chair Professor, Department of Chemistry, Faculty of Science

APDO Organizing Committee Members

Co-Chairs: Prof. Masato Kasuga, National Center for Global Health and Medicine, Japan
Prof. David James, University of Sydney, Australia

Members: Prof. Lee-Ming Chuang, National Taiwan University Hospital, Taiwan
Prof. Mark Febbraio, Baker IDI Heart and Diabetes Institute, Australia
Prof. Youfei Guan, Dalian Medical University, China
Prof. Weiping Han, Singapore Bioimaging Consortium, Singapore
Prof. Jae Bum Kim, Seoul National University, Korea
Prof. Karen Lam, University of Hong Kong, Hong Kong
Prof. Peter Shepherd, University of Auckland, New Zealand

Symposium Organizing Committee

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Director, the State Key Laboratory of Pharmaceutical Biotechnology
Professor, Departments of Medicine, and Pharmacology & Pharmacy
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The University of Hong Kong

Members: Connie Wai Hong Woo
Assistant Professor, Department of Pharmacology and Pharmacy,
LKS Faculty of Medicine,
The University of Hong Kong

Miss Lily Li
Executive Assistant, the State Key Laboratory of Pharmaceutical Biotechnology
LKS Faculty of Medicine,
The University of Hong Kong

Our Speakers (Alphabetical Order)

Dr. Anna Calkin (Baker Heart and Diabetes Institute, Australia)

Prof. Ajay Chawla (University of California, San Francisco, US)

Prof. Sung Hee Choi (Seoul National University, Korea)

Dr. Kae Won Cho (Soonchunhyang University, Korea)

Prof. Mark Febbraio (Garvan Institute of Medical Research, Australia)

Prof. Josephine Forbes (Mater Research Institute, Australia)

Prof. Youfei Guan (Dalian Medical University, China)

Prof. Weiping Han (Singapore Bioimaging Consortium, A*STAR, Singapore)

Prof. Debbie Hay (University of Auckland, New Zealand)

Prof. Min-Seon Kim (University of Ulsan, Korea)

Prof. Jae Bum Kim (Seoul National University, Korea)

Prof. Seung-Hoi Koo (Korea University, Korea)

Dr. Yun Hee Lee (Yonsei University, Korea)

Dr. Paul Lee (University of Hong Kong, Hong Kong SAR)

Prof. Yong Liu (Wuhan University, China)

Dr. Sean McGee (Deakin University, Australia)

Dr. Andrew Murphy (Baker Heart and Diabetes Institute, Australia)

Prof. Wataru Ogawa (Kobe University, Japan)

Prof. XiongZhong Ruan (University College London, UK)

Dr. Chen-Yang Shen (Institute of Biomedical Sciences, Academia Sinica, Taiwan)

Dr. Chia-Ning Shen (Genomics Research Centre, Academia Sinica, Taiwan)

Prof. Iichiro Shimomura (Osaka University, Japan)

Dr. Brie Sorrenson (University of Auckland, New Zealand)

Dr. Yu Wang (University of Hong Kong, Hong Kong)

Dr. Feng Xu (Singapore Institute for Clinical Sciences, Singapore)

Dr. Toshimasa Yamauchi (Tokyo University, Japan)

Prof. Ying Yu (Tianjin Medical University, China)

Prof. Weiping Zhang (The Second Military Medical University, China)

Program at a Glance

Time	*Invited speaker/Lecture Title*
Day 1:	
8:45– 9:15	Opening Ceremony: ***Prof. Andy Hor*** *(Vice-President and Pro-Vice-Chancellor, University of Hong Kong)* ***Prof. Masato Kasuga*** *(President, National Center for Global Health and Medicine, Japan)*
9:15– 9:55	**Plenary Lecture:** Chairman: Prof. Masato Kasuga **Prof. Ajay Chawla:** Host Immunity and Energetics
	Section 1: New Remedy for Diabetes and Obesity Chairman: Prof. Iichiro Shimomura
9:55 – 10:15	Prof. Debbie Hay: Towards next generation amylin agonists for diabetes and obesity
10:15 – 10:35	Dr. Chia-Ning Shen: Lineage reprogramming-based strategies for the treatment of Type 1 diabetes mellitus
10:35 – 10:55	Prof. Josephine Forbes: Advanced glycation and RAGE in diabetes: From complications to initiation
10:55 – 11:10	Coffee break
	Section 2: Insulin Signaling and Regulation of Glucose metabolism Chairman: Prof. Debbie Hay
11:10 – 11:30	Prof. Wataru Ogawa: Insulin signaling in adipocytes and metabolic control
11:30 – 11:50	Prof. Seung Hoi Koo: Intestinal CRTC2 is critical in regulating glucose metabolism
11:50 – 12:10	Dr. Brie Sorrenson: The importance of beta-catenin to beta-cell function
12:10 – 12:30	Prof. Weiping Han: Regulation of GLUT4 translocation in muscle cells
12:30 – 13:30	Lunch *(Short talk) Dr. Jessie Wang (Biogene): Opening up live-cell kinetic windows by applying metabolic readouts to fundamental immune processes*
	Section 3: Lipid Metabolism in obesity and diabetes Chairman: Prof. Xiongzhong Ruan
13:30 – 13:50	Prof. Youfei Guan: Novel Lipid droplet-associated proteins in non-alcoholic fatty liver disease
13:50 – 14:10	Dr, Anna Calkin : Novel Regulation of Lipid Metabolism
14:10 – 14:30	Prof. Weiping Zhang: Transcriptional regulation of hepatic lipogenesis
14:30 – 14:50	Prof. Jae Bum Kim: Lipid Dysregulation and Adipose Tissue Inflammation in Obesity
14:50 – 15:05	Coffee break
	Section 4: Biology of Adipokines and Adipose inflammation Chairman: Prof. Weiping Han
15:05 – 15:25	Prof. Iichiro Shimomura: Adiponectin/T-cadherin system exerts vascular protection and exosome biogenesis

15:25 – 15:45	Prof. Toshimasa Yamauchi: Development of a small-molecule AdipoR agonist AdipoRon as exercise mimetics
15:45 – 16:05	Dr. Kae Won Cho: Crosstalk between innate and adaptive immune cells in adipose tissue during obesity
16:05 – 16:25	Prof. Yong Liu: Macrophage IRE1 promotes adipose inflammation and energy imbalance
16:25 – 16:45	Prof. Xiongzhong Ruan: CD36 palmitoylation disrupts free fatty acid metabolism and promotes tissue inflammation in non-alcoholic steatohepatitis
	Dinner at 18:30pm
Day 2:	
9:00– 9:40	**Plenary Lecture:** Chairman: Prof. Karen Lam (*University of Hong Kong*) **Prof. Mark Febbraio:** How Do Macrophages Sense Nutrient Overload to Induce an Inflammatory Response?
	Section 5: Immunometabolic complication of Obesity and Diabetes Chairman: Dr. Chen-Yang Shen
9:40 – 10:00	Dr. Sean Mcgee: Unexpected roles for the Alzheimer's disease protein Ab42 in peripheral metabolism
10:00 – 10:20	Dr. Yu Wang: Lipocalin-2 in obesity-related cardiometabolic syndrome: from risk prediction to therapeutic intervention
10:20 – 10:40	Dr. Andrew Murphy: Hyperglycaemic spikes promote monocytosis and atherosclerosis IN A S100A8/A9 / RAGE dependent manner
10:40 – 10:55	Coffee break
	Section 6: Energy Dynamics in Obesity Chairman: Mark Febbraio
10:55 – 11:15	Dr. Feng Xu: Narciclasine Attenuates Diet-Induced Obesity by Promoting Oxidative Metabolism in Skeletal Muscle
11:15 – 11:35	Prof. Min-Seon Kim: Peripheral metabolic effects of hypothalamic mitochondrial stress
11:35 – 11:55	Dr. Yun Hee Lee: Roles of connexin 43 in brown adipose tissue metabolism
	Section 7: Emerging Biomarkers of Diabetes and Obesity Chairman: Jae Bum Kim
12:00 – 12:20	Dr. Paul Lee: Adipocyte fatty acid binding protein, diabetic complications and mortality
12:20 – 12:40	Prof. Sung Hee Choi: Comprehensive analysis of human ectopic fats by multiomics approach
12:40 – 13:00	Dr. Chen-Yang Shen: Mendelian Randomization Analysis to Explore Causal Relation between Triglyceride and HBA1c- An Example of using Taiwan Biobank
13:00 – 13:10	Closing remark *(Light lunch will be provided)*
	Departure

Plenary Lectures

Ajay Chawla

Cardiovascular Research Institute, Departments of Physiology and Medicine, University of California San Francisco, USA

Professor Chawla received his B.Sc. from Johns Hopkins University in Biomedical Engineering in 1989, and his M.D., Ph.D. degrees from the University of Pennsylvania in 1996. He completed his graduate work in the laboratory of Dr. Mitch Lazar, and joined the laboratory of Dr. Ronald Evans at the Salk Institute for his postdoctoral studies. He became an Assistant Professor in 2003 at Stanford University, and is currently Professor of Physiology and Medicine in Cardiovascular Research Institute of the University of California San Francisco. His laboratory focuses on the innate mechanisms of tissue homeostasis. Work form his laboratory has contributed to our understanding of how innate immune cells and signals mitigate dietary and environmental stress maintains metabolic homeostasis, and how innate immunity orchestrates tissue regeneration after injury. He has received many awards acknowledging his outstanding work in the field, including NIH Director's Pioneer Award, AHA Innovative Science Award, NIDDK Young Investigator Award, Rita Allen Scholar, and Culpepper Medical Sciences Scholar. He is a member of American Society of Clinical Investigation and Association of American Physicians.

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Host Immunity and Energetics

Organisms acquire energy from their environment, which they allocate to growth, reproduction, and somatic maintenance. In energy-rich environments, investment in reproduction and growth is favored, whereas in energy-limiting environments, organisms favor investment in somatic maintenance programs. For example, when confronted with energy-constraining periods, such as cold weather, food shortage or natural disasters, many endothermic mammals abandon homeothermy, lower their core temperature, and enter the hypo-metabolic state of torpor to conserve energy. Although torpid animals exhibit a dramatic decrease in their body temperature, heart, and respiratory rate, their tissues are resistant to the damaging effects of hypothermia, ischemia, hypoxia, toxins, and injury, suggesting that torpor might be a somatic maintenance program of tissue tolerance. The importance of opportunistic torpor is also highlighted by the observation that many avian and mammalian species (humming birds, rodents, bats, and non-human primates) use it daily during nutrient deprivation or to escape environmental adversities, and torpor-like states have been documented in some groups of humans, such as the Aboriginal Australians. Although torpor was proposed as a strategy of tissue tolerance over 200 years ago, the mechanisms that integrate environmental inputs into the coordinated physiological, metabolic, and molecular programs of torpor and tissue tolerance are largely unknown.

