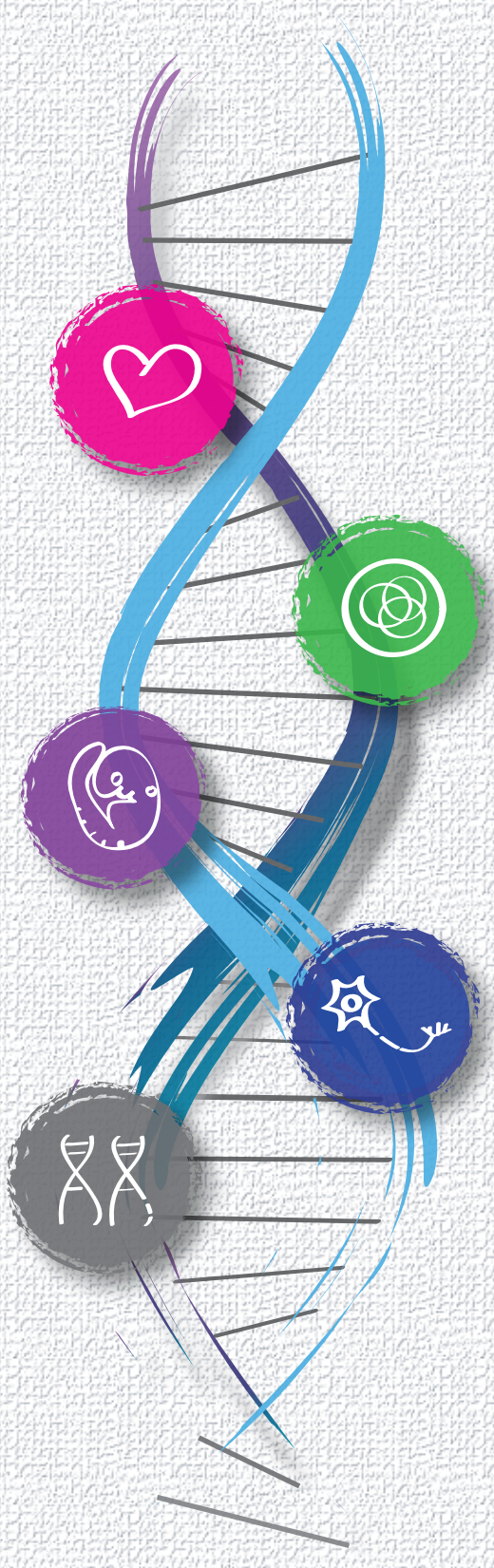


THE CHINESE UNIVERSITY OF HONG KONG

SCHOOL OF BIOMEDICAL SCIENCES

Research Day 2016

2-3 June, 2016

Lo Kwee-Seong Integrated Biomedical Sciences Building

香港中文大學
The Chinese University of Hong Kong

CU Medicine HONG KONG
香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

35th Anniversary
三十五週年

香港中文大學 生物醫學學院
CUSBS

School of Biomedical Sciences Research Day 2016

Members of the Organizing Committee

Professor Andrew M. Chan
Professor Wai Yee Chan
Professor Wing Tai Cheung
Professor Yu Huang (Chairman)
Professor Xiaohua Jiang
Professor Yiu Wa Kwan
Professor Sidney S.B. Yu

COVER: The five Thematic Research Programs of School of Biomedical Sciences, CUHK
Designed by Ms. Tai Fung Wan, School of Biomedical Sciences, CUHK

CONTENTS

Welcome Message from the Dean of Faculty of Medicine

I warmly welcome all of you to the School of Biomedical Sciences (SBS) Research Day 2016.

Since the formation of the School in 2009, the Research Day has been a signature event that draws hundreds of researchers from different research focuses to discuss and exchange findings and to formulate research directions. Having a platform to exchange ideas amongst participants from cross- and inter-disciplinary areas has been instrumental to provocation of fresh perspectives and insights.

The Faculty of Medicine has been supportive of junior faculty development. This year we invite our junior faculties to present their latest research and innovative ideas. I believe that new and early-stage investigators will take full advantage of this scientific forum to initiate fruitful exchange of ideas and to build collaborative networks with like-minded colleagues.

I would like to take this opportunity to thank the Organizing Committee of the Research Day and all the helpers for their efforts to ensure the success of this event.

I hope that at the end of this one-and-a-half day, you will bring home many useful ideas to help advance the frontiers of your respective research foci.

Professor Francis K.L. Chan
Dean, Faculty of Medicine
Choh-Ming Li Professor of Medicine & Therapeutics
The Chinese University of Hong Kong

Welcome Message from the Director of School of Biomedical Sciences

It gives me tremendous pleasure to welcome you to the School of Biomedical Sciences (SBS) Research Day 2016.

I am most delighted by the continuous support by our colleagues, associate members and friends from other local tertiary institutions in the past few years. Their presence makes this event even more joyous. Being one of our School's flagship events, every year the Research Day had successfully attracted over 250 participants to take part. When it comes to the seventh year, we would like to transform this event into a platform for our School members, especially the junior members, to share their research works and ideas. It is hoped that with more communications, more collaborations would be feasible. This year we have changed the Research Day into a 1.5-day programme which accommodates 22 oral presentations delivered by School members.

To foster collaborations among different research themes, this year's programme is divided into six sessions with presenters grouped according to their research topics rather than their affiliated thematic research programs. It is the Organizing Committee's hope that this new arrangement can stimulate new scientific ideas and encourage more interdisciplinary research efforts.

I would like to take this opportunity to sincerely thank members of the Organizing Committee for their efforts in organizing and thoughtful planning of the event, along with the helpers' outstanding support in making the event a success. I hope the programme would be inspiring to every participant and a wonderful experience to all of you.

Wai-Yee Chan, Ph.D.
Professor of Biomedical Sciences
Director, School of Biomedical Sciences
The Chinese University of Hong Kong

SBS Research Day 2016 Programme
2 June 2016 (Thursday)

Venue: Room G02, Lo Kwee-Seong Integrated Biomedical Sciences Building

13:30-13:45 **Opening Ceremony:**
Prof. CHAN Ka Leung Francis (Dean of Faculty of Medicine) &
Prof. CHAN Wai Yee (Director of School of Biomedical Sciences)

13:45-14:00 **Photo taking**

Time	*Title of Presentation*	*Speaker*	*Abstract No.*
Session I (Stem cell and cancer) ***Chairpersons: Prof. LUI Wai Yan Vivian & Prof. CHAN Leung Franky***			
14:00-14:25	Epigenetic regulation in dedifferentiation-mediated MSC reprogramming: application in tissue repair and cancer targeting	JIANG Xiaohua (SCR)	S1-01
14:25-14:50	Explore the molecular mechanism of neural crest development	ZHAO Hui (RDE)	S1-02
14:50-15:15	Novel therapeutic targets for pancreatic cancer	CHEN Yangchao (C&I)	S1-03
15:15-15:40	Functional liver cancer epigenomics	CHENG Sze Lok Alfred (C&I)	S1-04
15:40-16:00	***Tea Break***		
Session II (Technology frontiers) ***Chairpersons: Prof. LEE Ka Ho Kenneth & Prof. TANG Leung Sang Nelson***			
16:00-16:25	An empirical Bayes approach to polygenic risk prediction using summary statistics	SO Hon Cheong (RDE)	S2-01
16:25-16:50	Knock-in of large reporter genes in human cells via CRISPR/Cas9-induced homology-dependent and independent DNA repair	FENG Bo (SCR)	S2-02
16:50-17:15	Herbalog: a virtual herbal screening method for drug discovery and development	WAN Chi Cheong David (NDDR)	S2-03
17:15-17:40	Liquid biopsy of circulating-microRNA promotes precision medicine in neurological diseases	LU Gang (SCR)	S2-04

Thematic Research Programs:

- ✧ Cancer and Inflammation (C&I)
- ✧ Neuro-degeneration, -development and Repair (NDDR)
- ✧ Reproduction, Development and Endocrinology (RDE)
- ✧ Stem Cells and Regeneration (SCR)
- ✧ Vascular and Metabolic Biology (VMB)

SBS Research Day 2016 Programme
3 June 2016 (Friday)

Venue: Room G02, Lo Kwee-Seong Integrated Biomedical Sciences Building

Time	*Title of Presentation*	*Speaker*	*Abstract No.*
Session III (Reproductive biology) ***Chairpersons: Prof. SHUM Sau Wun Alisa & Prof. MA Ching Wan Ronald***			
09:00-09:25	Unexpected and forgotten events in the male gamete factory	FOK Kin Lam Ellis (RDE)	S3-01
09:25-09:50	The epithelial sodium channel (ENaC) in pregnancy	RUAN Yechun (RDE)	S3-02
09:50-10:15	Revealing developmental progression of undifferentiated spermatogonia by single cell genomics	LEE Tin Lap (RDE)	S3-03
10:15-10:45	***Tea Break***		
Session IV (Molecular pathogenesis I) ***Chairpersons: Prof. LEUNG Po Sing & Prof. CHAN Chung Ngor Juliana***			
10:45-11:10	Is bone more than just a structural organ?	MAK King Lun Kingston (SCR)	S4-01
11:10-11:35	Distinct mode of insulin and IGF-1 actions on Glut1 expression in chondrocytes: Implications for diabetic bone repair	WAN Chao (SCR)	S4-02
11:35-12:00	Myeloid specific disruption of circadian rhythm promotes atherosclerosis	TIAN Xiao Yu (VMB)	S4-03
12:00-12:25	Glucose-sensitivity of CFTR and its role in pancreatic insulin and glucagon secretion	CHAN Hsiao Chang (RDE)	S4-04
12:30-14:00	***Lunch at C.W. Chu College (敬文書院) Canteen***		
Session V (Molecular pathogenesis II) ***Chairpersons: Prof. CHENG Hon Ki Christopher & Prof. LAU Hang Yung Alaster***			
14:00-14:25	Dragon inhibits necroptosis in renal tubular cells during acute kidney injury	XIA Yin (RDE)	S5-01
14:25-14:50	The regulation of lipid droplet homeostasis by TRAPP complex	YU Siu Bun Sidney (RDE)	S5-02
14:50-15:15	TM9SF4 is a novel protein crucial for starvation-induced autophagy in renal cells	YAO Xiaoqiang (VMB)	S5-03
15:15-15:45	***Tea Break***		
Session VI (Neurological and developmental disorders) ***Chairpersons: Prof. CHAN Sun On & Prof. CHOI Chung Hang Jonathan***			
15:45-16:10	Modeling Werner syndrome and autism spectrum disorder with iPSC	CHEUNG Hoi Hung Albert (RDE)	S6-01
16:10-16:35	Platelets mediate protective neuroinflammation and promote neuronal plasticity at the site of brain injury	PONOMAREV Eugene (NDDR)	S6-02
16:35-17:00	Neuromotor modules as markers of diseased states and progress of motor recovery	CHEUNG Chi Kwan Vincent (NDDR)	S6-03
17:00-17:25	Whole exome sequencing to dissect the genetic factors behind developmental delay and learning difficulties	TSUI Kwok Wing Stephen (C&I)	S6-04
17:30	***Closing Ceremony***		
18:30	***Conference Dinner (by invitation)***		

Session (I) Stem cell and cancer

Speaker Biography

Prof. JIANG Xiaohua (蔣曉華) graduated from Shanghai Second Medical University (currently School of Medicine, Shanghai JiaoTong University), and completed her internship and residency at RuiJin Hospital in Shanghai. She obtained her PhD degree in cell biology from the University of Hong Kong in 2003. Dr. Jiang undertook her postdoctoral training at the Department of Medicine, UCLA from 2003-2006. Her work focused on the role of protein kinase cascades in cancer development. After that, she joined the University of Southern California as a CIRM (California Institute for Regenerative Medicine) fellow and her research focused on cellular and molecular basis of Ewing sarcoma by using human embryonic stem cells as an innovative model. Currently, Dr. Jiang is an Assistant Professor in the Stem Cells and Regeneration Program at the School of Biomedical Sciences.

Her main research interests are impact of epigenetics on mesenchymal stem cell (MSC) biology, MSC therapy in tissue repair and cancer targeting, application of embryonic stem cells (ESC) in developmental biology and disease modeling. Dr. Jiang has published more than 50 peer-reviewed papers, including Stem Cells, Scientific Reports, Cancer Research, Gastroenterology and Oncogene.

Five recent representative publications

1. Zhang J, Weng Z, Tsang K, Tsang L, Chan HC, **Jiang XH**. "MycN is critical for the maintenance of human embryonic stem cell-derived neural crest stem cells." ***PLoS ONE,*** 2016; 11(1):e0148062.
2. Rui Y, Xu L, Chen R, Zhang T, Lin S, Hou Y, Liu Y, Meng F, Liu Z, Ni M, Tsang KS, Yang F, Wang C, Chan HC, **Jiang XH**[#], Li G[#]. "Epigenetic memory gained by priming with osteogenic induction medium improves osteogenesis and other properties of mesenchymal stem cells." ***Scientific Reports***, 2015; 5:11056. ([#]Co-corresponding author)
3. Huang B, Li G, **Jiang XH**. "Fate determination in Mesenchymal Stem Cells: a perspective from histone modifying enzymes." ***Stem Cell Res Ther***, 2015; 19:6:35.
4. Xie C, Sun X, Chen J, Ng CF, Lau KM, Cai ZM, **Jiang XH**[#], Chan HC[#]. "Down-regulated CFTR during aging contributes to benign prostatic hyperplasia through upregulation of NF-κB/COX2/PGE2." ***J Cell Physiol***, 2015; 230(8):1906-15. ([#]Co-corresponding author)
5. Sun TT, Wang Y, Cheng H, Zhang XH, Xiang JJ, Zhang JT, Yu SB, Martin TA, Ye L, Tsang LL, Jiang WG#, **Jiang XH**[#], Chan HC. "Disrupted interaction between CFTR and AF-6/afadin aggravates malignant phenotypes of colon cancer." ***Biochim Biophys Acta***, 2014; 1843(3):618-28. ([#]Co-corresponding author)

Technical expertise

- ✧ Multi-lineage differentiation of human embryonic stem cells
- ✧ Stem cell therapy for ischemic brain diseases and brain tumor

Epigenetic regulation on dedifferentiation-mediated MSC reprogramming: application in tissue repair and cancer targeting

CHEN Rui, XU Liangliang, YANG Fuyuan, JIANG Xiaohua

Stem Cells and Regeneration Program, School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, P.R. China.

Stem cells offer a unique and powerful tool for use in regenerative medicine. However, major challenges still exist in understanding the biology and function of these cells to enable safe and effective translation of their use into the clinical setting. Our fields of interest and expertise extend from embryonic stem cells to adult stem cells, the basic biology of stem cells to their clinical applications.

