香港大學心臟血管研究所
THE UNIVERSITY OF HONG KONG
INSTITUTE OF CARDIOVASCULAR SCIENCE AND MEDICINE

26th Annual Scientific Meeting of ICSM

Translational Science Transforming Cardiovascular Medicine

In conjunction with

Hong Kong College of Cardiology Seminar

Optimizing the Journey and Outcome for Patients with Chest Pain

4th Nov 2023, LKS Faculty of Medicine, HKU

Table of Contents

Meeting Details

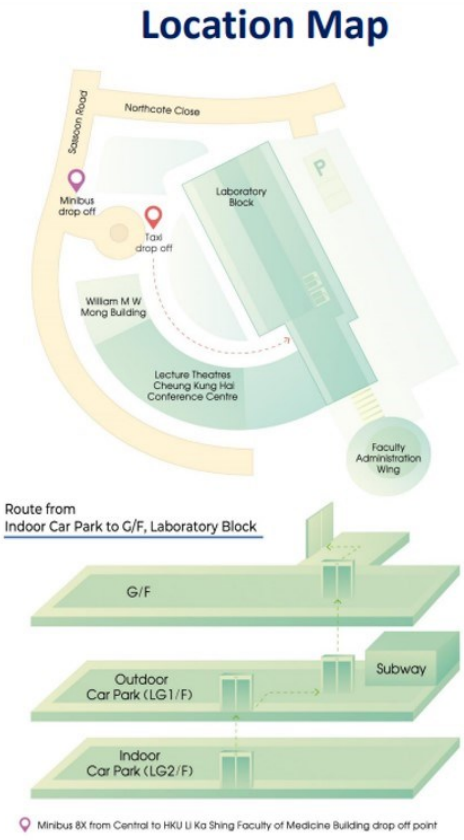
ICSM

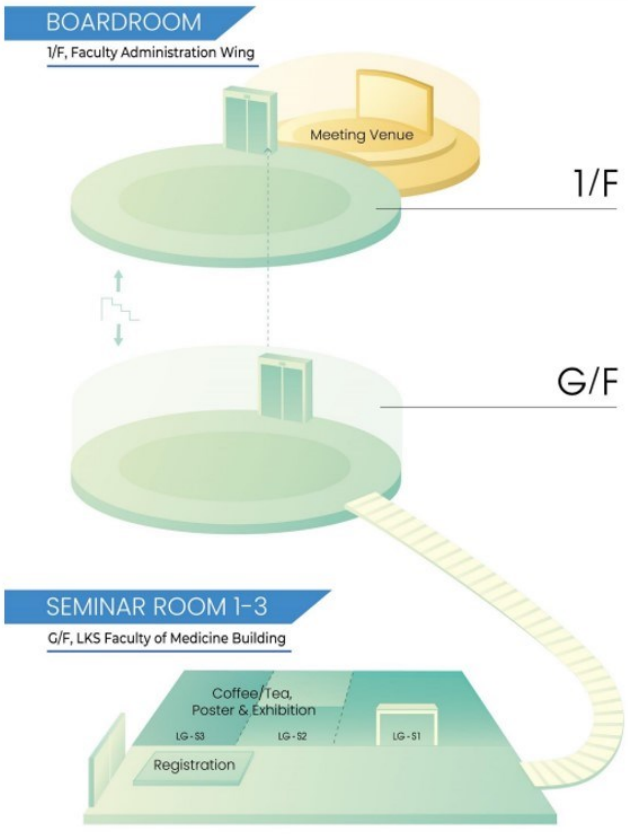
Date: 4 November 2023

Time: 08:55 to 18:00 (Registration starts at 08:30)

Venue: LKS Faculty of Medicine Building, The University of Hong Kong, 21 Sassoon Road, Hong Kong

Registration	Seminar Room 2-3 Foyer, G/F
Coffee/Tea, Posters & Exhibitions	Seminar Room 2-3, G/F
Main Meeting & Lunch	Boardroom, 1/F, Faculty Administration Wing
Annual General Meeting	Boardroom, 1/F, Faculty Administration Wing





Organizing Committee

Co-Chairpersons:	Dr. C.L. Cheung Prof. Kelvin KH Yiu
Members:	Prof. Bernard Cheung Prof. Yu Huang Dr. George Leung Dr. Susan Leung Dr. Gloria Li Dr. Judith Mak Prof. David CW Siu Prof. Xiaoqiang Yao

Supporting Organizations

The Organizing Committee would like to extend their sincere thanks to the supporting organizations for their supports to the 26th Annual Scientific Meeting of ICSM.