Here, we asked whether torpor could be induced in mice by creating competition between somatic maintenance programs for energy. We tested this idea by activating the energy intensive trait of immunity in mice, who had a competing need for energy to maintain homeothermy. We found that activation of immunity led to induction of opportunistic torpor, which enhanced organismal fitness. These and other related findings will be presented at this meeting.

Mark A Febbraio

Molecular Metabolism Laboratory, Diabetes and Metabolism Division, Garvan Institute of has Medical Research, Sydney, Australia

Prof Mark Febbraio is a Senior Principal Research Fellow of the NHMRC, is the Head of the Cellular and Molecular Metabolism Laboratory and Head of the Diabetes and Metabolism Division at the Garvan Institute for Medical Research. He is also the Chief Scientific Officer of N-Gene Research Laboratories Inc, a USA based Biotechnology Company. His research is focused on understanding cellular and molecular mechanisms associated with obesity and type 2 diabetes, and his aim is to develop novel drugs to treat metabolic disease. He has authored over 200 peer reviewed papers in leading journals and has over 12,000 career citations. Mark has won prizes at international, national and institutional levels, including the A K McIntyre Prize for significant contributions to Australian Physiological Science (1999), the Colin I Johnson Lectureship by the High Blood Pressure Research Council of Australia (2006) the ESA/ADS Joint Plenary Lecture (2009) and the Sandford Skinner Oration (2011). He is on the Editorial Board of Diabetes, The American Journal of Physiology Endocrinology & Metabolism, and the Journal of Applied Physiology. He has also been a Councillor and Treasurer of the Australian Diabetes Society. Mark is also dedicated to health and fitness. He was a full time triathlete before embarking on his scientific career, and continues to compete in running races and multi-sport events. Mark co-hosts the radio program "The Science of Sport" on the SEN radio network in Melbourne, Australia

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How Do Macrophages Sense Nutrient Overload to Induce an Inflammatory Response?

Inflammation been recognized as a core component of obesity-induced metabolic disease. However, a major question in biology is how is inflammation sensed in circumstances of obesity and nutrient overload? It has become widely accepted that the activation of toll-like receptor 4 (TLR4) in immune cells such as macrophages, links obesity to the development of chronic tissue inflammation and metabolic disease. Specifically, it is thought that long chain saturated free fatty acids (LCSFA), such as palmitate, are agonistic ligands for TLR4 in macrophages, initiating inflammation and consequently promoting the development of obesity related pathologies via TLR4 signaling. Using several different experimental approaches, we provide compelling evidence that LCSFA, such as palmitate are, in fact, not ligands for TLR4 in macrophages. Paradoxically, we have demonstrated that bone marrow-derived macrophages from TLR4 knockout or C3H/HeJ (which have a naturally occurring mutation of TLR4) mice display abrogated palmitate-induced JNK activation, supporting previous observations (Shi et al. J Clin Invest 2006). Importantly, however, using genomic and lipidomic screens, we show that the absence of TLR4 genetically reprograms macrophages to increase lipid oxidation and decrease lipid esterification and subsequent accumulation of specific lipid species known to activate JNK. Moreover, this effect in TLR4 deficient cells can be completely reversed by priming the cells with ligands known to activate other TLR family members. These data shed novel insights into the link between lipids and inflammation in settings of nutrient overload.

Speakers and Abstracts (Chronological order)

Debbie Hay

Department of Biology Sciences, Faculty of Science, University of Auckland, New Zealand

Debbie Hay is Professor of Biochemistry and Pharmacology at the University of Auckland, New Zealand. She is a current James Cook Research Fellow (Royal Society of New Zealand), with a particular interest in amylin and related class B G protein-coupled receptors. Her team had made contributions to determining the pharmacology, mode of ligand binding and signalling, and in vivo expression of these receptors, and is developing novel amylin analogues. Professor Hay chairs the NC-IUPHAR subcommittee on calcitonin family receptors, has >100 publications and has won awards for research, teaching and service to her discipline.

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Towards next generation amylin agonists for diabetes and obesity

The pancreatic peptide hormone amylin plays a critical role in the control of appetite, and synergises with other key metabolic hormones such as glucagon-like peptide 1 (GLP-1). An amylin analogue, pramlintide is an FDA-approved therapeutic for insulin-requiring diabetes. The development of more potent and longer-acting analogues of amylin or dual agonists between these and GLP-1 mimetics for treating diabetes or obesity requires interrogation of how the 37 amino acid amylin peptide engages with its complex receptor system. We have extensively profiled the human amylin sequence, determining the role of its disulphide loop, amidated C terminus and receptor “capture” and “activation” regions in receptor signalling. We determined potential bias between ligands, at four signalling pathways and multiple receptor subtypes, plus selectivity determinants between related receptors. We identified distinct roles for parts of the peptide in receptor binding and activation, and identified peptides with greater activity than the native sequence. Receptor mapping studies are informing the binding site of amylin and interpretation of our data using full-length active receptor models is guiding the synthesis of novel amylin analogues and dual agonists of GLP-1 and amylin receptors.

Chia-Ning Shen

Genomics Research Center, Academia Sinica, Taipei, Taiwan

Dr. Chia-Ning Shen obtained his Ph.D. in 2002 from Developmental Biology Program, University of Bath, United Kingdom and then had his postdoctoral training at the Center of Regenerative Medicine, University of Bath, United Kingdom. Since 2004, Dr. Shen joined the Genomics Research Center of Academia Sinica. Dr. Shen is now an Associate Research Fellow and Deputy Director of Genomics Research Center of Academia Sinica and also serve as adjunct associate professor at National Yang-Ming University and Taipei Medical University. Dr. Shen is focusing on investigating whether cell fate switches is important for improving our ability to reprogram somatic cells for the purposes of therapeutic transplantation and also for understanding the rules for transdifferentiation (metaplasia) between cell types which can possibly lead to identifying targets for disease diagnosis and therapeutics.

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Lineage reprogramming-based strategies for the treatment of Type 1 diabetes mellitus

Type 1 diabetes mellitus is characterized by complete loss of beta-cells due to T-cell mediated autoimmune attacking leading to a deficiency of insulin. Islet transplantation is the potential way to sustainably modulate glycemic status. However, the shortage of donor islets and poor islet graft survival limit the potential use of islet transplantation to treat patients with type 1 diabetes. Moreover, patients received the allogeneic islet transplantation were still suffering from side effects of the immunosuppressive medications. Hence, the possibility of producing immune-tolerable β-cells from autologous resources would be a key challenge for developing cell-based therapeutics for type 1 diabetic patients.

We had previously demonstrated ABCG2-positive cells derived from acinar cell reprogramming can be triggered by GLP-1 to differentiate into insulin-producing β-cells. However, these cells were not able to survival in autoimmune status. Since the liver has remarkable capacities to regenerate after injury and immune privileged properties, we therefore hypothesize β-cells derived from hepatocyte reprograming may display immune-tolerable features. We performed direct conversion approaches by introducing Pdx1, Ngn3, and PDGFRα to primary hepatocytes of Non-obese diabetic (NOD) mice which spontaneously develop autoimmune diabetes. We demonstrated that transduction of Adeno-Pdx1, -Ngn3, and -PDGFRα efficiently reprogrammed hepatocytes to glucose-responsive β-like cells. Autologous transplantation of hepatocyte-derived β-like cells to diabetic NOD mice significantly improved hyperglycemic status without needs of tolerogenic treatments. Further characterization experiments demonstrated that β-like cells derived from hepatocyte reprogramming displayed reduced levels of MHC class I molecules and autoantigens. Importantly, hepatocyte-derived β-like cells expressed several immune negative regulators including programmed death-ligand 1 (PD-L1), Galectin-3 and Galectin-9. We demonstrated induced expression of PD-L1 and galectin-3 in hepatocyte-derived β-like cells could trigger apoptosis of autoreactive T-cells. The results raises the possibility of developing cell therapeutic strategy for patients with type 1 diabetes via autologous hepatocyte reprogramming.

Josephine Forbes

Mater Research Institute - Translational Research Institute, University of Queensland, Australia

Prof Forbes completed her PhD in Paediatric Nephrology in 2000 at the University of Melbourne and Royal Children's Hospital in Melbourne, Australia. She then continued her training as a post-doctoral fellow in diabetes and kidney disease at both Austin Health and Baker IDI Heart and Diabetes Institute in Melbourne, Australia. Currently she is a Professorial Research Fellow at Mater Research Institute-UQ in Brisbane, Australia where she also leads the Chronic Disease Biology and Care Program. She holds/has received research grants from NH&MRC of Australia, Kidney Health Australia, NIH/NIDDK and the Juvenile Diabetes Research Foundation (JDRF). She is board member of the Australian Diabetes Society and is the co-chair of the Diabetes Australia Research Program and a Founding Council Member of the EASD Reactive Metabolites Study Group. Her work to date has resulted in more than 140 publications in highly ranked journals which have been cited > 6500 times (H-index of 44; i10 of >106). Her primary research focuses on the pathological mechanisms that contribute to diabetes and its complications including advanced glycation and mitochondrial energy production. She has received numerous awards for her research including the Commonwealth Health Minister's Award for Excellence in Medical Research in Australia, The TJ Neale Award from the ANZSN for outstanding contribution to Nephrological Science and a Young Researcher Award from the International Diabetes Federation.

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Advanced glycation and RAGE in diabetes: From complications to initiation

Advanced glycation end products (AGEs) are formed in the body when lysine and arginine residues in proteins and peptides become irreversibly modified by reactive sugars or carbonyls. AGEs can also be absorbed from dietary sources, in particular in westernised diets as a result of modern food processing or cigarettes. Traditionally, AGEs have been investigated as contributors to diabetic complications since their production is facilitated by hyperglycaemia and the generation of reactive oxygen species. This is particularly evident in studies using inhibitors of advanced glycation to improve these disorders. There is also some evidence that AGE concentrations may serve as biomarkers for progressive injury at sites of diabetic complications and within the circulation. However, there has been a paradigm shift which suggests that AGEs may be modulators of insulin secretion and peripheral insulin sensitivity as well as cellular energetics and as such, may play a crucial role in the development of obesity and diabetes per se. This will be discussed in this presentation.

