2016 11th APDO SYMPOSIUM

Asia-Pacific Diabetes and Obesity Study Group
Joint with the 11th IDF-WPR Congress 2016 & 8th AASD Scientific Meeting

October 29 Sat. › 30 Sun.

Taipei International Convention Center (TICC), Taipei, Taiwan

President : Lee-Ming Chuang, MD, PhD

Department of Internal Medicine and Graduate Institute of Clinical Medicine,
College of Medicine, National Taiwan University

11th APDO symposium

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Welcome Message from President of APDO 2016

Oct. 29, 2016

On behalf of the local organizing committee, we sincerely welcome you to the 11th Symposium of Asia-Pacific Diabetes and Obesity Study Group in Taipei, Taiwan.

It is our honor to host the APDO Symposium for the first time in Taiwan. With pleasure, we invite representatives from each country from Australia, China, Hong Kong, Japan, Korea, New Zealand, Singapore and Taiwan to form this year's symposium as traditionally. This year's APDO program is organized as two full days meeting in conjunction with the 11th IDF-WPR Congress 2016 & 8th AASD Scientific Meeting, covering both basic and clinical researches in field of obesity and diabetes. As a hope to make better communication and exchange of research data among this region and the world, I believe that all the participants will benefit from the program. I wish everyone can get more insight and knowledge, and enjoy a great stay at Taipei.

Lee-Ming Chuang, MD, PhD

President, the 11th Symposium of Asia-Pacific Diabetes and Obesity Study Group in Taipei, Taiwan
Chair Professor, Department of Internal Medicine and Graduate Institute of Clinical Medicine,
College of Medicine, National Taiwan University, Taipei, Taiwan

Welcome Message from Co-chairs of the APDO

Oct. 29, 2016

The Asia Pacific Diabetes Obesity Study group or APDO was founded in 2004. 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 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.

It is our great pleasure to host the 11th APDO meeting in Taipei, October 2016. We sincerely thank Prof. Lee-Ming Chuang, Prof. Wayne H-H Sheu and Prof. Shih-Te Tu for their efforts in organizing the APDO meeting in Taipei. The APDO meeting will run concurrent with the 11th IDF-WPR Congress and the 8th Scientific Meeting of the AASD. Therefore, this an ideal opportunity to forge new friendships and collaborations with researchers throughout the region.

We welcome all of you to Taipei and thank each of you for taking time out of your busy schedules to attend the meeting.

David James and Masato Kasuga

Co-chairs of the APDO

About APDO Symposium 2016

President

Lee-Ming Chuang, MD, PhD

Department of Internal Medicine and Graduate Institute of Clinical Medicine,
College of Medicine, National Taiwan University

Organizer

Chinese Taipei Diabetes Association

Abstract Publication

The congress abstracts (incl. speech, oral, poster) are also published in Diabetes Research and Clinical Practice (DRCP). Please view the electronic version here:

http://11thIDF-WPR-8thAASD2016-abstracts.elsevierdigitaledition.com

About APDO

Drs. Masato Kasuga and David James have initiated APDO (Asia-Pacific Diabetes and Obesity) meeting in 2004. Its vision is to promote research and collaboration in our region in the areas of diabetes, obesity and metabolism. The focus of the APDO meeting is basic and clinical researches on metabolic complications. The APDO is annually held among Australia, China, Hong Kong, Japan, Korea, New Zealand, Singapore and Taiwan.

APDO Official Website

http://apdo.umin.jp/

APDO Committee

Co-Chairs:

David James	University of Sydney, Australia
Masato Kasuga	National Center for Global Health and Medicine, Japan

Members:

Lee-Ming Chuang	National Taiwan University Hospital, Taiwan
Mark Febbraio	Baker IDI Heart and Diabetes Institute, Australia
Youfei Guan	Shenzhen University Medical School, China
Weiping Han	Singapore Bioimaging Consortium, Singapore
Takashi Kadowaki	University of Tokyo, Japan
Jae Bum Kim	Seoul National University, Korea
Karen Lam	University of Hong Kong, Hong Kong
Peter Shepherd	University of Auckland, New Zealand

Day 1

Symposium 13 (The APDO symposium 1)

29 Oct, 2016 (Day 1)	Symposium 13 ***Obesity and Diabetes***

Room 102
09:00-10:45

Moderator: Jae Bum Kim (Korea); Yu-Hua Tseng (USA)

S13-1 **Roles for adipose ceramides in metabolic homeostasis**
Scott Summers (Australia)

S13-2 **Roles of G6PD in ROS and inflammatory responses of obese adipose tissue**
Jae Bum Kim (Korea)

S13-3 **Obesity, inflammation and diabetic kidney disease**
Chi Ho Lee (Hong Kong)

S13-4 **The relationship between obesity and insulin resistance in Asian patients**
E.Shyong Tai (Singapore)

S13-5 **17β-hydroxysteroid dehydrogenase-13 is a lipogenic lipid droplet-associated protein and is regulated by an LXR-SREBP1c axis in the liver**
Xiao-yan Zhang (China)*
Apology for absence due to unanticipated reason

Day 1

Symposium 20 (The APDO symposium 2)

29 Oct, 2016 (Day 1)	Symposium 20 ***Adipocyte Biology and Insulin Resistance***
Room 102 14:15-16:00	**Moderator: Huey-Kang Sytwu (Taiwan); Peter Shepherd (New Zealand)**
Special Lecture 20-1	**Lipid dynamics in brown fat-mediated thermogenesis and energy metabolism** Yu-Hua Tseng (USA)
S20-2	**HOXC10 suppresses browning of white adipose tissues** Weiping Han (Singapore)
S20-3	**Inactivation of the E-Prostanoid 3 receptor gene causes adiposity and insulin resistance via altering white adipose tissue metabolism** Youfei Guan (China)
S20-4	**Regulation of hepatosteatosis and obesity by sphingolipids** Tae-Sik Park (Korea)
S20-5	**Targeting fat metabolism and energy expenditure in metabolic disease** Kyle Hoehn (Australia)

Day 1

Symposium 24 (The APDO symposium 3)

29 Oct, 2016 (Day 1)	Symposium 24 ***Hot Topics in Diabetes and Obesity (I)***
Room 102 16:20-18:05	**Moderator: Karen SL Lam (Hong Kong); Youfei Guan (China)**
S24-1	**Molecular mapping of insulin action and insulin resistance** David E. James (Australia)
S24-2	**The metabolic consequences of fecal microbiota transplantation (FMT) in mice** Darren Henstridge (Australia)
S24-3	**Chronic exercise alleviates obesity-related metabolic dysfunction by enhancing FGF21 sensitivity in adipose tissues** Aimin Xu (Hong Kong)* Apology for absence due to unanticipated reason
S24-4	**Laparoscopic sleeve gastrectomy versus Roux-en-Y gastric bypass for the treatment of type 2 diabetes: 12 month results of a double-blind, randomised trial** Rinki Murphy (New Zealand)

Day 2

Symposium 30 (The APDO symposium 4)

30 Oct, 2016 (Day 2)	Symposium 30 ***Incretin/Islet Biology and Insulin Secretion***
Room 102 08:00-09:45	**Moderator: David E. James (Australia); Weiping Han (Singapore)**
Special Lecture 30-1	**β-cell glutamate signaling in insulin secretion: The physiological and pathophysiological roles** Susumu Seino (Japan)
S30-2	**Intracellular membrane trafficking and insulin secretion** Wanjin Hong (Singapore) Apology for absence due to unanticipated reason
S30-3	**Sorcs1: From diabetes quantitative trait locus to cellular function** Melkam Kebede (Australia)
S30-4	**New insights into mechanisms regulating insulin secretion** Peter Shepherd (New Zealand)
S30-5	**Role of activin B/FSTL3 axis in the control of glucose homeostasis** Kohjiro Ueki (Japan)

Day 2

Symposium 35 (The APDO symposium 5)

30 Oct, 2016 (Day 2)	Symposium 35 ***Hot Topics in Diabetes and Obesity (II)***

Room 102
13:30-15:15

Moderator: Norikazu Maeda(Japan); Yi-Cheng Chang (Taiwan)

S35-1 **Role of CRTC2 in the control of glucose metabolism**
Seung-Hoi Koo (Korea)

S35-2 **Analysis of lipidomic profiling from ectopic fats in patients with coronary artery disease**
Sung Hee Choi (Korea)

S35-3 **Significance of adiponectin accumulation in vasculature**
Norikazu Maeda (Japan)

S35-4 **Hypothalamic inflammation in high fat diet-induced obesity**
Min-Seon Kim (Korea)

Day 2

Symposium 38 (The APDO symposium 6)

30 Oct, 2016 (Day 2)	Symposium 38 ***Hot Topics in Diabetes and Obesity (III)***

Room 102
15:35-17:20

Moderator: Masato Kasuga (Japan); Lee-Ming Chuang (Taiwan)

S38-1 **Feeding-induced activation of beta-catenin/ TCF signal transduction in hypothalamic neurons**
David R. Grattan (New Zealand)

S38-2 **Insulin signaling in adipocytes and metabolic control**
Wataru Ogawa (Japan)

S38-3 **Maternally inherited mitochondrial dysfunction causes insulin resistance**
Yi-Cheng Chang (Taiwan)

S38-4 **Role of mitochondrial quality control in hyperglycemic neuroprotection**
Daniel Hesselson (Australia)

Prof. Scott Summers

Current Position	Professor and Chair, Nutrition and Integrative Physiology, University of Utah

AFFILIATIONS

2015-2016	Baker IDI Heart and Diabetes Institute, Melbourne, Australia
2008-2015	Duke University, Durham, NC and the Duke-NUS Graduate Medical School, Singapore
2004-2008	University of Utah, Salt Lake City, UT
1999-2004	Colorado State University, Fort Collins, CO
1995-1999	University of Pennsylvania, Philadelphia, PA

EDUCATION

5/1989	BS - Indiana University, Bloomington, IN
8/1995	PhD - Southern Illinois University
6/1999	PostDoc - University of Pennsylvania

RESEARCH INTERESTS

My entire professional career has been devoted to the study of diabetes, with my interest having been born shortly after my father's diagnosis with the disease. My laboratory has become particularly interested in the relationship between dyslipidemia and metabolic disease and much of our current work derives from the observation that sphingolipids (e.g. ceramide) contribute to insulin resistance and beta cell failure, which are important features of the disease. Our current research efforts seek to identify the (a) site of sphingolipid function, (b) their mechanism of action, and (c) the regulatory events controlling sphingolipid accumulation. Moreover, (d) we seek to develop drugs targeting enzymes in the ceramide-synthesizing pathway, which hold enormous potential in a broad spectrum of metabolic disorders.

SELECTED PUBLICATION (Pertinent to your presentation)

1. Chaurasia B, Kaddai VA, Lancaster GL, Henstridge DC, Srirah S, Galam DAL, Gopalan, V, BPrahkash KNB, Velan SS, Bulchand S, Tson TJ, Wang M, Siddique MM, Yuguang G, Sigmundsson K, Mellet NA, Weir JM, Meikle PJ, Shabeeer BMMY, Shabbir A, Shayman JA, Hirabahashi Y, Shio SATE, Sugii S, and Summers SS (2016) Adipocyte ceramides regulate subcutaneous adipose browning, inflammation and metabolism (in press)
2. Chavez JA, Siddique MM, Wang ST, Ching J, Shayman JA, and Summers SA (2014) Ceramides and Glucosylceramides are Independent Antagonists of Insulin Signaling. Journal of Biological Chemistry 289(2),723-34
3. Holland WL, Brozinick JT, Wang LP, Hawkins ED, Sargent KM, Liu Y, Narra K, Hoehn KL, Knotts TA, Siesky A, Nelson DH, Karathanasis SK, Fontenot GK, Birnbaum MJ and Summers SA (2007) Inhibition of ceramide synthesis ameliorates glucocorticoid-, saturated-fat-, and obesity-induced insulin resistance. Cell Metabolism 5(3), 167-79
4. Holland WL and Summers SA (2008) Sphingolipids in insulin resistance and metabolic disease: New insight from in vivo manipulation of sphingolipid synthesis. Endocrine Reviews 29(4), 381–402

S13-1

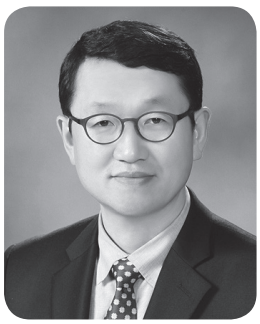
Roles for adipose ceramides in metabolic homeostasis

S. A. Summers[1]

[1]Department of Nutrition and Integrative Physiology, University of Utah, Salt Lake City, UT USA

Adipocytes package incoming fatty acids into triglycerides and other glycerolipids, with only a fraction spilling into a parallel biosynthetic pathway that produces sphingolipids. During obesity, the excessive entry of lipid into this pathway leads to the aberrant accumulation of biosynthetic intermediates such as ceramides that impair tissue metabolism and function. Notably, genetic or pharmacological inhibition of enzymes that drive ceramide synthesis (e.g. serine palmitoyltransferase, dihydroceramides desaturase, etc.) in mice ameliorates virtually all complications of obesity including insulin resistance, steatosis, diabetes, hypertension, cardiomyopathy, and atherosclerosis. To dissect the tissue-specific roles for ceramides in nutrient homeostasis, we have produced mice lacking serine palmitoyltransferase, the rate-limiting enzyme in the ceramide biosynthesis cascade,.in various body locales. Using these mice, we determined that newly-synthesized adipocyte sphingolipids drive profound changes in the adipose phenotype to influence whole-body energy expenditure and nutrient metabolism.