In mammals, the differentiation process was thought to be irreversible. However, recent studies have demonstrated that dedifferentiation may function as an alternative mechanism to achieve tissue regeneration in mammals. Can we induce dedifferentiation readily in culture without gene manipulation and obtain reprogrammed stem cells with improved therapeutic potential? Our previous study demonstrated that MSCs could be reprogrammed *in vitro* via neural differentiation and dedifferentiation with enhanced therapeutic efficacy in a rat model with hypoxia ischemic brain disease (Stem Cells, 2011). This is of particular interest, since the finding provides a potential approach to overcome some of the major hurdles faced by current MSC-based therapy. Apart from neural lineage, we have found that after *in vitro* induction of osteogenic differentiation, MSCs can also be reverted to a primitive stem cell population (dedifferentiated osteogenic MSCs) with enhanced stem cell potency as demonstrated by improved cell survival, colony formation, osteogenic potential and increased expression of pluripotency genes. In addition, we demonstrate that Nanog plays critical role in maintaining the dedifferentiation phenotype, since knockdown of Nanog in MSCs completely reverses the enhanced cell survival and differentiation in De-Os-MSCs. More interestingly, we reveal that the increased expression of Nanog and Oct4 is attributed to the epigenetic activation involving both DNA methylation and histone modifications, as evidenced by decreased methylation and promoter accrual of activating histone marks, such as H3K4me3 and H4ac on gene promoters. Our findings indicate that dedifferentiation can be achieved after different lineage commitment in MSCs (Sci Reports, 2015). Recently, following our previous study, we evaluated the effect of dedifferentiation on the migratory capability of MSCs and their homing ability to glioma. Our results show that dedifferentiation strategy dramatically enhances the migratory and tumor targeting ability of MSCs both *in vitro* and *in vivo*. Furthermore, we reveal a novel epigenetic regulatory mechanism involving histone modification on the CCL5/CCR1/ERK axis during dedifferentiated-mediated reprogramming. Taken together, these studies reinforce the potential therapeutic benefit of *in vitro* dedifferentiation strategy, which may have broad impact on the application of MSCs in regenerative medicine and cancer targeting.

Session (I) Stem cell and cancer

Speaker Biography

Prof. ZHAO Hui (趙暉) received his Ph.D. degree from the University of Essen in Germany in 2002 and completed postdoctoral training at National Institutes of Health in the US. In 2008, he joined The Chinese University of Hong Kong as a Research Assistant Professor (RAP) in the former Department of Anatomy. Since 2009, he has been a member of Reproduction, Development and Endocrinology Program of the newly formed School of Biomedical Sciences (SBS). Dr. Zhao Hui was promoted as an Assistant Professor in 2013.

His research interests focus on the early embryonic development using *Xenopus* and zebrafish as the model systems. His laboratory studies the mechanism of neural crest differentiation, germ layer formation and cell migration, and how these multiple events affect the embryonic patterning. In the past few years, his group has been studying the molecular mechanisms that are involved in oncogenesis of neuroblastoma. He also studies the signal transduction to explore the regulatory network in regulation of cell differentiation using *Xenopus* and zebrafish embryos. Recently his group established TALEN and CRISPR/Cas9 nucleases for gene targeting in *Xenopus* and cancer cells in his lab. His research also covers the tissue regeneration and organogenesis.

Five recent representative publications

1. Wang CD, Kam RTK, Shi WL, Xia Y, Chen XF, Cao Y, Sun J, Du Y, Lu G, Chen ZJ, Chan WY, Chan SO, Deng Y, and **Zhao H**. "The proto-oncogene transcription factor Ets1 regulates neural crest development through Histone Deacetylase 1 to mediate output of bone morphogenetic protein signaling." ***J Biol Chem***, 2015; 290: 21925-21938.
2. Shi WL, Xu G, Wang CD, Sperber SM, Chen YL, Zhou Q, Deng Y, and **Zhao H**. "Heat shock 70kDa protein 5 (Hspa5) is essential for pronephros formation by mediating retinoic acid signaling." ***J Biol Chem***, 2015; 290: 577-589.
3. Kam RKT, Shi W, Chan SO, Chen Y, Xu G, Lau CBS, Fung KP, Chan WY, **Zhao H**. "dhrs3 attenuates the retinoic acid signaling and is required for early embryonic patterning." ***J Biol Chem***, 2013; 288: 31477-31487.
4. Lei Y, Guo XG, Liu Y, Cao Y, Deng Y, Chen XF, Cheng HKC, Dawid IB., Chen YL and **Zhao H**. "Efficient targeted gene disruption in Xenopus embryos using engineered transcription activator-like effector nucleases (TALENs)." ***Proc Natl Acad Sci USA***, 2012; 109(43): 17484-9.
5. **Zhao H**, Han D, Pieler T and Chen Y. "Homeoprotein hhex-induced conversion of intestinal to ventral pancreatic precursors results in the formation of giant pancreata in Xenopus embryos." ***Proc Natl Acad Sci USA***, 2012; 109: 8594-8599.

Technical expertise

- ✧ Whole mount in situ hybridization, immunostaining, and confocal imaging
- ✧ Genome editing mediated by TALEN and CRISPR/Cas9
- ✧ Methodology involved in signaling transduction

Explore the molecular mechanism of neural crest development

WANG Chengdong, LIU Zhongzhen, WONG Chi Bun Thomas, ZHAO Hui

Reproduction, Development and Endocrinology Program, School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, P.R. China.

The neural crest (NC) is a transient, migratory cell population that differentiates into a large variety of tissues including craniofacial cartilage, melanocytes, and peripheral nervous system. NC is initially induced at the border of neural plate and non-neuralectoderm by balanced regulation of multiple signaling pathways, among which an intermediate bone morphogenetic protein (BMP) signaling is essential for NC formation. We performed Affymetrix microarray to identify genes that are essential for NC development. Among the candidate genes, *Ets1*, a proto-oncogene playing important roles in tumor invasion, has also been implicated in delamination of NC cells. In this study, we investigated Ets1 function in NC formation using *Xenopus*. Overexpression of *ets1* repressed NC formation through down-regulation of BMP signaling. Moreover, *ets1* repressed the BMP-responsive gene *id3* that is essential for NC formation. Conversely, overexpression of *id3* can partially rescue the phenotype of NC inhibition induced by ectopic *ets1*. Mechanistically, we found that Ets1 binds to *id3* promoter as well as Histone Deacetylase 1 (HDAC1), suggesting that Ets1 recruits HDAC1 to the promoter of *id3,* thereby inducing Histone deacetylation of the *id3* promoter.

The RNA guided CRISPR/Cas9 nucleases have been proven to be effective for gene disruption in various animal models. We utilized CRISPR/Cas9 to disrupt genes that are involved in NC formation in *Xenopus* embryos. Total 16 target sites in 15 genes were targeted by CRISPR/Cas9 and resulted in successful indel mutations at 14 loci with disruption efficiencies in a range from 9.3% to 57.8%. Duplex mutations were induced by CRISPR/Cas9 and corresponding single guide RNAs (sgRNAs). Furthermore, we demonstrated the feasibility of generation of large segmental deletions and inversions by Cas9 and a pair of sgRNAs.

Our study shed light on epigenetic regulation involving with both HDAC1 and Ets1 during NC development, and set up a basis for studying NC development using genetic approach.

Session (I) Stem cell and cancer

Speaker Biography

Prof. CHEN Yangchao (陳揚超) is currently an Associate Professor in School of Biomedical Sciences, The Chinese University of Hong Kong. He obtained his PhD from Zhongshan University in 2003 and later on obtained his postdoctoral training at University of Washington, Seattle.

His research interests include epigenetics in cancer, histone modification particularly methylation, long and short non-coding RNAs, development of novel therapeutics for liver and pancreatic cancer. The ultimate goal of his lab is aimed at the identification of novel diagnostic markers and therapeutic targets for pancreatic and liver cancer.

Five recent representative publications

1. Xiao Z, Li CH, Chan SL, Xu F, Feng L, Wang Y, Jiang JD, Sung JJY, Cheng CHK, **Chen Y**. "A small molecule modulator of the tumor suppressor miRNA-34a inhibits the growth of hepatocellular carcinoma." ***Cancer Res***, 2014; 74:6236-47.
2. Li CH, Xu F, Chow SC, Feng L, Yin D, Ng TB, **Chen Y**. "Hepatitis B virus X protein promotes hepatocellular carcinoma transformation through interlukin-6 activation of microRNA-21 expression." ***Eur J Cancer***, 2014; 50:2560-9.
3. Xiao ZG, Chow SC, Li CH, Tang SC, Tsui SKW, Lin ZX, **Chen Y**. "Role of microRNA-95 in the anticancer activity of Brucein D in hepatocellular carcinoma." ***Eur J Pharmacol***, 2014; 728:141-150.
4. Li CH, **Chen Y**. "Targeting long non-coding RNAs in cancer: progress and perspective." Int ***J Biochem Cell Biol***, 2013; 45:1895-1910.
5. Li CH, To KF, Tong JH, Xiao Z, Xia T, Lai PB, Chow SC, Zhu YX, Chan SL, Marquez VE, **Chen Y**. "Enhancer of Zeste Homolog 2 Silences microRNA-218 in Human Pancreatic Ductal Adenocarcinoma Cells by Inducing Formation of Heterochromatin." ***Gastroenterology***, 2013; 144:1086-1097.

Technical expertise

✧ Lentiviral vector mediated gene expression, RNAi and CRISPR

Novel therapeutic targets for pancreatic cancer

CHEN Yangchao

Cancer and Inflammation Program, School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, P.R. China.

The dysregulation of microRNA expression in pancreatic ductal adenocarcinoma (PDAC) has been well documented. However, the underlying mechanism is not fully explored. Enhancer of zeste homolog 2 (EZH2) is a histone methyltransferase and is overexpressed in PDAC. To explore the role of EZH2 in regulating miRNAs expression, we performed genomic miRNAs profiling in PDAC cells with EZH2 inhibition. MiR-218 was repressed by EZH2 in PDAC cells and UDP-glycosyltransferase 8 (UGT-8) was identified as a novel target of miR-218. UGT-8 was overexpressed in over 70% of PDAC tumor samples and was associated with progression of tumors in patients. Therefore, we identified a novel EZH2/miR-218/UGT-8 pathway associated with progression of PDAC. We further found that EZH2 silenced miR-218 by promoting heterochromatin formation (***Gastroenterology*** *2013*). We also found that miR-34a was regulated by EZH2 in PDAC cells and demonstrated that EZH2 suppressed miR-34a expression through trimethylation of H3K27 and heterochromatin formation (***Int J Can*** *2016*). Therefore, EZH2-induced heterochromatin formation is a general mechanism leading to tumor suppressor microRNAs silencing in PDAC.

We isolated a natural product which inhibited cancer cell growth *in vitro* and tumor growth *in vivo* by targeting EZH2 (***Tumour Biol*** *2014*). Recently, we identified a small molecule modulator of miR-34a which could selectively restore the expression of miR-34a in cancer cells in which miR-34a was silenced. The *in vitro* and *in vivo* anti-cancer activities of the small molecule were demonstrated in cell and animal models (***Cancer Res*** *2014*). Taken together, targeting non-coding RNAs might represent novel therapeutic strategies for PDAC.

Session (I) Stem cell and cancer

Speaker Biography

Prof. CHENG Sze Lok Alfred (鄭詩樂) is an Associate Professor in the School of Biomedical Sciences at The Chinese University of Hong Kong (CUHK). He completed his Ph.D. under the supervision of Prof. Joseph Sung in the Department of Medicine and Therapeutics at CUHK in 2002 and went on his postdoctoral training to characterize the roles of cyclooxygenase-2 in hepatitis B-induced hepatocarcinogenesis. From 2004 to 2007, he was trained as a postdoctoral researcher in Prof. Tim Huang's lab in the Ohio State University, USA, where he developed an integrative genome-wide and bioinformatics approach to interrogate gene regulatory network in cancer.

His current research focuses on the transcriptional and epigenetic mechanisms in liver carcinogenesis. Dr. Cheng has published in international journals including *Molecular Cell, Nature Genetics, Journal of Clinical Investigation, Cancer Cell, Cancer Research, Gastroenterology, Gut and Journal of Hepatology*. He has received several scientific awards including three consecutive American Association of Cancer Research (AACR) Scholar-in-Training Awards (2004-2006) and Travel Grants/Oral Free Paper Prizes from the United European Gastroenterology (UEG) for three years (2011-2013). He was also a recipient of the Most Promising Young Investigator Award by the Food and Health Bureau, the Government of Hong Kong SAR in 2014 and the Young Researcher Award by CUHK in 2015. From 2008 to 2016, he has presided as PI capacity in 12 competitive research projects (RGC-CRF, GRF, RFCID, HMRF, NSFC and CUHK Focused Innovations Scheme).

Five recent representative publications

1. Tian Y, Wong VW, Wong GL, Yang W, Sun H, Shen J, Tong JH, Go MY, Cheung YS, Lai PB, Zhou M, Xu G, Huang TH, Yu J, To KF, **Cheng ASL***, Chan HL*. "Histone deacetylase HDAC8 promotes insulin resistance and ß-catenin activation in NAFLD-associated hepatocellular carcinoma." ***Cancer Research***, 2015; 75(22):4803-4816.
2. Feng H, Yu Z, Tian Y, Lee YY, Li MS, Go MY, Cheung YS, Lai PB, Chan AM, To KF, Chan HL, Sung JJ, **Cheng ASL***. "A CCRK-EZH2 Epigenetic Circuitry Drives Hepatocarcinogenesis and Associates with Tumor Recurrence and Poor Survival of Patients." ***Journal of Hepatology***, 2015; 62(5):1100-11.
3. Yu Z, Gao YQ, Feng H, et al., **Cheng ASL***. "Cell cycle-related kinase mediates viral-host signalling to promote hepatitis B virus-associated hepatocarcinogenesis." **Gut**, 2014; 63(11):1793-804. (Editorial: **Gut,** 2014;63:1688-9)
4. **Cheng ASL***, Li MS, Kang W, et al., Chan FK*. "Helicobacter pylori causes epigenetic dysregulation of FOXD3 to promote gastric carcinogenesis." ***Gastroenterology***, 2013; 144(1):122-133.e9. (Coverage/Editorial: Gastroenterology, 2013; 144:22-5; F1000 Faculty, http://f1000.com/prime/717963965)
5. Feng H, **Cheng ASL***, Tsang DP, et al, Sung JJ*. "Cell cycle–related kinase is a direct androgen receptor-regulated gene driving β-catenin/T-cell factor-dependent hepatocarcinogenesis." ***Journal of Clinical Investigation,*** 2011; 121(8):3159-75. (Coverage/Editorial: ***Nature China,*** 2011; doi:10.1038/nchina.2011.58; **Hepatology** 2012; 55:970-3.)

Technical expertise

✧ Genome-wide transcriptional and epigenetic analyses

Functional liver cancer epigenomics

CHENG Sze Lok Alfred

Cancer and Inflammation Program, School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, P.R. China.

DNA and histones are targets of multiple modifications that convey flexibility to the genome. However, these epigenetic events are often hijacked in carcinogenesis. While chronic hepatitis B remains the major etiology of hepatocellular carcinoma (HCC), non-alcoholic fatty liver disease caused by the growing epidemics of obesity and diabetes has emerged as an important risk factor. Accumulating evidence suggest that epigenetics converts the hostile inflammatory and metabolic microenvironments into aberrant transcriptional activities, which underscore the fundamental roles of epigenetic regulation in HCC pathogenesis. In the pursuit of molecular vulnerabilities in HCC, we have applied multiple genome-wide epigenetic analyses in clinical specimens and various cell and mouse models with genetic and dietary modifications, followed by rigorous functional investigations. It is now apparent that the interconnected epigenetic mechanisms comprise complex signaling networks which modify susceptibility to molecular targeted therapy. Through seamless integration of the complementary epigenome, genome and transcriptome information, the long-term goal of our efforts is to derive the next generation of effective targeted therapeutics to reverse transcriptional abnormalities that are inherent to the HCC epigenome.