Wataru Ogawa

Division of Diabetes and Endocrinology, Kobe University Graduate School of Medicine, Kobe, Japan

Professor Ogawa completed his medical training in Kobe University in 1991 and pursued his postdoctoral fellowship in Stanford University in molecular pharmacology. After that, he was recruited to his mother school as an assistant professor, and now is the Chair of the Division of Diabetes and Endocrinology, Kobe University Graduate School of Medicine. His team provides specialized treatment for various metabolic diseases and also conducts a broad range of research spanning from basic to clinical fields in order to provide the best treatment possible Under his leadership, the success of the Division in treating hypothalamic and pituitary gland diseases, and abnormalities of calcium and bone metabolism is of international renown, with a great deal of experience and success in treating growth disorders and advanced medical treatment. Professor Ogawa have been devoting to his research in diabetes and endocrinology, and made several significant findings and helped the bench-to-bed translation of science. He also serves as a council member in Japan Diabetes Society Medical Affairs and Japan Society for the Study of Obesity (JASSO), and the Delegate of Japan Endocrine Society.

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Insulin signaling in adipocytes and metabolic control

Insulin signaling in adipocytes is thought to play a key role in the control of energy metabolism. The pathophysiological significance of insulin resistance in adipocytes remains ambiguous, however. To understand the physiological impact of insulin resistance in adipocytes in living animals, we generated mice lacking PDK1 selectively in adipocytes. Insulin-induced biological actions in adipose tissue, including the stimulation of glucose uptake and of lipogenesis as well as the inhibition of lipolysis, were almost completely prevented in adipocyte-specific PDK1 deficient mice (A-PDK1KO mice). The mass of adipose tissue as well as the plasma levels of adiponectin and leptin were decreased in A-PDK1KO mice. A-PDK1KO mice manifest severe insulin resistance, glucose intolerance, and dyslipidemia under normal chow feeding. Moreover, A-PDK1KO mice naturally develop nonalcoholic steatohepatitis (NASH) within ~35 weeks of age. A transcription factor FoxO1 is a negative regulator of insulin action. To investigate whether the activation of the FoxO1 pathway contributes to the metabolic abnormalities of A-PDK1KO mice, we have additionally disrupted FoxO1 selectively in adipocytes in A-PDK1KO mice. The additional disruption of FoxO1 markedly ameliorated metabolic abnormalities in A-PDK1KO mice including insulin resistance, glucose intolerance and the liver disease without affecting the mass of adipose tissue, the plasma levels of the adiponectin and leptin. Our results suggest that the impairment of insulin action in adipocytes contributes not only to the pathogenesis of insulin resistance and glucose intolerance, but also to that of NASH. Furthermore, the FoxO1-dependent transcriptional pathway appears to be attributable to these pathological conditions. Mechanism by which the FoxO1 pathway contributes to the development of insulin resistance and NASH will be discussed.

Seung Hoi Koo

Division of Life Sciences, Korea University

Dr, Koo was trained as a biochemist and obtained his PhD in University Minnesota, US. He further pursued his postdoctoral training in Stanford University and Salk Institute for Biological Studies. In 2005, he was recruited back to Korea and started his academic position at Sungkyunkwan University School of Medicine. He is now a Professor in Division of Life Sciences, Korea University. Throughout his academic career, Prof. Koo has made several major findings in the field of metabolism. He has particular interests in glucose homeostasis, cAMP signaling and transcriptional regulation. He demonstrated the critical function of ER-bound transcription factor, CREBH, in the regulation of hepatic gluconeogenesis, and discovered the novel role of TCF7L2 in hepatic glucose metabolism.

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Intestinal CRTC2 is critical in regulating glucose metabolism

GLP-1 is a major incretin that controls glucose homeostasis. The secretion of mature GLP-1 is regulated in part via a bile acid receptor GPBAR1, which utilizes cAMP signaling to enhance the exocytosis of GLP-1-containing vesicles. However, the role of cAMP-mediated transcription has not been demonstrated to date. In this study, we would like to explore the role of CREB/CRTC2-dependent transcription on GLP-1 secretion in the L cells. We found that the reduced CRTC2 activity impaired cAMP-dependent GLP-1 secretion, while expression of constitutively-active CRTC2 increased GLP-1 exocytosis from the L cells. Close investigation revealed that expression of not only proglucagon but also PC1/3, an endopeptidase for GLP-1 maturation, is transcriptionally regulated by CREB/CRTC2. Furthermore, expression of PGC-1α is also reduced upon depletion of CRTC2, leading to the decreased expression of OxPhos genes, reduced ATP levels, and decreased calcium concentrations in the L cells. Finally, we observed that intestine-specific CRTC2 knockout mice displayed reduced GLP-1 levels, leading to the impaired glucose tolerance, and decreased insulin-containing beta cells in pancreatic islets. Our data provide that CREB/CRTC2-dependent transcriptional pathway is critical in the regulation of glucose homeostasis by controlling production of GLP-1 from the L cells at the level of transcription, maturation, and exocytosis.

Brie Sorrenson

Department of Molecular Medicine and Pathology, Faculty of Medical and Health Sciences, University of Auckland, New Zealand

Dr. Sorrenson completed my PhD in the Department of Biochemistry at the University of Otago, New Zealand, in 2012 and was placed on the Dean's list of Excellent Theses. Gaining a National Heart Foundation Fellowship in 2013, she then joined Professor Peter Shepherd's group at the Faculty of Medical and Health Sciences at the University of Auckland and became interested in the Wnt signalling pathway and the potential link it provides between the high blood glucose levels seen in Type-2 diabetes and the increased risk of cardiovascular disease associated with this condition. Over time her research interests have evolved to encompass the cell biology of pancreatic beta-cells and determining the exact mechanisms of insulin secretion from these cells. Gaining a Rutherford Postdoctoral Fellowship in 2015 the main areas of her current research are investigating the role of the Wnt signalling protein beta-catenin in vesicle secretion across various cell types and using induced pluripotent stem cells to study beta-cell development and function in a human context.

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The importance of β-catenin to β-cell function

Defective glucose-stimulated insulin secretion from β-cells is a critical step in the development of overt type-2 diabetes and while many of the processes controlling insulin release from β-cells have been characterized, many remain not well understood. We have recently provided evidence that the Wnt signaling protein β-catenin is required for insulin secretion in rodent pancreatic β-cells and isolated islets. We find that this occurs via a role in the acute events regulating insulin vesicle trafficking and have also identified that changes in actin polymerisation are important in mediating this effect. Using induced pluripotent stem cells differentiated into cells that contain and secrete insulin in response to stimulation (β-like cells), we have now demonstrated that β-catenin is also important for insulin secretion in a human context. Parallel to the requirement for β-catenin in β-cell insulin secretion, we observe that the level of β-catenin protein and specific post-translational modifications on β-catenin can be dynamically regulated by changes in glucose and nutrient levels. In particular, the level of Serine 552 phosphorylation is increased by glucose and incretin hormones. Our evidence show this phosphorylation to correlate with insulin secretion function of β-cells and to be dependent on a pathway involving protein kinase A, exchange protein directly activated by cAMP and p-21 associated kinase 1.

Weiping Han

Institute of Molecular and Cell Biology, Singapore Bioimaging Consortium, A*STAR, Singapore

Prof. Weiping Han obtained his Ph.D. in Physiology from Cornell University in 1996. He 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). 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 and Professor in the Program of Cardiovascular and Metabolic Disorders at Duke-NUS Graduate Medical School.

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Regulation of GLUT4 translocation in muscle cells

Insulin regulates the translocation of glucose transporter 4 (GLUT4) to the plasma membrane for glucose uptake into skeletal muscles and adipose tissues under nutrient-abundant (hyperglycemic) conditions. The core signaling pathway for this process is well understood, which includes the activation of PI3K/Akt. It is less clear, however, on the identities of PI3K/Akt substrates that are responsible for the final steps of GLUT4 trafficking and exocytosis near the plasma membrane. We previously identified Tropomodulin3 (Tmod3), an actin capping protein that blocks the elongation and de-polymerization of actin filaments at the pointed end, as a novel Akt2 substrate, and showed that Tmod3 plays a vital role in GLUT4 translocation and glucose uptake under insulin stimulation. Recently, we focused on the regulation of GLUT4 translocation during muscle contraction, a process under the control of AMPK (5' adenosine monophosphate-activated protein kinase) signaling. Although the role of AMPK in this process is well documented, the precise mechanisms governing AMPK-medicated GLUT4 translocation are not clearly elucidated. Here we present our latest results that identify Tmod3 as an AMPK substrate and Ser25 as the phosphorylation site on Tmod3 by AMPK signaling. We further show that phosphorylation of Ser25 is required for AMPK-induced GLUT4 translocation and glucose uptake in L6 myoblasts. Tmod3 phosphorylation by AMPK leads to actin re-modeling and promotes GLUT4 translocation and glucose uptake. These findings support that Tmod3 is a key downstream effector of AMPK in the regulation of GLUT4 translocation and glucose homeostasis in muscle cells.

Youfei Guan

Advanced Institute for Medical Sciences, Dalian Medical University, Department of Physiology, AstraZeneca–Shenzhen University Joint Institute of Nephrology, Shenzhen University Health Science Center, Shenzhen

Professor Guan Youfei is currently vice president of Dalian Medical University. He obtained his B.S. and M.S. from Nantong Medical College and his PhD degree from Beijing Medical University. He received his postdoctoral training in Division of Nephrology and Hypertension at Vanderbilt University. In 1999, he was appointed as research assistant professor and tenure-track assistant professor in Department of Medicine and Diabetes Center at Vanderbilt. Then he became Professor of Department of Physiology and Pathophysiology in Peking University Health Science Center since 2002. He was appointed to Changjiang Professor of the Ministry of Education from 2005. Now Professor Guan Youfei is "Yangtze River Scholars" Distinguished Professor of Chinese Ministry of Education, winner of the National Science Fund for Outstanding Young Scholars, Chief Scientist of the National Basic Research Program of China (973 Program) held by Chinese Ministry of Science and Technology. He is also a member of American Physiological Society, American Society of Nephrology, American Diabetes Association, National Nature Science Foundation of China and Ministry of Education. His research focus on the role of prostaglandin receptors (including PGE2 receptors) and other metabolic nuclear receptors (such as peroxisome proliferator-activated receptor gamma) in diabetes, hypertension, lipid metabolic disorder, obesity and its related renal complications.