Sun Chieh Yeh Heart Foundation
Sponsored the Young Investigator Awards

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Director of cardiac catheterization laboratory
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Dr. Ada KC Cheung
Resident Specialist
Department of Medicine and Geriatrics
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Dr. Chung-Leung Tang
Consultant
Accident & Emergency Department
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Dr. Chiu-Sun Yue
Consultant and Head
Division of Cardiology Dept of Medicine & Geriatrics
United Christian Hospital

Programme

ICSM

4 November 2023 (Sat)

Time	Faculty Boardroom, Li Ka Shing Medical Faculty, HKU	
09:00-09:12	Cardiovascular Translational Research: A Brief Introduction to Our Work *Prof. Guowei He, Tianjin University*	
09:12-10:00	**Young Investigator Oral Presentation** *Chairs: Prof. Xiaoqiang Yao, Dr. Judith Mak* *Judges: Dr. Susan Leung, Dr. Gloria Li*	
	OP1	Thioridazine Alleviates Disturbed Flow-Induced Endothelial Inflammation and Atherosclerosis Via Inhibition of Rhoa-Yap Axis *Minchun Jiang*
	OP2	Concomitant Aortic Stenosis and Left Ventricular Mass Predict Postoperative Adverse Outcomes Regardless of Valvular Morphology in Patients With Aortic Regurgitation *Ching-Yan Zhu*
	OP3	Homocysteine Compromises the Function Of Perivascular Adipose Tissue Surrounding Human Internal Mammary Artery *Jia-Hui Wei*
	OP4	Retinol Dehydrogenase 10 Reduction Promotes Diabetic Cardiomyopathy via Disturbed Cardiac Retinol Metabolism *Yandi Wu*
	OP5	Endothelial SIRT1 Regulates the Circadian Rhythms of Cardiovascular and Metabolic Function by Enhancing Leucine Catabolism in Brown Adipose Tissue *Zhongyan Zhou*
	OP6	Prognostic Implication of Novel Computational Pressure-Flow Dynamics Derived Fractional Flow Reserve (CaFFR) in Patients with Non-Obstructive Coronary Artery Disease (NOCAD) *Yik-Ming Hung*
10:00-10:40	Coffee break / Poster viewing	
10:00-10:40	Poster Presentations (3 mins each) Judges: Dr. David Cai, Dr. Susan Leung, Dr Gloria Li, Dr. Judith Mak	
	Session 1 **Chairs: Prof. Yu Huang, Dr. Susan Leung**	
10:40-11:10	KChIP2 Regulation and Arrhythmia *Prof. Jie Liu, Shenzhen University*	
11:10-11:40	Brown Adipose Tissue: A Hidden Asset in Cardiovascular Medicine *Dr. Hannah Hui, CUHK*	
	Session 2 **Chair: Prof. Kelvin Yiu**	
11:40-12:10	Ultrafast Echocardiography and Its New Opportunities with Artificial Neural Networks *Dr. Wei-Ning Lee, HKU*	
12:10-12:40	A Pair of Adaptor Proteins APPL1 & APPL2 in Control of Metabolic and Vascular Diseases *Dr. Kenneth KY Cheng, PolyU*	

12:40-14:00	Lunch break
	Optimizing the Journey and Outcome for Patients with Chest Pain *Chair: Prof. Bernard Cheung and Dr. Kin-Lam Tsui*
14:00-14:30	Pre-hospital and Emergency Department Management of Acute Chest Pain *Dr. Chung-Leung Tang, QMH*
14:30-15:00	*Symposium sponsored by Amgen* *Optimizing LDL-C Management Post MI: From Clinical Evidences to Patient Cases* *Dr. Lap-Tin Lam, GH*
15:00-15:30	Minimizing Door-to-Balloon Time in Primary Percutaneous Coronary Intervention *Dr. Alan KC Chan, QEH*
15:30-15:45	Break
15:45-16:15	Maximizing the Uptake Rate for Cardiac Rehabilitation *Dr. Chiu-Sun Yue, UCH*
16:15-16:45	Case presentations *Dr. Ada Cheung, PMH & Dr. Raymond Cheung, TMH*
16:45-16:50	Young Investigator Awards Presentation *Prof. Kelvin Yiu*
16:50-17:00	Closing Remarks by *Prof. Kelvin Yiu*
17:00-17:05	Break
17:05-17:35	**AGM**