Session (II) Technology frontiers

Speaker Biography

Prof. SO Hon Cheong (蘇漢昌) received his Bachelor of Medicine and Bachelor of Surgery (MBBS) degree together with a PhD degree in 2012 from University of Hong Kong (HKU). His PhD research focused on statistical and psychiatric genomics. He has received numerous awards for his academic achievement, including the Croucher Foundation Scholarship and the Dr. Stephen KP Chang Gold Medal for the best PhD thesis in the Faculty of Medicine. Prior to taking up the current academic post, he worked as a resident psychiatrist in Queen Mary Hospital and Castle Peak Hospital. He joined the School of Biomedical Sciences of The Chinese University of Hong Kong as an Assistant Professor in Jan 2016.

His main research interests include the development and application of novel statistical and computational methodologies to "omics" and clinical data in general. In particular, he is interested in uncovering the genetic architecture of complex diseases and predicting disease risk and phenotypes based on bioinformatics and clinical data. He has developed methodologies for evaluating the heritability explained by individual genetic variants and the entire set of markers on a genome-wide association study (GWAS) panel. He has also developed novel methods to combine genetic information with family history in improving risk prediction, and found potential application of the method to breast and prostate cancer screening. He has also participated in a GWAS of schizophrenia in Chinese population, leading to discovery of a novel susceptibility loci on the X chromosome.

Five recent representative publications

1. **So HC**, Sham PC. "A unifying framework for evaluating the predictive power of genetic variants based on the level of heritability explained." ***PLoS Genet***, 2010; 6: e1001230.
2. **So HC**, Gui AH, Cherny SS, Sham PC. "Evaluating the heritability explained by known susceptibility variants: a survey of ten complex diseases." ***Genet Epidemiol***, 2011; 35:310-7.
3. **So HC**, Kwan JS, Cherny SS, Sham PC. "Risk prediction of complex diseases from family history and known susceptibility loci, with applications to cancer screening." ***American Journal of Human Genetics***, 2011; 88(5):548-65
4. **So HC**, Li MX and Sham PC. "Uncovering the total heritability explained by all true susceptibility variants in a genome-wide association study." ***Genetic Epidemiol***, 2011; 35:447-56.
5. Wong EH*, **So HC***, Li M, Wang Q, Butler AW, Paul B, Wu HM, Hui TC, Choi SC, So MT et al. "Common variants on Xq28 conferring risk of schizophrenia in Han Chinese." ***Schizophr Bull***, 2014; 40(4):777-8 (*equal first author)

Technical expertise

✧ Statistical genomics, bioinformatics, neuro-psychiatric genomics

An empirical Bayes approach to polygenic risk prediction using summary statistics

SO Hon Cheong[1], **SHAM Pak C.**[2,3,4,5]

[1] Reproduction, Development and Endocrinology Program, School of Biomedical Sciences, The Chinese University of Hong Kong, Hong Kong SAR, P.R. China.
[2] Department of Psychiatry, University of Hong Kong, Pokfulam, Hong Kong SAR
[3] Centre for Genomic Sciences, University of Hong Kong, Pokfulam, Hong Kong SAR
[4] State Key Laboratory for Cognitive and Brain Sciences, University of Hong Kong, Pokfulam, Hong Kong SAR
[5] Centre for Reproduction, Development and Growth, University of Hong Kong, Pokfulam, Hong Kong SAR

Genome-wide association studies (GWAS) have become increasingly popular and a large number of susceptibility variants have been identified for a number of complex diseases. One important clinical application is in disease risk prediction.

While traditionally only the top established variants are considered, it was found that variants with smaller effect sizes may also improve prediction and polygenic risk scores (PRS) have been widely used in recent years. Typically a number of different *p*-value thresholds are tested, and the predictive performances of the model at various thresholds are assessed by cross-validation (CV) or in a separate validation set. However, such an approach can become computationally expensive when sample size get larger, and thresholds are usually chosen in an arbitrary manner.

Another crucial question is how to improve the prediction power of PRS. In most studies, PRS are weighted by the log odds ratios or regression coefficients. However, the observed effect sizes might not reflect the true underlying effects due to selection bias. How to improve the weighting of effect sizes remains an open question.

With the above questions in mind, we propose two contributions to the PRS methodology. Firstly, we propose a methodology to estimate the predictive performance of PRS analytically at *any* *p*-value thresholds, using a *single* set of summary statistics only. We propose empirical Bayes estimates of the underlying true effect sizes and use them to derive the predictive power of standard PRS at different *p*-value thresholds.

Secondly, we directly employed the corrected effect size estimates to construct new versions of PRS, with an aim to improving predictive power and testing if satisfactory performance can be achieved with all variants. We applied the new PRS to twelve anthropometric and metabolic traits in the Northern Finland Birth Cohort and showed significant improvements in predictive power (as measured by R^2) when compared to the best performance achieved by standard PRS. In addition, for more than a half of the traits studied, the predictive performance from the entire set of markers are very close to or outperform the best R^2 from standard PRS with threshold selected by CV. Our method is computationally simple and requires no assumptions of effect size distributions.

Session (II) Technology frontiers

Speaker Biography

Prof. FENG Bo (馮波) graduated from Nankai University with B.Sc. (1993) and M.Sc (1996), and received her Ph.D. (2006) from National University of Singapore. In 2007, she joined in Genome Institute of Singapore and started her postdoctoral research on stem cells and reprogramming with Prof. Ng Huck-Hui. She set up a platform to screen for novel factors that contribute to the reprogramming of fibroblasts into induced pluripotent stem cells (iPSCs), and identified orphan nuclear receptor Esrrb, Nr5a2 as well as PRDM14 in human as a novel reprogramming factors. Her works during this period have been published in *Nature Cell Biology*, *Cell Stem Cell* and *Nature*, respectively.

In Nov 2010, Prof. Feng joined the School of Biomedical Sciences, The Chinese University of Hong Kong. Her current research interest lies within the molecular mechanism that controls pluripotency and differentiation of ESCs/iPSCs, as well as development of new tools for stem cell manipulation. Recently, her group have adapted the cutting edge gene targeting technologies, demonstrated the direct activation of endogenous Oct4 gene by TALE and CRISPR/Cas9 activators, as well as established the efficient CRISPR/Cas9-induced NHEJ-based knock-in approach, which have been published in *Nucleic Acids Res* in 2014 and 2016, respectively. Prof. Feng has received funding support by GRF grants (2012, 2014, 2015), ECS grant (2013), NSFC grant (2012), and in part by CRF grant (C4014-14G, co-I), 973-grant (2015CB964700, co-I) and TBR grant (T13-607/12R, co-I).

Five recent representative publications

1. He X, Tan C, Wang F, Wang Y, Zhou R, Cui D, You W, Zhao H, Ren J, **Feng B**[#]. "Knock-in of large reporter genes in human cells via CRISPR/Cas9-induced homology-dependent and independent DNA repair." ***Nucleic Acids Res***, 2016; (Advance access, doi: 10.1093/nar/gkw064). ([#]Corresponding author)
2. Liu S, Xu Y, Zhou Z, **Feng B**[#], Huang H[#]. "Progress and challenges in generating functional hematopoietic stem/progenitor cells from human pluripotent stem cells." ***Cytotherapy***, 2015; 17, 344-58 *Review*. ([#]Co-corresponding author)
3. Hu J, Lei Y, Wong WK, Liu S, Lee KC, He X, You W, Zhou R, Guo JT, Chen X, Peng X, Sun H, Huang H, Zhao H, **Feng B**[#]. "Direct activation of human and mouse Oct4 genes using engineered TALE and Cas9 transcription factors." ***Nucleic Acids Res***, 2014; 42(7):4375-90. ([#]Corresponding author)
4. Lu X, Goke J, Sachs F, Jacques PE, Liang H, **Feng B**, Bourque G, Bubulya PA & Ng HH. "SON connects the splicing-regulatory network with pluripotency in human embryonic stem cells." ***Nat Cell Biol***, 2013; 15, 1141-1152.
5. Tsang WH, Wang B, Wong WK, Chen X, Shen G, Hu J, Wang C, He X, Liu PC, Lu G, Zhao H, Poon WS, Chan WY[#] & **Feng B**[#]. "Lif-dependent primitive neural stem cells derived from mouse ES cells represent a reversible stage of neural commitment." ***Stem Cell Res***, 2013; 11:1091-102. ([#]Co-corresponding author)

Technical expertise

- ✧ Techniques related to research on human/mouse embryonic stem cells/induced pluripotent stem cells, such as ESC culture, lentivirus packaging, primary fibroblast culture & iPSC generation.
- ✧ Molecular biology technologies, such as CRISPR/Cas9-mediated genome editing (knock-out & knock-in) and subsequent genome analysis.

Knock-in of large reporter genes in human cells via CRISPR/Cas9-induced homology-dependent and independent DNA repair

FENG Bo

Stem Cells and Regeneration Program, School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, P.R. China.

In human cells, efficient knock-in of foreign DNA into a selected genomic locus has been long awaited. It is anticipated to facilitate various applications, ranging from gene function study to therapeutic genome editing. Currently, most studies focused on homology-directed repair (HDR)-based strategies, and the rate of targeted integration was reported to be low. Notably, in human embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs), which are pluripotent and possess unprecedented potentials for basic research and cell-based therapies, gene targeting via HDR is found to be particularly difficult and has impeded applications of these cells.

Recently, CRISPR/Cas9 technology has achieved great success in introducing site-specific DNA double-strand breaks (DSBs) with high accuracy and efficiency. The CRISPR/Cas9-induced DSBs can be repaired by either HDR or non-homologous end joining (NHEJ) pathways. In this study, we construct a universal reporter system and systematically investigate into the potentials of both HDR and NHEJ repair in mediating CRISPR/Cas9-induced reporter integration. We found that NHEJ pathway mediates efficient rejoining of genome and plasmids following CRISPR/Cas9-induced DNA DSBs, and promotes high-efficiency DNA integration in various human cell types. With this homology-independent knock-in strategy, integration of a 4.6 kb promoterless ires-eGFP fragment into the GAPDH locus yielded up to 20% GFP+ cells in somatic LO2 cells, and 1.70% GFP+ cells in human embryonic stem cells (ESCs). Quantitative comparison demonstrates that the NHEJ-based knock-in is more efficient than HDR-mediated gene targeting in all the human cell types examined. These data support that CRISPR/Cas9-induced NHEJ provides a valuable new path for efficient genome editing in human ESCs and somatic cells.

In this study, for the first time, by using promoterless fluorescent reporters targeted to the GAPDH locus, we present direct quantification and comparison of CRISPR/Cas9-induced gene targeting via HDR and NHEJ repair pathways in human ESCs and somatic cell lines. Furthermore, our quantitative analysis provided direct evidence showing that intrinsic restrictions may exist in human ESCs to hamper efficient gene targeting, which suggests a new angle for further investigation into the unique DNA repair mechanisms in pluripotent cells.

Session (II) Technology frontiers

Speaker Biography

Prof. WAN Chi Cheong David (溫志昌) is the Associate Professor of the School of Biomedical Sciences at The Chinese University of Hong Kong (CUHK). He graduated from Department of Biochemistry at CUHK and received his PhD degree from University of Melbourne, Australia in 1989. He did his post-doctoral as research scientist at Burroughs Wellcome Research Laboratories in North Carolina, USA and then joined CUHK as Assistant Professor in 1993.

His research interests include: (i) Drug discovery and assay platform development using cell cultures and fluorescent proteins as biosensors; (ii) Recombinant expression of therapeutic enzymes (human AChE, BChE, tyrosinase) and proteins (heat shock protein HSP90, AhR) using bacterial and insect (silkworm) expression system; (iii) Computational virtual drug screening and natural product data mining for therapeutic mechanisms of herbal remedies on neuroprotection and against cancer and HIV infection. Prof. Wan has published more than 90 scientific papers and book chapters. He is the principal investigator of eight research grants funded by Research Grant Council, Innovation Technology Fund and Health Science Research Fund and numerous contract research. He has held 4 patents (US and European patents) and on the discovery of the first orange fluorescent protein from anemone and herbal medicine on Alzheimer's disease. The fluorescent protein technology has been patented and licensed to Invitrogen/Thermo Fisher non-exclusively since 2006.

Five recent representative publications

1. Wang Y, Lin HQ, Law WK, Liang WC, Zhang JF, Hu JS, Ip TM, Waye MMY, **Wan DCC.** "Pimozide, a Novel Fatty Acid Binding Protein 4 Inhibitor, Promotes, Adipogenesis of 3T3-L1 Cells by Activating PPAR gamma." ***Acs Chemical Neuroscience***, 2015; 6: 211-218.
2. Wang Y, Liang WC, Pan WL, Law WK, Hu JS, Ip DT, Waye MM, Ng TB, **Wan DC**. "Silibinin, a novel chemokine receptor type 4 antagonist, inhibits chemokine ligand 12-induced migration in breast cancer cells." ***Phytomedicine***, 2014; 21: 1310-1317.
3. Wang Y, Law WK, Hu JS, Lin HQ, Ip TM, **Wan DC**. "Discovery of FDA-approved drugs as inhibitors of fatty acid binding protein 4 using molecular docking screening." ***J Chem Inf Model***, 2014; 54: 3046-3050.
4. Gu WG, Zhang X, Ip DT, Yang LM, Zheng YT, **Wan DC**. "Discovery of a novel HIV-1 integrase inhibitor from natural compounds through structure based virtual screening and cell imaging." ***FEBS Lett***, 2014; 588: 3461-3468.
5. Wang Y, Pan WL, Liang WC, Law WK, Ip DTM, Ng TB, Waye MMY, **Wan DCC**. "Acetylshikonin, a Novel AChE Inhibitor, Inhibits Apoptosis via Upregulation of Heme Oxygenase-1 Expression in SH-SY5Y Cells." ***Evidence-Based Complementary and Alternative Medicine***, 2013; 937370.

Technical expertise

- ✧ Biochemical assay platform development using fluorescent proteins as probes, computational docking analysis of herbal medicine; therapeutic protein expression

Herbalog: a virtual herbal screening method for drug discovery and development

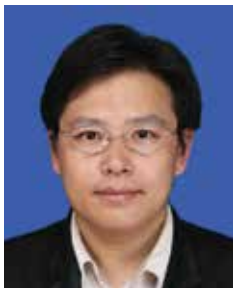
WANG Yang, HU Jian-Shu, IP Tsz-Ming Denis, WAN Chi Cheong David

Neuro-degeneration, -development and Repair Program, School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Shatin, Hong Kong SAR, P.R. China.

Molecular docking or virtual screening has been increasingly popular as screening tools in pharmaceutical and academic arena for new drug discovery. Conventional virtual screening aims at large databases of synthetic drugs for their predicted binding affinity towards target proteins. Here we described an automated algorithm, named Herbalog, as a powerful virtual herbal screening tool. This method is aimed to facilitate the identification new drug targets for evidence-based TCM research. Herbalog consists of a natural product database containing 5,112 phytochemicals from 197 commonly used herbs, and a script that automatically counts the number of hits from docking screening in each herb and calculates the hit rate of herbs. Herbs can be prioritized according to their hit rates; and top herbs candidates should contain large repertoire of hits. We evaluated the usefulness of this screening algorithm using the validated drug target acetylcholinesterase for potential herbs for Alzheimer's disease treatment. We then extended the analysis on other potential drug targets of interest. Using Herbalog, we have successfully identified *andrographis paniculata* for the first time that contain large repertoire of potential FABP4 inhibitors. This herb worth further exploration for treatment of diabetes and obesity.