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The role of novel lipid droplet-associated proteins in the pathogenesis of non-alcoholic fatty liver disease.

Nonalcoholic fatty liver disease (NAFLD) is characterized by a massive accumulation of lipid droplets (LDs). By using 2D LC-MS/MS, we identified two novel liver-specific lipid droplet-associated proteins, 17β-hydroxysteroid dehydrogenase-13 (17β-HSD13) and cytochrome P450 4A11 (CYP4A11) in healthy human livers. Hepatic expression of both 17β-HSD13 and CYP4A11 was significantly upregulated in the livers of patients with NAFLD. Increased expression of hepatic 17β-HSD13 and CYP4A14 (a homolog of human CYP4A11 in mice) was confirmed in type 2 diabetic db/db mice and high-fat diet-fed mice. Adenovirus-mediated hepatic overexpression of 17β-HSD13 and CYP4A14 resulted in a fatty liver phenotype in C57BL/6 mice. 17β-HSD13 overexpression-induced fatty liver was associated with a significant increase in mature sterol regulatory element-binding protein 1 (SREBP1) and fatty acid synthase levels, while hepatic CYP4A14 overexprssion led to a marked induction of CD36, a fatty acid transporter. Moreover, mice with either 17β-HSD13 or CYP4A14 gene deficiency exhibited attenuated hepatic lipid accumulation, inflammation and fibrosis. These findings demonstrate that 17β-HSD13 and CYP4A14 play an important role in liver lipid homeostasis and dysfunction of these tow novel lipid droplet-associated proteins may contribute to the pathogenesis of NAFLD. 17β-HSD13 and CYP4A14 may represent potential therapeutic targets for the treatment of NAFLD.

Anna Calkin

Baker Heart & Diabetes Institute,
Monash University, Australia

Dr Anna Calkin is a National Heart Foundation Future Leader Fellow and Head of the Lipid Metabolism and Cardiometabolic Disease Laboratory at the Baker Heart and Diabetes Institute. She has developed a research program that focuses on preventing the onset of cardiometabolic diseases driven by excess lipid accumulation, including obesity and diabetes-associated cardiomyopathy, atherosclerosis, hepatic steatosis and insulin resistance. In addition, she has an interest in identifying novel regulators of lipid metabolism using a novel discovery platform she has established with several collaborators, which combines cutting edge proteomics and lipidomics across strains of genetically diverse inbred mice. This has led to the identification of many novel and exciting targets, including those linked to the regulation of cholesterol, diacylglycerols and ceramides. Prior to this, Anna undertook post-doctoral studies at UCLA with Professor Peter Tontonoz, where she defined the E3 ligase, IDOL, as an evolutionarily conserved mechanism for the regulation of lipid metabolism and demonstrated its importance in regulating cholesterol levels in humans. She also modulated this pathway to develop a novel mouse model of atherosclerosis, currently available from Jackson Laboratories. Previous to this she trained with Professor Shaun Jackson at the Australian Centre for Blood Diseases, where she demonstrated a potent anti-thrombotic role for reconstituted HDL in individuals with type 2 diabetes.

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Novel Regulation of Lipid Metabolism using a Trans-Omics Approach

Background: The liver controls numerous pathways central to the maintenance of whole body lipid metabolism. Dysregulation of these pathways can lead to increased levels of lipids such as cholesterol, triglycerides and diacylglycerols. This can have pathological consequences, promoting the onset of insulin resistance and the development of cardiovascular disease and hepatic steatosis. However, a greater understanding of the pathways mediating this dysregulation is required. *Aims:* We used a trans-omics approach combining genomics, phenomics, lipidomics and proteomics to identify novel pathways associated with the regulation of hepatic lipid metabolism. We utilised our exclusive access to a panel of >100 genetically inbred mouse strains, known as the hybrid mouse diversity panel (HMDP) at UCLA. *Methods:* We collected livers (n=3) from male mice of 107 HMDP strains that were housed and fed under the same conditions. We performed deep proteomic analysis on livers by performing 34 separate TMT-10 plex multidimensional LC-MS/MS experiments with SPS-MS3 acquisition on an Orbitrap Fusion (>5000 proteins). We also performed quantitative lipidomics analysis using LC-MS/MS on an AB Sciex API4000 Q/TRAP system (>300 lipids) on livers of the same mice. *Results:* Integration of proteomic and lipidomic data identified numerous proteins associated with hepatic lipid accumulation. In particular, we identified included the well-known lipid droplet protein perilipin 2 (plin2) and a novel dehydrogenase called acyl-CoA dehydrogenase family member 11 (acad11). Interestingly we also identifed a protein specifically associated with the abundance of pathological short-chain saturated diacylglycerol species (SCS-DGs). In vivo adenoviral expression of this target was associated with a significant upregulation of these SCS-DGs in various mouse strains. Moreover, this target was associated with onset as well as duration of diabetes in the San Antonio Family Heart Study. *Conclusion:* We have established a high-resolution trans-omics network for the identification of novel regulators of hepatic lipid metabolism.

Weiping Zhang

Department of Pathophysiology, Second Military Medical University, Shanghai, China

Professor Zhang Weiping is currently the Director of Department of Pathophysiology of the Secondary Military Medical University, where he leads the obesity and diabetes research group. He got his B.S. and PhD degree in the Secondary Military Medical University. Then he received his Post-doctoral training at Public Health Institute in Harvard University, USA. His research focus on the pathophysiology of obesity and diabetes and translational medicine. He has taken the National 863 Program, the National 973 Program and the National Natural Science Foundation of Key Projects. Professor Zhang Weiping firstly established the zinc finger protein ZBTB20 knockout mice model to elucidate its physiological functions and transcriptional regulations. Professor Zhang Weiping has won the seventh session of the China Youth Science and Technology Award and the People's Liberation Army General Logistics Department of Science and Technology Silver Star title. He is currently a final reviewer of the National Natural Science Foundation and Journal of Endocrinology, Journal of Molecular Endocrinology.

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Regulation of Lipid Homeostasis by the Zinc Finger Protein ZBTB20

The zinc finger protein ZBTB20 is highly expressed in the liver, and its nuclear localization and transcriptional activity are nutritionally regulated. The mice specifically lacking hepatic ZBTB20 exhibit hypolipidemia and reduced liver triglyceride accumulation, along with impaired hepatic lipogenesis and augmented plasma hydrolysis. Mechanistically, ZBTB20 acts as a transcriptional activator of *ChREBP-α*, thereby activating the relevant glycolytic and lipogenic genes including *Pklr*, *Fasn, Elovl6, Scd1*, and ChREBPβ. On the other hand, ZBTB20 is a transcriptional repressor of lipoprotein lipase (LPL) gene. As a result, the increased expression and plasma activity of LPL contributed to the hypotriglyceridemia in the absence of ZBTB20. Deletion of liver ZBTB20 in ob/ob mice could significantly improve hyperglycemia, hyperlipidemia, hepatic steatosis, and insulin resistance despite the persistent obesity. Lastly, the Together, our study points to ZBTB20 as a unique regulator of lipid homeostasis and may serve as a therapeutic target for metabolic syndrome.

Ying Yu

Department of Pharmacology, School of Basic Medical Sciences, Tianjin Medical University, China

Dr. Yu received his Bachelor degree from Medical college of Nanchang University in 1995, then got his Master degree in Tumor Immunology Department in the Medical College in 1998 and his PhD in tumor genetics from Cancer Research Institute in Xiangya Medical School in Central South University in 2001. He had his postdoctoral training in Pharmacology Department at University of Pennsylvania from 2002 to 2006, and then worked as Research Associate (2006) and Research Assistant Professor (2009) in the Institution for Translational Medicine and Therapeutics at University of Pennsylvania. He joined the Institute of Nutritional Sciences in 2010 and moved to Tianjin Medical University in 2016. Dr. Yu has been engaged in studying cyclooxygenases (COXs) and their down-stream pathways involved in inflammatory response and cardiometabolic diseases over 16 years. During the past several years, his work revealed the molecular mechanisms for COX-2 derived prostanglandin E2 (PGE_2) involvement in injury-induced arterial remodeling and pulmonary hypertension; and found the unique role of COX-2 in blood pressure regulation and thrombogenesis; discovered the mechanism for COX-2-derived PGD_2 –mediated resolution; uncovered the underlying mechanisms for COX-1 derived prostanoid in the pathogenesis of aspirin intolerant asthma and B cell development, discovered the mechanism for regulation of vitamin D on COX-2 expression in macrophage; and also revealed COX-derived PGI_2 in hepetocytes promotes gluconeogenesis response to fasting . Those works were published in Nat Med, Sci Transl Med. J Clin Invest. J Exp Med., Circ Res, J Allergy Clinc Immunol, Diabetes, Blood, Hepatology, ATVB, at al. Currently, research efforts in Dr. Yu's laboratory are mainly focused on: i) COX, Ω－3 fatty acid, PGs in cardiovascular remodeling; 2) PG and their receptors in metabolic disorders and related vascular complications; 3) Food contamination and cardiovascular toxicity.

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Prostaglandin E2, cholesterol metabolism and atherosclerosis

Prostaglandin E_2 (PGE_2) is an important lipid mediator of inflammation. However, whether and how PGE_2 regulates hepatic cholesterol metabolism remains unknown. We found that expression of the PGE_2 receptor, E prostanoid receptor 3 (EP3) expression is remarkably increased in hepatocytes in response to hyperlipidemic stress. Hepatocyte-specific deletion of EP3receptor ($EP3^{hep-/-}$) results in hypercholesterolemia and augments diet-induced atherosclerosis in low-density lipoprotein receptor knockout ($Ldlr^{-/-}$) mice. Cholesterol 7α-hydroxylase (CYP7A1) is down-regulated in livers of $EP3^{hep-/-}$ $Ldlr^{-/-}$ mice, leading to suppressed hepatic bile acid (BA) biosynthesis. Mechanistically, hepatic-EP3 deficiency suppresses CYP7A1 expression by elevating protein kinase A (PKA)-dependent Ser143 phosphorylation of hepatocyte nuclear receptor 4α (HNF4α). Disruption of the PKA-HNF4α interaction and BA sequestration rescue impaired BA excretion and ameliorated atherosclerosis in $EP3^{hep-/-}$ $Ldlr^{-/-}$ mice. Our results demonstrated an unexpected role of proinflammatory mediator PGE_2 in improving hepatic cholesterol metabolism through activation of the EP3-mediated PKA/HNF4α/CYP7A1 pathway, indicating that inhibition of this pathway may be a novel therapeutic strategy for dyslipidemia and atherosclerosis.