26th ICSM AGM

ICSM

Annual Report

CME Accreditations

College / Association	CME Points Accredited		
	Max. for whole functions	4 Nov 2023 (08:55-18:00)	Category
Hong Kong College of Community Medicine	6	6	PP-PP
Hong Kong College of Emergency Medicine	6	6	CME-PP
The Hong Kong College of Family Physicians	5	5	OEA-5.02
The Hong Kong College of Pathologists	6	6	CME-PP
Hong Kong College of Physicians	4	4	PP-PP
Hong Kong College of Radiologists	6	6	B-PP
The College of Surgeons of Hong Kong	6	6	CME-PP
MCHK Programme accredited by HKAM*	Pending	Pending	Pending

**CME accreditation as of 9 Nov 2023

Contact Us

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c/o Talent Consultants
Tel / WhatsApp: (852) 9257 8453
E-mail: icsm2023@talent-links.com

Young Investigator Award
Oral Presentations

OP1	**THIORIDAZINE ALLEVIATES DISTURBED FLOW-INDUCED ENDOTHELIAL INFLAMMATION AND ATHEROSCLEROSIS VIA INHIBITION OF RHOA-YAP AXIS** Minchun Jiang, Huanyu Ding, Xiaoqiang Yao, Li Wang, Yu Huang School of Biomedical Sciences, The Chinese University of Hong Kong, Hong Kon
OP2	**CONCOMITANT AORTIC STENOSIS AND LEFT VENTRICULAR MASS PREDICT POSTOPERATIVE ADVERSE OUTCOMES REGARDLESS OF VALVULAR MORPHOLOGY IN PATIENTS WITH AORTIC REGURGITATION** CY Zhu, JN Zhang, YK Tse, JY Huang, QW Ren, MZ Wu, KH Yiu Division of Cardiology, Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong
OP3	**HOMOCYSTEINE COMPROMISES THE FUNCTION OF PERIVASCULAR ADIPOSE TISSUE SURROUNDING HUMAN INTERNAL MAMMARY ARTERY** Jia-Hui Wei[1], Hang Qi[1], Yang Zhou[1], Hai-Tao Hou[1], Guo-Wei He[1,2], Qin Yang[1*] [1]Institute of Cardiovascular Diseases & Department of Cardiovascular Surgery, TEDA International Cardiovascular Hospital, Chinese Academy of Medical Sciences and Peking Union [2]Medical College & Tianjin University, Tianjin 300457, China Department of Surgery, Oregon Health and Science University, Portland, OR 97239-3098, USA
OP4	**RETINOL DEHYDROGENASE 10 REDUCTION PROMOTES DIABETIC CARDIOMYOPATHY VIA DISTURBED CARDIAC RETINOL METABOLISM** WU Yandi[1], CAI Weibin[2#] [1]Department of Biomedical Sciences, City University of Hong Kong, Hong Kong SAR [2]Zhongshan School of Medicine, Sun Yat-sen University, Guangzhou, Guangdong, China
OP5	**ENDOTHELIAL SIRT1 REGULATES THE CIRCADIAN RHYTHMS OF CARDIOVASCULAR AND METABOLIC FUNCTION BY ENHANCING LEUCINE CATABOLISM IN BROWN ADIPOSE TISSUE** Zhongyan Zhou, Yu Wang Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong SAR, China
OP6	**PROGNOSTIC IMPLICATION OF NOVEL COMPUTATIONAL PRESSURE-FLOW DYNAMICS DERIVED FRACTIONAL FLOW RESERVE (CAFFR) IN PATIENTS WITH NON-OBSTRUCTIVE CORONARY ARTERY DISEASE (NOCAD)** YM Hung, KH Yiu, HC Xuan Division of Cardiology, Department of Medicine, Queen Mary Hospital, University of Hong Kong, Hong Kong Division of Cardiology, Department of Medicine, The University of Hong Kong Shenzhen Hospital, Shenzhen, People's Republic of China

Young Investigator Award
Oral Presentations

OP1

THIORIDAZINE ALLEVIATES DISTURBED FLOW-INDUCED ENDOTHELIAL INFLAMMATION AND ATHEROSCLEROSIS VIA INHIBITION OF RHOA-YAP AXIS