Session (II) Technology frontiers

Speaker Biography



Prof. LU Gang (路鋼) B.Med., M.D., is an Assistant Professor in Stem Cells and Regeneration Program of School of Biomedical Sciences in The Chinese University of Hong Kong (CUHK). Dr. Lu has been trained in clinical and translational neuroscience in SDU and CUHK. Currently he has accumulated more than 1500 hours of classroom teaching especially on neuroscience and human anatomy, published 9 book chapters regarding this area.

His research interest is neural regenerative medicine including biomarkers screening and stem cell conversion for clinical application. His on-going research activities on neuroscience are related to both T1 (from laboratory to clinic) and T2 (from clinic to population) translational researches. He assists the collaboration between academicians, medical professionals, basic scientists, entrepreneurs and government officials in the field to organize collaborative studies, conferences and forums to optimize the resources and broaden the scope of human health. He worked as one of the founding members in the Executive Committee on the establishment of Life Science Conference in Boao Forum for Asia, which is the first of its kinds on biomedical sciences in Boao Forum. So far he published 60 research articles related to neuroscience in peer-reviewed journals, which have been cited for more than 1000 times with H-index 18. Being one of team members, he was awarded First Prize in Chinese Medical Science and Technology Award for project entitled "The mechanisms and clinical application of new technologies on stroke", in 2014.

Five recent representative publications

1. Su XW, Chan AH, **Lu G**, Lin M, Sze J, Zhou JY, Poon WS, Liu Q, Zheng VZ, Wong GK. "Circulating microRNA 132-3p and 324-3p Profiles in Patients after Acute Aneurysmal Subarachnoid Hemorrhage." ***PLoS ONE***, 2015; 10(12):e0144724.
2. Liu Y, Ao LJ, **Lu G**[#], Leong E, Liu Q, Wang XH, Zhu XL, Sun TF, Fei Z, Jiu T, Hu X, Poon WS. "Quantitative gait analysis of long-term locomotion deficits in classical unilateral striatal intracerebral hemorrhage rat model." ***Behav Brain Res***, 2013; 257:166-77. ([#]Co-corresponding author)
3. Wang XH, **Lu G***, Hu X, Tsang KS, Kwong WH, Wu FX, Meng HW, Jiang S, Liu SW, Ng HK, Poon WS. "Quantitative assessment of gait and neurochemical correlation in a classical murine model of Parkinson's disease." ***BMC Neurosci***, 2012; 13:142. (*Co-first author)
4. Zhang JF, Fu WM, He ML, Wang H, Wang WM, Yu SC, Bian XW, Zhou J, Lin MC, **Lu G**[#], Poon WS, Kung HF "MiRNA-637 maintains the balance between adipocyte and osteoblast by directly targeting osterix." ***Mol Biol Cell***, 2011; 22(21):3955-61. ([#]Co-corresponding author)
5. Liu AM, **Lu G**, Tsang KS, Li G, Wu Y, Huang ZS, Ng HK, Kung HF, Poon WS. "Umbilical cord-derived mesenchymal stem cells with forced expression of hepatocyte growth factor enhance remyelination and functional recovery in a rat intracerebral hemorrhage model." ***Neurosurgery***, 2010; 67(2):357-65; discussion 365-6.

Technical expertise

- ✧ Neuronal Cell Conversion
- ✧ *In vitro* and *in vivo* model for Parkinson's disease, Stroke and Brain Cancer
- ✧ Neurological Behavioral and neuro-electrophysiology evaluations on rodent models
- ✧ Bioinformatics Analysis on circulating non-coding RNA Next-generation sequencing

Liquid biopsy of circulating-microRNA promotes precision medicine in neurological diseases

LU Gang[1], LI Zhuo[2], SU Xianwei[2], WONG Kwok Chu George[2], POON Wai Sang[2]

[1] Stem Cell and Regeneration Program, School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, P.R. China.
[2] Neurosurgery, Department of Surgery, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, P.R. China.

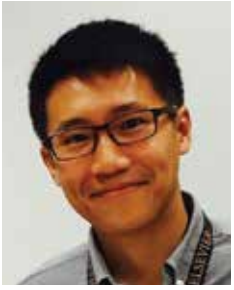
Liquid Biopsy from bodily fluids which including naked circulating cell-free DNA, exosomes and non-coding RNA like miRNAs can serve as biomarkers to predict disease progress and treatment responses, these are critical for the success of precision therapy and drug development. To comply with clinical practice and provide the clinicians with a quantitative method for assessing prognostic and predictive value of the particular subgroup, these biomarkers should be: (i) specificity and sensitivity associated with disease progression; (ii) techniques required as routinely used in clinical settings, feasibly matching to standard clinical practice; (iii) validated by independent groups.

miRNAs are found to be highly stable in peripheral blood due to its association with Argonaute protein and exosomes. Distinctive patterns of circulating miRNAs expression have been specifically discovered as discriminative classifiers to indicate progression of serval diseases. MiRNA-based classifier has been reported as reliable prognostic or predictive tools for several diseases. We postulate that combined with medical record data-based clinical phenotyping, expression patterns of multiple microRNAs could increase diagnostic value, improve patient stratification and classify patients between those could not be identified according to current clinical examination methods, that will lead to more precision targeted treatment.

Several key technological points to develop such miRNA-based classifiers on neurological diseases from our limited experiences are discussed in this presentation, which will include experimental process optimization, expression normalization with reference miRNA selection and bioinformatics analysis methods. Normally, such study should be designed as three phases including discovery, training and validation stages. Healthy controls, disease subgroups and at-risk controls from independent centers are required. The variations of reference miRNAs in difference neurological diseases are notable. Combination analysis methods such as k-Top Scoring Pair (k-TSP) algorithm, LASSO Cox regression model, area under the receiver operating characteristic curve (AUC) and Kaplan-Meier survival analysis could improve predictive power of sensitivity and specificity, positive predicted value (PPV) and negative predicted value (NPV) of selected miRNA-based classifiers. Clearly, further study about the insights into disease mechanisms involved selected microRNAs and models for validation are still required. Large-scale, multicentre, retrospective longitudinal studies are needed to validate the performance of serum miRNA classifiers. In the decades of traditional Chinese medicine which spotlights the world as one of the modern medical breakthroughs, it is worthy of pursuing our mentioned methods for validating the theory regarding the basic Chinese medicine philosophy, for instance in clarifying the Yin & Yang-syndrome of Ischemic Stroke by microRNA-expression pattern.

Session (III) Reproductive biology

Speaker Biography



Prof. FOK Kin Lam Ellis (霍建霖) obtained his Ph.D. in Physiology from the School of Biomedical Sciences (SBS), The Chinese University of Hong Kong in 2009. He continued his research after graduation and then moved to the Department of Medicine, McGill University in Canada as Post-doctoral Fellow in 2012. He has joined SBS as a Research Assistant Professor in 2015.

Dr. Fok's research mainly focuses on male reproduction and germline stem cell biology. His previous researches have uncovered the functions of a number of genes in spermatogenesis. He has also studied in-depth the sperm maturation process and uncovered the dual role of a small peptide human β-defensin 1 in regulating the motility and bactericidal activity of sperm. During his training at McGill University, Dr. Fok has also looked into the biology of spermatogonial stem cells and revealed the involvement of an ubiquitin ligase in regulating the establishment and maintenance of spermatogonial stem cells. Over the years, Dr. Fok has published over 30 peer-review articles in decent journals including *Science Translational Medicine* and *Cell Research*. Dr. Fok has served as invited reviewer for scientific journals including *PLoS ONE*, *Journal of Cell Sciences* and *Scientific Reports*. He is also the review editor for *Frontiers in Genetics* and *Frontiers in Cell and Developmental Biology*.

Five recent representative publications

1. Diao R*, **Fok KL***, Chen H*, Yu MK, Duan Y, Chung CM, Li Z, Wu H, Hu Z, Ji Z, Zhen W, Ng CF, Gui Y, Cai Z, Chan HC. (*Equal contribution). "Deficient human β-defensin-1 underlies male infertility associated with poor sperm motility and genital tract infection." ***Sci Transl Med***, 2014; 6(249):249ra108.
2. **Fok KL**, Chen H, Ruan YC, Chan HC. "Novel regulators of spermatogenesis. (Review)." ***Semin Cell Dev Biol***, 2014; 29:31-42
3. **Fok KL***, Chung CM*, Yi S, Jiang X, Chen YC, Kung HF, Tao Q, Diao R, Chan H, Zhang XH, Chung YW, Cai Z, Chan HC. (*Equal contribution) "STK31 maintains the undifferentiated state of colon cancer cells." ***Carcinogenesis***, 2012; 33(11):2044-53.
4. Lu Y*, Chen H*, **Fok KL***, Tsang LL, Yu MK, Zhang XH, Chen J, Jiang X, Chung YW, Ma AC, Leung AY, Huang HF, Chan HC. (*Equal contribution) "CFTR mediates bicarbonate-dependent activation of miR-125b in preimplantation embryo development." ***Cell Res***, 2012; 22(10):1453-1466.
5. Chen H*, **Fok KL***, Jiang X, Jiang J, Chen Z, Gui Y, Cai Z, Chan HC. (*Equal contribution) "CD147 regulates apoptosis in spermatocytes but not spermatogonia." ***Hum Reprod***, 2012; 27(6):1568-76.

Technical expertise

- ✧ Genetic engineering: CRISPR/Cas9, lentiviral gene delivery, mutagenesis
- ✧ Cell biology: primary spermatogonial stem cell culture, sperm analysis, flow cytometry
- ✧ Animal model: germ cell transplantation, conditional knock-out mice

Unexpected and forgotten events in the male gamete factory

FOK Kin Lam[1,2], BOSE Rohini[2], DIAO Ruiying[3], CHEN Hao[1,3], CAI Zhiming[3], WING S. Simon[2], CHAN Hsiao Chang[1]

[1] Reproduction, Development and Endocrinology Program; Epithelial Cell Biology Research Center, School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, P.R. China.
[2] Department of Medicine, McGill University & McGill University Health Centre Research Institute, Montreal, Quebec, Canada H4A 3J1.
[3] Shenzhen Key Laboratory of Genitourinary Tumor, Shenzhen Second People's Hospital, First Affiliated Hospital of Shenzhen University, Shenzhen 518035, P.R. China.

Spermatogenesis and sperm maturation are essential processes in maintaining male fertility and sustaining a species. Defects in these processes lead to male infertility that affects ~7.5% of couples. Spermatozoa are first produced in the testis and acquire motility and fertilizing capacity when transiting through the epididymis. Until now, the mechanisms underlying the regulation of spermatogenesis and sperm maturation remain elusive. In this seminar, I will present the findings from our previous and on-going researches on the unexpected and forgotten events during these processes.

Defending the male fertility: An unexpected dual role of β-defensin 1

Decreased sperm motility and genital tract infection are two common and often associated causes of male infertility. However, whether these two defects are stemmed from a common factor remains elusive. We have demonstrated that decreased levels of human β-defensin 1 (HBD-1), a small peptide produced in the epididymis, is associated with low sperm motility and bactericidal activity in infertile patients. Immunodepleting HBD-1 in sperm from normal individuals decreases motility and antibacterial activity while recombinant HBD-1 treatment in sperm from infertile patients significantly restored these properties. We have further identified the interaction of HBD-1 and chemokine receptor 6 in sperm that triggers calcium mobilization required for sperm motility. The demonstrated dual role of HBD-1 in maintaining motility and bactericidal activity of sperm may provide a feasible treatment approach for male infertility with poor motility and genital tract infection.

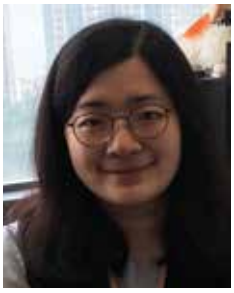
A forgotten question in the male germline: Where did spermatogonia come from?

Spermatogenesis is sustained by the spermatogonial stem cells (SSCs), a subpopulation of spermatogonia. Extensive studies have focused on the maintenance of SSCs, however, how the SSCs and other spermatogonia are established from their precursor remains elusive. We have recently uncovered an essential role of an ubiquitin E3 ligase, Huwe1, in the establishment and maintenance of spermatogonia. We have demonstrated that knockout of Huwe1 decreases the formation and causes the degeneration of spermatogonia. Loss of Huwe1 increased the level of H2Ax, a histone 2A variant, and led to the accumulation of phosphorylated H2Ax (γH2Ax) and ubiquitinated γH2Ax, two hallmark post-translational modifications of H2Ax in response to DNA damage, that in turn resulted in hyperactivated DNA damage response (DDR). These results suggest that precise DDR regulation by Huwe1 is essential for the establishment and maintenance of spermatogonia.

Further studies along these lines will provide insights into the physiology of male reproduction and the treatment of male infertility.

Session (III) Reproductive biology

Speaker Biography



Prof. RUAN Yechun (阮曄純) received her Ph.D. degree from Sun Yat-sen University in 2009 and afterwards went for postdoctoral study at Harvard Medical School for the next 4 years. In 2013, she was recruited as a Research Assistant Professor in the Epithelial Cell Biology Research Centre at The Chinese University of Hong Kong (CUHK).

Her research has been focused on ion channels in male and female reproduction and associated human diseases. Her work together with the research team's has yielded important research findings including 1) identifying the epithelial sodium channel (ENaC) as a crucial player in embryo implantation (***Nature Medicine, 2012***); 2) CFTR, another epithelial ion channel, in the development of male reproductive system (***J Cell Sci., 2014***) and metabolic diseases (***Nature Communications, 2014***). Currently, her research is extended to investigations into new roles of ion channels in reproductive diseases such as preterm labor and endometriosis, as well as bone-associated regenerative medicine. In addition, since joining CUHK, she has successfully obtained external funding support from agencies such as **RGC** (Hong Kong) and NSFC (China), and established collaborations with investigators within CUHK, in mainland and overseas.

Five recent representative publications

1. **Ruan YC**, Guo JH, Liu X, Zhang R, Tsang LL, Dong JD, Chen H, Yu MK, Jiang X, Zhang XH, Fok KL, Chung YW, Huang H, Zhou WL & Chan HC. "Activation of the epithelial Na^+ channel triggers prostaglandin E(2) release and production required for embryo implantation." ***Nature Medicine***, 2012; 18L 1112-1117, doi:10.1038/nm.2771.
2. **Ruan YC**, Chen H & Chan HC. "Ion channels in the endometrium: regulation of endometrial receptivity and embryo implantation." ***Human Reproduction Update***, 2014; 20:517-529, doi:10.1093/humupd/dmu006.
3. Guo JH, Chen H, **Ruan YC**, Zhang XL, Zhang XH, Fok KL, Tsang LL, Yu MK, Huang WQ, Sun X, Chung YW, Jiang X, Sohma Y, Chan HC. "Glucose-induced electrical activities and insulin secretion in pancreatic islet beta-cells are modulated by CFTR." ***Nature Communications***, 2014; 5:4420, doi:10.1038/ncomms5420.
4. **Ruan YC**, Wang Y, Da Silva N, Kim B, Diao RY, Hill E, Brown D, Chan HC, Breton S. "CFTR interacts with ZO-1 to regulate tight junction assembly and epithelial differentiation through the ZONAB pathway." ***Journal of Cell Science***, 2014; 127, 4396-4408, doi:10.1242/jcs.148098. *Cover-story*.
5. Sun X, **Ruan YC**, Guo J, Chen H, Tsang LL, Zhang X, Jiang X, Chan HC. "Regulation of miR-101/miR-199a-3p by the epithelial sodium channel during embryo implantation: involvement of CREB phosphorylation." ***Reproduction***, 2014; 148, 559-568, doi: 10.1530/REP-14-0386. Co-first author.