Iichiro Shimomura

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

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 been revealing 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.

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Adiponectin/T-cadherin system exerts vascular protection and exosome biogenesis

Our group discovered adiponectin from human adipose tissues as an adipocyte-specific secretory factor. Uniquely, circulating adiponectin concentration ranges 1-30 μg/mL, which is around 103~106-fold higher than ordinary hormones and cytokines. Decreased adiponectin concentration in obesity associates with many metabolic disorders and chronic organ diseases, especially atherosclerosis. Higher adiponectin concentration in blood, experimentally and clinically, has been shown to be protective against various organ damages.

We recently demonstrated the existence of adiponectin protein, not mRNA expression, in vasculature, demonstrating adiponectin's adherence to vascular component cells. Adiponectin required T-cadherin, a glycosylphosphatidylinositol (GPI)-anchored cadherin on membrane, to accumulate in cardiovasculature. Adiponectin accumulated endothelial cells (ECs) in normal artery, and synthetic smooth muscle cells (SMCs) as well, in atherosclerotic plaque. In T-cadherin (Tcad)/ApoE-double knockout (DKO) mice, there was no adiponectin protein in either ECs or synthetic SMCs, accompanying severer atherosclerosis on high cholesterol diet, than ApoE-KO mice, with five-fold increase of plasma adiponectin levels. These data indicate that T-cadherin controls adiponectin accumulation in vasculature and high circulating adiponectin level in blood, and that Adiponectin/T-cadherin system exerts vascular protection, targeting on ECs and SMCs. Our recent work revealed the sites of T-cadherin of adiponectin binding.

Related to protective effect of adiponectin on organ damage, we recently found the relationship between adiponectin and exosome biogenesis. We introduced native adiponectin rich physiologically in high-molecular multimers. 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. These enhancements accompanied the reduction of cellular ceramide and enhanced ceramide-release to exosome, which suggested excretion of cellular ceramide through the process of exosome biogenesis/secretion. Adiponectin/T-cadherin system may exert organ protection partly through exosome biogenesis.

Toshimasa Yamauchi

Department of Diabetes and Metabolic Diseases, Graduate School of Medicine, University of Tokyo, Japan

Dr. Yamauchi obtained his medical degree in Tokyo University Medical School in 1992 and his PhD in Graduate School of Medicine, the University of Tokyo in 1998. His academic service started in 2003 as an assistant professor in Department of Metabolic Diseases of the University of Tokyo, and he was promoted to associate professor in 2014. His research focuses on the physiology and biology of adiponectin receptors, and he has made several remarkable findings in the field. His prestigious discoveries were published in the top journals including Nature, Nature Medicine, Nature Genetics, etc. Through all these years, Dr. Yamauchi have been granted many awards and honors, including Science Prize in 1999, Lilly Award of the Japan Diabetes Society in 2006, Young Investigator's Award of the Japanese Society of Internal Medicine and Research Award of the Japan Endocrine Society in 2007, and JSPS (Japan Society for the Promotion of Science) PRIZE and Yomiuri Gold Medal in 2011.

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Novel structures and functions of adiponectin receptors

Adiponectin (Ad) is an antidiabetic adipokine, which binds to its receptors AdipoR1/R2, leading to activation of AMPK and PPAR pathways, respectively. Recently, small-molecule AdipoR agonist was shown to ameliorate diabetes and increase exercise endurance, and at the same time prolong shortened lifespan in obesity. Although AdipoRs are predicted to contain seven-transmembrane (7TM) domains, with an internal N-terminus and an external C-terminus, which is opposite to GPCRs, crystal structures of AdipoRs remained to be determined.

In this study, we successfully determined crystal structures of human AdipoR1/R2, and found that overall structures of AdipoRs are indeed distinct from those of GPCRs. Moreover, as for common functions of AdipoRs such as Ad binding, mutational analyses of conserved residues between AdipoR1/R2 shown by crystal structures revealed that Ad may broadly interact with extracellular surface of AdipoRs, in a different manner from previously anticipated. In contrast, as for specific functions of AdipoRs such as specific intracellular signal transduction pathways, mutational analyses of specific residues shown by crystal structures gave important insight into understanding each AdipoR specific intracellular signaling mechanisms.

The seven-transmembrane domain of both AdipoR1 and AdipoR2 was shown to have a cavity with a zinc-binding site, which contains unidentified extra electron densities. It was thus suggested that these electron densities may represent potential substrates for AdipoR hydrolytic activity or their products. For development of best-in-class AdipoR agonists, optimization of AdipoRon based on 3D structure of AdipoRon-AdipoR complex should be most important.

In conclusion, mutational analyses based on crystal structures revealed novel structural and functional properties of AdipoRs, including 7TM architecture and a putative Ad-binding surface, which are completely distinct from those of GPCRs, thus highlighting uniqueness of AdipoRs. This study should open new avenues toward elucidation of an unprecedented paradigm of signal transduction and development and optimization of AdipoR agonists.

Jae-bum Kim

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

Dr. Jae Bum Kim is Professor of Biological Sciences at Seoul National University and Director of Center for Adipose Tissue Remodeling, Creative Research Initiatives in Korea. He obtained his Bachelor and Master of Science at Seoul National University. Then, he earned his Ph. D. at Harvard University under the mentorship of Dr. Bruce Spiegelman, where he cloned and elucidated ADD1/SREBP1c as a key lipogenic transcription factor. After his postdoctoral fellowship training with Dr. Phillip Sharp at MIT, he joined the faculty at School of Biological Sciences, Seoul National University in 2000. His research group has investigated on gene expression regulation and signal transduction pathways of lipid and glucose metabolism, which are crucial to resolve the prevailing health issues such as obesity and diabetes. Recently, his research has focused on the molecular mechanisms of lipid and glucose homeostasis, adipose tissue inflammation, and insulin resistance, which would shed important insights on obesity and its related metabolic diseases.

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Lipid Dysregulation and Adipose Tissue Inflammation in Obesity

Adipose tissue plays key roles in whole body energy homeostasis. Accumulating evidence has suggested that obesity is characterized by chronic and low-grade inflammation accompanied by macrophage accumulation in the adipose tissue, which eventually leads to metabolic diseases, including insulin resistance and type 2 diabetes. The increased number of adipose tissue macrophages (ATMs) plays crucial roles in the altered production of proinflammatory cytokines in the fat tissue of obese individuals. In healthy lean mice, ATMs are mostly composed of alternatively activated (M2) type macrophages that express high levels of anti-inflammatory cytokines, such as IL-10, and specific enzymes, such as arginase 1 (ARG1), in addition to low levels of proinflammatory signals. It is likely that M2 ATMs contribute to metabolic homoeostasis by preventing adipose tissue inflammation. However, in the progression of obesity, some ATMs are polarized into the classically activated (M1) type. In the adipose tissue of obese individuals, M1 ATMs stimulate iNOS and the secretion of proinflammatory cytokines such as tumor necrosis factor alpha, interleukin 6, and IL-1 beta. Thus, the imbalance between M1- and M2-like ATMs appears to be crucial to stimulating pro-inflammatory responses in obese adipose tissue. In this presentation, I will discuss the novel mechanism by which alteration of lipid metabolism in ATMs would be crucial to induce inflammatory responses and insulin resistance in obesity.

Kae Won Cho

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

Dr. Kae Won Cho is an Assistant Professor in Soonchunhyang Institute of Medi-bio Science (SIMS) at Soonchunhyang University. He received PhD from Purdue University in 2006 and completed postdoctoral training at University of Michigan Medical School. From his PhD periods, his research has been focused on the molecular mechanisms underlying pathogenesis of type 2 diabetes. His current research interest is the inflammatory mechanisms by which obesity contributes to disease, with a particular emphasis on how adipose tissue immune cells such as macrophages and T cells contribute to adipose tissue function.

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Crosstalk between innate and adaptive immune cells in adipose tissue during obesity

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 chronic inflammation of hypertrophic adipose tissue depots in obese individuals leads to obesity-associated insulin resistance and is mediated by cells of the innate immune system, particularly adipose tissue macrophages (ATMs). Cells of the adaptive immune system, adipose CD8+ and CD4+ T lymphocytes (ATTs), have also emerged as important regulators of glucose homeostasis. However, it has been unresolved how ATMs interact with T lymphocytes and the importance in generating adipose tissue inflammation and contributing glucose homeostasis. Recently, we have demonstrated that ATMs directly interact with adipose tissue T cells and the antigen presentation property of ATM through MHC II is required to ATT development and obesity-induced insulin resistance. In this study, we investigated the regulatory mechanisms of antigen presentation ability of ATMs during obesity. ATMs from obese fat promote interferon-γ producing CD4+ T cells and CD8+ T cells, but inhibit the proliferation of regulatory T cells. In addition, obese ATMs have increased mass but higher pH of lysosomes where antigens are processed and loaded. In vitro experiments, induction of lysosomal stress to ATMs changes their antigen presentation function. Moreover, restoration of lysosomal stress in obese mice decreases adipose tissue inflammation and insulin resistance with alterations of ATTs. These results suggest that ATM lysosomal function would be one of regulatory mechanisms responsible for the crosstalk between innate and adaptive immune cells during obesity-induced inflammation. In this presentation, I will discuss novel mechanisms responsible for crosstalk of ATMs with ATTs during the development of obesity-induced inflammation and insulin resistance.

Yong Liu

Associate Dean, College of Life Sciences, Wuhan University, China

Dr. Yong Liu received his Bachelor and Master degrees in Biochemistry from Peking University in 1986 and 1989, respectively. He obtained his Ph.D. degree in 1995 in Microbiology and Molecular Genetics from Rutgers-The State University of New Jersey and UMDNJ-RWJ Medical School. After his post-doctoral training at University of California, Santa Barbara from 1995 to 2000, Dr. Liu worked as a Senior Scientist at the Immunology Section of AlleCure/Mankind Corp., a California-based biotechnology company. In 2003, Dr. Liu joined the Institute for Nutritional Sciences as a Principal Investigator at SIBS, Chinese Academy of Sciences in Shanghai. In 2015, he moved to Wuhan and joined the College of Life Sciences at Wuhan University as a Professor. Dr. Liu has received a number of awards, including the Distinguished Young Scientist Award from National Natural Science Foundation of China in 2009. He has also served as the Principal Investigator for a 973 research program from the Ministry of Science and Technology of China. Dr. Liu's research has focused upon elucidating the molecular and cellular mechanisms that link overnutrition, cellular stress pathways and metabolic disorders. Currently, Dr. Liu's group is interested in exploring the physiological actions of the IRE1α signaling arm of the cellular unfolded protein response (UPR) in nutrient-sensing and metabolic homeostasis.