Prof. JAE BUM KIM



Current Position Professor

AFFILIATIONS

2009 - present	Professor, School of Biological Sciences, Seoul National University, Seoul, Korea
2009 - 2011	Director, Institute of Laboratory Animal Research, Seoul National University, Seoul, Korea
2011 - 2012	Director, Institute of Molecular Biology and Genetics, Seoul National University, Seoul, Korea
2011 - present	Director, Center for Adipose Tissue Remodeling, Creative Research Initiatives
2015 - present	Member of Korean Academy of Science and Technology

EDUCATION

1984 -1988	B.S. Dept. of Zoology, Seoul National University, Seoul, Korea.
1988 -1990	M.A. Cell & Molecular Biology, Seoul National University, Seoul, Korea
1991 -1996	Ph.D. Dept. of Microbiology & Molecular Genetics, Harvard University, Boston, USA
1996 -1997	Postdoctoral Fellow. Dana-Farber Cancer Inst., Harvard Medical School, Boston, USA
1997 -2000	Postdoctoral Fellow. Center for Cancer Research, MIT, Cambridge MA, USA

RESEARCH INTERESTS

Mechanism of Adipocyte Differentiation
Lipid Metabolisms, Insulin Signaling
Obesity and Diabetes

SELECTED PUBLICATION (Pertinent to your presentation)

1. A. Y. Kim, Y. J. Park, X. Pan, K. C. Shin, S. H. Kwak, A. F. Bassas, R. M. Sallam, K. S. Park, A. A. Alfadda, A. Xu, and J. B. Kim*. Obesity-induced DNA hypermethylation of the adiponectin gene mediates insulin resistance. Nat Commun., 3:6:7585, 2015
2. J. I. Kim, J. Y. Huh, J. H. Sohn, S. S. Choe, Y. S. Lee, C. Y. Lim, A Jo, S. B. Park, W. Han, and J. B. Kim*. Lipid-overloaded enlarged adipocytes provoke insulin resistance independent of inflammation. Mol. Cell. Biol., 35:1686-99. 2015
3. I. Hwang, Y. J. Park, Y. R. Kim, Y. N. Kim, S Ka, H. Y. Lee, J. K. Seong, Y. J. Seok, and J. B. Kim*. Alteration of gut microbiota by vancomycin and bacitracin improves insulin resistance via glucagon-like peptide 1 in diet-induced obesity. FASEB J., 29:2397-411, 2015
4. J. H. Lee, J. Kong, J. Y. Jang, J. S. Han, Y. Ji, J. Lee, and J. B. Kim*. Lipid droplet protein LID-1 mediates ATGL-1-dependent lipolysis during fasting in Caenorhabditis elegans. Mol. Cell. Biol., 34:4165-76. 2014
5. S. S. Choe, K. C. Shin, S. Ka, Y. K. Lee, J. S. Chun, and J. B. Kim*. Macrophage HIF-2α Ameliorates Adipose Tissue Inflammation and Insulin Resistance in Obesity. Diabetes, 63:3359-71. 2014

S13-2

Roles of G6PD in ROS and inflammatory responses of obese adipose tissue

Sung Sik Choe[1], Mira Ham[1], Kyung Cheul Shin[1], Goun Choi[1], Jae Bum Kim[1]

[1]Department of Biological Sciences, Institute of Molecular Biology and Genetics, National Creative Research Initiatives Center for Adipose Tissue Remodeling, Seoul National University, Seoul, Korea

Glucose-6-phosphate dehydrogenase (G6PD), a rate-limiting enzyme of the pentose phosphate pathway, plays important roles in redox regulation along with de novo lipogenesis. Recently, it has been demonstrated that abnormal increase of G6PD in obese adipose tissue mediates insulin resistance due to imbalanced energy metabolism and oxidative stress. However, it remains elusive whether the G6PD deficiency in vivo may relieve obesity-induced insulin resistance. In this study, we have shown that hematopoietic G6PD defect alleviates insulin resistance in obesity, accompanied with reduced adipose tissue inflammation. Compared to WT littermates, G6PD-deficient mutant (G6PDmut) mice were glucose tolerant upon high fat diet (HFD) feeding. Intriguingly, the expression of NADPH oxidase genes to produce ROS was alleviated whereas that of anti-oxidant genes was enhanced in adipose tissue from HFD-fed G6PDmut mice. In diet-induced obesity (DIO), adipose tissue of G6PDmut mice decreased expression of inflammatory cytokines, accompanied with down-regulated pro-inflammatory macrophages. In accordance with these, macrophages from G6PDmut mice greatly suppressed LPS-induced pro-inflammatory signaling cascades, leading to enhance insulin sensitivity in adipocytes and hepatocytes. Furthermore, adoptive transfer of G6PDmut bone marrow into wild type mice attenuated adipose tissue inflammation and improved glucose tolerance in DIO. Collectively, these data suggest that down-regulation of macrophage G6PD would ameliorate insulin resistance in obesity through suppression of pro-inflammatory responses.

Dr. LEE, Chi Ho

Current Position	Clinical Assistant Professor Department of Medicine The University of Hong Kong

AFFILIATIONS

2007-2013	Resident, Hospital Authority, Hong Kong
2013-2015	Resident Specialist, Hospital Authority, Hong Kong
2015-Present	Clinical Assistant Professor, The University of Hong Kong

EDUCATION

2016	MBBS (HK), The University of Hong Kong
2009	MRCP (UK), Royal Colleges of Physicians, United Kingdom
2013	FHKCP (Endocrinology / Diabetes / Metabolism), Hong Kong College of Physicians
2013	FHKAM (Medicine), Hong Kong Academy of Medicine
2014	FHKCP (Advanced Internal Medicine), Hong Kong College of Physicians

RESEARCH INTERESTS

Adipokines and other endocrine biomarkers in obesity, diabetes and their complications

Genetics of phaeochromocytoma and paraganglioma in Chinese patients

SELECTED PUBLICATION (Pertinent to your presentation)

1. Lee CH, Hui EYL, Woo YC, Yeung CY, Chow WS, Yuen MMA, Fong CHY, Xu A, Lam KSL. Circulating fibroblast growth factor 21 levels predict progressive kidney disease in subjects with type 2 diabetes and normoalbuminuria. J Clin Endocrinol Metab 2015 Apr; 100:1368-1375. (Impact factor: 6.209)
2. Lee CH, Lam KS. Biomarkers of progression in diabetic nephropathy – the past, present and future. J Diabetes Investig 2015 May; 6:247-249. (Impact Factor: 1.825)
3. Lee CH, Woo YC, Wang Y, Yeung CY, Xu A, Lam KS. Obesity, adipokines and cancer: an update. Clin Endocrinol (Oxf). 2015 Aug; 83:147-156. (Impact Factor: 3.457)
4. Hui E, Yeung CY, Lee CH, Woo YC, Fong CH, Chow WS, Xu A, Lam KS. Elevated circulating pigment epithelium-derived factor predicts the progression of diabetic nephropathy in patients with type 2 diabetes. J Clin Endocrinol Metab 2014; 99:E2169-E2177 (Impact factor: 6.209)
5. Lee CH, Woo YC, Fong CHY, Lam JKY, Cheung BMY, Lam KSL, Tan KCB. Validation of the Pooled Cohort equations in a long-term cohort study of Hong Kong Chinese. J Clin Lipidol 2015 Sep-Oct; 9: 640-646. (Impact factor: 3.904)
6. Lee CH, Cheung CYY, Chow WS, Woo YC, Yeung CY, Lang BHH, Fong CHY, Kwok KHM, Chen SPL, Mak CM, Tan KCB, Lam KSL. Genetics of apparently sporadic phaeochromocytoma in a Chinese population. Horm Metab Res 2015 Oct; 47:833-838. (Impact factor: 2.121)
7. Woo YC, Cheung BMY, Yeung CY, Lee CH, Hui EYL, Fong CHY, Tso AWK, Tam S, Lam KSL. Cardiometabolic risk profile of subjects with prediabetes diagnosed by HbA1c criteria in an urban Hong Kong Chinese population over 40 years of age. Diabet Med 2015; 32: 1207-1211 (Impact factor: 3.115)
8. Hui E, Xu A, Chow WS, Lee CH, Fong HY, Cheung CW, Tse HF, Chau MT, Cheung BMY, Lam KSL. Hypoadiponectinaemia as an independent predictor for the progression of carotid atherosclerosis: a 5-year prospective study. Metab Syndr Relat Disord 2014; 12: 517-522 (Impact factor: 1.976)

S13-3

Obesity, inflammation and diabetic kidney disease

Chi Ho Lee[1]

[1]University of Hong Kong, Hong Kong

Obesity has become an epidemic, globally. In parallel with this is a rapid surge in the prevalence of both type 2 diabetes mellitus and its related complications. Although mortality from macro-vascular complications like coronary heart disease and stroke has improved with the advent of potent statins, the incidence of diabetic kidney disease is still on the rise and it remains a major cause of end-stage renal failure worldwide.

Obesity causes dysfunction of adipose tissue, resulting in chronic inflammation and an imbalance of various adipokines. Over the past decade, the role of inflammation in diabetic kidney disease has been increasingly recognized. These have facilitated not only the improved understanding of the complex pathogenic mechanisms of diabetic kidney disease, but also the development of novel therapeutic strategies in tackling this devastating complication of diabetes.

In this short talk, the association between inflammation and diabetic kidney disease will be discussed. Furthermore, as some adipokines or obesity related markers, such as adipocyte fatty acid-binding protein and fibroblast growth factor 21, have been recently investigated as renal biomarkers, their roles as potential useful candidate markers of diabetic kidney disease will also be presented.

Dr. Tai E Shyong

Current Position Professor, Yong Loo Lin School of Medicine,
National University of Singapore

AFFILIATIONS

Cardiovascular and metabolic disease program, Duke-NUS graduate medical school
Saw Swee Hock School of Public Health, National University of Singapore

EDUCATION

2009	PhD
1990	MB ChB

RESEARCH INTERESTS

Diabetes mellitus
genetics
Insulin resistance

SELECTED PUBLICATION (Pertinent to your presentation)

1. Fuchsberger C et al. The genetic architecture of type 2 diabetes. Nature. 2016 Jul 11;536(7614):41-47. doi: 10.1038/nature18642
2. Mahajan et al. Genome-wide trans-ancestry meta-analysis provides insight into the genetic architecture of type 2 diabetes susceptibility. Nat Genet. 2014 Mar;46(3):234-44
3. Khoo CM et al. Body fat partitioning does not explain the interethnic variation in insulin sensitivity among Asian ethnicity: the Singapore adults metabolism study. Diabetes. 2014 Mar;63(3):1093-102.

S13-4

The relationship between obesity and insulin resistance in Asian patients

E. S. Tai[1,2,3]

[1]Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[2]Cardiovascular and Metabolic Program, Duke-National University of Singapore Graduate Medical School, Singapore
[3]Genome Institute of Singapore, Singapore

Obesity and insulin resistance are key pathophysiologic features of type 2 diabetes (T2D). Obesity and insulin resistance are correlated. However, insulin resistance and features of the metabolic syndrome are manifest a relatively low levels of body mass index in Asians than they are in populations of European ancestry. It has been suggested that this relates to the fact that body mass index under-estimates the degree of adiposity in Asians. Others have suggested that this relates to the relatively greater proportion of visceral fat related to total adiposity in Asians. We have found that the ethnicity modulates the relationship between obesity and insulin resistance. In South Asians, insulin resistance is present even at low body mass index, suggesting that in this ethnic group, insulin resistance does not require the presence of obesity. In contrast, while Chinese and Malays are very insulin sensitive when they are lean, with increasing levels of obesity, insulin sensitivity rapidly declines so that at a BMI in the region of 27-28 kg/m^2, there is no difference between Chinese, Malays and South Asians in relation to insulin sensitivity. This suggests that obesity may have a greater impact in Chinese and Malays than in South Asians. These provides unique opportunities to dissect out obesity dependent and obesity independent pathways leading to insulin resistance.