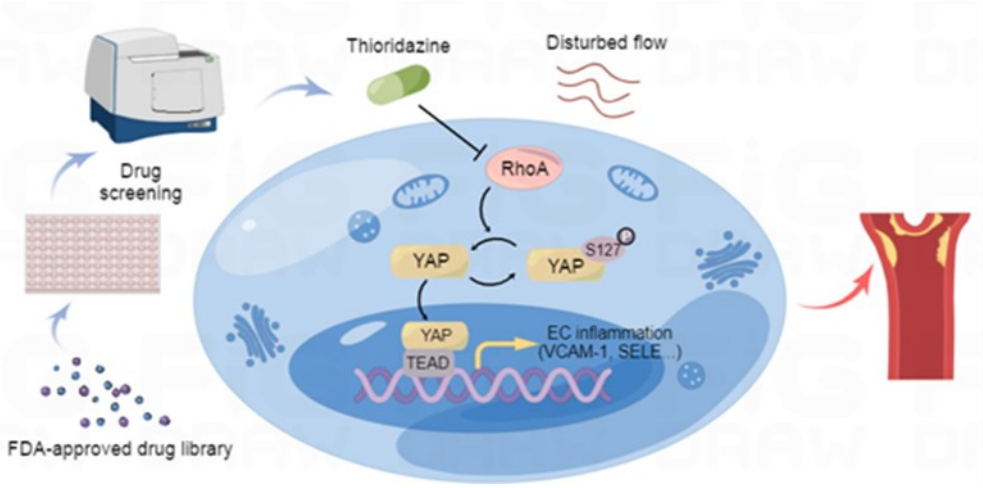
Minchun Jiang, Huanyu Ding, Xiaoqiang Yao, Li Wang, Yu Huang

School of Biomedical Sciences, The Chinese University of Hong Kong, Hong Kong

Objectives: Atherosclerotic diseases remain a prominent cause of adult mortality and pose significant challenges to global healthcare systems. Our previous studies have unveiled the role of disturbed flow- induced YAP (Yes-associated protein) activation in endothelial inflammation and atherosclerosis. Targeting YAP has emerged as a promising strategy to alleviate endothelial inflammation and atherogenesis. In light of these findings, we established a luciferase reporter assay -based drug screening platform to identify novel YAP inhibitors with potential anti-atherosclerotic properties.

Methods and Results: Through screening the FDA-approved drug library, we found that thioridazine, a known antipsychotic medication, effectively suppressed YAP activity in human endothelial cells. Further investigations demonstrated that thioridazine exerted a substantial inhibitory effect on disturbed flow- induced endothelial inflammatory responses, both in vitro and in vivo. Mechanistically, we found that thioridazine's anti-inflammatory properties were mediated through inhibiting YAP nuclear translocation, achieved by restricting RhoA activity. Importantly, administration of thioridazine attenuated atherosclerosis in two distinct mouse models induced by partial carotid ligation and a western diet.

Conclusions: This study opens up the possibility of repurposing thioridazine for intervention of atherosclerotic diseases. Furthermore, our investigation has provided insights into the mechanisms underlying thioridazine's capacity to attenuate endothelial activation and atherogenesis, primarily through the repression of the RhoA-YAP axis. As a new YAP inhibitor, thioridazine necessitates further investigation to assess its suitability for clinical use in treating atherosclerotic diseases.



OP2

CONCOMITANT AORTIC STENOSIS AND LEFT VENTRICULAR MASS PREDICT POSTOPERATIVE ADVERSE OUTCOMES REGARDLESS OF VALVULAR MORPHOLOGY IN PATIENTS WITH AORTIC REGURGITATION

CY Zhu, JN Zhang, YK Tse, JY Huang, QW Ren, MZ Wu, KH Yiu

Division of Cardiology, Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Background: Bicuspid aortic valve (BAV) predicts adverse cardiac remodelling and postoperative heart failure in patients with severe aortic stenosis. Whether BAV predicts left ventricle (LV) remodelling and adverse outcomes in aortic regurgitation (AR) patients undergoing aortic valve replacement (AVR) remains unclear. Using clinical, laboratory, echocardiographic, and surgical data, we explored the preoperative and surgical differences between BAV and tricuspid aortic valve (TAV) patients with AR, and differences in postoperative adverse outcomes.