Technical expertise

- ✧ Patch-clamp, short-circuit current, Ca^{2+}/pH/membrane-voltage imaging, muscle contractility measurement, immunofluorescence and confocal imaging, protein and molecular assays, and implantation and preterm labor mouse models.

The epithelial sodium channel (ENaC) in pregnancy

RUAN Yechun

Reproduction, Development and Endocrinology Program, School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, P.R. China.

Pregnancy in mammals is a complex and highly regulated reproduction process that involves a series of events including fertilization, embryo implantation, placentation, embryo/fetus development and eventually ends by parturition. Malfunctions of the female reproductive system during these events could result in serious outcomes in humans including implantation failure, miscarriage and preterm labor. We have previously discovered an essential role of endometrial ENaC in transducing signals from the implanting embryo into a series of uterine changes resulting in upregulation of COX-2/PGE_2 required for embryo implantation. We have now extended the research into novel role of ENaC in regulating two COX-2-targeting microRNAs as well as the multi-drug resistant protein IV (MRP4), a membrane transporter of prostaglandins, critically involved in embryo implantation. Further, given these identified roles of ENaC in signalling transduction, we have explored potential involvement of ENaC in labor or parturition, and shown that ENaC, through its mechano-sensitivity, plays a key role in the switching of uterine state from quiescent to contractive, from anti-inflammatory to pro-inflammatory, leading to labor at both term or preterm. These findings have provided new insights into the molecular mechanisms underlying physiological events during pregnancy, embryo implantation and parturition in particular, and, therefore, suggested novel diagnostic/therapeutic targets for associated human diseases.

Session (III) Reproductive biology

Speaker Biography

Prof. LEE Tin Lap (李天立) is an Associate Professor in the School of Biomedical Sciences, Faculty of Medicine at The Chinese University of Hong Kong. He has previously conducted research at National Institutes of Health (NIH) in the United States for 10 years and was a Staff Scientist at the Laboratory of Clinical Genomics, National Institutes of Child Health and Human Development (NICHD) and Project Coordinator at National Center for Biotechnology Information (NCBI).

His research interests include germ cell and stem cell biology, nanomedicine and biomedical informatics. He identified various non-coding RNA and epigenetic regulations that contribute to normal or disease states in germ cell and stem cell development. He also developed algorithms and databases to facilitate genomic data mining, including GermSAGE, GonadSAGE. TileMapper and the GermlncRNA. His works have been recognized NIH Merit Award, The NIH Fellows Award for Research Excellence and young scholar awards from American Association for Cancer Research and American Nanomedicine Society.

Five recent representative publications

1. Tu J, Ng SH, Luk AC, Liao J, Jiang XH, Feng B, Mak KKL, Rennert OM, Chan WY, **Lee TL**. "MicroRNA-29b/Tet1 regulatory axis epigenetically modulates mesendoderm differentiation in mouse embryonic stem cells." ***Nucleic Acids Res***, 2015; 43(16):7805-22.
2. Luk AC, Gao H, Xiao S, Liao J, Wang D, Tu J, Rennert OM, Chan WY, **Lee TL**. "GermlncRNA: a unique catalogue of long non-coding RNAs and associated regulations in male germ cell development." ***Database (Oxford)***, 2015; 2015:bav044.
3. Qian Y, Tu J, Tang NL, Kong GW, Chung JP, Chan WY, **Lee TL**. "Dynamic changes of DNA epigenetic marks in mouse oocytes during natural and accelerated aging." ***Int J Biochem Cell Biol***, 2015; pii: S1357-2725(15)00126-0.
4. Luk AC, Chan WY, Rennert OM, **Lee TL**. "Long noncoding RNAs in spermatogenesis: insights from recent high-throughput transcriptome studies." ***Reproduction***, 2014; 147(5):R131-41.
5. Cheung HH, Davis AJ, **Lee TL***, Pang AL, Nagrani S, Rennert OM, Chan WY. "Methylation of an intronic region regulates miR-199a in testicular tumor malignancy." ***Oncogene***, 2011; 30(31).

Technical expertise

- ✧ Germline stem cell transplantation and transdifferentiation
- ✧ Non-coding RNA characterization
- ✧ Single cell genomics
- ✧ Bioinformatics

Revealing developmental progression of undifferentiated spermatogonia by single cell genomics

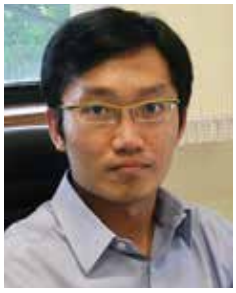
LEE Tin Lap

Reproduction, Development and Endocrinology Program, School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, P.R. China.

Precise cell fate determination in the neonatal testes is critical for generation of initial functional stem cell pool for establishing the first wave of spermatogenesis and subsequent development of adult spermatogonial stem cells (SSCs). It is believed that the process is supported by undifferentiated spermatogonia populations. However, the exact molecular identities and regulations governing self-renewal or differentiation in neonatal spermatogonia remain largely elusive. While SSCs and other undifferentiated spermatogonia population can be isolated effectively by established markers like THY1 and PLZF, the true SSC biology may be misrepresented by this bulk-cell population approach. Therefore, the absence of bona fide SSC marker poses a significant challenge to delineate precise biology in SSC development. Here we set out to reconstruct the developmental process of neonatal mouse spermatogonia by whole-genome transcriptome analysis at both population and single-cell levels. Using FACS-enriched populations representing early stages of neonatal spermatogonia differentiation, we uncovered two modes of molecular regulations governing spermatogonia KIT transition. In addition, we leveraged the power of single-cell RNA-Seq to address hidden heterogeneity at the single-cell level in the most undifferentiated spermatogonia and successfully identified four distinct subpopulations with different cellular identities, including a primitive undifferentiated cell population harboring SSCs, an “transiting” stem cell population committed to differentiation initiation, a differentiation-primed population and a population prone to apoptosis. We further defined neonatal spermatogonia ontogeny and provided a detailed view of molecular cascades governing neonatal spermatogonia development by gene network and pseudotime ordering analysis. Our study unravels cell state transitions and sequential activation of biological events during undifferentiated spermatogonia development, which would serve as a comprehensive resource for dissecting spermatogonia differentiation, identifying the origin of SSCs and addressing the fundamental questions related to stem cell self-renewal.

Session (IV) Molecular pathogenesis I

Speaker Biography



Prof. MAK King Lun Kingston (麥經綸) received his BSc (Hon) and Ph.D. degree from The University of Hong Kong. Prior to joining CUHK, he was a postdoctoral fellow in National Human Genome Research Institute, National Institute of Health, US. During his training, he focused on dissecting the differential roles of signaling networks during endochondral bone formation and bone remodeling.

Currently, Mak and his team study the roles of important signaling pathways in Mesenchymal Stem cell (MSCs) differentiation and renewal for the development of skeletal related cell lineages. He is interested in dissecting the mechanisms for cell fate determination including the regulation and regeneration of chondrocytes, osteoblasts, adipocytes and tenocytes. Mak is also interested in studying the interactions between bone and energy metabolism. He aims to identify additional secretory factors derived from the bones that will regulate the metabolism of other organs. These findings will significantly advance the field of integrative physiology and delineate the important physiological functions of the bones, which previously misinterpreted as an inert organ.

Five recent representative publications

1. Deng Y, Wu A, Li PS, Li G, Qin L, Song H, **Mak KK**. "Yap1 regulates multiple steps of chondrocyte differentiation during skeletal development and repair." ***Cell Reports***, 2016; 14: 2224-37.
2. Tu J, Ng, SH, Luk ACS, Liao JJ, Jiang X, Feng B, **Mak KK**, Rennert O, Chan WY, Lee TL. "MicroRNA-29b/Tet1 regulatory axis epigenetically modulates mesendoderm differentiation in mouse embryonic stem cells." ***Nucleic Acids Res***, 2015; 43(16): 7805-22.
3. Li P, Chen Y, **Mak KK,** Wong CK, Wang CC, Yuan P. "Functional role of Mst1/Mst2 in embryonic stem cell differentiation." ***PLoS ONE***, 2013; 8(11): e79867.doi:10.1371/journal.pone.0079867.
4. Chan LH, Wang W, Yeung W, Deng Y, Yuan P, **Mak KK**. "Hedgehog signaling induces osteosarcoma development through Yap1 and H19 overexpression." ***Oncogene***, 2014; 33:4857-66.
5. Yang Y, Zhou L, Jian P, Wang L, Hu L, Li X, Chan LKY, Yu J, Kwong J, Cheung TH, Chung TKH, **Mak KK**, Sun H, Wang H. "A Novel miR-193a-5p-yy1-APC Regulatory Axis in Human Endometrioid Endometrial Adenocarcinoma." ***Oncogene***, 2013; 32:3432-42.

Technical expertise

- ✧ Skeletal biology and bone endocrinology
- ✧ Skeletal tissue regeneration
- ✧ Skeletal diseases and cancers
- ✧ Transgenic and knockout technology
- ✧ Mouse genetics

Is bone more than just a structural organ?

ZHANG Xu, MAK King Lun Kingston

Stem Cells and Regeneration Program, School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, P.R. China.

Bone is often considered simply as a supportive and protective organ. However, it is actually a very dynamic organ that is constantly remodeling to adapt the needs of our body. It has been recently shown that bone plays a role in glucose homeostasis but the interplay between bone and other organs in regulating energy metabolism is not completely understood. Here, we show that upregulated Hedgehog (Hh) signaling in mature osteoblasts enhances whole body energy expenditure. Hh signaling induces secretion of Parathyroid Hormone related Peptide (PTHrP) from bones causes white adipose tissue (WAT) browning through increased expression of Uncoupling Protein 1 (Ucp1). Mutant mice with upregulated Hh signaling also display hypoglycemia, which is independent of insulin and osteocalcin secretion. Injection of PTHrP neutralizing antibody or high fat diet attenuates WAT browning and improves circulating blood glucose level. Bone-derived PTHrP also induces adiponectin secretion from WAT and results in skeletal muscle atrophy. Mechanistically, PTHrP induced WAT browning is mediated through both PKA/cAMP and Akt/Foxo pathways. Skeletal muscle atrophy is caused by elevated β-oxidation through AMPK/ACC pathway mediated by adiponectin stimulation. Our findings establish a bone-adipose-muscle hormonal relay that regulates whole body energy metabolism and unravel new regulatory network in bone endocrinology.

Session (IV) Molecular pathogenesis I

Speaker Biography

Prof. WAN Chao (萬超) obtained Bachelor of Medicine from Shandong University of Traditional Chinese Medicine (1995), Master of Medicine from Shanghai University of Traditional Chinese Medicine (1999), and PhD from Shanghai Jiaotong University School of Medicine (former Shanghai Second Medical University) (2002). He then worked as a resident Orthopaedic surgeon in Shanghai Longhua Hospital, and pursued postdoctoral training in School of Medicine, Queen's University of Belfast, UK, and in School of Medicine, University of Alabama at Birmingham, USA. He was appointed as an Instructor in School of Medicine, University of Alabama at Birmingham, and an Instructor in The Johns Hopkins University School of Medicine. Currently, Dr. Wan is an Associate Professor in the Stem Cells and Regeneration Thematic Research Program of School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong.

His research interests include the molecular and cellular mechanisms of the oxygen sensing and growth factor pathways in stem cell biology and exploring novel therapies for skeletal tissue regeneration.

Five recent representative publications

1. Wang PZ, Zhang F, Shu Y, Shiu HT, He Q, Tsang WP, **Wan C**. "Flavonoid compound Icariin activates hypoxia inducible factor-1α in chondrocytes and promotes articular cartilage repair." ***PLoS ONE***, 2016; 11(2):e0148372.
2. Su X, Zuo W, Wu Z, Chen J, Wu N, Ma P, Xia Z, Jiang C, Ye Z, Liu S, Liu J, Zhou G, **Wan C,** Qiu G. "CD146 as a new marker for an increased chondroprogenitor cell sub-population in the later stages of osteoarthritis." ***J Orthop Res***, 2015; 33(1):84-91.
3. Wan L, Zhang F, He Q, Tsang WP, Lu L, Li Q, Liu Z, Qiu G, Zhou G, **Wan C**. "EPO promotes bone repair through enhanced cartilaginous callus formation and angiogenesis." ***PLoS ONE***, 2014; 9 (7):e102010.
4. Zhang F, He Q, Tsang WP, Garvey WT, Chan WY, **Wan C**. "Insulin exerts direct, IGF-1 independent actions in growth plate chondrocytes." ***Bone Research***, 2014; 2(2): 14012.
5. Tsang WP, Shu Y, Kwok PL, Zhang F, Lee KKH, Tang MK, Li G, Chan KM, Chan WY, **Wan C**. "CD146^{+} human umbilical cord perivascular cells maintain stemness under hypoxia and as a cell source for skeletal regeneration." ***PLoS ONE***, 2013; 8(10):e76153.

Technical expertise

- ✧ Skeletal repair and regeneration animal models
- ✧ Stem cell based therapy and tissue engineering technique for tissue regeneration

Distinct mode of insulin and IGF-1 actions on Glut1 expression in chondrocytes: Implications for diabetic bone repair

ZHANG Fengjie, TSANG Wing Pui, WAN Chao

Stem Cells and Regeneration Program, School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, P.R. China.

Insufficient insulin action in diabetes is associated with growth retardation and impaired bone repair or non-union. The pathology of impaired diabetic bone repair is characterized by alterations in cartilaginous or bony callus formation, cell proliferation, differentiation and metabolism associated with hyperglycemia. However, the mechanisms responsible for these abnormalities remain unclear. In this study, we examined the roles of insulin and IGF-1 during diabetic bone repair. We established streptozotocin (STZ)-induced diabetic mouse model, in which the serum glucose level was elevated. A femur mid-shaft fracture model was performed in these diabetic mice. Insulin or IGF-1 was locally delivered to the fracture site every other day for five injections after day 4 post-surgery, with non-treatment as control. Radiographic and histomorphometric analysis showed that diabetic group had decreased cartilaginous callus formation and bony callus volume, local injection of insulin or IGF-1 dramatically increased cartilaginous callus and bony callus formation. The phenotype is accompanied by upregulation of insulin receptor (IR) and chondrogenic marker genes expression (Sox9, Col2α1 and ALP) in the cartilaginous callus at day 14 post-surgery. Local delivery of insulin or IGF-1 significantly increased proliferating nuclear antigen positive ($PCNA^{+}$) cell numbers and decreased the expression of glucose transporter-1 (Glut-1) in chondrocytes of the cartilaginous callus compared with the diabetic control. At the end of consolidation, both insulin and IGF-1 increased the radiographic score and bone volume of the healing bone. *In vitro*, high glucose decreased chondrogenic differentiation and increased chondrocyte proliferation. High glucose elevated phosphorylation of cyclin D1 and the level of Glut1 in chondrocytes. Interestingly, both IR and IGF-1R were shown to function in regulation of Glut-1 expression in chondrocytes, while IGF-1R seemed to exert more sensitive response than that of IR. Insulin and IGF-1 showed differential effect on Glut1 expression mediated by distinct mode of IR/IGF-1R action. The results indicate that the enhanced diabetic bone repair by insulin or IGF might be associated with their distinct regulation of Glut1expression during cartilaginous callus formation. Local delivery of insulin or IGF-1 might serve as a therapy for promoting skeletal repair for diabetic patients with impaired bone healing.