Prof. Xiao-yan Zhang

Current Position Professor

AFFILIATIONS

2016,01- present Professor, Dalian Medical University
2013,10-2015,12 Associate Professor, Shenzhen University
2011,10-2013,09 Assistant Researcher ,Peking University First Hospital
2009,08-2011,09 Postdoctoral Fellow, Peking University

EDUCATION

1999,08 -2004,07 M.D. in Medicine, Peking University
2004,08- 2009,07 Ph.D. in Pathophysiology, Peking University
2007,08- 2008,05 Exchange Research visitor, University of pittburgh

RESEARCH INTERESTS

Nuclear receptor biology
Kidney diseases
Metabolic syndrome

SELECTED PUBLICATION (Pertinent to your presentation)

1. Han Q#, Zhang X#, Xue R, Yang H, Zhou Y, Kong X, Zhao P, Li J, Yang J, Zhu Y, Guan Y *. AMPK potentiates hypertonicity-induced apoptosis by suppressing NF κ B/COX-2 in medullary interstitial cells. J Am Soc Nephrol. 2011;22:1897-911;
2. Zhang X #, Shizheng Huang#, Min Gao, Jia Liu, Xiao Jia, Qifei Han, Senfeng Zheng, Yifei Miao, Shuo Li, Haoyu Weng, Xuan Xia, Shengnan Du, Jan-Åke Gustafsson, Youfei Guan* (#Equal contribution). Farnesoid X receptor (FXR) gene deficiency impairs urine concentration in mice. Proc Natl Acad Sci. 2014 Feb 11;111(6):2277-82;
3. Su W, Wang Y, Jia X, Wu W, Li L, Tian X, Li S, Wang C, Xu H, Cao J, Han Q, Xu S, Chen Y, Zhong Y, Zhang X, Liu P, Gustafsson JÅ, Guan Y*. Comparative proteomic study reveals 17 β -HSD13 as a pathogenic protein in nonalcoholic fatty liver disease. Proc Natl Acad Sci U S A. 2014 Aug 5;111(31):11437-42;
4. Xu H, Fu J, Miao Y, Wang C, Han Q, Li S, Huang S, Du S, Qiu Y, Yang J, Gustafsson J-Å, Breyer R, Zheng F, Wang N, Zhang X, Guan Y*. Prostaglandin E2 receptor EP3 regulates adipogenesis and lipolysis in mice white adipose tissue. J Mol Cell Biol. 2016(accepted).

S13-5

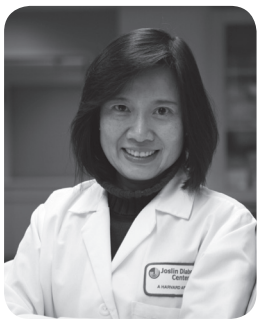
17β-hydroxysteroid dehydrogenase-13 is a lipogenic lipid droplet-associated protein and is regulated by an LXRα-SREBP1c axis in the liver

Xiao-yan Zhang[1,2], Wen Su[2], Bing Wang[1], You-fei Guan[1,2]

[1]Advanced Institute for Medical Sciences, Dalian Medical University, Dalian, Liaoning 116044, China
[2]Department of Physiology, AstraZeneca–Shenzhen University Joint Institute of Nephrology, Shenzhen University Health Science Center, Shenzhen, 518060, China

Nonalcoholic fatty liver disease (NAFLD) is characterized by a massive accumulation of lipid droplets (LDs). By using 2D LC-MS/MS, we identified a novel liver-specific lipid droplet-associated protein, 17β-hydroxysteroid dehydrogenase-13 (17β-HSD13). 17β-HSD13 expression was significantly upregulated in the livers of patients and mice with NAFLD. Increased hepatic 17β-HSD13 and its LD surface location were confirmed in type 2 diabetic db/db (diabetic) mice and high-fat diet-fed mice. Adenovirus-mediated hepatic overexpression of human 17β-HSD13 induced a fatty liver phenotype in C57BL/6 mice, with a significant increase in mature sterol regulatory element-binding protein 1 (SREBP1) and fatty acid synthase levels. These findings demonstrate that 17β-HSD13 is a pathogenic protein in the development of NAFLD. To further characterize the molecular mechanisms involved in the regulation of 17β-HSD13 gene expression,we determined the effect of liver X receptors on 17β-HSD13 expression. We found that treatment with T0901317, a non-specific LXR agonist for both LXRα and LXRβ, increased both 17β-HSD13 mRNA and protein levels in cultured hepatocytes. It also significantly upregulated hepatic 17β-HSD13 expression in wild-type (WT) and LXRβ-/- mice but not in LXRα-/- mice. Basal expression of 17β-HSD13 in the livers of LXRα-/- mice was lower than that in the livers of WT and LXRβ-/- mice. Moreover, induction of hepatic 17β-HSD13 expression by T0901317 was almost completely abolished in SREBP-1c-/- mice. Bioinformatics analysis revealed a consensus sterol regulatory element (SRE)-binding site in the promoter region of the 17β-HSD13 gene. A 17β-HSD13 gene promoter-driven luciferase reporter and ChIP assays further confirmed that 17β-HSD13 gene was under direct control of SREBP-1c. Collectively, these findings demonstrate that 17β-HSD13 is a lipogenic lipid-droplet protein which expression is regulated by the LXRα-SREBP1c axis. 17β-HSD13 may represent a potential therapeutic target for the treatment of NAFLD.

Dr. Yu-Hua Tseng



Current Position	Associate Professor of Medicine, Harvard Medical School Investigator, Joslin Diabetes Center, Boston, MA

AFFILIATIONS

2011-present	Principal Faculty, Harvard Stem Cell Institute, Cambridge, MA
2012-present	Investigator, Section on Integrative Physiology and Metabolism, JDC
2014-present	Faculty, Biological and Biomedical Sciences, Harvard Medical School
2014-present	Associate Professor of Medicine, Harvard Medical School

EDUCATION

06/1989	B.S., National Taiwan University, Taipei, Taiwan
06/1991	M.S., National Taiwan University, Taipei, Taiwan
06/1991	Ph.D., University of Wisconsin-Madison, Madison, WI
06/2004	Postdoc., Joslin Diabetes Center/ Harvard Medical School, Boston, MA

RESEARCH INTERESTS

I have dedicated my career to obesity and diabetes research, and have integrated a large variety of cellular, molecular and physiological techniques in my laboratory to understand the mechanisms underlying the regulation of energy homeostasis. I am particularly intrigued by the unique nature of the energy-burning brown fat, and its related 'beige' fat. Targeting brown and beige fat content or activity has therapeutic potential for treating obesity, diabetes and the metabolic syndrome by increasing energy expenditure.

Current ongoing projects in my laboratory aim to determine the role of the biomarkers in brown and beige adipocyte differentiation and functions, as well as to investigate the role of secreted factors, including proteins and lipids, in regulation of brown fat thermogenic activity.

SELECTED PUBLICATION (Pertinent to your presentation)

1. Xue R, Lynes MD, Dreyfuss JM, Shamsi F, Schulz TJ, Zhang H, Huang TL, Townsend KL, Li Y, Takahashi H, Weiner LS, White AP, Lynes MS, Rubin LL, Goodyear LJ, Cypess AM Tseng YH. Functional and Clonal Analyses of Human Brown and White Fat Progenitors Identify Markers that Predict Thermogenic Capacity of Mature Adipocytes. Nat Med 2015; 21(7):760-768.
2. Zhang H, Guan M, Townsend KL, Huang TL, An D, Yan X, Xue R, Schulz TJ, Winnay J, Mori M, Hirshman MF, Kristiansen K, Tsang JS, White AP, Cypess AM, Goodyear LJ, Tseng YH. MicroRNA-455 regulates brown adipogenesis via a novel HIF1an-AMPK-PGC1 α signaling network. EMBO Reports 2015; 16(10):1378-93
3. Townsend KT, Tseng YH. Brown fat fuel utilization and thermogenesis. Trends Endocrinol Metab 2014; 25(4):168-177
4. Cypess AM, White AP, Vernochet C, Schulz TJ, Xue R, Sass C, Huang TL, Roberts-Toler C, Weiner LS, Sze C, Chacko A, Deschamps LN, Herder LM, Truchan N, Glasgow AL, Holman AR, Gavrila A, Hasselgren P-O, Mori MA, Molla M, Tseng YH. Anatomical localization, gene expression profiling, and functional characterization of human neck brown fat. Nat Med 2013; 19(5):635-9
5. Schulz TJ, Huang P, Huang TL, Xue R, McDougall LE, Townsend KL, Cypess AM, Mishina Y, Gussoni E, Tseng YH. Brown fat paucity due to impaired BMP signaling induces compensatory browning of white fat. Nature 2013; 495(7441):379-83

Special Lecture 20-1

Lipid dynamics in brown fat-mediated thermogenesis and energy metabolism

Yu-Hua Tseng[1]

[1]Joslin Diabetes Center and Harvard Medical School, Boston, MA, USA

Obesity is a pandemic and major contributor to metabolic disorders. Increased adiposity is the main characteristic of obesity. In mammals, there are two functionally distinct types of fat tissue: white adipose tissue (WAT), which is specialized for energy storage, and brown adipose tissue (BAT), which dissipates energy for thermogenesis via uncoupling protein 1(UCP1). In addition to the classical brown adipocytes, UCP1-positive "beige" or "brite" adipocytes can be recruited within WAT upon cold exposure. Increasing the amount or activity of brown/beige fat has been considered as an appealing approach for the treatment or prevention of obesity and related metabolic disorders. The energetic processes executed by BAT require a readily available fuel supply, which includes glucose and fatty acids (FAs). FAs become available by cellular uptake, de novo lipogenesis, and from release of fat stored in multilocular lipid droplets in brown adipocytes. BAT also possesses a great capacity for glucose uptake and metabolism, as well as an ability to regulate insulin sensitivity. I will discuss our recent findings on cold-induced lipid dynamics in brown and white adipose tissue of mice using highly sensitive liquid chromatography coupled with mass spectrometry lipidomics analyses.

Dr. Weiping Han

Current Position Deputy Director, Singapore Bioimaging Consortium

AFFILIATIONS

2012-now Deputy Director, Singapore Bioimaging Consortium, A*STAR

2008-now Head, Laboratory of Metabolic Medicine, Singapore Bioimaging Consortium, A*STAR

EDUCATION

1992-1996 Cornell University, Ph.D.

RESEARCH INTERESTS

Regulated exocytosis and membrane trafficking
Diabetes and diabetic complications

SELECTED PUBLICATION (Pertinent to your presentation)

Wu et al., PNAS 112(32):9996-10001, 2015
Lim et al., Nature Comm 6:5951, 2015
Li et al., EMBO Reports 15(6):714-722, 2014
Yang et al., Human Mol Gen 23(2):502-513, 2014
Gustavsson et al., PNAS 105:3992-3997, 2008

S20-2

HOXC10 suppresses browning of white adipose tissues

Weiping Han[1]

[1]Joslin Diabetes Center and Harvard University, Boston, MA, USA

As increased thermogenesis in white adipose tissue (WAT), or browning, promotes energy expenditure, significant efforts have been invested to determine the molecular players involved in this process. Here, we show that HOXC10, a homeobox domain-containing transcription factor expressed in subcutaneous (SubQ) WAT, is a suppressor for genes involved in the process of browning. Ectopic expression of HOXC10 in adipocytes suppresses brown fat genes. Conversely, depletion of HOXC10 in adipocytes and myoblasts increases expression of brown fat genes. HOXC10 protein level inversely correlates with brown fat genes in SubQ WAT of cold exposed mice. Expression of HOXC10 in mice suppresses cold-induced browning in SubQ WAT and abolishes the beneficial effect of cold exposure on glucose clearance. HOXC10 exerts its effect, at least in part, by suppressing PRDM16 expression. Taken together, we propose that HOXC10 is a key negative regulator of the process of browning in WAT.

Prof. Youfei Guan

Current Position Vice President of Dalian Medical University
Dean of Advanced Institute for Medical Science (AIMS)

AFFILIATIONS

2015,05-present	Vice President of Dalian Medical University Dean of Advanced Institute for Medical Sciences (AIMS)
2013,04- 2015,05	Director of Shenzhen University Health Sciences Medical Center Dean of Shenzhen University Medical College Distinguished Professor, Director of AstraZeneca-Shenzhen University Joint Institute of Nephrology
2008, 07- 2013,05	Associate Dean for Education, School of Basic Medical Sciences Peking University Health Science Center
2006, 08-2013.5	Chair of Department of Physiology and Pathophysiology Peking (Beijing) University Health Science Center
2002,09-2013.5	Professor of Physiology Peking (Beijing) University Health Science Center
1999,09-2002,09	Assistant Professor of Medicine, Division of Nephrology, Department of Medicine Vanderbilt University Medical Center
1989,08-1991,07	Lecturer and Resident Physician, Division of Nephrology, Department of Internal Medicine The Affiliated Hospital of Nantong Medical College

EDUCATION

1994-1999	Division of Nephrology, Department of Medicine, Vanderbilt University Medical Center, Postdoctoral Research Fellow
1991-1994	Institute of Nephrology, Beijing Medical University, Ph.D. in Nephrology
1986-1989	Department of Internal Medicine, Nantong Medical College, Master degree in Nephrology
1981-1986	Department of Internal Medicine, Nantong Medical College, M.D. in Medicine

RESEARCH INTERESTS

Prof. Guan's research mainly focuses on the biological roles of membrane-associated prostaglandin receptors and related nuclear receptor transcription factors in metabolic syndrome , especially the pathogeneses and therapies of diabetes, hypertension, fatty liver disease and their complications.