Methods: Three-hundred twenty-three patients with moderate to severe AR without severe AS undergoing AVR were included, with either BAV (n=70) or TAV (n=253). Baseline clinical, laboratory, medication, and echocardiographic data, as well as surgical data, were analysed. Follow-up data was collected and analysed for adverse events, defined as the composite outcome of all-cause mortality and heart failure rehospitalization. Kaplan-Meier and interaction analyses were performed, as well as Cox regression analysis adjusted for age, sex, diabetes, hypertension, euroSCORE II, LV ejection fraction (LVEF) and LV end-systolic dimension (LVESD).

Results: Patients with BAV were a decade younger ($p<0.001$) and had more concomitant AS ($p<0.001$). They also had lower surgical risk scores ($p<0.001$) and shorter aortic cross-clamp durations during AVR ($p=0.036$). AV morphology significantly interacts with LVESD on LVEF, where patients with TAV showed greater LVEF decline with LVESD elevation ($p_{interaction} = 0.004$). Patients with BAV experienced less adverse events than those with TAV (HR: 0.50 (1.07 – 3.80), log-rank $P = 0.03$). After multivariable Cox regression analysis, significant predictors of adverse events were indexed aortic valve area (AVAi) ($p = 0.042$), indexed left ventricular mass (LVMi) ($p = 0.013$), and indexed left atrial volume (LAVi) ($p = 0.031$). The presence of BAV or TAV did not independently predict adverse outcomes.

Conclusion: Patients with BAV were younger and had more concomitant AS, as well as better surgical characteristics and less postoperative adverse events than those with TAV. Systolic function was more preserved in patients with BAV with LV dilation. However, adverse outcomes were significantly predicted by the degree of concomitant aortic stenosis, LV hypertrophy, and left atrial dilation, regardless of aortic valve morphology

Young Investigator Award
Oral Presentations

OP3

HOMOCYSTEINE COMPROMISES THE FUNCTION OF PERIVASCULAR ADIPOSE TISSUE SURROUNDING HUMAN INTERNAL MAMMARY ARTERY

Jia-Hui Wei[1], Hang Qi[1], Yang Zhou[1], Hai-Tao Hou[1], Guo-Wei He[1,2], Qin Yang[1*]

[1]Institute of Cardiovascular Diseases & Department of Cardiovascular Surgery, TEDA International Cardiovascular Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College & Tianjin University, Tianjin 300457, China

[2]Department of Surgery, Oregon Health and Science University, Portland, OR 97239-3098, USA

Objectives: Perivascular adipose tissue (PVAT) surrounding human internal mammary artery (IMA) possesses anticontractile property. The function of PVAT surrounding the IMA (IMA-PVAT) under pathological conditions is barely studied. We previously reported that homocysteine, a risk factor for cardiovascular disease, impairs the vasodilator function of IMA through endothelium and smooth muscle- dependent mechanisms. In this study, we investigated the effect of homocysteine on the function of IMA- PVAT and the associated mechanisms.

Methods: Residual IMA tissues were collected from patients undergoing coronary artery bypass grafting. The tissue from each individual patient was divided into control group and homocysteine-exposed group. Anticontractile and vasorelaxing activity of IMA-PVAT was studied using myograph. Adiponectin content in the PVAT was measured by ELISA. Expressions of adiponectin receptors (AdipoR1 and AdipoR2), eNOS, and p-eNOS in IMA were determined by RT-qPCR and Western-blot.

Results: Exposure to homocysteine augmented the contractile responses of PVAT-intact (PVAT+) IMA to U46619 and KCl, regardless with (E+) or without (E-) endothelium. “PVAT transfer” experiments showed that U46619 and KCl elicit greater contractile response in “skeletonized IMA + homocysteine-exposed PVAT” group than in “skeletonized IMA + control PVAT” group. A certain degree of relaxant response to acetylcholine was observed in PVAT+E- IMA and such PVAT-mediated relaxation was attenuated by homocysteine in terms of both magnitude (Rmax: 8.28±1.53% vs. 18.59±3.06% in control, P=0.027) and the sensitivity to acetylcholine (EC50: -6.10±0.23 vs. -6.79±0.20 LogM in control, P=0.045). Moreover, homocysteine weakened the relaxant response of skeletonized IMA to adiponectin receptor agonist AdipoRon (P=0.0009, two-way repeated measures ANOVA) with maximal relaxation decreased from 65.14±4.90% to 45.69±5.99% (P=0.027, Students’ t-test). Homocysteine lowered adiponectin content in IMA-PVAT, and downregulated the expression of AdipoR1 and AdipoR2 in skeletonized IMA with or without endothelium. Homocysteine exposure also decreased eNOS and p-eNOS in skeletonized IMA. The relaxant response of skeletonized IMA to AdipoRon was blunted by eNOS inhibitor (P<0.0001, two-way repeated measures ANOVA; Rmax: 51.17±4.33% vs. 68.78±3.43% in control, P=0.0078), and homocysteine significantly attenuated the inhibitory effect of eNOS inhibitor on AdipoRon-induced relaxation.