Session (IV) Molecular pathogenesis I

Speaker Biography

Prof. TIAN Xiao Yu (田小雨) got her PhD in Physiology from The Chinese University of Hong Kong in 2011, when she studied various aspects of vascular dysfunction in type 2 diabetes. She did postdoctoral training with Prof. Ajay Chawla in UCSF Cardiovascular Research Institute in 2012, and later with Prof. John Cooke in Houston Methodist Department of Cardiovascular Sciences in 2014. She re-joined Prof. Huang Yu's lab as Research Assistant Professor in May 2015.

Her current research interests are transcriptional control of macrophage and endothelial cell function in atherosclerosis and vascular inflammation, and intrinsic metabolic regulation of macrophage function in atherosclerosis. She has over 10 first/co-first author papers in high-impact journals, and >40 co-author papers, including *Cell Metabolism*, *Diabetes*, *Circulation Research, ATVB*, Antioxid *Redox Signal*, etc.

Five recent representative publications

(* first/co-first author)

1. Ma S*, **Tian XY***, Zhang Y, Mu C, Shen H, Bismuth J, Pownall HJ, Huang Y, Wong WT. "E-selectin-targeting delivery of microRNAs by microparticles ameliorates endothelial inflammation and atherosclerosis." ***Scientific Reports***, 2016; 6:22910.
2. **Tian XY***, Ganeshan K*, Hong C*, Nguyen KD, Qiu Y, Kim J, Tangirala RK, Tontonoz P, Chawla A. "Thermoneutral housing accelerates metabolic inflammation to potentiate atherosclerosis but not insulin resistance." ***Cell Metabolism***, 2016; 23(1):165–178.
3. **Tian XY***, Wong WT, Wang N, Lu Y, Liu J, Cheang WS, Liu L, Liu Y, Lee SST, Chen ZY, Yao X, Cooke JP, Huang Y. "PPARdelta activation protects endothelial function in diabetic mice." ***Diabetes***, 2012; 61(12):3285-93.
4. **Tian XY***, Wong WT, A Xu, Lu Y, Wang L, Zhang Y, Cheang WS, Wang Y, Yao X, Huang Y. "Uncoupling protein-2 protects endothelial function in diet-induced obese mice." ***Circulation Research***, 2012; 110(9):1211-6.
5. Wong WT*, **Tian XY***, Xu A, Yu J, Lau CW, Hoo RCL, Wang Y, Lee VWY, Lam KSL, Vanhoutte PM, Huang Y. "Adiponectin is required for PPARγ-mediated improvement of endothelial function in diabetic mice." ***Cell Metabolism***, 2011; 14(1):104-15.

Technical expertise

- ✧ Vascular biology
- ✧ Macrophage biology
- ✧ Immunophenotyping

Myeloid specific disruption of circadian rhythm promotes atherosclerosis

HUANG Yuhong, HUO Mingyu, HUANG Yu, TIAN Xiao Yu

Vascular and Metabolic Biology Program, School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, P.R. China.

Backgrounds: Peripheral cell-intrinsic clock is present in all types of cells and is important for synchronization of physiological function and homeostasis in response to the ever-changing environment. Bmal (encoded by *Arntl* gene) is a transcription factor that forms complex with Clock and induces rhythmic transcription of many genes. Peripheral clock has been demonstrated in monocytes to regulate inflammatory responses. We postulate that the dysfunction of circadian rhythm in myeloid cells enhances atherosclerosis in atherosclerotic mice.

Methods and Results: Myeloid cell-specific Bmal knockout mice ($Arntl^{LoxP/LoxP}Lyz2^{Cre}$) as $Bmal^{MKO}$ and Bmal wild type ($Arntl^{LoxP/LoxP}$) as $Bmal^{MWT}$ were crossbred with $Apoe^{-/-}$ to generate Apoe-$Bmal^{MKO}$ and Apoe-$Bmal^{MWT}$ mice. Mice with disruption of myeloid circadian rhythm (Apoe-$Bmal^{MKO}$) on Western diet showed enhanced atherosclerotic plaque formation by en face oil red o staining, compared with their WT control. The plaque of Apoe-$Bmal^{MKO}$ mice contains almost twice more macrophages than that from Apoe-$Bmal^{MWT}$ mice, accompanied with more infiltrating monocyte-macrophages. This increase was accompanied by an enhanced adaptive immune response reflected by the increases of T cells. The anti-inflammatory maker CD206 diminished in macrophages from $Bmal^{MKO}$ mice. Gene expression analysis showed upregulation of pro-inflammatory genes and downregulation of anti-inflammatory genes. More macrophages by CD68 staining, and more $Ly6c^{+}$ infiltrating monocyte-derived macrophages were present in aortic roots from Apoe-$Bmal^{MKO}$ mice. Proliferation rates were similar between two genotypes, indicating monocyte trafficking and infiltration is the major course of enhanced atherosclerosis. *In vitro* culture of bone marrow derived macrophage from Apoe-$Bmal^{MKO}$ and Apoe-$Bmal^{MWT}$ mice demonstrated that deletion of myeloid Bmal impaired rhythmic transcription of circadian genes and upregulation of chemokine Ccl2. Meanwhile, lipid profile were unaltered in Apoe-$Bmal^{MKO}$ compared with Apoe-$Bmal^{MWT}$ mice.

Conclusions: Our data showed disruption of myeloid circadian rhythm increased inflammation and enhanced atherosclerosis.

Session (IV) Molecular pathogenesis I

Speaker Biography

Prof. CHAN Hsiao Chang (陳小章) received her B.S. in Bioengineering (1983) and Ph.D. in Biophysics (1988) from the University of Illinois, Urbana-Champaign (USA) and went on her postdoctoral training at the University of Chicago (1989-1993). She joined the Department of Physiology, Faculty of Medicine at The Chinese University of Hong Kong in 1993 and is currently Li Ka Shing Professor of Physiology at the School of Biomedical Sciences. She also holds visiting professorships or honorary positions at over 20 institutions / universities in mainland China.

Professor Chan has broad interests in epithelial cells related interdisciplinary research, including epithelial ion channels in reproduction, development, cancer metastasis and metabolic diseases; defensins in sperm functions and male fertility and infertility. She has over 227 publications and contributed to a number of discoveries, including a cell shrinkage-activated cation channel (Science 1992); β-defensins in defending male fertility (Science 2001, Nature Cell Biology 2004, Science Translational Medicine 2014), the role of CFTR in male and female fertility and infertility (Nature Cell Biology 2003, PNAS 2007) and insulin secretion (Nature Communication 2014); ENaC in signaling mechanism underlying embryo implantation (Nature Medicine 2012). She has received a number of awards including the National Natural Sciences Award of China (1997, 2008), Distinguished Young Investigator (National Science Foundation of China, 2000), Croucher Senior Research Fellowship (2007) and Chang Jiang Scholars Achievement Award (2008).

Five recent representative publications

1. Diao R, Fok KL, Chen H, Yu MK, Duan Y, Chung CM, Li Z, Wu H, Li Z, Zhang H, Ji Z, Zhen W, Ng CF, Gui Y, Cai Z, **Chan HC**. "Deficient human β-defensin 1 underlies male infertility associated with poor sperm motility and genital tract infection." ***Sci Transl Med***, 2014 Aug 13; 6(249):249ra108.
2. Guo JH, Chen H, Ruan YC, Zhang XL, Zhang XH, Fok KL, Tsang LL, Yu MK, Huang WQ, Sun X, Chung YW, Jiang X, Sohma Y, **Chan HC**. "Glucose-induced electrical activities and insulin secretion in pancreatic islet β-cells are modulated by CFTR." ***Nat Commun***, 2014 Jul 15; 5:4420. doi: 10.1038/ncomms5420. PMID: 25025956
3. Ruan YC, Guo JH, Liu X, Zhang R, Tsang LL, Dong JD, Chen H, Yu MK, Jiang X, Zhang XH, Fok KL, Chung YW, Huang H, Zhou WL, **Chan HC**. "Activation of the epithelial Na(+) channel triggers prostaglandin E(2) release and production required for embryo implantation." ***Nat Med***, 2012 Jul; 18(7):1112-1118.
4. Zhou CX, Zhang YL, Xiao LQ, Zheng M, Leung KM, Chan MY, Lo PS, Wong HY, Ho LS, Chung YW, **Chan HC**. "An epididymis-specific-defensin involved in initiation of sperm maturation." ***Nat Cell Biol***, 2004; 6:458-464.
5. Wang XF, Zhou CX, Shi QX, Yuan YY, Yu MK, Ho LS, Ajonuma LC, Lo PS, Lam SY, Tsang LL, Chan LN, Zhao WC, Chung YW, **Chan HC**. "Involvement of CFTR in uterine bicarbonate secretion and the fertilizing capacity of sperm." ***Nat Cell Biol***, 2003; 5:902-906.

Technical expertise

- ✧ Patch-clamp, short-circuit current, sperm function assays, male and female reproductive tract primary epithelial cultures, intracellular signalling imaging, PCOS and preterm labour animal models.

Glucose-sensitivity of CFTR and its role in pancreatic insulin and glucagon secretion secretion

CHAN Hsiao Chang, GUO Jing Hui, HUANG Wenqing, RUAN Yechun

Reproduction, Development and Endocrinology Program; Epithelial Cell Biology Research Center, School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, P.R. China.

Glucose exerts opposing effects on insulin and glucagon secretion, by pancreatic β and α cells, respectively; however, the detailed mechanism underlying the action of glucose remains controversial. Up to 50% of adult patients with cystic fibrosis (CF), a disease caused by mutations in the gene encoding the CF transmembrane conductance regulator (CFTR), develop CF-related diabetes (CFRD) with most patients exhibiting insulin insufficiency and decreased glucose-induced suppressibility of glucagon secretion. However, the underlying cause remains poorly understood. The expression of CFTR in the islet β and α cells prompted us to examine the role of CFTR in the regulation of glucose-dependent electrical activities in β and α cells, as well as its effect on insulin and glucagon secretion, respectively. We have demonstrated that glucose-elicited whole-cell currents, membrane depolarization, electrical bursts or action potentials, Ca^{2+} oscillations and insulin secretion are abolished or reduced by inhibitors or knockdown of CFTR in primary mouse β-cells or RINm5F β-cell line, or significantly attenuated in CFTR mutant (DF508) mice compared to wildtype mice. VX-809, a corrector of DF508 mutation, successfully rescues the defects in DF508 β-cells. On the other hand, elevated glucagon secretion, together with increased glucose-induced membrane depolarization and Ca^{2+} response, is found in CFTR mutant (DF508) mice/islets compared to the wildtype. Overexpression of CFTR in AlphaTC1-9 cells results in membrane hyperpolarization and reduced glucagon release, which can be reversed by CFTR inhibition. AlphaTC1-9 cells overexpressed with wildtype CFTR, but not DF508, when patch-clamped, exhibit enhanced whole-cell K^+ currents with sensitivity to glucose and K_{ATP} channel blocker, which can be abolished by knockdown of SUR1, a functional unit of K_{ATP} channels. K_{ATP} knockdown also reverses the CFTR-overexpression-induced glucagon suppression. Thus, it appears that CFTR may respond to blood glucose and regulate glucose-induced electrical activities in both β and α cells, defect of which may lead to impaired insulin secretion and reduced suppressibility of glucagon secretion seen in CFRD.

Session (V) Molecular pathogenesis II

Speaker Biography

Prof. XIA Yin (夏銀) received his PhD degree in 2002 from The University of New England, Australia. Dr. Xia undertook his postdoctoral training at Massachusetts General Hospital, Harvard Medical School (2002-2008) before he was promoted to an Instructor of Harvard Medical School (2008-2010). He is currently an Assistant Professor in the School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong (CUHK).

His main research interests lie in the molecular mechanisms of kidney injury and repair, metabolic signaling pathways in the liver, and spermatogenesis and follicle development.

In 2015, Dr. Xia received fund from the Incentive Scheme for High Impact Factor Publication from School of Biomedical Sciences, CUHK, for his Blood paper. This highlights his research excellence.

Five recent representative publications

1. Meng C, Liu W, Huang H, Wang Y, Chen B, Freeman GJ, Schneyer A, Lin HY, **Xia Y** "Repulsive guidance molecule b (RGMb) is dispensable for normal gonadal function in mice." ***Biol Reprod***, 2016; 94:78, 1-10.
2. Zhao Y, Meng C, Wang Y, Huang H, Liu W, Zhang JF, Zhao H, Feng B, Leung PS, **Xia Y** "Interleukin (IL)-1b inhibits b-Klotho expression and FGF19 signaling in hepatocytes." ***Am J Physiol Endocrinol Metab***, 2016; 310:E289-300.
3. Wu XG, Wang Y, Wu Q, Cheng WH, Liu W, Zhao Y, Mayeur C, Schmidt PJ, Yu PB, Wang F, **Xia Y.** "HFE interacts with the BMP type I receptor ALK3 to regulate hepcidin expression." ***Blood***, 2014; 124:1335-43. *With an inside Blood commentary.*
4. Zhao Y, Xiao X, Frank SJ, Lin HY, **Xia Y** "Distinct mechanisms of induction of hepatic growth hormone resistance by endogenous IL-6, TNF-a and IL-1b." ***Am J Physiol Endocrinol Metab***, 2014; 307:E186-98.
5. Liu W, Li X, Zhao Y, Meng XM, Wan C, Yang B, Lan HY, Lin HY, **Xia Y.** "Dragon (RGMb) inhibits E-Cadherin expression and induces apoptosis in renal tubular epithelial cells." ***J Biol Chem***, 2013; 288:31528-39.

Technical expertise

- ✧ Use genetically modified mouse models to study the role of novel genes in kidney function and injury, and in spermatogenesis.

Dragon inhibits necroptosis in renal tubular cells during acute kidney injury

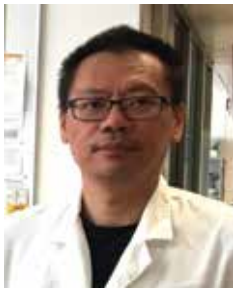
LIU Wenjing, CHEN Binbin, WANG Yang, XIA Yin

Reproduction, Development and Endocrinology Program, School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, P.R. China.

Acute kidney injury (AKI) is an important cause of morbidity and mortality in hospitalized patients, but there are no effective treatment strategies available. Therefore, there is a pressing need to enhance our understanding of the pathogenesis of AKI. It is well accepted that tubular epithelial cell death plays an active role in the development of AKI with acute tubular necrosis being a key feature of AKI. Recent studies have found that necrosis can be a programed process in various pathological and physiological conditions. Many extrinsic signals including TNF-α can trigger programed necrosis i.e., necroptosis. Importantly, it has been recently found that necroptosis is predominant over apoptosis in a number of mouse models of AKI including ischemia/reperfusion injury (IRI), and that necroptosis contributes significantly to AKI. Necroptosis is executed by mixed lineage kinase domain-like protein (MLKL). Phosphorylation of MLKL by receptor-interacting protein kinase (RIP) 3 and RIP1 induces MLKL oligomerization. Oligomerized MLKL is translocated to the plasma membrane to induce membrane rupture and necrosis. However, how the RIP1/RIP3/MLKL pathway is regulated during AKI is largely unknown. Dragon (a.k.a, repulsive guidance molecules b) is a membrane-associated glycoprotein. Our previous study demonstrated that Dragon is highly expressed in the tubular epithelial cells of the kidney. We now have identified a novel role for Dragon in renal tubular epithelial cells, which is that Dragon inhibits necroptosis by reducing membrane-associated MLKL. Specific ablation of Dragon in kidney tubular epithelial cells in mice resulted in increased tubular cell necroptosis and kidney injury compared to wild type mice after ischemia/reperfusion. Our results suggest that Dragon inhibits necroptosis and ameliorates acute kidney injury.