SELECTED PUBLICATION (Pertinent to your presentation)

1. Gao M, Cao R, Du S, Jia X, Zheng S, Huang S, Han Q, Liu J, Zhang X, Miao Y, Kang J, Gustafsson JÅ, Guan Y*. Disruption of prostaglandin E2 receptor EP4 impairs urinary concentration via decreasing aquaporin 2 in renal collecting ducts. Proc Natl Acad Sci U S A. 2015 Jul 7;112(27):8397-402. doi: 10.1073/pnas.1509565112 ;
2. Su W, Wang Y, Jia X, Wu W, Li L, Tian X, Li S, Wang C, Xu H, Cao J, Han Q, Xu S, Chen Y, Zhong Y, Zhang X, Liu P, Gustafsson JÅ, Guan Y*. Comparative proteomic study reveals 17 β-HSD13 as a pathogenic protein in nonalcoholic fatty liver disease. Proc Natl Acad Sci U S A. 2014 Aug 5;111(31):11437-42;

S20-3

Inactivation of the E-Prostanoid 3 Receptor gene causes adiposity and insulin resistance via altering white adipose tissue metabolism

Hu Xu[1], Xiaoyan Zhang[1], Youfei Guan[1]

[1]Advanced Institute for Medical Sciences, Dalian Medical University, Dalian, China

Prostaglandins E2 (PGE2) is the predominant prostaglandin produced in white adipose tissue (WAT) and plays an important role in adipogensis and adiposity. Among four PGE2 receptors, the EP3 receptor is most abundantly expressed in WAT. In mice, the EP3 gene gives rise to three isoforms, namely EP3α, EP3β and EP3γ, which differ only at their C-terminal tails and are produced by alternative splicing. To date, the role of the EP3 and each of its isoforms in the regulation of WAT remains incompletely characterized. In the present study, we found that the expression of all EP3 isoforms were significantly down-regulated in WAT of several obese murine models including db/db mice and high-fat diet-induced obese mice. Genetic ablation of total EP3 receptor gene (EP3-/- mice) or selective deletion of the EP3α and EP3γ isoforms (EP3β mice) led to an obese phenotype, with increased food intake, decreased motor activity, reduced insulin sensitivity and imbalanced lipid metabolism featured as enhanced adipogenesis. Terminal differentiation of preadipocytes and mouse embryonic fibroblasts (MEFs) was markedly facilitated by either pharmacological blockade of the EP3 receptor or genetic targeting of the EP3α and EP3γ isoforms. The inhibition of adipogenesis by the EP3 and the EP3α and EP3γ was mainly through the cAMP/PKA/CREB pathway. In addition, the EP3-/- and EP3β mice also exhibited increased lipolysis in WAT, which is mainly mediated by the suppression of the cAMP/PKA/HSL pathway. Taken together, the EP3 receptor is critical for the maintenance of normal WAT function, where inactivation of the EP3 promotes adiposity via facilitating adipogenesis and increases insulin resistance via enhancing lipolysis.

Prof. Tae-Sik Park

Current Position Associate Professor

AFFILIATIONS

2002-2005	Postdoctoral scientist, Cardiovascular Pharmacology, Pfizer. Ann Arbor, MI, USA
2005-2007	Associate Research Scientist, Department of Medicine, Columbia University, New York, NY, USA
2007-present	Associate Professor, Department of Life Science, Gachon University, Sungnam, South Korea

EDUCATION

1989-1995	B.S. Department of Life Science, Korea University, Seoul, Korea
1995-2001	Ph.D Department of Food Science, Rutgers University, New Brunswick, NJ, USA

RESEARCH INTERESTS

Sphingolipid biosynthesis
Hepatosteatosis
Obesity and diabetes
Natural product

SELECTED PUBLICATION (Pertinent to your presentation)

1. Lee SY, Hong IK, Kim BR, Shim SM, Sung Lee J, Lee HY, Choi CS, Kim BK, Park TS. Activation of sphingosine kinase 2 by endoplasmic reticulum stress ameliorates hepatic steatosis and insulin resistance in mice. Hepatology. 2015. 62(1):135-46
2. Lee KP, Won KJ, Lee DH, Lee DY, Jung SH, Baek S, Park TS, Kim B. DJ-1-mediated upregulation of serine palmitoyltransferase 2 controls vascular neointima via S1P autocrine. Int J Cardiol. 2015 . 191:220-2.
3. Yang UJ, Maeng H, Park TS, Shim SM. Houttuynia cordata Extract Improves Physical Endurance Performance by Regulating Endothelial Production of Nitric Oxide. J Med Food. 2015. 18(9):1022-31.
4. Tran NK, Kwon JE, Kang SC, Shim SM, Park TS. Crassaostrea gigas oyster shell extract inhibits lipogenesis via suppression of serine palmitoyltransferase. Nat Prod Commun. 2015. 10(2):349-52.

S20-4

Regulation of hepatosteatosis and obesity by sphingolipids

Tae-Sik Park[1]

[1]Department of Life Science, Gachon University, Sungnam, Gyeonggido, Korea

Sphingolipids are implicated in etiology of chronic metabolic diseases including cardiovascular diseases and diabetes. In this study, we investigated whether de novo sphingolipid biosynthesis is associated with development of adipose tissues. SPTLC2, a subunit of serine palmitoyltransferase, was transcriptionally upregulated in adipose tissues of obese mice and during differentiation of 3T3-L1 cells. SPTLC2 knockdown suppressed expression of adipogenic genes and lipid accumulation in 3T3-L1 cells. To confirm this, we have developed adipocyte-specific SPTLC2 deficient (aSPTLC2 KO) mice that have lipodystrophic phenotype even with high fat diet feeding. The cell size and mass of adipocyte tissue were reduced dramatically and expression of adipogenic genes was downregulated. Whereas, the fatty acids destined to the adipose tissue were accumulated by increased uptake into liver and caused hepatic steatosis. aSPTLC2 KO mice fed a high fat diet did not increase the body weight but fasting glucose levels were elevated and developed systemic insulin resistance. Although adenoviral SPHK2 overexpression in liver did not recover lipodystrophic phenotype, the floxed mice showed increased fat mass. This is in part due to downregulation of S1P receptor 1 in adipose tissue of aSPTLC2 KO mice and SPTLC2-suppressed 3T3-L1 cells. Collectively, our observations suggest that tight regulation of de novo sphingolipid biosynthesis and S1P signaling plays an important role in adipogenesis and hepatosteatosis.

Dr. Kyle Hoehn

Current Position Lab Head

AFFILIATIONS

2014-Present	University of New South Wales, Sydney, Australia
2009-Present	University of Virginia, Charlottesville, Virginia, USA
2005-2009	Garvan Institute of Medical Research, Sydney, Australia

EDUCATION

2000-2005	PhD in Biochemistry, Colorado State University, Colorado, USA

RESEARCH INTERESTS

The Hoehn laboratory investigates the pathophysiology and treatment of obesity-related disorders including insulin resistance and diabetes.

SELECTED PUBLICATION (Pertinent to your presentation)

1. Kenwood BM, ⋯ and Hoehn KL. Identification of a novel mitochondrial uncoupler that does not depolarize the plasma membrane. Molecular Metabolism. Nov 28;3(2):114-23. 2014.
2. Chow JD, ⋯ and Hoehn KL. Genetic inhibition of hepatic acetyl-CoA carboxylase activity increases liver fat and alters global protein acetylation. Molecular Metabolism. Mar 12;3(4):419-31. 2014.
3. Hoehn KL, Turner N, ⋯ James DE, and Cooney GJ. Acute or chronic upregulation of mitochondrial fatty acid oxidation has no net effect on whole-body energy expenditure or adiposity. Cell Metabolism. Jan;11(1):70-6. 2010.
4. Hoehn KL, ⋯ and James DE. Insulin resistance is a cellular antioxidant defense mechanism. PNAS. Oct 20;106(42):17787-92. Sep 30. 2009.

S20-5

Targeting fat metabolism and energy expenditure in metabolic disease

Kyle Hoehn[1]

[1]Garvan Institute of Medical Research, Sydney, Australia

Excess fat accumulation in peripheral tissues is a risk factor for insulin resistance and type 2 diabetes. Calorie restriction and exercise are the safest and most effective ways to decrease excess lipid storage; however, poor patient compliance and disability limit the effectiveness of these approaches. Therefore, there is an unmet medical need to develop drugs that promote fat loss. My laboratory has investigated three approaches to reduce fat mass including increasing fat oxidation, reducing lipogenesis, and increasing energy expenditure. We have found that increasing fat oxidation or reducing lipogenesis by targeting acetyl-CoA carboxylase enzymes is not sufficient to promote fat loss because tissues compensate by altering carbohydrate metabolism and fat uptake. However, increasing energy expenditure by mitochondrial uncoupling represents a viable approach if safety can be improved through the development of mitochondria-specific small molecule mitochondrial uncouplers.

Prof. David E James

Current Position

Leonard P Ullmann Chair in Molecular Systems Biology

Domain Leader for Biology at the Charles Perkins Centre, Sydney University

David James was awarded a PhD in 1985 from UNSW.

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

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

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

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

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

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

S24-1

Molecular mapping of insulin action and insulin resistance

David E. James[1]

[1]Charles Perkins Centre, School of Life and Environmental Science, Sydney University, Sydney, Australia

We have utilized global unbiased phosphoproteomic analysis of insulin responsive tissues to construct a large scale map of the insulin regulated signaling network. This has revealed key regulatory nodes together with novel substrates of major insulin regulated kinases such as Akt. Using machine learning we have discovered several new Akt substrates that have revealed novel aspects of insulin action, several of which will be discussed. We have also applied similar approaches to examine changes in insulin signaling and the total proteome in adipocytes rendered insulin resistant using a range of physiological perturbations. These studies have revealed novel insights into the mechanism of insulin resistance, which appears to involve the induction of an insulin sensitive pathway in adipocytes that impairs insulin regulated glucose metabolism.

Dr. Darren Henstridge

Current Position
Senior Research Officer
Cellular and Molecular Metabolism Laboratory Baker IDI Heart and Diabetes Institute
Melbourne, VIC, Australia

AFFILIATIONS

2007-2016	Baker IDI Heart and Diabetes Institute
2015-2016	Monash University

EDUCATION

2004-2007	Monash University: PhD
2003	Monash University: BSc Honours
2000-2002	Monash University: BSc

RESEARCH INTERESTS

Metabolism, Type 2 diabetes, obesity, Alzheimer's disease, exercise physiology

S24-2

The metabolic consequences of fecal microbiota transplantation (FMT) in mice

Jeroen Zoll[1], Sarah E Heywood[1], Helene L Kammoun[1], Jessica Marshall[1], Emma Estevez[1,2], Borivoj Zivanovic[1], Tamara L Allen[1], Mark A Febbraio[1,2], Darren C Henstridge[1]

[1]Baker IDI Heart and Diabetes Institute, Melbourne, Australia
[2]Garvan Institute of Medical Research, Sydney, Australia

Background: The gastrointestinal microbiota is a community of microorganisms that reside in the digestive tract. Studies have suggested that the microbiota composition may contribute to the development of obesity and the metabolic syndrome. Exercise has been shown to alter the microbiota composition by increasing diversity and altering specific bacteria species. We tested whether fecal microbiota transplantation (FMT) from exercise-trained mice to recipient mice alters body composition and metabolism.

Methods: C57BL6/J mice were fed a chow or high fat diet (HFD) for 4-weeks to induce obesity and insulin resistance. Mice were further divided into sedentary or exercise training groups (treadmill training for 6-weeks) while maintaining their respective diets (four groups of donor mice; chow sedentary or exercised and HFD sedentary or exercised). Recipient mice were inoculated with the faeces from the respective donor groups once a week for 6-weeks and body composition and metabolism assessed.

Results: While the HFD led to glucose intolerance and obesity, exercise training resulted in a small decrease in body fat and improved glucose tolerance. FMT from the donor groups did not alter body composition (weight, fat mss, lean mass) in any of the recipient groups. Unexpectedly given the lack of an effect on adiposity, glucose tolerance was disrupted in the mice inoculated with faeces derived from mice on a HFD irrespective of exercise status and this was associated with a decrease in insulin-stimulated glucose clearance into white adipose tissue and the large intestine.

Conclusion: FMT can transmit HFD-induced aspects of disrupted glucose metabolism to recipient mice independently of any change in adiposity. However, FMT from exercise trained donor mice appears to elicit no beneficial effect.