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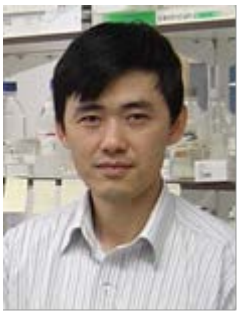
Macrophage IRE1α Promotes Adipose Inflammation and Energy Imbalance

Accumulation of unfolded/misfolded proteins in the endoplasmic reticulum (ER) of eukaryotic cells results in ER stress, thus activating an adaptive cellular response termed the unfolded protein response (UPR). IRE1 (inositol-requiring enzyme 1) is an ER-localized transmembrane signal transducer that possesseses both protein Ser/Thr kinase and endoribonuclease (RNase) activities. IRE1 initiates a critical branch of the UPR through unconventional splicing regulation of the transcription factor XBP1 (X-box binding protein 1). IRE1 can also degrade select mRNA species to exert its UPR actions through a mechanism referred to as regulated IRE1-dependent decay (RIDD).

Obesity is associated with chronic metabolic inflammation and ER stress that are believed to promote metabolic disease progression. Adipose tissue macrophages (ATMs) are key players in orchestrating metabolic inflammation. ATM M1 polarization is thought to promote insulin resistance and type 2 diabetes, whereas M2 polarization has been shown to enhance activation of brown adipose tissue (BAT) and browning/beiging of white adipose tissue (WAT). ER stress is able to enhance macrophage activation; however, the role of individual UPR pathways in M1/M2 polarization and ATM regulation of energy metabolism is poorly understood. Here we present evidence suggesting that IRE1α acts as a critical switch in regulating M1/M2 polarization and energy homeostasis. The IRE1α-XBP1 pathway in ATMs was aberrantly activated in obese mice. Myeloid-specific ablation of IRE1α largely reversed high-fat diet (HFD)-induced M1/M2 imbalance in WAT, and blocked HFD-induced obesity, insulin resistance, hepatic steatosis, and hyperlipidemia. BAT activity, WAT browning, and energy expenditure were all significantly higher in IRE1α-deficient mice, thus protecting against obesity and obesity-associated metabolic disease. Abrogation of macrophage IRE1α cell-autonomously decreased M1 polarization, and enhanced M2 polarization in response to IL-4, which was able to activate the IRE1α-XBP1 pathway in macrophages. Thus, IRE1α links metabolic ER stress to imbalance of macrophage polarization, adipose inflammation, and disruption of energy expenditure in obesity. Aberrant activation of macrophage IRE1α drives obesity and metabolic syndrome, at least in part through impairing BAT activity and WAT browning. Our findings suggest that IRE1α may serve as a valuable target for development of therapeutics against obesity and metabolic disease.

Xiongzhong Ruan

Lipid Research Unit, Centre for Nephrology, University College London, UK



Professor Xiong Z. Ruan, National '1000 Talent Plan' expert, is currently the Director of Centre for Lipid Research in Chongqing Medical University and University College London (UCL). He received his Msc in Peking Union Medical College Hospital (PUMCH) in 1994 and PhD from University College London (UCL) in 1999. His main goal has been to develop an academic research programme for 'Fatty Kidney/Liver Disease' in UK and China that investigates the regulatory mechanisms for the crosstalk between lipid homeostasis and inflammation. He has demonstrated for the first time that inflammatory stress modifies lipid homeostasis by increasing cellular cholesterol uptake mediated by the lipoprotein receptors, inhibiting cholesterol efflux mediated by the ABCA1 and increasing cholesterol synthesis in peripheral cells. As a result of these inflammation-mediated events, cholesterol re-distributes from circulation to the renal, vascular and hepatic tissues (first redistribution), and from the cytoplasm to the ER and the mitochondria (second redistribution). These important findings support the new concept that cholesterol locations (in tissue compartments) are more important than plasma cholesterol levels; this challenges the classic setting of risk assessment and contributes the change of the AHA guideline by removing target of LDL level in plasma (as an indicator) for lipid lowering treatment. He is the Vice-Chairman of Chinese Association of Renal Physiology, Chinese Medical Doctor Association of Fatty Liver Disease. He has published more than 90 papers in Nature Rev Nephrol, Lancet Diabetes Endocrinology, J Am Soc Nephrol, Kidney Int, Am J Physiol, Arterioscler Thromb Vasc Bio, and Hepatology etc. He acts as the associate editor for BMC Nephrology.

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CD36 palmitoylation disrupts free fatty acid metabolism and promotes tissue inflammation in non-alcoholic steatohepatitis

Fatty acid translocase CD36 (CD36) is a multifunctional immuno-metabolic receptor with many ligands. CD36 expression is abnormally upregulated and it is mainly located at the plasma membrane of hepatocytes in patients with NASH. Palmitoylation has been suggested to regulate subcellular distribution of CD36, but little is known about its significance in NASH.

Human liver tissue samples were obtained from patients undergoing liver biopsy for diagnostic purposes. C57BL/6J and CD36 knockout mice were injected with lentivirus vectors expressing wild type CD36 and palmitoylation sites mutated CD36. Liver histology, immunohistochemistry, mRNA expression profile, subcellular distributions and functions of CD36 protein were assessed.

Hepatic CD36 expression was significantly higher in patients with NASH compared to patients with normal liver and those with simple steatosis. CD36 was predominantly located at the plasma membrane of hepatocytes in subjects with NASH with a strong inflammatory responese. Hepatic CD36 palmitoylation was induced in mice with NASH, and the inhibition of CD36 palmitoylation protected mice from developing NASH by inhibiting lipid accumulation and also metabolic inflammation. In addition, blocking of palmitoylation, either by mutation or by pharmacological inhibition, caused intracellular accumulation of hepatic CD36 and decreased its localization on the plasma membrane. A lack of palmitoylation decreased the formation of CD36/Fyn complex, with the consequent activation of the AMPK pathway and inhibition of the JNK pathway. Consistently, inhibition of CD36 palmitoylation ameliorated fatty acids metabolic disorders and inflammatory response in animal models of NASH and HepG2 cells.

Conclusions: Our findings demonstrate the key role of palmitoylation in regulating CD36 distributions and its functions in NASH. Inhibition of CD36 palmitoylation may represent an effective therapeutic strategy in patients with NAFLD/NASH.

Yu Wang

Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong SAR

After obtaining PhD degree in Proteomics and Biomedical Sciences from the University of Auckland, Dr Wang worked as a research Fellow in Maurice Wilkins Centre for Molecular Biodiscovery and helped with the establishment of the Proteomics Research Facility. In 2004, Dr Wang joined Genome Research Center [now known as: Center for Genomic Sciences] and Department of Biochemistry in University of Hong Kong. She had made a major contribution to the development of Proteomics Research and the establishment of various biomarker discovery platforms. In 2008, Dr Wang joined Department of Pharmacology and Pharmacy in University of Hong Kong as a faculty member. Dr Wang has published four book chapters and over 130 research articles in internationally peer-reviewed journals, with an average citation of 35.78/article, and obtained five US patents. Her research on aging, obesity and diabetes has been well recognized internationally. Dr Wang is among the top 1% highly cited scientists according to ISI Essential Science Indicators.

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Lipocalin-2 in obesity-related cardiometabolic syndrome: from risk prediction to therapeutic intervention

Lipocalin-2 or neutrophil gelatinase-associated lipocalin (NGAL) is a proinflammatory molecule exhibiting a diversified structure-functional relationships. The circulating levels of lipocalin-2 are significantly upregulated in obese human populations and positively correlated with cardiometabolic risk factors including hypertension, hyperglycemia, hyperlipidemia and insulin resistance. Animal studies demonstrate that lipocalin-2 plays a causative role in the development of obesity-associated pathologies, including endothelial dysfunction, adipose tissue inflammation, cardiac and renal injuries.

Human and murine lipocalin-2 is post-translationally modified by polyamination. Non-polyaminated lipocalin-2 exhibits a prolonged circulating half-life, thus increasing the risks of tissue accumulation. Pericardial expression and accumulation of non-polyaminated lipocalin-2 contributes to the development of heart failure. Moreover, measuring both polyaminated and non-polyaminated lipocalin-2 is useful for the stratification of heart failure patients with preserved or reduced ejection fractions. Long-term elevation of non-polyaminated lipocalin-2 derived from adipose tissue causes chronic kidney injuries and renal fibrosis.

In conclusion, targeting non-polyaminated lipocalin-2 represents a promising approach for obesity-related cardiometabolic complications.

Andrew Murphy

Baker Heart & Diabetes Institute,
Monash University, Australia

Andrew Murphy is NHMRC Career Development Fellow and National Heart Foundation Future Leader Fellow, and head of the Haematopoiesis and Leukocyte Biology laboratory at the Baker. Andrew completed is PhD in 2008 in Prof Jaye Chin-Dusting's laboratory at the Baker and postdoc'd in Prof. Alan Tall's group at Columbia University. In 2013 he returned to Australia to begin his own group. His work largely focuses on how inflammatory diseases associated with cardiovascular disease, including diabetes, obesity and rheumatoid arthritis cause the overproduction of innate immune cells and how this contributes to atherogenesis or impaired lesion regression. Furthermore, his laboratory studies fundamental biological process regulating haematopoiesis. He has published a number of manuscripts in leading journals including Nature Medicine, Cell Stem Cell, Cell Metabolism and the JCI.