Conclusions: Homocysteine impairs the anticontractile/vasorelaxing activity of PVAT surrounding the IMA through inhibiting adiponectin/adiponectin receptor/eNOS//NO signaling pathway. Results derived from this study enriched our understanding of the unfavorable effect of homocysteine on IMA vasoreactivity and provided additional evidence in support of the discussion that if preserving the PVAT could help prevent postoperative vasospasm of the arterial grafts and potentially improve their physiological properties.

Young Investigator Award
Oral Presentations

OP4

RETINOL DEHYDROGENASE 10 REDUCTION PROMOTES DIABETIC CARDIOMYOPATHY VIA DISTURBED CARDIAC RETINOL METABOLISM

WU Yandi[1], CAI Weibin[2#]

[1]Department of Biomedical Sciences, City University of Hong Kong, Hong Kong SAR
[2]Zhongshan School of Medicine, Sun Yat-sen University, Guangzhou, Guangdong, China

Background: Diabetes mellitus (DM) is an independent risk factor for cardiovascular diseases and can independently induce structural and functional disruptions in the heart, leading to diabetic cardiomyopathy (DCM). With the application of new therapies, most complications of DM have been effectively controlled, and the life expectancy of DM patients has been extended, while hidden myocardial injury has become the leading cause of death in DM patients. Mechanistic studies are key to improving the prevention and treatment of DCM. Retinol (vitamin A, Rol) and all-trans retinoic acid (atRA) are metabolites of retinol metabolism that have been shown to have altered levels in diseases. The study demonstrated that retinoic acid receptors (RARs) were reduced in the hearts of diabetic rats and activating these receptors by atRA or other activators prevented myocardial injury; however, it remains unknown whether cardiac retinol metabolite levels are altered and whether these alterations are involved in DCM.

Methods: LC-MS/MS, WB, and IHC assays were performed in type 2 diabetic (T2DM) mice and patients to identify disordered cardiac retinol metabolism in DCM; db/db mice were supplemented with Rol or atRA to demonstrate the differential effects of retinol (Rol) and all-trans retinoic acid (atRA) on DCM; and RDH10 cardiomyocyte-specific knockout (RDH10-cKO) mice and db/db mice injected with RDH10 overexpressing adeno-associated virus were used to validate the role and importance of RDH10 in cardiac retinol metabolism and DCM.

Results: With this study, we demonstrated that in T2DM, impaired cardiac retinol metabolism caused by cardiac RDH10 reduction results in DCM through Rol overload-induced cardiotoxicity and atRA deficiency-induced lipotoxicity and ferroptosis.

Conclusion: In summary, in this study, we report for the first time that in T2DM, RDH10 reduction leads to cardiac retinol metabolism disorder characterized by Rol overload, atRA deficiency, and RARs reduction, and promotes diabetic cardiomyopathy through Rol overload-induced cardiotoxicity and atRA deficiency-induced lipotoxicity and ferroptosis. Based on these findings, we suggest that atRA and RDH10 could be potential targets for the prevention and treatment of DCM by correcting disordered retinol metabolism, whereas retinol, as known as vitamin A, should be avoided in patients with type 2 diabetes because of its deleterious effects on the heart in excess.