Disclosure: No conflict of interest

Prof. Aimin Xu

Current Position Director

AFFILIATIONS

2013-	Director, State Key Laboratory of Pharmaceutical Biotechnology, University of Hong Kong
2011-	Professor, Department of Medicine, and Department of Pharmacology and Pharmacy, University of Hong Kong

EDUCATION

1984-1989	Bachelor of Medicine, Anhui Medical University, China
1989-1992	Master of Medicine, the third Medical University, China
1996-1999	PhD in Biochemistry, University of Auckland, New Zealand

RESEARCH INTERESTS

Obesity and its related medical complications; adipocyte biology, biomarker discovery and assay development

SELECTED PUBLICATION (Pertinent to your presentation)

1. Hui X, Gu P, Zhang J, Nie T, Pan Y, Wu D, Feng T, Zhong C, Wang Y, Lam KS, Xu A*, Adiponectin Enhances Cold-Induced Browning of Subcutaneous Adipose Tissue via Promoting M2 Macrophage Proliferation. Cell Metabolism. 2015 22(2):279-90
2. Lin Z, .. Li X, Xu A*. Fibroblast Growth Factor 21 Prevents Atherosclerosis by Suppression of Hepatic Sterol Regulatory Element-Binding Protein-2 and Induction of Adiponectin in Mice. Circulation, 2015; 131(21):1861-71
3 Ye D, .. Lam KSL, Xu A*. Fibroblast growth factor 21 protects against acetaminophen-induced hepatotoxicity by potentiating peroxisome proliferator-activated receptor coactivator protein-1 α -mediated antioxidant capacity in mice. Hepatology. 2014 Sep;60(3):977-989.
4. Liang Q, Z⋯, Lam KS, Xu A. FGF21 Maintains Glucose Homeostasis by Mediating the Cross Talk Between Liver and Brain During Prolonged Fasting. Diabetes. 2014 Dec;63(12):4064-75

5. Lin Z, Tian H, Lam KS.., Xu A*,. Adiponectin mediates the metabolic effects of FGF21 on glucose homeostasis and insulin sensitivity in mice. Cell Metabolism. 2013, 17(5) 779-789

S24-3

Chronic exercise alleviates obesity-related metabolic dysfunction by enhancing FGF21 sensitivity in adipose tissues

Aimin Xu[1]

[1]State key laboratory of Pharmaceutical Pharmacology, and Department of Medicine, University of Hong Kong, Hong Kong

Chronic exercise has beneficial effects on protecting against obesity-related metabolic dysfunction. However, the underlying molecular mechanisms are incompletely understood. Fibroblast growth factor 21 (FGF21) is a hormone mainly derived from liver and acts on adipocytes by activating the FGF21 receptor complex (FGFR1 and β-Klotho)-mediated intracellular signalling. FGF21 has pleiotropic effects on regulating glucose homeostasis, lipid metabolism and insulin actions. Here we show that chronic exercise improves FGF21 sensitivity by upregulating the expression of FGFR1 and β-Klotho in adipose tissues of diet-induced obese mice. FGF21 knockout mice were refractory to several benefits of chronic exercise, including alleviation of glucose intolerance and insulin resistance. Exercised FGF21 knockout mice show augmented lipolysis and free fatty acids (FFA) accumulation in liver and muscle compared with the wild type littermates. Furthermore, the effects of chronic exercise on enhancement of adiponectin production and fatty acids oxidation were abrogated in FGF21 knockout mice. Additionally, adipose tissue β-Klotho specific knockout mice are also refractory to the beneficial effects of exercise on attenuating diet-induced systemic lipotoxicity, glucose intolerance and insulin resistance. Collectively, chronic exercise-induced improvement of FGF21 sensitivity in adipose tissues can prevent excessive FFA influx and promote FFA oxidation in liver and muscle, leading to reduced lipotoxicity and enhanced systemic glucose tolerance and insulin sensitivity.

Dr. Rinki Murphy

Current Position	Endocrinologist
	Senior Lecturer in Medicine
	University of Auckland, New Zealand

AFFILIATIONS

2008	Adult diabetes physician at Auckland District Health board
2008	Adolescent diabetes physician at Counties Manukau District Health Board
2008	Senior Lecturer in Medicine, University of Auckland
2013	Principal investigator at Maurice Wilkins Centre

EDUCATION

1999	MBChB, University of Auckland
2005	FRACP, Adult medicine and endocrinology
2007	PhD, Genetics and epgigenetics of young adult onset diabetes, University of Exeter and Plymouth, UK

RESEARCH INTERESTS

Broad clinical research expertise in diabetes and obesity, particularly (a) monogenic diabetes and severe insulin resistance, (b) treatments for obesity and diabetes, including probiotics, bariatric surgery, text mobile support, hepatic denervation, fecal transplantation (c) risk factors for diabetes and obesity, involving multiple prospective birth and adult cohorts

SELECTED PUBLICATION (Pertinent to your presentation)

1. Murphy R. Evennett NJ, Clarke MG, Robinson SJ, Humphreys L, Jones B, Kim DD, Cutfield R, Plank LD, Hammodat H, Booth MWC. Sleeve gastrectomy versus Roux-en-Y gastric bypass for type 2 diabetes and morbid obesity: double-blind randomised clinical trial protocol. BMJ Open 2016;6:e011416.
2. Gounder ST, Wijayanayaka D, Murphy R, Armstrong D, Cutfield R, Kim DD, Clarke MG, Evennett NJ, Humphreys ML, Robinson SJ, Booth MWC. Costs of bariatric surgery in a RCT comparing Roux-en-Y gastric bypass vs sleeve gastrectomy in morbidly obese diabetic patients. NZMJ in press 2016.
3. Nemati R, Lu J, Tura A, Smith G, Murphy R. Acute changes in non-esterifed free fatty acids in patients with type 2 diabetes receiving bariatric surgery. Obesity Surg 2016: doi 10.1007/s11695-016-2323-9
4. Thomas F, Smith G, Babor R, Booth M, Beban G, Chase JG, Murphy R. Differential acute impacts of sleeve gastrectomy, Roux-en-Y gastric bypass surgery and matched caloric restriction diet on insulin secretion, insulin effectiveness and non-esterified fatty acid levels among patients with type 2 diabetes. Obesity Surgery 2016 doi:10.1007/s11695-015-2083-3
5. Murphy R, Jiang Y, Booth M, Babor R, MacCormick A, Beban G, Barnes R, Vincent A. Progression of diabetic retinopathy after bariatric surgery. Diab Med 2015 doi: 10.1111/dme.12727
6. Jullig M, Yip S, Xu A, Smith G, Middleditch M, Booth M, Babor R, Beban G, Murphy R. Lower Fetuin A, retinol-binding protein 4 and several metabolites after gastric bypass compared to sleeve gastrectomy in patients with type 2 diabetes. PLOS one

S24-4

Laparoscopic sleeve gastrectomy versus Roux-en-Y gastric bypass for the treatment of type 2 diabetes: 12 month results of a double-blind, randomised trial

R. Murphy[1], N.J. Evennett[2], M.G. Clarke[2], S.J. Robinson[2], B. Jones[2], D.D. Kim[3], R. Cutfield[3], L.D. Plank[4], H. Hammodat[2], and M.W.C. Booth[2]

[1]Department of Medicine, University of Auckland, Auckland, New Zealand
[2]Department of Surgery, North Shore Hospital, Auckland, New Zealand
[3]Department of Endocrinology, North Shore Hospital, Auckland, New Zealand
[4]Department of Surgery, University of Auckland, Auckland, New Zealand

Introduction: It is unclear which of the two most commonly performed types of bariatric surgery, laparoscopic sleeve gastrectomy (LSG) or laparoscopic Roux-en-Y gastric bypass (LRYGB), is most effective for obese patients with type 2 diabetes (T2D).

Objectives: To examine the comparative ad interim effectiveness of LSG or LRYGB at 1 year in achieving improvement in T2D using different HbA1c thresholds.

Methods: Single-centre, double-blind (assessor and patient), parallel, randomized, clinical trial conducted in Auckland, New Zealand. Eligibility criteria included age 20-55 years, T2D of at least 6 months duration and BMI 35-65kg/m^2 for at least 5 years. Recruitment of 114 patients completed in October 2014. Randomization 1:1 to LSG (n=58) or LRYGB (n=56) used random number codes disclosed to the operating surgeon after induction of anesthesia. A standard medication adjustment schedule was used during post-operative metabolic assessments scheduled for 5 years when primary outcome of T2D remission defined by HbA1c <42mmol/mol without diabetes medications, is to be analysed.

Results: Ad interim analysis at 1 year showed 109/114 completed 12 month follow up. Participants included 17% Maori, 8% Pacific and 55% were women. Mean (±standard deviation) HbA1c pre-operatively was 63mmol/mol ±16 with 29% on insulin therapy and 65% on oral glucose lowering therapy alone. Proportions achieving HbA1c <39mmol/mol, <42mmol/mol, <48mmol/mol, or <53mmol/mol without the use of diabetes medication in LSG vs LRYGB were 43% vs 38% (p=0.56), 49% vs 52% (p=0.85) and 72% vs 75% (p=0.83), and 77% vs 80% (p=0.82) respectively. Mean (±standard deviation) weight loss at 1 year was less after LSG than after LRYGB: 34.0±13.1kg and 39.6±11.6 kg respectively, (p=0.02).

Conclusions: LSG and LRYGB achieve similar prevalence of T2D remission despite significantly greater weight loss at 1 year after LRYGB. Longer term follow up is required to determine the durability of these results.

Dr. Susumu Seino

Current Position
Professor and Head
Division of Molecular and Metabolic Medicine Kobe University Graduate School of Medicine

AFFILIATIONS

Dr. Susumu Seino graduated from Kobe University School of Medicine, Japan (received M.D., 1974). After being trained as resident, clinical fellow and research fellow, he received Doctor of Medical Science (D.M.Sci.=Ph.D.) from Kyoto University in 1982. He then moved to the United States as postdoctoral fellow and research associate at University of Michigan and at University of Chicago, and, eventually, held faculty position (Research Associate Professor) at University of Chicago. While Dr. Seino stayed in the States, he (with Prof. Graeme Bell) cloned many important genes involved in glucose metabolism, including various human glucose transporters, human insulin receptor gene and its mutation in diabetes with severe insulin resistance (with Prof. Don Steiner), somatostatin receptors, and many others. After spending 10 years in the U.S., he returned to Japan as a full professor at Chiba University in 1991, and moved to Kobe University in 2003.

Dr. Seino pioneered to apply molecular biology to ß-cell research. He has been investigating mechanisms of insulin secretion. Dr. Seino's group first discovered that ATP-sensitive K^+ channel, a crucial molecule for glucose-induced and sulfonylurea-induced insulin secretions, is composed of the K^+ channel member Kir6.2, and the sulfonylurea receptor SUR1. This study provided the ground work for discovery of neonatal diabetes later. His group has also found Epac2 (or cAMP-GEF II) plays a critical role in incretin / cAMP-induced insulin secretion. He recently found that ß-cell glutamate produced through glucose metabolism acts as a key signal in incretin /cAMP-induced insulin secretion. He has published more than 360 peer-reviewed papers and his citation index is more than 23,000.

He received many awards and honors including Asia and Oceania Medal (currently International Medal) from the Society for Endocrinology in UK, Hagedorn Award from the Japan Diabetes Society, Donald Steiner Award from University of Chicago and Albert Renold Prize from EASD. He was also granted the Medal of Honor with Purple Ribbon by the Emperor of Japan in 2011.

Special Lecture 30-1

β-cell glutamate signaling in insulin secretion: the physiological and pathophysiological roles

Susumu Seino[1]

[1]Division of Molecular and Metabolic Medicine, Kobe University Graduate School of Medicine, Kobe, Japan

Insulin secretion from pancreatic β-cells plays the central role in the maintenance of glucose homeostasis; impaired insulin secretion contributes to the pathogenesis and pathophysiology of diabetes. Glucose-induced insulin secretion (GIIS) is the primary mechanism of insulin secretion, in which glucose metabolism in β-cells is prerequisite. In addition to GIIS, neuro-hormonal amplification of insulin secretion is also critical in normal regulation of insulin secretion. Incretins such as glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), which are released from enteroendocrine cells in response to meal ingestion, potentiate insulin secretion primarily through cAMP signaling in pancreatic β-cells. The glucose-dependent action of incretin in insulin secretion provides the basis for the recently developed incretin-based anti-diabetic drugs. However, the mechanism of the link between glucose metabolism and incretin/cAMP action in insulin secretion was not clear. Using a metabolomics-based approach, we recently found that cytosolic glutamate produced through the malate-aspartate shuttle links glucose metabolism to cAMP action in insulin release, acting as a key cell signal in incretin-induced insulin secretion (IIIS). We also investigated the pathophysiological role of glutamate signaling in insulin secretion using various rat models of diabetes and obesity. The insulin secretory responses to glucose and the incretins GLP-1 and GIP were assessed by batch incubation of isolated pancreatic islets. Contents of glutamate isotopomers were measured by 13C-enrichment analysis with uniformly-labeled [U-13C]-glucose as a substrate using capillary electrophoresis mass spectrometry (CE-MS). Pancreatic islets of control Wistar rats exhibited both GIIS and IIIS. However, in islets of Goto-Kakizaki (GK) rats, a model of diabetes with impaired insulin secretion, GIIS was markedly decreased while IIIS was somewhat retained. In contrast, in Zucker fatty (ZF) rats, a model of obesity, GIIS was evident, but there was no IIIS. The islets of Zucker fatty diabetes mellitus rats (ZFDM, a model of diabetes with obesity) at 11 weeks of age were found to comprise a mixture of relatively larger and smaller islets. Interestingly, while the smaller islets (<100 m in diameter) exhibited IIIS, the larger islets (>300m) did not. Glutamate production in GK islets was slightly but significantly increased by glucose stimulation. In contrast, glutamate production in neither ZF islets nor the larger ZFDM islets was increased by glucose stimulation, although it was increased in the smaller islets of ZFDM rats. These data indicate that IIIS is well correlated with glutamate production by glucose in β-cells. Our findings serve to clarify the mechanism of impaired IIIS in type 2 diabetes and to suggest novel therapeutic strategies.