Session (V) Molecular pathogenesis II

Speaker Biography



Prof. YU Siu Bun Sidney (余小彬) received his bachelor degree in Molecular and Cell Biology from the University of California, Berkeley. He did his Ph.D. study at the University of Texas, Southwestern Medical Centre at Dallas. During his Ph.D. study, he was first under the supervision of David G. Garbers, studying guanylyl cyclase receptor family in C. elegans, and later under Michael G. Roth, studying the structure and function of ArfGAP1 in vesicular transport. He then did his postdoctoral research studying vesicular transport under the mentorship of Susan Ferro-Novick at Yale. He was among the first to study the TRAPP (transport protein particle) complex in mammalian cells. After joining The Chinese University of Hong Kong, he continues to investigate this topic of research and expands into other related areas including the cell biology aspects of hepatitis C virus pathogenesis.

Five recent representative publications

1. Siu KY, Zhou F, Yu M, Zhang L, Wang T, Liang YH, Chen Y, Chan HC and **Yu S**. "Hepatitis C virus NS5A protein cooperates with phosphatidylinositol 4-kinase III to induce mitochondria fragmentation." ***Scientific Reports***, 2016; 6: 23464
2. Zou S, Liu Y, Zhang C, **Yu S**, Liang Y. "Bet3 participates in autophagy through GTPase Ypt1 in *Saccharomyces cerevisiae*." ***Cell Biology International***, 2015; 39(4):466-74
3. Zou S, Chen Y, Liu Y, Segev N, **Yu S**, Liu Y, Min G, Ye M, Zeng Y, Zhu X, Hong B, Björn LO, Liang Y, Li S and Xie Z "Trs130 participates in autophagy through GTPases Ypt31/32 in *Saccharomyces cerevisiae*." ***Traffic***, 2013; 14(2):233-246
4. Zong M, Satoh A, Yu MK, Siu KY, Ng WY, Chan HC, Tanner TA, and **Yu S**. "TRAPPC9 mediates the interaction between $p150^{Glued}$ and COPII vesicles at the target membrane." ***PLoS ONE***, 2012; 7(1): e29995
5. Zong M, Wu XG, Chan CWL, Choi MY, Chan HC, Tanner JA, and **Yu S**. "The Adaptor Function of TRAPPC2 in Mammalian TRAPPs Explains TRAPPC2-Associated SEDT and TRAPPC9-Associated Congenital Intellectual Disability." ***PLoS ONE***, 2011; 6(8): e23350.

Technical expertise

- ✧ Confocal microscopy and related imaging techniques
- ✧ Electron microscopy
- ✧ Protein purification
- ✧ Various biochemical assays

The regulation of lipid droplet homeostasis by TRAPP complex

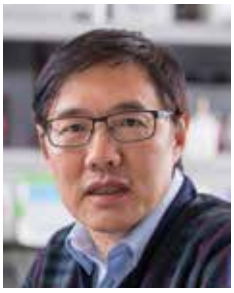
YU Sidney

Reproduction, Development and Endocrinology Program, School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, P.R. China.

The Transport protein particle was initially identified as a vesicle tethering factor for COPII coated vesicles in yeast. Three forms of TRAPP (TRAPPI, II, and III) have been discovered and they are responsible for various trafficking functions. In mammals, structures and functions of various TRAPP complexes are beginning to be understood. We have been studying the structures and functions of the TRAPP in vesicular transport in mammalian cells but have recently discovered that mammalian TRAPPII is involved in regulation of lipid droplet metabolism, a vital process in energy homeostasis. Such regulation appears to rely on the function of TRAPPII as an activator of a small GTPase well-characterized in regulating lipid droplet metabolism. COPI coatomers have been reported to regulate lipid droplet metabolism. The interaction between COPI and TRAPPII is required for TRAPPII to exert its regulatory effect on lipid droplet. These results reveal a novel function of TRAPPII in mammalian cells.

Session (V) Molecular pathogenesis II

Speaker Biography



Prof. YAO Xiaoqiang (姚曉強) received his B.S. in Biology (1978-1981), Hangzhou University, P.R. China; M.Phil. (1982-1984), Chinese Academy of Sciences; Ph.D. (1986-1991), Department of Biological Sciences, The State University of New York at Buffalo, Buffalo, New York, USA; Postdoctoral Associate (1992-1996), Department of Internal Medicine, Yale University School of Medicine, Connecticut, USA.

Professional Experiences:
Assistant Professor (1996-1999); Associate Professor (1999-2002), Department of Physiology, The Chinese University of Hong Kong; Professor (2002-now), School of Biomedical Sciences, The Chinese University of Hong Kong.

Research Interests:
My research interest is mostly on ion channels in cardiovascular system and cancer cells. These include TRP channels and K^+ channels. I published more than 200 original articles with a total citation of more than 4,400 and an H factor of 36 (ISI Web of Science), including those in *Proc Natl Acad Sci USA*, *Journal of Clinical Investigation*, *Circulation Research*, and *Trends in Pharmacological Sciences*.

Five recent representative publications

1. Wang Y, Li ZC, Zhang P, Poon E, Kong CW, Boheler KR, Huang Y, Li RA, **Yao X**. "Nitric oxide-cGMP-PKG pathway acts on Orai1 to inhibit the hypertrophy of human embryonic stem cell-derived cardiomyocytes." ***Stem Cells***, 2015; 33(10):2973-84.
2. Ma X, Chen Z, Hua D, He D, Wang L, Zhang P, Wang J, Cai Y, Gao C, Zhang X, Zhang F, Wang T, Hong T, Jin L, Qi X, Chen S, Gu X, Yang D, Pan Q, Zhu Y, Chen Y, Chen D, Jiang L, Han X, Zhang Y, Jin J, **Yao X**. "Essential role for TrpC5-containing extracellular vesicles in breast cancer with chemotherapeutic resistance." ***The Proceedings of the National Academy of Sciences, U.S.A.***, 2014 Apr 29; 111(17):6389-94.
3. Ma X, Cai Y, He D, Zou C, Zhang P, Lo CY, Xu Z, Chan FL, Shan Yu, Chen Y, Zhu R, Lei J, Jin J, **Yao X**. "Transient receptor potential channel TRPC5 is essential for P-glycoprotein induction in drug-resistant cancer cells." ***The Proceedings of the National Academy of Sciences, U.S.A.***, 2012; 109(40):16282-7.
4. Du J, Wong WY, Sun L, Huang Y, **Yao X**. "Protein kinase G regulates flow-induced Ca^{2+} entry in M1-CCD cells." ***Journal of the American Society of Nephrology***, 2012; 23:1172-80.
5. Kwan HY, Shen B, Ma X, Kwok YC, Huang Y, Man YB, Yu S, **Yao X**. "TRPC1 Associates With BKCa Channel to Form a Signal Complex in Vascular Smooth Muscle Cells." ***Circulation Research***, 2009; 104:670-678.

Technical expertise

✧ Ca^{2+} signaling, patch clamp, protein phosphorylation, signal transduction.

TM9SF4 is a novel protein crucial for starvation-induced autophagy in renal cells

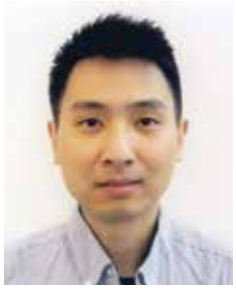
SUN Lei, MENG Zhaoyue, LI Leo, YJONG Jeff, YAO Xiaoqiang

Vascular and Metabolic Biology Program, School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, P.R. China.

TM9SF4 is a transmembrane protein that is evolutionary conserved across unicellullar organisms, plants and animals. Functionally, TM9SF4 is involved in phagocytosis and cannibalistic activity. In this study, we made several surprising new findings. 1) Overexpression of TM9SF4 resulted in an electrical current, which was inhibited by broad-spectrum K^+ channel inhibitors Cs^+ and Ba^{2+}. Preliminary ion permeability assay showed that this electrical current was more permeable to K^+ than to Na^+ and Cl^-. Furthermore, a putative K^+ selection filter sequence VHGD was identified in TM9SF4 protein sequence. Mutation at this K^+ selection filter abolished the electrical current. 2) TM9SF4 proteins were abundantly expressed in renal proximal tubular cells of rats and mice, but not in those cells of TM9SF4 knockout mice. 3) At subcellular level, they are localized on Endoplasmic reticulum, Golgi, Late endosome, and Autophagosome. 4) Nutrient starvation stimulated the autophagy. Knocking-down of TM9SF4 with TM9SF4-siRNA reduced the starvation-induced autophagy. The mechanism may involve TM9SF4-related changes in cytosolic Ca^{2+} level, followed by alteration in mTOR activity. Taken together, these data suggest that TM9SF4 is a novel K^+-selective ion channel which plays a critical role in promoting autophagy in renal cells. It is well known that autophagy can protect renal proximal tubules from degeneration, ischemic kidney injury and sepsis. Therefore, the results from this study should provide important information as to whether TM9SF4 is indeed a key component in kidney autophagy and whether TM9SF4 could potentially become a molecular target for the treatment of autophagy-related kidney diseases.

Session (VI) Neurological and developmental disorders

Speaker Biography



Prof. CHEUNG Hoi Hung Albert (張凱鴻) was graduated from The Chinese University of Hong Kong (CUHK). He received his Ph.D. through the CUHK-NIH Graduate Partnership Program. After obtaining his doctoral degree, he continued his postdoctoral research at Dr. Owen Rennert's laboratory, National Institute of Child Health and Human Development. During his postdoctoral training, he initiated two projects on modeling human diseases using induced pluripotent stem cells, and received the American Society of Human Genetics (ASHG) Trainee Award and the NIH Fellows Award for Research Excellence (FARE).

In 2014, he joined the School of Biomedical Sciences, CUHK as a Research Assistant Professor. He is currently working at the CUHK-GIBH, CAS Joint Research Laboratory on Stem Cell and Regenerative Medicine and the CUHK-Shandong University Joint Laboratory on Reproductive Genetics. His research interest is to establish stem cell models for studying complex human diseases, differentiating to specific cell types for disease modeling as well as elucidating the mechanism leading to stem cell aging.

Currently, he is a member of the International Society for Stem Cell Research (ISSCR).

Five recent representative publications

1. **Cheung HH**, Yang Y, Lee TL, Rennert OM, Chan WY. "Hypermethylation of genes in testicular embryonal carcinomas." ***Br J Cancer***, 2016 Jan 19; 114(2):230-6. doi: 10.1038/bjc.2015.408.
2. **Cheung HH**, Pei D, Chan WY. "Stem cell aging in adult progeria." ***Cell Regen (Lond)***, 2015 Oct 3; 4:6. doi: 10.1186/s13619-015-0021-z.
3. **Cheung HH**, Liu X, Canterel-Thouennon L, Li L, Edmonson C, Rennert OM. "Telomerase protects Werner Syndrome lineage-specific stem cells from premature aging." ***Stem Cell Reports***, 2014 Mar 27; 2(4):534-46.
4. **Cheung HH**, Davis AJ, Lee TL, Pang AL, Nagrani S, Rennert OM, Chan WY. "Methylation of an intronic region regulates miR-199a in testicular tumor malignancy." ***Oncogene***, 2011 Aug 4; 30(31):3404-15.
5. **Cheung HH**, Lee TL, Davis AJ, Taft DH, Rennert OM, Chan WY. "Genome-wide DNA methylation profiling reveals novel epigenetically regulated genes and non-coding RNAs in human testicular cancer." ***Br J Cancer***, 2010 Jan 19; 102(2):419-27.

Technical expertise

- ✧ Stem cell and differentiation (induced pluripotent stem cell, embryonic stem cell, mesenchymal stem cell etc)
- ✧ Epigenetics
- ✧ miRNA biology

Modeling Werner syndrome and autism spectrum disorder with iPSC

CHEUNG Hoi Hung Albert

Reproduction, Development and Endocrinology Program, School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, P.R. China.

We are interested in understanding the molecular and genetic factors leading to syndromic and idiopathic diseases. In particular, we have been working on the premature aging disease Werner syndrome (WS), which is caused by germline mutations on the WRN DNA helicase, and idiopathic autism spectrum disorder (ASD), which is a complex neurodevelopmental disorder. We established human iPSC models for WS and ASD respectively, by reprogramming patient-derived fibroblasts. Genomic profiling of the transcriptome revealed high similarity between normal and WS or ASD iPSC. However, when differentiating to specific lineages of cells, we observed differential properties relating to aging (for WS) and neurophysiology (for ASD). For WS, mesenchymal progenitor cells entered senescence prematurely, with obvious accelerated shortening of telomeres and loss of sister telomeres at lagging strand. In ASD, mature neurons showed aberrant expressions of genes related to ligand-receptor interaction, ECM-receptor interaction and ion channel function. Taken together, the iPSC-based disease models for WS and ASD provide insights into the pathogenesis of progeroid and neurodevelopmental disorders.

Session (VI) Neurological and developmental disorders

Speaker Biography

Prof. PONOMAREV Eugene (龐佑信) is currently appointed to the School of Biomedical Sciences, The Chinese University of Hong Kong, and his research interest is related to the immunological aspects of inflammation in the central nervous system (CNS) associated with neurodegenerative disease such as multiple sclerosis and Alzheimer's disease. Particularly he is interested in 1) epigenetic and transcriptional control of microglia/macrophage activation and polarization during CNS inflammation and 2) the role of platelets in the initiation of neuroinflammation. Both directions of his research program are currently supported by RGC and HMRF grants. Dr. Ponomarev is well known scientist in field of neuroinflammation and neurodegeneration and he is an author of more than 25 publications in top academic journals such as *Nature Medicine*, *Journal of Immunology* and *Journal of Neuroscience, Circulation Research*. Dr. Ponomarev serves in the editorial boards of number of International academic journals such as *Journal of Immunology*, *Journal of Neuroscience*, *Journal of Clinical Immunology*, *Annals of Neurology*, *Journal of Neuroinflammation*, *PLoS ONE* etc. Before his relocation to Hong Kong, Eugene Ponomarev spent 12 years in the USA working as a scientist in top academic institutions such as Brigham and Women's Hospital, Harvard Medical School (Boston MA) where he held the position of Assistant Professor and his work was supported by RO1 grant form National Institute of Health.