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Hyperglycaemic spikes promote monocytosis and atherosclerosis IN A S100A8/A9 / RAGE dependent manner

Background: Postprandial hyperglycaemic spikes are a major cardiovascular risk factor in diabetes. We have previously shown that hyperglycaemia in diabetic mice increases monocytosis and atherosclerosis through S100A8/A9 signalling via the receptor for advanced glycation end-products (RAGE). Aims: We aimed to determine whether hyperglycaemic spikes alone promote S100A8/A9-RAGE signalling to increase monocytosis and thus atherosclerosis, and if blocking this pathway could thereby act to reduce hyperglycaemia-associated monocytosis and prevent atherosclerosis. *Methods:* Wildtype C57Bl/6 (WT) as well as WT mice transplanted with Rage-/- bone marrow (BM) were given 4 intraperitoneal glucose injections (2mg/kg, every 2hrs) to induce hyperglycaemic spikes (>15mM) and sacrificed after 1 and 7 days of normoglycaemia. We quantified common myeloid (CMPs) and granulocyte-monocyte precursors (GMPs) and circulating monocyte subsets (Ly6Chi and lo) with flow cytometry. To determine if this translated into accelerated atherosclerosis, we induced weekly hyperglycaemic spikes for 10 weeks in Apoe-/- mice or Rage-/-Apoe-/- mice, as well as Apoe-/- mice treated with a S100A8/A9 inhibitor, ABR-215757. *Results:* We found in the BM that CMPs and GMPs were increased 2.2 and 1.3 fold after 1 day and normalized 7 days after glucose spiking. This translated to significantly increased monocytes after 7 days (especially Ly6Chi subset). Interestingly, 1 day after glucose spiking, the expression of the RAGE ligand S100A8/A9 in white blood cells and expression of RAGE on CMPs were increased. Mice lacking S100a8, S100a9 and myeloid Glut-1 were all protected from glucose spike-driven monocytosis. Assessing neutrophil metabolism, it appeared that increased glucose promoted glycolysis, which was linked to neutrophil S100a9 expression. Mice transplanted with Rage-/- BM were protected against monocytosis induced by hyperglycaemic spikes. In Apoe-/- mice, hyperglycaemic spikes increased atherosclerotic burden in the aortic arch by 2-fold, and this was abolished by the deletion of RAGE. Intervention with ABR-215757 inhibited hyperglycaemic spike-induced monocytosis, and atherosclerosis, noted by a decreased plaque size, lipid content and macrophage content. *Conclusions:* These results highlight the potential harm of poor glyceamic control by stimulating myelopoiesis and enhanced atherogenesis, dependent on RAGE-S100A8/A9 signaling. Blocking this signaling by treatment with the novel S100A8/A9-RAGE pathway inhibitor, ABR-215757, conferred protection against hyperglycemic spikes and reduced atherosclerosis.

Feng Xu

Singapore Institute for Clinical Sciences, Agency for Science, Technology and Research (A*STAR), Singapore

Dr. Feng Xu has been a principal investigator at the Agency for Science, Technology and Research (A*STAR) since 2009. Now he works in the Institute of Molecular and Cell Biology (IMCB). He was trained as a chromatin biologist at University of California, Los Angeles before establishing his independent lab 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 in treating 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.

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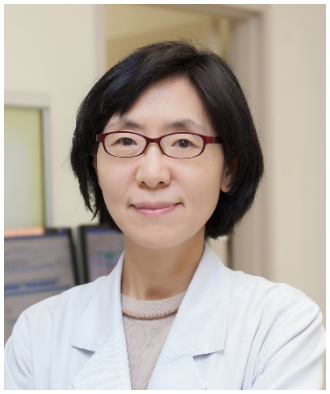
Narciclasine Attenuates Diet-Induced Obesity by Promoting Oxidative Metabolism in Skeletal Muscle

Obesity develops when caloric intake exceeds metabolic needs. Promoting energy expenditure represents an attractive approach in the prevention of this fast-spreading epidemic. Here we report a novel pharmacological strategy in which a natural compound, narciclasine (ncls), attenuates diet-induced obesity (DIO) in mice by promoting energy expenditure. Moreover, ncls promotes fat clearance from peripheral metabolic tissues, improves blood metabolic parameters in DIO mice and protects these mice from the loss of voluntary physical activity. Further investigation suggested that ncls achieves these beneficial effects by promoting a shift from glycolytic to oxidative muscle fibers in the DIO mice thereby enhancing mitochondrial respiration and fatty acid oxidation (FAO) in the skeletal muscle. Moreover, ncls strongly activates AMPK signaling specifically in the skeletal muscle. The beneficial effects of ncls treatment in fat clearance and AMPK activation were faithfully reproduced in vitro in cultured murine and human primary myotubes. Mechanistically, ncls increases cellular cAMP concentration and ADP/ATP ratio, which further lead to the activation of AMPK signaling. Blocking AMPK signaling through a specific inhibitor significantly reduces FAO in myotubes. In summary, our results indicated the therapeutic potential of ncls in combating obesity by increasing energy expenditure through enhancing FAO in skeletal muscle.

Min-Seon Kim

Division of Endocrinology and Metabolism, Department of Internal Medicine, University of Ulsan College of Medicine, Korea



Min-Seon Kim received her M.D. and Ph.D. from the Seoul National University College of Medicine. She trained research fellowship at Imperial College School of Medicine, UK. She is currently the Professor and Director of Division of Endocrinology and Metabolism at the University of Ulsan, College of Medicine. Her research interest is on the molecular mechanisms by which the CNS regulates systemic energy metabolism. She published over 100 original papers and received many awards including the Bunch Award, Hamchun Award, and Yonkang Award.

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Role for hypothalamic neuronal cilia in obesity and metabolic regulation

The primary, non-motile cilium is a specialized organelle found at the almost every eukaryotic cells. The cilium consists of 9+0 microtubule-based axoneme, an extension of mother centriole, in a plasma membrane sheath. Recently, the cilium has become the focus of intensive studies for its role in the transduction of extracellular signals and in a constellation of genetic disorders. Interestingly, human genetic ciliopathies (Bardet-Biedel Syndrome (BBS) and Alström syndrome, etc) commonly manifest obesity and diabetes mellitus. Similarly, mice deficient BBS protein-2,-4, and -6 display obese phenotype and leptin resistance. These mice develop central leptin resistance before the establishment of obesity, suggesting that BBS proteins are critical for central leptin signaling pathway. On the other hand, defective ciliogenesis in hypothalamic neurons causes hyperphagia and obesity, indicating that cilia of hypothalamic neurons play an important role in the maintenance of normal energy metabolism. Hypothalamic pro-opiomelanocortin (POMC) neurons are known as a key player in the central regulation of energy and glucose metabolism. To investigate a role of primary cilia of POMC neurons in the maintenance of energy balance, we generated the mice lacking Kif3a and IFT88, key components for ciliary growth, in POMC cells by using cre-lox system. I will present our recent findings which suggest an importance of cilia-mediated signaling in neuronal circuit formation during the early postnatal development.

Yun Hee Lee

College of Pharmacy, Yonsei University, Korea

I received a Master's degree in Pharmacy from Seoul National University, where I investigated molecular mechanisms of novel insulin-sensitizing compounds, and then worked as a Tenured Researcher in the Drug Evaluation Department, Ministry of Food and Drug Safety (MFDS) in South Korea. For my Doctoral research at Wayne State University, I joined the Center for Integrative Metabolic and Endocrine Research to work with Dr. James Granneman on the therapeutic remodeling of adipose tissue. This work led to the discovery of adipocyte progenitors that can become brown or white adipocytes depending on the nature of the stimulus (Cell Metab 2012; 15:480-91). More recently, as an independent scientist at Yonsei University, I currently work on characterization of molecular markers that can distinguish differentiation-primed progenitors from quiescent progenitors, which will allow analysis of the earliest stages of adipocyte progenitor activation and fate choice in vivo.

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The Role of Connexin43 in Adipose Tissue Metabolism

We investigated the role of connexin 43 (Cx43) in maintaining the integrity of mitochondria in brown adipose tissue (BAT). The functional effects of Cx43 were evaluated using inducible, adipocyte-specific Cx43 knockout in mice (Gja1adipoqKO) and by overexpression and knockdown of Cx43 in cultured adipocytes. Mitochondrial morphology was evaluated by electron microscopy and mitochondrial function and autophagy were assessed by immunoblotting, immunohistochemistry, and qPCR. The metabolic effects of adipocyte-specific knockout of Cx43 were assessed during cold stress and following high fat diet feeding. Cx43 expression was higher in BAT compared to white adipose tissue. Treatment with the β3-adrenergic receptor agonist CL316,243 increased Cx43 expression and mitochondrial localization. Gja1adipoqKO mice reduced mitochondrial density and increased the presence of damaged mitochondria in BAT. Moreover, metabolic activation with CL316,243 further reduced mitochondrial integrity and upregulated autophagy in the BAT of Gja1adipoqKO mice. Inhibition of Cx43 in cultured adipocytes increased the generation of reactive oxygen species and induction of autophagy during β-adrenergic stimulation. Gja1adipoqKO mice were cold intolerant, expended less energy in response to β3-adrenergic receptor activation, and were more insulin resistant after a high-fat diet challenge. Collectively, our data demonstrate that Cx43 is required for maintaining the mitochondrial integrity and metabolic activity of BAT.

Paul Lee

Department of Medicine, Li Ka Shing Faculty of Medicine, the University of Hong Kong, Hong Kong SAR

Dr. Lee joined the Department of Medicine as Clinical Assistant Professor in July 2015. He obtained his MBBS degree from the University of Hong Kong in 2006. Dr. Lee received his training in internal medicine, endocrinology and diabetes in Queen Mary Hospital. Research interests of Dr. Lee include adipokines and other endocrine biomarkers in obesity, diabetes and their complications. He is also interested in the genetics of phaeochromocytoma and paraganglioma, as well as other endocrine disorders, in Chinese patients

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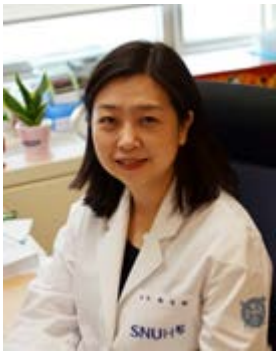
Adipocyte fatty acid-binding protein, diabetic complications and mortality

Type 2 diabetes (T2DM) increases mortality. Importantly, not only does it associate with substantial excess risks of cardiovascular and renal complications, studies from both Asian and the Western populations had found that T2DM also significantly raises mortality rates related to non-vascular causes like cancer and infectious diseases. On the other hand, adipocyte fatty acid-binding protein (AFABP) are lipid chaperones that are abundantly secreted from adipocytes and highly expressed in macrophages. High circulating AFABP levels have been reported in subjects with incident metabolic syndrome, T2DM and CV events in population based cohorts. This talk will illustrate the performance of circulating AFABP as a potential marker to predict various complications and mortality in T2DM.

Sung Hee Choi

Endocrinology and Metabolism, Internal Medicine, Seoul National University, Korea



Dr. Choi was treated as a medical doctor in Yonsei University in 1997, and she pursued research training in the same university and obtained her PhD in 2006. She also served as a clinical fellow at Schwabinger Krankenhaus, Munich, Germany (under the guidance of Dr. Hubert Stiegler, and a visiting research scholar at Columbia University Medical Center, Irving Institute for Clinical and Translational Research, in Henry Ginsberg's lab. She started her academic appointment as an assistant professor in Seoul National University College of Medicine, and was promoted to full Professor in 2017. She has been actively taking up the leading role in several professional societies to promote the research and clinical practice of diabetes and endocrinology, including Korean Diabetes Association, Korean Lipid & Atherosclerosis Society and Korean Endocrine Society. Her research interests include diabetes-induced cardiovascular complications, proteomics and lipidology.