Prof. Hong Wanjin

Current Position

Professor and Executive Director, Institute of Molecular and Cell Biology, A*STAR, Singapore

AFFILIATIONS

2008 -	Editor-in-Chief, Bioscience Reports, Portland Press for UK Biochemical Society
2005 -	Editorial Board, Traffic
2011 -	Academic Editor, PLoS ONE

EDUCATION

1988 - 1989	Postdoctoral fellow, The Department of Biological Sciences, State University of New York at Buffalo, USA (under the supervision by Dr. Darrell Doyle)
1983 - 1987	Ph.D. student in Cell Biology, The Department of Biological Sciences, State University of New York at Buffalo, USA (under the supervisor by Dr. Darrell Doyle)
1978 - 1982	B.S. student, Biology Department, Xiamen University, Fujian, China

RESEARCH INTERESTS

Protein Trafficking and Cancer Cell Biology

SELECTED PUBLICATION (Pertinent to your presentation)

1. Li, H., Wei, S., Cheng, K., Gounko, N.V., Ericksen, R.E., Xu, A., Hong, W., and Han, W. BIG3 inhibits insulin granule biogenesis and insulin secretion. EMBO Rep. (2014) 15, 714-722. . (Identified BIG3 as a negative regulator of insulin secretion in beta cells)
2. Loo, L.S., Tang, N., Al-Haddawi, M., Dawe, G.S., and Hong, W. A role of sorting nexin 27 in AMPA receptor trafficking. Nature Commun. (2014) Jan 24;5:3176. doi: 10.1038/ncomms4176. (Revealed a role of SNX27 in postsynaptic recycling of neurotransmitter receptors)
3. Zhu, D., Zhang, Y., Lam, P.P., Dolai, S., Liu, Y., Cai, E.P., Choi, D., Schroer, S.A., Kang, Y., Allister, E.M., Qin, T., Wheeler, M.B., Wang, C.C., Hong, W., Woo, M., Gaisano, H.Y. Dual Role of VAMP8 in Regulating Insulin Exocytosis and Islet β Cell Growth. Cell Metabolism (2012) 16, 238-249.
4. Zong, H., Wang, C.C., Vaitheesvaran, B., Kurland, I.J., Hong, W., and Pessin J.E. Enhanced energy expenditure, glucose utilization and insulin sensitivity in VAMP8 null mice. Diabetes (2011) 60, 30-38.
5. Zhao, P., Yang, L., Lopez, J.A., Fan, J., Burchfield, J.G., Bai, L., Hong, W., Xu, T., and James, D.E. Variations in the requirement for v-SNAREs in GLUT4 trafficking in adipocytes. J. Cell Sci. (2009) 122, 3472-8340.
6. Wang, C.C., Ng, C.P., Lu, L., Atlashkin, V., Zhang, W., Seet, L.F., and Hong, W. A role of endobrevin/VAMP8 in regulated exocytosis of pancreatic acinar cells. Dev. Cell (2004) 7, 359-371.

S30-2

Intracellular membrane trafficking and insulin secretion

Wanjin Hong[1]

[1]Institute of Molecular and Cell Biology, A*STAR, Singapore

My lab has been interested in defining the underlying mechanisms governing membrane trafficking in mammalian cells. Over the years, we have identified over half of mammalian SNARE proteins, defined several SNARE complexes and identified downstream effectors for small GTPases Arl1, Rab34 and Rab7. In addition, we have discovered that PX domain is a novel motif capable of interacting with phosphoinositides. Other regulators of membrane trafficking such as BIG3 and p125A and Tom1L1 were discovered. In addition to the overview of the research, I will discuss our work on VAMP8 and BIG3 in insulin secretion.

Dr. Melkam Kebede

Current Position Research Fellow

AFFILIATIONS

2015-Current	Research Fellow, Charles Perkin Centre, University of Sydney, Sydney, Australia
2012-2015	Post-Doctoral Research Associate, Department of Biochemistry, University of Wisconsin, Madison, USA
2007-2012	Post-Doctoral Research Fellow, Montreal Diabetes Research Center, Montreal, Canada

EDUCATION

2004-2007	PhD, Department of Medicine, University of Melbourne, Melbourne, Australia
1999-2003	Bachelor of Science, Degree with Honours, University of Melbourne, Melbourne, Australia

RESEARCH INTERESTS

Islet Biology
Obesity-induced type 2 diabetes
Proinsulin processing
Trafficking of insulin secretory granules
Lysosomes

SELECTED PUBLICATION (Pertinent to your presentation)

1. Melkam A. Kebede, Angie T. Oler, Trillian Gregg, Allison J. Balloon, Adam Johnson, Kelly Mitok, Mary Rabaglia, Kathryn Schueler, Donald Stapleton, Candice Thorstenson, Lindsay Wrighton, Brendan J. Floyd, Oliver Richards, Summer Raines, Kevin Eliceiri, Nabil G. Seidah, Christopher Rhodes, Mark P. Keller1, Joshua L. Coon, Anjon Audhya, Alan D. Attie. Sorcs1 is Necessary for Normal Insulin Secretory Granule Biogenesis in Metabolically Stressed Beta-Cells. J Clin Invest. 2014 Oct 1; 124 (10) 4242-4256.
2. Ghislain, J.; Fontes, G.; Tremblay, C.; Kebede, M. A.; Poitout, V. Dual reporter-beta-cell specific male transgenic rats for the analysis of beta-cell functional mass and enrichment by flow cytometry Endocrinology (2015) en20151550 P13253412
3. Kebede MA and Attie AA. Insights into obesity and diabetes at the intersection of mouse and human genetics. Trends Endocrinol Metab. 2014 Oct;25(10):493-501.
4. O'Halloran TV, Kebede M, Philips SJ, Attie AD. Zinc, insulin, and the liver: a ménage à trois. J Clin Invest. 2013 Oct 1;123(10):4136-9.
5. M. Kebede, M. Ferdaoussi, A. Mancini, T. Alquier, R. N Kulkarni, M. D Walker, V. Poitout. Glucose activates free fatty acid receptor 1 gene transcription via phosphatidylinositol-3-kinase-dependent O-GlcNAcylation of pancreas-duodenum homeobox-1. Proc Natl Acad Sci U S A. 2012 Feb 14;109(7):2376-81.

S30-3

Sorcs1: From diabetes quantitative trait locus to cellular function

Melkam A. Kebede[1]

[1]School of Life and Environmental Sciences, Charles Perkin Centre University of Sydney, Sydney, Australia

Type 2 diabetes occurs when pancreatic β-cells are unable to produce enough insulin to meet the increased demand for insulin brought about by insulin resistance. Most of the genetic loci that have been discovered through genome-wide association studies in humans point to defects that affect β-cell mass or β-cell function. Using mouse genetics, we positionally cloned a diabetes susceptibility locus and identified the causal gene, Sorcs1. Subsequent studies show that Sorcs1 is involved in type 2 diabetes and diabetes complications in humans. Sorcs1 is a member of the Vacuolar protein sorting-10 (Vps10) gene family. Vps10 was originally discovered in yeast where it is a receptor for carboxypeptidase Y and is essential for its transport to the yeast vacuole (equivalent to the mammalian lysosome). We derived a mouse with a deletion of the Sorcs1 gene. When made obese, the mouse develops severe diabetes. This is due to a defect in the production of insulin granules and a dramatic increase in the post-translational degradation of insulin. Our preliminary studies point to a second vps10 protein, which plays an important role in post-translational degradation of proteins, by targeting to the lysosome. We are currently investigating the role of this second vps10 family member on insulin degradation in pancreatic β -cells. In this seminar I will describe the methods we used to identify Sorcs1 as a T2D gene and describe what we have learn from the phenotype of the Sorcs1 KO mouse and our preliminary data on receptor mediated degradation of insulin in pancreatic β-cells.

Prof. Peter Shepherd

Current Position
Professor of Cellular Signalling, Dept of Molecular Medicine
University of Auckland

AFFILIATIONS

1990-1993	Fellow, Beth Israel Hosp, Harvard Med School, Boston
1993-1996	Fellow, Clinical Biochemistry, Cambridge University
1996-2004	Faculty, University College London
2004-	Professor, University of Auckland, NZ

EDUCATION

1989	PhD, Massey University, NZ

RESEARCH INTERESTS

Cell signaling pathways in disease, drug discovery and development

SELECTED PUBLICATION (Pertinent to your presentation)

1. Emmanuelle Cognard, Coralie G. Dargaville, Deborah L. Hay and Peter R. Shepherd, Identification of a pathway by which glucose regulates β-catenin signalling via the cAMP/protein kinase A pathway in β-cell models , Biochemical Journal (2013) 449 803-811 doi:10.1042/BJ20121454

S30-4

New insights into mechanisms regulating insulin secretion

Peter Shepherd[1]

[1]University of Auckland, New Zealand

The capacity of β-cells to secrete insulin is reduced during the development of type-2 diabetes but the mechanisms regulating insulin secretion in response to glucose and incretins remains only partially understood. This presentation will describe our evidence indicating that β-catenin and proteins that associate with it represent an important component of the nutrient responsive insulin secretory mechanism. We find that β-catenin is necessary for insulin secretion in response to both these glucose and GLP-1. What is more we find β-catenin levels change in β-cells in response to changes in glucose levels indicating this is part of the way β-cells regulate insulin secretion in response to changes in glucose. A potential role for this in vivo is supported by the finding that number of SNPs associated with increased risk of type-2 diabetes have been identified in genes that regulate β-catenin function (e.g. TCF7L2, CTNNA2, BTRC, IGFBP2 and MAGI1). Our mechanistic information suggests that β-catenin is acting as rheostat to regulate the amount of insulin that can be secreted at any one time. This presentation will describe the evidence supporting this.

Dr. Kohjiro Ueki

Current Position

Director, Diabetes Research Center, Research Institute, National Center for Global Health and Medicine

Education and Appointments

1987	M.D. in Faculty of Medicine, the University of Tokyo
1987-1988	Resident in Internal Medicine, Tokyo University Hospital, Tokyo
1988-1989	Resident in Internal Medicine, Jichi Medical School Hospital, Tochigi
1990-1991	Clinical Fellow, the Third Department of Internal Medicine, the University of Tokyo, Tokyo
1991-1997	Clinical and Research Staff, the Third Department of Internal Medicine, the University of Tokyo, Tokyo
1992-1997	Research Staff, Institute for Diabetes Care and Research, Asahi Life Foundation, Tokyo
1998	Ph.D. Graduate School of Medicine, the University of Tokyo (Medical Science)
1997-2000	Research Fellow, Cellular and Molecular Physiology, Joslin Diabetes Center, Harvard Medical School
2001-2003	Instructor in Medicine, Harvard Medical School and Cellular and Molecular Physiology, Joslin Diabetes Center
2004-2007	Associate Professor at 21st Century Centre of Excellence Program, Graduate School of Medicine, the University of Tokyo
2007-2014	Associate Professor at Department of Diabetes and Metabolic Diseases, Graduate School of Medicine, the University of Tokyo
2011-2014	Director, Department of Diabetes and Metabolic Diseases, the University of Tokyo Hospital
2014-2016	Professor, Department of Molecular Sciences on Diabetes, Graduate School of Medicine, the University of Tokyo
2016-present	Director, Diabetes Research Center, Research Institute, National Center for Global Health and Medicine

Activities in Academic Societies

2014-present	Executive Director of Board, Japan Diabetes Society
2014-present	Academic Council Member, Japan Endocrine Society
2010-present	Academic Council Member, Japan Society for the Study of Obesity
2010-present	Secretary General, Asian Association for the Study of Diabetes

Awards

2006 Young Investigator Award, Japan Society of Diabetic Complications
2010 Research Award, Japan Society of Experimental Diabetes and Obesity

S30-5

Role of Activin B/FSTL3 axis in the control of glucose homeostasis

Kohjiro Ueki[1]

[1]Department of Molecular Sciences on Diabetes, the University of Tokyo, Tokyo, Japan

Activins, members of TGFβ superfamily proteins, are known to play a pivotal role in the reproductive and developmental processes and their variety of functions have recently been explored in many cells and tissues, while the role in glucose metabolism is poorly understood. Here we show that administration of Activin B, which is mainly produced in liver in the fasted state, significantly reduces blood glucose levels in both obese diabetic mice and insulin deficient diabetic mice, while this effect is completely canceled by co-administration of FSTL-3, known as an inhibitory molecule for TGFβ superfamily proteins. Activin B exerts glucose lowering effects through suppression of gluconeogenesis, induction of FGF21 and increased insulin secretion. Although expression of Activin B is not altered by obesity, expression of FSTL-3 in adipocytes, strongly correlates with BMI and insulin resistance in mice and humans. Indeed, suppression of FSTL-3 markedly improves glucose homeostasis in obese mice. Thus, Activin B produced by the liver contributes to the maintenance of glucose levels and insulin sensitivity under the lean condition and obesity increases the production of FSTL3 thereby suppressing the functions of Activin B leading to insulin resistance and dysregulation of glucose homeostasis.