Young Investigator Award
Oral Presentations

OP5

ENDOTHELIAL SIRT1 REGULATES THE CIRCADIAN RHYTHMS OF CARDIOVASCULAR AND METABOLIC FUNCTION BY ENHANCING LEUCINE CATABOLISM IN BROWN ADIPOSE TISSUE

Zhongyan Zhou, Yu Wang

Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong SAR, China

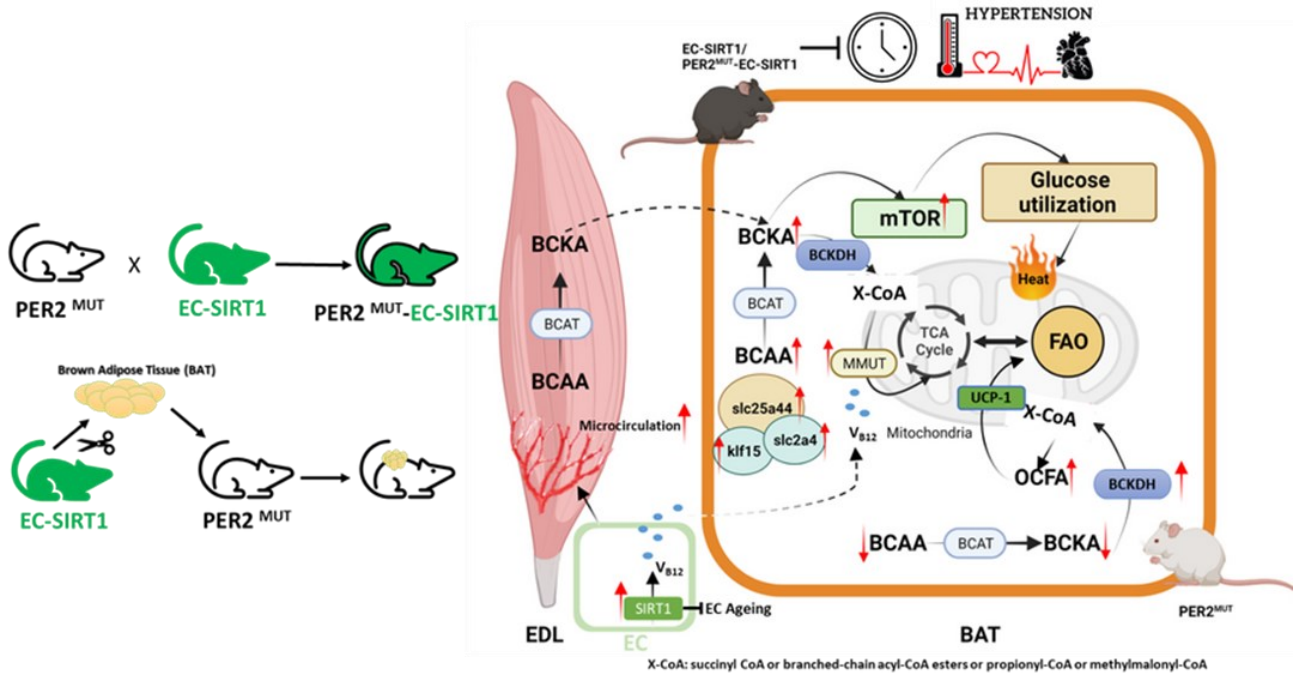
Background: Mutation of period-2 (PER2), one of the key clock genes, leads to abnormal circadian rhythmicity, cardiovascular and metabolic dysfunction. Sirtuin 1 (SIRT1) is a positive regulator of the circadian clock circuitry and promotes cardiometabolic homeostasis. However, the mechanisms underlying the regulation and coordination of the cardiovascular and metabolic circadian rhythms by PER2 and SIRT1 remain largely unknown.

Objective: The present study aims to investigate whether and how endothelial overexpression of SIRT1 restores the circadian rhythms of cardiovascular and metabolic function in PER2 mutant mice (PER2MUT).

Methods: PER2MUT were crossbred with EC-SIRT1, a transgenic mouse model with overexpression of human SIRT1 selectively in endothelial cells, to produce PER2MUT/EC-SIRT1. The implantable radio - telemetry and indirect calorimetry were applied to monitor the circadian rhythms of blood pressure (BP), heart rate (HR) and body core temperature. The Comprehensive Lab Animal Monitor System (CLAMS) was used for the measurement of oxygen consumption (VO2), carbon dioxide production (VCO2), respiratory exchange ratio (RER) and energy expenditure. The mitral inflow, left ventricular (LV) filling and diastolic cardiac function were examined by pulsed doppler and echocardiography. The metabolites were detected by gas chromatography-mass spectrometry (GC-MS). Transplantation of BAT was performed for assessing the effect of endothelial SIRT1 on circadian rhythms of cardiovascular and metabolic function.