Five recent representative publications

1. Starossom SC, Veremeyko T, Dukhinova M, Yung AWY, Weiner HL, **Ponomarev ED**. "Platelets Play Differential Role in the Regulation of the Initiation and Progression of Autoimmune Neuroinflammation." ***Circulation Research***, 2015; 117(9): 779-792
2. Starossom SC, Veremeyko T, Dukhinova M, Yung AWY, **Ponomarev ED**. "Glatiramer acetate (Copaxone) modulates platelet activation and inhibits thrombin-induced calcium influx: possible role of Copaxone in targeting platelets during autoimmune neuroinflammation." ***PLoS ONE***, 2014; 9(5): e96256.
3. Veremeyko T, Siddiqui S, Sotnikov I, Yung A and **Ponomarev ED**. "IL-4/IL-13-Dependent and Independent Expression of miR-124 and its Contribution to M2 Phenotype of Monocytic Cells in Normal Conditions and During Allergic Inflammation." ***PLoS ONE***, 2013; 8(12): e81774.
4. Sotnikov I, Vermeyko T, Starossom SC, Barteneva N, Weiner HL and **Ponomarev ED**. "Platelets recognize brain-specific glycolipid structures, respond to neurovascular damage and promote neuroinflammation." ***PLoS ONE***, 2013; 8(3): e58979.
5. **Ponomarev ED**, Veremeyko T, Krichevsky AK and Weiner HL. "MicroRNA-124 promotes microglia quiescence and suppresses EAE by deactivating macrophages via the CEBPalpha-PU.1 pathway." ***Nat Med***, 2011; 17:64-70

Technical expertise

- ✧ Immune cell isolation from different organs and their identification
- ✧ Cell cultures: neuronal and immune cells
- ✧ Experimental Autoimmune Encephalitis (EAE)
- ✧ FACS analysis (cell subsets, intracellular staining)
- ✧ microRNA
- ✧ Platelets / Glycolipids

Platelets mediate protective neuroinflammation and promote neuronal plasticity at the site of brain injury

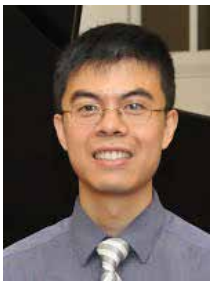
DUKHINOVA Marina, KUZNETSOVA Inna, VEREMEYKO Tatyana, YOUNG Amanda, KOPEIKINA Ekaterina, PONOMAREV Eugene

Neuro-degeneration, -development and Repair Program, School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, P.R.China.

Despite it is widely accepted that inflammation in the central nervous system (CNS) contributes to neurodegenerative diseases such as Alzheimer's disease (AD) and multiple sclerosis, it is not clear how inflammation in CNS is initiated during neurodegerative process in the absence of infection. It is also not clear whether inflammation in the CNS is beneficial or detrimental in case of AD or traumatic injury. Our laboratory is interested in earliest events of initiation of neuroinflammmation. One of the cells types that have capacity to immediately respond to neurovascular damage are platelets. Platelets are known to respond to a vascular damage, but their role in the neurodegenerative and neuroinflammatory diseases is not well known. We have previously found that administration of brain lipid rafts induced a massive platelet activation and degranulation. The brain-specific glycolipids (gangliosides) within brain lipid rafts were specifically recognized by the platelets and this recognition occurred during disruption of blood brain barrier, a hallmark of CNS inflammation. We compared inflammatory response in the CNS of wild-type (WT) vs. $ST3^{-/-}$ mice that lack of major brain-specific gangliosides. Our study revealed that level of microglia activation and leukocyte infiltration was substantially lower in $ST3^{-/-}$ animals. In addition, we found that after traumatic injury, ST3KO mice had substantially larger area of damage with dramatic neuronal loss. Interaction of platelets with brain lipid rafts in WT mice resulted in release of serotonin and platelet-activation factor that mediated recruitment of peripheral leukocytes and decreased CNS hemorrhage. Thus, these studies determined a new role of platelets as "innate immune cells" that directly recognize a neuronal damage and contribute to inflammation in the CNS. Our further studies indicated that interaction of platelets with brain lipid rafts in WT, but not $ST3^{-/-}$ mice resulted in increased growth of axons, increased number of dendritic spines leading to formation of new neuronal synapses at the area of neuronal damage. Platelet-derived factors also induced expression of early response genes in neurons: c-Fos, c-June, and BDNF. Collectively all these data indicate the role of platelet-brain lipid raft interactions in induction of protective neuroinflammation that restrict area of damage and promote neuronal plasticity.

Session (VI) Neurological and developmental disorders

Speaker Biography



Prof. CHEUNG Chi Kwan Vincent (張智鈞) is a native of Hong Kong. At present he is an Assistant Professor at the School of Biomedical Sciences of The Chinese University of Hong Kong. He obtained his bachelor degree in Mathematics and Pharmacology & Therapeutics from the University of British Columbia, Vancouver, and subsequently, Ph.D. in Neuroscience and Biomedical Engineering from MIT and the Harvard Medical School, and postdoc at the McGovern Institute for Brain Research of MIT. Over the last decade, Vincent's research has focused on understanding how the nervous system controls voluntary movement and enables learning of motor skills. On the applied side, Vincent is interested in exploring how knowledge of movement modules may be translated into a new rehabilitation strategy for stroke survivors. He and his collaborators at the Spaulding Rehabilitation Hospital, Boston, and the San Camillo Rehabilitation Hospital, Venice, have recently proposed that distinctive muscle-synergy patterns may be used as markers of motor cortical damage in stroke patients. In addition to his physiological and computational studies, Vincent has worked with Prof. Ki Goosens of MIT on motor cortical gene expression dynamics during motor skill acquisition using molecular and behavioral approaches. Vincent's papers have appeared in *Journal of Neuroscience*, *Journal of Neurophysiology*, *PNAS*, *PLoS ONE*, and *Neural Computation*. He has been invited to speak at conferences of the Neural Control of Movement Society, Society for Neuroscience USA, and World Congress for Neurorehabilitation.

Five recent representative publications

1. **Cheung VCK**, d'Avella A, Tresch MC, Bizzi E. "Central and sensory contributions to the activation and organization of muscle synergies during natural motor behaviors." ***Journal of Neuroscience***, 2005; 25(27): 6419-6434.
2. **Cheung VCK**, Piron L, Agostini M, Silvoni S, Turolla A, Bizzi E. "Stability of muscle synergies for voluntary actions after cortical stroke in humans." ***Proceedings of the National Academy of Sciences***, USA, 2009; 106(46): 19563-19568.
3. **Cheung VCK**, Turolla A, Agostini M, Silvoni S, Bennis C, Kasi P, Paganoni S, Bonato P, Bizzi E. "Muscle synergy patterns as physiological markers of motor cortical damage." ***Proceedings of the National Academy of Sciences***, USA, 2012; 109(36): 14652-14656. [Recommended by Faculty of 1000]
4. **Cheung VCK**, DeBoer C, Hanson E, Tunesi M, D'Onofrio M, Arisi I, Brandi R, Cattaneo A, Goosens KA. "Gene expression changes in the motor cortex mediating motor skill learning." ***PLoS ONE***, 2013; 8(4): e61496.
5. Devarajan K, **Cheung VCK.** "A quasi-likelihood approach to non-negative matrix factorization." ***Neural Computation***, 2016; in press.

Technical expertise

- ✧ electromyography (EMG) (humans / rodents)
- ✧ computational analysis of high-dimensional data and complex physiological and behavioral data sets
- ✧ Matlab software programming for analysis and data acquisition
- ✧ musculoskeletal and movement simulations using computers (e.g., OpenSim platform)
- ✧ human motion capture (VICON cameras; MotionCap)
- ✧ human and rodent motor behaviors (reaching; locomotion)
- ✧ optogenetics (mouse)

Neuromotor modules as markers of diseased states and progress of motor recovery

CHEUNG Vincent C.K.[1], **SEVERINI Giacomo**[2], **BONATO Paolo**[3], **TUROLLA Andrea**[4], **CHEUNG Roy T.H.**[5]

[1] Neuro-degeneration, -development and Repair Program, School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, P.R. China.
[2] School of Electrical and Electronic Engineering, University College Dublin, Dublin, Ireland.
[3] Department of Physical Medicine and Rehabilitation, Harvard Medical School, Boston MA, USA.
[4] IRCCS Fondazione Ospedale San Camillo, Venice, Italy.
[5] Department of Rehabilitation Sciences, The Hong Kong Polytechnic University, Hong Kong SAR, P.R. China.

It has been suggested that the combination of discrete motor modules is a viable framework for mechanistically understanding how the immense variety of movement patterns are generated by the CNS. In most formulations, a motor module consists of a set of time-invariant activation weights across many muscles (widely called a "muscle synergy"), and a time-varying coefficient that scales the muscle weights across time. Experiments performed using techniques ranging from multi-channel EMG recordings to optogenetics have provided evidences that support the neural origin of motor modules. If motor modules are indeed neurophysiological entities employed by the CNS for control, characterizing their deviations in diseased conditions should not only offer insights into the underlying pathology responsible for the dysfunctional movement, but also suggest how an effective intervention may be rationally designed. At the very least, distinctive patterns of abnormal motor modules may be robust signatures of particular diseased states, and thus be potentially used as markers for diagnosing a condition, or for evaluating the progress of recovery. Here, we argue, with two examples, that abnormal patterns of either the muscle weights or temporal activations of the motor modules may serve as markers of diseased states. The first example concerns upper-limb modules observed in stroke survivors. We have previously shown that severe post-stroke motor impairment is associated with merging of the modules' muscle weights, while the chronicity of stroke is reflected as fractionation of the muscle weights. Our preliminary results from chronic survivors undergoing rehabilitative training indicate that enhanced post-rehab motor recovery is associated with the activation of a specific module in the affected arm after rehab, one that can be regarded as a marker of post-training recovery. The second example concerns lower-limb modules observed in infants with delayed-onset locomotion, a condition with variable causes that affects up to 5-15% of newborns. We found in our pilot data that in these children, the temporal activation burst of one module was consistently time-shifted to the right relative to the burst of another module. Children responsive to physiotherapy displayed a post-rehab temporal activation pattern similar to that observed in age-matched, normally developed children. The above two examples illustrate the potential of using either the muscle weights or temporal activations of specific modules for early detection and/or evaluation of recovery progress for different movement disorders.

Session (VI) Neurological and developmental disorders

Speaker Biography

Prof. TSUI Kwok Wing Stephen (徐國榮) is currently a professor in the School of Biomedical Sciences and directors of the Hong Kong Bioinformatics Centre and the Centre for Microbial Genomics and Proteomics in The Chinese University of Hong Kong (CUHK). In 1992, he started his M.Phil. study and later received his Ph.D. degree from the Biochemistry Department of CUHK in 1995 under the supervision of Professor Mary Miu-Yee Waye and Professor Cheuk-Yu Lee. The topic of his thesis was related to the study of the human genome and the expression of cardiovascular genes. After two-year post-doctoral training in the same department, he was appointed as an Assistant Professor in 1997 and promoted to the full professorship in 2004. He was also a former member of the International HapMap Consortium and worked on the single nucleotide polymorphisms of human chromosome 3p. During the SARS outbreak in 2003, his team was one of the earliest teams that cracked the complete genome of the SARS-coronavirus. Totally, he has published more than 180 scientific papers in international referred journals, including *Nature, New England Journal of Medicine*, *Lancet, PNAS*, *Circulation*, *Journal of Allergy and Clinical Immunology*, *Genome Biology and Nucleic Acid Research* (*H index* = 32 and cumulative citations >9,900). He is very interested in clinical and microbiological genomics and bioinformatics. In 2015, his team cracked the genome, transcriptome and microbiome of *Dermatophagoides farinae*, an important species that can be linked to the house dust mite allergy.

Five recent representative publications

1. Yang KY, Chen Y, Ng PKS, Zhou WJ, Chen JY, Mao BY, **Tsui SKW**. "Transcriptome analysis of different developmental stages of amphioxus reveals dynamic changes of distinct classes of genes during development." ***Sci Rep***, 2016; 6:23195.
2. Fung ELW, Kwok JSL, **Tsui SKW**. "SCN8A mutations in Chinese children with early onset epilepsy and intellectual disability." ***Epilepsia***, 2015; 56(8):1319-20.
3. Zhang Y, Li SK, Yang KY, Liu MH, Lee N, Tang X, Wang H, Liu L, Chen Z, Zhang CY, Wang JH, **Tsui SKW**. "Whole genome methylation array reveals the down-regulation of IGFBP6 and SATB2 by HIV-1." ***Sci Rep***, 2015; 5:10806.
4. Chan TF, Ji KM, Yim AKY, Liu XY, Zhou JW, Li RQ, Yang KY, Li J, Li M, Law PTW, Wu YL, Cai ZL, Qin H, Bao Y, Leung RKK, Ng PKS, Zou J, Zhong XJ, Ran PX, Zhong NS, Liu ZG, **Tsui SKW**. "The draft genome, transcriptome and microbiome of Dermatophagoides farinae reveal a broad spectrum of dust mite allergens." ***J Allergy Clin Immunol***, 2015; 135:539-548.
5. Chan TM, Leung KS, Lee KH, Wong MH, Lau CK, **Tsui SKW**. "Subtypes of associated Protein-DNA (TF-TFBS) patterns." ***Nucleic Acid Res***, 2012; 40(19):9392-403.

Technical expertise

- ✧ Genomics and bioinformatics

Whole exome sequencing to dissect the genetic factors behind developmental delay and learning difficulties

KWOK Sui Lam Jamie[1], HAU Wai Lok Edgar[2], ZUO Xiang[3], FUNG Lai Wan Eva[4], LO Fai Man Ivan[2], TSUI Kwok Wing Stephen[1,3,5].

[1] Cancer and Inflammation Program, School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, P.R. China.
[2] Clinical Genetic Service, Department of Health, Hong Kong SAR, P.R. China.
[3] Division of Genomics and Bioinformatics, Innovation Institute of Trans-omics, The Chinese University of Hong Kong, Hong Kong SAR, P.R. China.
[4] Department of Paediatrics, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, P.R. China.
[5] Hong Kong Bioinformatics Centre, The Chinese University of Hong Kong, Hong Kong SAR, P.R. China.

Developmental disorders (DD) affect 1-3% of children worldwide. DD is defined as a disorder in which the most prominent pathogenetic mechanism occurs during embryogenesis or early brain development. Therefore, the majority of children with DD have an abnormality of the nervous system, including autism and developmental delay, defined as significant impairment in two or more of the following developmental domains: motor, language, cognition, social, or activities of daily living. In Hong Kong, a crude statistical assessment indicated that the total number of persons with intellectual disability was likely to be in the range of 71,000 to 101,000. Current understanding of the various DD is limited due to its genotypic and phenotypic heterogeneity. Traditional first-tier tests such as G-banded karyotype and array comparative genomic hybridization (aCGH) have a diagnosis rate of approximately 15%. Chromosomal microarray was developed later, and large studies have reported diagnostic rates for patients of developmental delay/intellectual disability of 19%. In spite of the improvements, this leaves the remaining majority of cases having no diagnosis. Recently, researchers and clinicians are turning towards whole exome sequencing (WES) for DD cases with negative results from traditional tests. There is consensus that *de novo* mutations are one of the causes of DD according to multiple studies. In this study, we have successfully found *de novo* mutations (DNM) in 24 of 30 trios that previously failed to be diagnosed using traditional methods. For Patients 4, 10, 14, 16, 23, 24 and 26, we have found compelling evidence showing that the identified genes are probably causative because their DNM could explain these patients' phenotypes and the genes in which their DNM occur have been previously confirmed to be a DD gene in DDG2P database of genotype-phenotype correlation of DD. For Patients 3, 6, 12, 15, 20 and 27, their DNM is in a gene that is a related family member of known DD genes. In fact, Patients 4, 10, 16 and 26 also have another DNM that is a related family member of known DD genes, suggesting that modifier effects may be present to contribute to the deviation of phenotypes from other cases diagnosed with the same primary DNM. For the remaining patients, either evidence of the causation of the DNM and phenotype are not as certain, or no DNM was found at all. In conclusion, WES is a better method to confirm diagnosis for those patients with diseases of unknown causes.

Acknowledgements

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