Prof. Seung-Hoi Koo

Current Position
Professor, Division of Life Sciences, Korea University
Seoul, Korea

AFFILIATIONS

2013-Present	Professor, Division of Life Sciences, Korea University
2005-2013	Assistant/Associate Professor, Sungkyunkwan University School of Medicine
2002-2005	Research Associate, Salk Institute for Biological Studies
2000-2001	Postdoctoral Associate, Stanford University

EDUCATION

1995-2000	Ph.D. (Biochemistry), University of Minnesota, Minneapolis, MN, USA
1993-1995	M.S. (Biochemistry), Dept of Chemistry, Seoul National University, Seoul, Korea
1988-1992	B.S. (Chemistry), Dept of Chemistry, Seoul National University, Seoul, Korea

RESEARCH INTERESTS

Glucose homeostasis
cAMP signaling
Transcriptional regulation

SELECTED PUBLICATION (Pertinent to your presentation)

1. Salt-Inducible Kinase 1 Terminates cAMP Signaling by an Evolutionarily Conserved Negative-Feedback Loop in β-Cells. Kim MJ, Park SK, Lee JH, Jung CY, Sung DJ, Park JH, Yoon YS, Park J, Park KG, Song DK, Cho H, Kim ST, Koo SH. Diabetes. 2015 Sep;64(9):3189-202
2. SIK2 is critical in the regulation of lipid homeostasis and adipogenesis in vivo. Park J, Yoon YS, Han HS, Kim YH, Ogawa Y, Park KG, Lee CH, Kim ST, Koo SH. Diabetes. 2014 Nov;63(11):3659-73
3. Arginine methylation of CRTC2 is critical in the transcriptional control of hepatic glucose metabolism. Han HS, Jung CY, Yoon YS, Choi S, Choi D, Kang G, Park KG, Kim ST, Koo SH. Sci Signal. 2014 Feb 25;7(314):ra19.
4. TCF7L2 modulates glucose homeostasis by regulating CREB- and FoxO1-dependent transcriptional pathway in the liver. Oh KJ, Park J, Kim SS, Oh H, Choi CS, Koo SH. PLoS Genet. 2012 Sep;8(9):e1002986.
5. Protein arginine methyltransferase 1 regulates hepatic glucose production in a FoxO1-dependent manner. Choi D, Oh KJ, Han HS, Yoon YS, Jung CY, Kim ST, Koo SH. Hepatology. 2012 Oct;56(4):1546-56.
6. Regulation of hepatic gluconeogenesis by an ER-bound transcription factor, CREBH. Lee MW, Chanda D, Yang J, Oh H, Kim SS, Yoon YS, Hong S, Park KG, Lee IK, Choi CS, Hanson RW, Choi HS, Koo SH. Cell Metab. 2010 Apr 7;11(4):331-9.

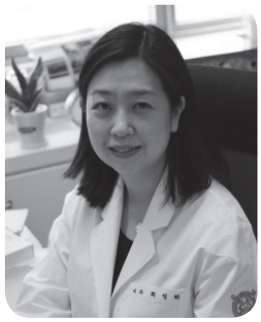
S35-1

Role of CRTC2 in the control of glucose metabolism

Hye-Sook Han[1], Byeong Hun Choi[1], Jun Seok Kim[1], Geon Kang[1], Seung-Hoi Koo[1]

[1]Division of Life Sciences, College of Life Sciences & Biotechnology, Korea University, Seoul, Korea

Liver plays a major role in maintain glucose homeostasis in mammals. Under the starvation, glucose production is increased in the liver to provide enough fuels for critical organs such as brain and red blood cells. Short-term fasting mainly activates glycogenolysis in the liver, and a longer-term fasting triggers the activation of gluconeogenesis that utilizes various non-carbohydrate precursors such as lactate, amino acids, and glycerol to meet the body's need for glucose. Interestingly, activation of gluconeogenesis is in large part achieved by a transcriptional mechanism in response to pancreatic hormone glucagon and adrenal glucocorticoid. While glucocorticoid signals through a nuclear receptor glucocorticoid receptor, glucagon elicits its effects by inducing cAMP-dependent pathway in the liver, utilizing CREB and CREB regulated transcription coactivator 2 (CRTC2) as proximal transcriptional complex. Increased hepatic glucose production under insulin resistance or type 2 diabetes is one of the major causes for hyperglycemia, and it was shown that hyperactivation of CREB/CRTC2 signals could be in part responsible for such phenomenon. In this talk, we would like to delineate the mechanistic insight into the role of CRTC2 in the control of hepatic glucose metabolism by using in vivo mouse models.



Prof. Sung Hee Choi

Current Position

Associate Professor, Seoul National University, Seoul National University College of Medicine, Seoul, Korea, & Bundang SNU Hospital (SNUBH), Seongnam, Korea

EDUCATION

1991-1993	Yonsei University College of Medicine, Pre-medicine, Seoul, Korea
1993-1997 M.D.	Yonsei University College of Medicine, Medicine, Seoul, Korea
1998-2001 M.S.	Yonsei University College of Medicine, Internal Medicine, Seoul, Korea : "The Effects of Recombinant Human Parathyroid Hormone [rhPTH (1-84)] on Bone Change Induced by Glucocorticoids with Different Action Mechanisms in Mice"
2001.9-2006.2 Ph.D.	Yonsei University College of Medicine, Internal Medicine, Seoul, Korea : "The Effects of Peroxisome Proliferator Activated Receptor-gamma Agonist on the Endothelial Dysfunction in Metabolic Syndrome and Type 2 Diabetic Patients"

Postgraduate Training and Fellowship Course

1997-1998	Rotating Internship, Severance Hospital, Yonsei Medical Center, Seoul, Korea
1998-2002	Residency in Internal Medicine, Severance Hospital, Yonsei Medical Center, Seoul, Korea
2002-2003.8	Clinical and Research Fellow in Division of Endocrinology and Metabolism, Internal Medicine, Severance Hospital, Yonsei Medical Center, Seoul, Korea
2002.4-8	Clinical fellow, Color-Doppler Ultrasound at Angiology Department, Schwabinger Krankenhaus, Munich, Germany (under the guidance of Dr. Hubert Stiegler)
2009~2011	Visiting Research Scholar, Columbia University, Columbia University Medical Center, Irving Institute for Clinical and Translational Research, New York, USA (Henry Ginsberg's lab)

Faculty and Academic Appointments

2003.9-2004.9	Faculty, Division of Endocrinology and Metabolism, Internal Medicine, National Health Insurance Hospital (NHIH), Ilsan, Korea
2004.10~2007.9	Medical Instructors, Seoul National University College of Medicine, Seoul Korea & Bundang Hospital, Seongnam, Korea
2007. 10~ Assistant	Professor, Seoul National University College of Medicine, Seoul, Korea, & Bundang Hospital, Seongnam, Korea

S35-2

Analysis of lipidomic profiling from ectopic fats in patients with coronary artery disease

Sung Hee Choi[1]

[1]Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Korea and Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Korea

The accumulation of ectopic fat is a key feature of many metabolic diseases such as obesity, diabetes, cardiovascular diseases based on insulin resistance. There are many evidences that active hormone or protein secretion from each fat tissues, which are called as “adipokines”. Visceral fats or other ectopic fats are known as “bad fats” to aggravate metabolic signals. In clinical settings, the higher amount of ectopic fat accumulation in patients with metabolic diseases is common and there is unsolved question about those ectopic fats are same fat in different location or different fat in different location? However, underlying mechanisms of ectopic fat are poorly understood and especially, there is limited data of lipidomic signatures of human fat tissues.

We investigated the differences of subcutaneous, visceral and pericardial lipidomes and compared their lipidomic signatures in patients with severe coronary artery disease. Liquid chromatography/mass spectrometry was used for lipid profiling in different fat tissues from patients with NGT (n = 22) and T2DM (n = 27) who underwent coronary artery bypass graft. Principal component analysis was performed to compare lipidomic signatures between tissues and between patient groups.

Total 26 lipid classes and more than 400 lipid species were identified. The diacylglycerol (DG), dihydroceramide, and sphinganine in the visceral fat tissue were significantly lower in the T2DM group than the NGT group. However, the DG level in pericardial fat tissue was higher in the T2DM group than the NGT group. At the lipid species level, lipidomic signatures of DG, and lysophosphatidylserine distinguished the presence of T2DM.

In this lipidomic analysis, the selective enrichment of lipidomic signatures was observed between T2DM and NGT. Further validation will provide a novel insight for characteristics of ectopic fat in subjects with T2DM.

Prof. Norikazu Maeda

Current Position

Associate Professor,Department of Metabolism and Atherosclerosis, Graduate School of Medicine, Osaka University

EDUCATION

1989-1995	Faculty of Medicine, Osaka University
1999-2003	Graduate student (Ph.D. Course) ,Internal Medicine and Molecular Science,Osaka University. Work supervised by Professor Yuji Matsuzawa.
2004-2006	Research fellow of the Japan Society for the Promotion of Science Department of Internal Medicine and Molecular Science, Osaka University.
2006-2009	Research fellow Department of Metabolic Medicine, Osaka University.
2009-2015	Assistant Professor
2016- present	Associate Professor Department of Metabolism and Atherosclerosis, Osaka University

POSTDOCTORAL EXPERIENCES:

1995.6.1-1996.5.31	Second Department of Internal Medicine, Osaka University Hospital Clinical Internship
1996.6.1-1999.5.31	Division of Internal Medicine and Cardiology, Kobe Kawasaki Hospital Residency

SOCIETY MEMBERSHIPS:

Japanese Society of Internal Medicine
Japan Diabetes Society
Japanese Circulation Society
Japan Society for the Study of Obesity
Japan Endocrine Society
Japan Atherosclerosis Society

AWARDS:

2003.5.11	Young Investigator Award in Japan Endocrine Society
2003.6.13	Travel Grant from American Diabetes Association
2003.11.14	Young Investigator Award in Japan Society for the Study of Obestiy
2004.1.10	24th Shuzo Kozawa Research Award
2004.9.4	Japan Heart Foundation Grant for Research on Arteriosclerosis Update
2005.2.4	Inoue Research Award for Young Scientists
2005.7.16	Young Investigator Award in The 3rd Metabolic Syndrome Conference
2005.7.31	Japan Heart Foundation for Research Award on Molecular and Cellular Cardiology
2005.9.2	Okamoto Research Award for Young Scientists
2006.1.14	26th Shuzo Kozawa Research Award
2010.10.2	Research Award in Japan Society for the Study of Obestiy
2012.4.19	Research Award in Japan Endocrine Society
2014.7.8	Research Award in the President of Osaka University

S35-3

Significance of adiponectin accumulation in vasculature

Norikazu Maeda[1,2], **Iichiro Shimomura**[1]

[1]Department of Metabolic Medicine, Graduate School of Medicine, Osaka University, Osaka, Japan
[2]Department of Metabolism and Atherosclerosis, Graduate School of Medicine, Osaka University, Osaka, Japan

Our group discovered adiponectin from human fat tissue in 1996 and established the measurement of circulating adiponectin concentration by using ELISA in 1999. Adiponectin is characterized as follows: (1) Plasma concentration range from 1 to 30 μg/mL in human adults, which is 103- to 106-fold higher than the levels of ordinary cytokines and hormones. (2) Circulating adiponectin levels paradoxically decrease in obesity, especially in visceral fat-accumulated obesity. Clinical and experimental studies evidently showed that adiponectin directly effects on cardiovascular tissues and exhibits cardiovascular protective function, suggesting the direct axis of fat and cardiovascular system. Importantly, we recently demonstrated the existence of adiponectin protein in the cardiovascular tissues and its localization was changed when these tissues were injured. However, molecular mechanism for the adiponectin accumulation in cardiovascular tissues has not been fully understood. Lodish's group previously demonstrated that T-cadherin is a receptor for multimeric forms of adiponectin (Hug C et al. PNAS 2004). T-cadherin is an atypical glycosylphosphatidylinositol (GPI)-anchored cadherin cell surface glycoprotein. Interestingly, T-cadherin knockout mice mimick the adiponectin knockout cardiovascular phenotype (Denzel MS et al. JCI 2010). In this symposium, I would like to talk about recent advances of adiponectin research in view of the cardiovascular protective action of adiponectin via T-cadherin.

Prof. Min Seon Kim

Current Position Director, Asan Diabetes Center

EDUCATION

1984 - 1990: Seoul National University College of Medicine, MD
1993 - 1995: Graduate School, Seoul National University, MS
1995 - 2000: Graduate School, Seoul National University, PhD

Postgraduate Professional Training

1990 - 1991:	Intern, Seoul National University Hospital
1991 - 1995:	Resident, Department of Internal Medicine Seoul National University Hospital
1996-2000:	Research fellow, Endocrine Unit Hammersmith Hospital Imperial College School of Medicine (Mentor: Stephen R. Bloom)
2000 -2001:	Fellow in Division of Endocrinology and Metabolism Department of Internal Medicine Seoul National University Hospital
2002.6 – 2008.2:	Assistant professor, Division of Endocrinology and Metabolism Department of Internal Medicine University of Ulsan College of Medicine
2008. 3- 2014. 5	Associate professor, Division of Endocrinology and Metabolism Department of Internal Medicine University of Ulsan College of Medicine
2014. 6- present:	Professor, Division of Endocrinology and Metabolism Department of Internal Medicine University of Ulsan College of Medicine

2014. 9- present: Director, Asan Diabetes Center

S35-4

Hypothalamic inflammation in high fat diet-induced obesity

Min-Seon Kim[1]

[1]Division of Endocrinology and Metabolism, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

A prolonged consumption of high fat diet (HFD) leads to hypothalamic inflammation in rodents. HFD-fed rats displayed increased expression of proinflammatory cytokines [interleukin-1 (IL-1), IL-6 and tumor necrosis factor-α (TNFα)] and activation of inflammatory signaling [c-Jun N-terminal kinase (JNK) and the IκB kinase-β/nuclear factor-κB (IKKβ-NFκB)] in their hypothalamus. Activation of hypothalamic inflammatory signaling pathways is suggested as an important mechanism underpinning overnutrition-induced leptin and insulin resistance. While it is evident that HFD induces hypothalamic inflammation, a relative contribution and interactions of neurons, glial cells, and immune cells in this process are not largely unveiled. A recent study has reported a rapid activation of hypothalamic microglia upon HFD feeding, which is evidenced by morphological changes and increased number. In my talk, I will present our recent data which suggest a critical contribution of hypothalamic macrophages in hypothalamic inflammation observed in HFD- induced obesity.