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Comprehensive analysis of human ectopic fats by multiomics approach

Ectopic fat accumulation is considered is an important feature in type 2 diabetes mellitus (T2DM) and cardiovascular diseases based on the atherosclerosis. However, current study in human about ectopic fat accumulation has been more focusing the difference in the amount of ectopic fat accumulation in patients with metabolic disease, but not enoughly explored its pathophysiological characteristics such as lipid composition or extensive profiling in secretory proteins.

In this talk, I want to present the result from lipidomics and proteomics approach to analyze the pathophysiological difference in three different site of fats (subcutaneous, pericardial, and visceral fats) in human with cardiovascular diseases. We collected the samples from patients with coronary artery bypass graft, 3 different fat depots from one patient.

The lipidomic profile of PAT showed significant distinction in phospholipids and sphingolipids compared to those of SAT and the VAT. The lipid species belonging to the sphingolipid of ectopic fats (PAT & VAT) showed a marked difference from those of SAT. The sphingolipid of the VAT was also different between subjects with T2DM and NGT.

Chen-Yang Shen

Division of Epidemiology and Genetics, Institute of Biomedical Sciences, Academia Sinica, Taiwan

Dr. Shen is the Professor of Institute of Biomedical Sciences with the research interested in molecular epidemiology and Cancer Genetics of Breast Cancers and personalized Medicine. Professor Chen-Yang Shen received his B.Sc. (1983) and M.P.H. (1987) from National Taiwan University, and Ph.D. (1992) in epidemiology form the University of North Carolina at Chapel Hill. He then worked as an assistant research fellow (1994-2000), associated research fellow (2000-2007) and research fellow (since 2007) of Academia Sinica, Taiwan. He was appointed as the deputy director in the Institute of Biomedical Sciences of Academia Sinica. He is now the chief executive of Taiwan Biobank, Academia Sinica. Prof. Shen has dedicated himself to molecular and genomic epidemiological research on breast cancer for 20 years. His laboratory is a member of interactional breast cancer consortium, using the genome-wide association study and successfully identifying multiple genomic loci important in determining genetic susceptibility of breast cancer.

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Mendelian Randomization Analysis to Explore Causal Relation between Triglyceride and HBA1c- An Example of using Taiwan Biobank

We describe here an investigation of causal link between triglyceride and HBA1c, a more reliable marker of type-2 diabetes (T2D). This hypothesis stems from PheWas based on more than 10-thousand participants of the Taiwan Biobank (TWB). TWB aims to build a nationwide research database that integrates genomic/epigenomic profiles, lifestyle patterns, dietary habits, environmental exposure history and long-term health outcomes of 300,000 residents of Taiwan. Because observational studies have shown that either positive or negative association between triglyceride and T2D. Furthermore, observational data are prone to confounding and reverse causation. We used 20 single-nucleotide polymorphisms (SNPs) that are each specifically associated with triglyceride in eastern Asian population, 16 of which are in our genome-wide genotyping chip and 4 of which are from imputation. We purposely excluded self-reported T2D or hyperlipidemia, giving that the use of prescribed drugs by them might confound the level of HBA1c. After excluding the SNPs show strong linkage disequilibrium and pleiotropic effect, seven SNPs were examined for their association with HBA1c, among which five show statistically significant with HBA1c. In addition, Mendelian randomization estimates reveal a significant beta value (10.59, 95%CI, 1.65-13,39). Considering the contribution of other risk factor, multivariate analysis shows a significant odds ratio (1.07, 95%CI, 1.01-1,17) between genetic risk score representing triglyceride in association with the level of HBA1c. This Mendelian randomization study supports the hypothesis that higher triglyceride increases the level of HBA1c. These findings may highlight the use of triglyceride as a predicative marker of T2D.

List of participants

Dr.	Chi Bun	Chan	chancb@hku.hk
Dr.	Chung Ying Kathy	Chan	kchych@hku.hk
Mr.	Hau Tak	Chau	duck@hku.hk
Dr.	Guanghua	Chen	dr.g.chen@hku.hk
Mr.	Guolin	Chen	593609423@qq.com
Dr.	Haiyong	Chen	haiyong@hku.hk
Ms.	Xin Yi	Chen	chenxyi@hku.hk
Dr.	Kenneth King Yip	Cheng	kenneth.ky.cheng@polyu.edu.hk
Ms.	Lai Yee	Cheong	u3003285@hku.hk
Ms.	Jamie	Cheung	jamie.cheung@hku.hk
Mr.	Hou In Oscar	Chou	oscarchou211@yahoo.com.hk
Ms.	Chujun	Deng	569213236@qq.com
Dr.	Ben Yuk Fai	Fong	yffong@speed-polyu.edu.hk
Mr.	Wai Lun	Fung	wf0416@hku.hk
Mr.	Yuan	Gap	ygaobio@outlook.com
Mr.	Leiluo	Geng	u3003135@hku.hk
Ms.	Cordelia Yee Ching	Ho	cordelia0526@gmail.com
Dr.	King Lun	Ho	dominicho@me.com
Dr.	Ruby	Hoo	rubyhoo@hku.hk
Dr.	Yusei	Hosokawa	yusei719@med.kobe-u.ac.jp
Dr.	Tetsuya	Hosooka	thosooka@med.kobe-u.ac.jp
Mr.	Yue	Hu	alexhy@hku.hk
Dr.	Yuhong	Huang	wishes68@sina.com
Dr.	Zhe	Huang	huangzhe@hku.hk
Mr.	Shuwen	Jiang	1031449531@qq.com
Dr.	Xue	Jiang	xue0129@hku.hk
Mr.	Leigang	Jin	jinlg520@hku.hk
Dr.	Alice Pik Shan	Kong	alicekong@cuhk.edu.hk
Mr.	Kam Ching	Ku	kcku@connect.ust.hk
Dr.	Mei Kwun	Kwok	mkkwok@hku.hk
Dr.	Maria	Lam	19710901marialam@gmail.com
Ms.	Phoebe Cheuklam	Lam	phoebecl@connect.hku.hk
Dr.	Chi Wai	Lee	chiwai.lee@hku.hk
Dr.	Dong-Hwa	Lee	roroko0902@gmail.com
Mr.	Tsz Hang Jimmy	Lee	jimmylee@hku.hk
Ms.	Yann Yin	Lee	yannyin@connect.hku.hk
Dr.	Fung Ping Christina	Leung	christina_leungfp@cuhk.edu.hk
Ms.	Hei Ming Judy	Leung	judyming@hku.hk
Mr.	Bin	Li	u3004620@hku.hk
Ms.	Lily	Li	lily46@hku.hk
Mr.	Rodger	Li	rodgerli@hku.hk
Ms.	Xiang	Li	xiangli722@hotmial.com
Ms.	Boya	Liao	liaoboya@hku.hk
Dr.	Rui	Liao	rayliao1985@163.com
Dr.	Lee Ling	Lim	leelinglimll@gmail.com
Ms.	Huige	Lin	lin.ge.lin@connect.polyu.hk

Ms.	Haiyan	Liu	56235211@qq.com
Ms.	Jingjing	Liu	liujj93@hku.hk
Dr.	Yan	Liu	liuyan27@hku.hk
Mr.	Zhuohao	Liu	lchouhoo@gmail.com
Mr.	Kekao	Long	kklong@polyu.edu.hk
Mr.	Ka Wang Kelvin	Lui	kwklui@connect.hku.hk
Dr.	Judith Choi Wo	Mak	judithmak@hku.hk
Mr.	Ka Chun Eugene	Mak	u3549226@hku.hk
Dr.	Chun Laam Roy	Ng	royclng@hku.hk
Mr.	Yong	Pan	panicy0322@hotmail.com
Dr.	Antonio	Perfecto	perfecto.a@gmail.com
Ms.	Xingxing	Qian	u3005106@connect.hku.hk
Ms.	Han	Qiu	532665779@qq.com
Mr.	Haoyu	She	henryshe@hku.hk
Prof.	Peter	Shepherd	peter.shepherd@auckland.ac.nz
Dr.	Lingling	Shu	shinyshu@hku.hk
Dr.	Parco	Siu	pmsiu@hku.hk
Dr.	Tianhe Michael	Song	thsongm@gmail.comm
Dr.	Kel Vin	Tan	kvtan@hku.hk
Dr.	Zhi	Tang	tangzhi@szcdc.net
Dr.	Xiaoyu	Tian	xytian@cuhk.edu.hk
Dr.	Baile	Wang	blwong@connect.hku.hk
Mr.	Lin	Wang	wanglin9@connect.hku.hk
Mr.	Yao	Wang	yaowang@hku.hk
Dr.	Yu	Wang	yuwanghk@hku.hk
Mr.	Chi Wut	Wong	cwwong13@connect.hku.hk
Dr.	Chi-Ming	Wong	wispwong@hku.hk
Dr.	Ho Yee	Wong	vicwhy@connect.hku.hk
Mr.	Siu Cheung	Wong	anson.ascwong@gmail.com
Dr.	Wing Tak Jack	Wong	jack_wong@cuhk.edu.hk
Ms.	Xiaoping	Wu	xpwu@hku.hk
Ms.	Zhengyun	Xia	cherryxia64@gmail.com
Ms.	Xingqun	Yan	xqyanhku@hku.hk
Ms.	Chunxue	Yang	15484971@life.hkbu.edu.hk
Dr.	Kwok Ming	Yao	kmyao@hku.hk
Dr.	Rita	Yim	ritayim@hku.hk
Mr.	Jensen	Yiu	jensenhc@connect.hku.hk
Dr.	Yongke	You	yongke@hku.hk
Ms.	Qian	Yu	u3004582@hku.hk
Mr.	Hin Hei Samson	Yum	samsonyum@gmail.com
Dr.	Susan	Yung	ssyyung@hku.hk
Dr.	Ling	Zhong	kelsey@hku.hk
Mr.	Jie	Zhou	jzhou329@hku.hk
Mr.	Pengcheng	Zhou	zhoupc@hku.hk
Ms.	Wenli	Zhou	zwl1993@connect.hku.hk
Ms.	Yawen Eva	Zhou	evazyw@hku.hk

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