Prof. David R. Grattan

Current Position Professor

AFFILIATIONS

2009-present	Professor, Department of Anatomy, University of Otago, New Zealand
2006-Present	Centre for Neuroendocrinology, University of Otago
2014-Present	Maurice Wilkins Centre for Molecular Biodiscovery
1995-2009	Lecturer-Associate Professor, Department of Anatomy, University of Otago

EDUCATION

1991-1995	Postdoctoral Fellow, University of Maryland School of Med, Baltimore, USA
1985-1990	Ph.D., Victoria University of Wellington, New Zealand

RESEARCH INTERESTS

Neuroendocrinology
Obesity and diabetes
Reproduction

SELECTED PUBLICATION (Pertinent to your presentation)

1. Ladyman SR, Augustine RA, Scherf E, Phillipps HR, Brown CH, Grattan DR. Attenuated hypothalamic responses to α-melanocyte stimulating hormone during pregnancy in the rat. J Physiol. 594:1087-101. 2016
2. Benzler J, Andrews ZB, Pracht C, Stöhr S, Shepherd PR, Grattan DR, Tups A. Hypothalamic WNT signalling is impaired during obesity and reinstated by leptin treatment in male mice. Endocrinology 154(12):4737-45. 2013
3. Benzler J, Ganjam GK, Krüger M, Pinkenburg O, Kutschke M, Stöhr S, Steger J, Koch CE, Olkrug R, Schwartz MW, Shepherd PR, Grattan DR, Tups A.Hypothalamic glycogen-synthase-kinase 3 β has a central role in the regulation of food intake and glucose metabolism. Biochemical Journal 447(1):175-84, 2012
4. Ladyman SR, Fieldwick DM, Grattan DR. Suppression of leptin-induced hypothalamic JAK/STAT signaling and feeding response during pregnancy in the mouse. Reproduction 144(1):83-90, 2012
5. Ladyman SR, Sapsford TJ, Grattan DR. Loss of acute satiety response to cholecystokinin in pregnant rats. Journal of Neuroendocrinology 23(11):1091-8. 2011
6. Koch C, Augustine RA, Steger J, Ganjam GK, Benzler J, Pracht C, Lowe C, Schwartz MW, Shepherd PR, Anderson GM, Grattan DR and Tups A. Leptin rapidly improves glucose homeostasis in obese mice by increasing hypothalamic insulin sensitivity. Journal of Neuroscience 30, 16180-16187 2010

S38-1

Feeding-induced activation of beta-catenin/TCF signal transduction in hypothalamic neurons

Dave Grattan[1]

[1]University of Otago, New Zealand

Polymorphisms in the TCF7L2 gene are associated with increased risk of type-2 diabetes and obesity. TCF7L2 is a transcriptional co-factor that binds with β-catenin to promote gene transcription in the canonical Wnt/β-catenin pathway, and studies have focused on this pathway in the pancreas as a causal link to type-2 diabetes. The role of the brain in glucose homeostasis is increasingly recognised, however, and impaired neuronal Wnt signalling may contribute to development of diabetes. Here, we investigated whether the Wnt/β-catenin pathway is regulated in the hypothalamus during the normal physiological responses to food intake. We observed that feeding acutely induced stabilisation of β-catenin in neurons in specific hypothalamic nuclei involved in metabolic regulation, associated with increased transcription of TCF-responsive genes. The effect of feeding was mimiced by specific metabolic hormones, including GLP1 and insulin. Finally, experimental modification of β-catenin levels in a hypothalamic cell line altered neuropeptide secretion. The data suggest that both transcriptional and non-transcriptional effects of β-catenin in the hypothalamus might be involved in the regulation of body weight and glucose homeostasis, and highlights the potential role of altered hypothalamic function in contributing to the risk of diabetes conferred by specific genetic polymorphisms of TCF7L2 in human populations.

Prof. Wataru Ogawa

Current Position
Professor, Division of Diabetes and Endocrinology, Kobe University Graduate School of Medicine

AFFILIATIONS

1997-2003	Assistant Professor, Second Department of Internal Medicine, Kobe University School of Medicine
2003-2009	Associate Professor, Department of Diabetes, Digestive and Kidney Diseases, Kobe University School of Medicine
2009-2014	Associate Professor, Division of Diabetes and Endocrinology, Kobe University Graduate School of Medicine
2014-	Professor, Division of Diabetes and Endocrinology, Kobe University Graduate School of Medicine

EDUCATION

1979-1984	Kobe University School of Medicine, MD
1987-1991	Kobe University Graduate School of Medicine, Ph. D
1991-1994	Postdoctoral fellow, Department of Molecular Pharmacology、Stanford University Medical School

RESEARCH INTERESTS

Molecular mechanism of insulin action and Insulin resistance
Pathogenesis of type 2 diabetes

SELECTED PUBLICATION (Pertinent to your presentation)

1. Ohashi K, et al. Glucose Homeostatic Law: Insulin Clearance Predicts the Progression of Glucose Intolerance in Humans. PLoS One. 2015; 10, e0143880
2. Uchimura K, et al. The serine protease prostasin regulates hepatic insulin sensitivity by modulating TLR4 signalling. Nat Commun. 2014; 5: 3428
3. Takashima M, et al. Role of KLF15 in regulation of hepatic gluconeogenesis and metformin action. Diabetes. 2010 ; 59: 1608-15.
4. Hosooka T, et al. Dok1 mediates high-fat diet-induced adipocyte hypertrophy and obesity through modulation of PPAR-gamma phosphorylation. Nat Med. 2008 ;14: 188-93
5. Inoue, H et al. Role of hepatic STAT3 in brain-insulin action on hepatic glucose production. Cell Metab. 2006; 3: 267-75.

S38-2

Insulin signaling in adipocytes and metabolic control

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Insulin signaling in adipocyte is thought to play a key role in the control of energy metabolism in living animals. The pathophysiological significance of insulin resistance in adipocyte remains ambiguous, however. To understand the physiological impact of insulin resistance in adipocytes in living animals, we have generated mice lacking PDK1, a key molecule in insulin signaling, selectively in adipocytes. Insulin-induced biological actions in adipose tissue, including the stimulation of glucose uptake and 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. Insulin-induced phosphorylation of FoxO1 was abolished in the adipose tissue of A-PDK1KO mice, indicating that the FoxO1-dependent pathway is constantly activated. 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 NASH 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 greatly attributable to these pathological conditions. Further analysis of the PDK1-FoxO1 pathway in adipocytes may shed light on the pathogenesis of NASH and may lead to the development of a novel therapeutic approach for this global health problem.

Dr. Yi-Cheng Chang

Current Position
- Assistant professor, Graduate Institute of Medical Genomics and Proteomics, NTU
- Joint-appointment assistant research fellow, Institute of Biomedical Science, Academia

Education and employment:

1994-2001:MD,College of Medicine, National Taiwan University (NTU)

2010-2013PhD, Program of Translational Medicine, NTU & Academia Sinica

2015-: Attending physician, Department of Internal Medicine, NTU hospital

2014-: Assistant professor, Graduate Institute of Medical Genomics and Proteomics, NTU

2016-: Joint-appointment assistant research fellow, Institute of Biomedical Science, Academia Sinica

Selected Publications:

1. Chang YC, et al. Association Study of the Genetic Polymorphisms of the Transcription Factor7- like 2 (TCF7L2) Gene and Type 2 Diabetes in the Chinese Population. Diabetes 56:2631-7, 2007
2. Chang YC, et al. Common Variation in the FTO Gene Confers Risk of Obesity and Modulates Body Mass Index in the Chinese Population. Diabetes 57:2245-52, 2008
3. Liu PH, Chang YC (co-first author), et al. Genetic Variants of TCF7L2 are Associated with Insulin Resistance and Related Metabolic Phenotypes in Taiwanese Adolescents and Caucasian young adults. Journal Clinical Endocrinology Metabolism 94:3575-82, 2009
4. Lin JW, Chang YC(co-first author), et al. Cross-Sectional Validation of Diabetes Risk Scores for Predicting Diabetes, Metabolic Syndrome, and Chronic Kidney Disease in Taiwanese. Diabetes Care 32: 2294-6, 2009
5. Chang YC, et al. The Associations of LPIN1 Gene Expression in Adipose Tissue with Metabolic -Phenotypes in the Chinese Population. Obesity 18: 7-12, 2010
6. Chang YC, et al. Common PCSK1 Haplotypes are Associated with Obesity in the Chinese Population. Obesity 18:1404-9, 2010
7. Cho YS, Chen CH, Hu C, Long J, Hee Ong RT, Sim X, Takeuchi F, Wu Y, Go MJ, Yamauchi T, Chang YC(co-first author) , et al. Meta-analysis of genome-wide association studies identifies 8 new loci for type 2 diabetes in East Asians. Nature Genetics 44:67-72, 2011
8. Chang YC, et al. Deficiency of NPGPx, an oxidative stress sensor, leads to obesity in mice and human. EMBO Molecular Medicine 5:1165–1179, 2013
9. Chang CH, Chang YC(co-first author), et al. Cardiovascular Risk Associated with Acarbose versus Metformin as the First-line Treatment in Patients with Type 2 Diabetes: a Nationwide Cohort Study Journal Clinical Endocrinology Metabolism 100:1121-9, 2015

S38-3

Maternally inherited mitochondrial dysfunction causes insulin resistance

Yi-Cheng Chang[1]

[1]Natiotnal Taiwan University Hospital

Type 2 diabetes is a major threat to global health. The main pathophysiological feature of type 2 diabetes is insulin resistance. However, the underlying cause by which insulin resistance develops is still not fully elucidated. In past human studies, a strong correlation between mitochondrial dysfunction and insulin resistance has been observed. Nevertheless, the casual relationship and the molecular mechanism remained to be explored.

SUV3 is a conserved nuclear-encoded mitochondrial RNA helicase, a component of mitochondrial RNA degradesome. SUV3 is essential for mitochondrial RNA homeostasis. In mammalian cells, deficiency of SUV3 causes mitochondrial RNA accumulation, DNA instability, reduction of mitochondrial copy number, and lower respiration. Deficiency of SUV3 in mice cause accelerated mitochondrial DNA mutation, reduced mitochondrial DNA copy numbers, and mitochondrial dysfunction. These phenotypes could be maternally inherited.

Using a purely maternally inherited mitochondrial dysfunction model, we proved that mitochondrial dysfunction lead to insulin resistance and glucose intolerance without changes in body weight. Insulin signaling is impaired and transcriptome analysis revealed that pathway involved in DNA repair and insulin signaling is down-regulated in the skeletal muscle of mutant mice. These mice have elevated circulating fatty acid level and impaired exercise tolerance. Indirect calorimetry showed that the elevated respiratory quotient in these mutant mice. These data suggest maternally-inherited mitochondrial function lead to insulin resistance, probably owing to impaired fatty acid oxidation.

Dr. Dan Hesselson

Current Position Laboratory Head

AFFILIATIONS

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

St. Vincent's Clinical School, UNSW Australia, Sydney, Australia

EDUCATION

2006	PhD. University of Wisconsin- Madison
2001	BSc. (honours) University of Alberta

RESEARCH INTERESTS

Pancreatic development and beta cell regeneration

Role of hyperglycemia in neurodegeneration

SELECTED PUBLICATION (Pertinent to your presentation)

Malle et al., (2015) Journal of Experimental Medicine 212(8):1239-1254

Ninov et al., (2013) Current Biology 23:1242-1250

Gut et al., (2013) Nature Chemical Biology 9(20):97-104

Hesselson et al., (2011) Current Biology 21:712-717

Hesselson et al., (2009) PNAS 106(35):14896-14901

S38-4

Role of mitochondrial quality control in hyperglycemic neuroprotection

Daniel Hesselson[1]

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Population based studies have identified a link between Diabetes mellitus (DM) and the risk of developing Parkinson's disease (PD). The duration of prior DM has emerged as an independent risk factor for PD suggesting that dopaminergic neurons are susceptible to repeated hyperglycemic insults. Recent large-scale studies in the Taiwanese population have strengthened this association and further suggested that selected oral anti-hyperglycemic agents offer partial protection. However, the molecular mechanisms underlying DM-associated PD risk remain unclear. One possibility is that both diseases share common genetic and environmental risk factors. Alternatively, exposure to hyperglycemic conditions may trigger neurodegeneration in susceptible individuals. We have developed cell and animal (zebrafish) models to investigate the role of PD-associated mitochondrial quality control pathways in the neuronal response to hyperglycemia using unbiased proteomic approaches. As the repertoire of anti-hyperglycemic agents expands it will be essential to identify which drugs offer additional neuroprotective benefit to aging populations.

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