Results: Endothelial overexpression of human SIRT1 prevented the loss-of-cardiovascular and metabolic rhythmicity, the development of hypertension, vascular and cardiac dysfunctions in PER2 mutant mice. Mechanistically, PER2 mutation caused microvascular rarefaction in skeletal muscle and reduced the systemic delivery of branched-chain α-keto acids (BCKA), the metabolites of branched-chain amino acids (BCAA), for gluconeogenesis in liver and substrate utilization in brown adipose tissue (BAT). Overexpression of endothelial SIRT1 enhanced leucine catabolism, which then facilitated the thermogenic utilization of glucose in BAT of EC-SIRT1 and PER2MUT/EC-SIRT1, especially during the transition from day/light (inactive) to night/dark (active) cycles. By promoting the thermogenic oscillations in BAT, endothelial SIRT1 restored the circadian rhythmicity and cardiometabolic homeostasis in PER2 mutant mice. Transplantation of BAT from EC-SIRT1 restored the circadian oscillation of cardiovascular function, and prevented the development of hypertension and cardiac abnormalities in PER2 mutant mice.

Conclusion: PER2 mutation affected the cardiovascular and metabolic circadian rhythms by disruption of the leucine catabolism in BAT, which was ameliorated by endothelial overexpression of SIRT1. Endothelial SIRT1 acts as a peripheral circadian clock to synchronize the metabolic flux between different organs, in turn maintaining cardiovascular as well as energy rhythmicity and homeostasis thus preventing the development of cardiometabolic diseases.



Young Investigator Award
Oral Presentations

OP6

PROGNOSTIC IMPLICATION OF NOVEL COMPUTATIONAL PRESSURE-FLOW DYNAMICS DERIVED FRACTIONAL FLOW RESERVE (CAFFR) IN PATIENTS WITH NON-OBSTRUCTIVE CORONARY ARTERY DISEASE (NOCAD)

YM Hung, KH Yiu, HC Xuan

Division of Cardiology, Department of Medicine, Queen Mary Hospital, University of Hong Kong, Hong Kong
Division of Cardiology, Department of Medicine, The University of Hong Kong Shenzhen Hospital, Shenzhen, People's Republic of China

Objectives: A novel index named caFFR has demonstrated its remarkable precision to align with FFR measurements in coronary arteries based on coronary angiography. While several FFR studies have proved its importance in patients with coronary artery disease, its relevance in NOCAD patients has yet to be explored. Due to its minimally invasive nature, our objective was to assess the clinical value of caFFR measurement in NOCAD patients.

Methods: From 2014 to 2017, we enrolled patients with ≤ 50% diameter stenosis and underwent successful caFFR measurement with a value ≥ 0.8 in all three major coronary arteries on coronary angiography. In this study, a total of 490 NOCAD patients (mean age 64.39 ± 11.16, 55.5% male) were included. The sum of caFFR values in the three vessels was calculated for each patient. We categorized the patients based on the following criteria: the median value (0.93) of the left anterior descending (LAD) artery, the number of arteries with a value less than the median of all coronary arteries (0.93), and the median value (2.78) of the total 3-vessel (3V). The 3V grouping can reflect the total physiologic atherosclerotic burden. The primary endpoint of this study was major adverse cardiac events (MACE) at 5 years, defined as a composite of cardiac death, myocardial infarction, and ischemia-driven revascularization.

Results: In LAD analysis, the p-value of using median to predict 5-year MACE rate in low and high caFFR group is insignificant. In multi-vessel analysis, patients with 2-3 vessels lower than median value of all coronary arteries show an increased risk of 5-year MACE than patients with only 0-1 vessel (8.60% vs. 3.32%; hazard ratio [HR] 2.648, 95% confidence interval [CI] 1.141 - 6.145, P = 0.023). In 3-vessel analysis, patients in the low 3V-caFFR group demonstrated a higher risk of 5-year MACE compared to those in the high 3V-caFFR group (8.58% vs. 3.6%; [HR] 2.43, 95% [CI] 1.087 - 5.433, P = 0.031).

Conclusion: Among NOCAD patients, those with a higher number of vessels with low caFFR value and lower sum of caFFR values exhibited increased clinical outcomes at a 5-year rate of MACE. Unlike single- vessel caFFR, both multiple-vessel and 3V caFFR measurements serve as valuable prognostic indicators for NOCAD patients.

Young Investigator Award
Poster Presentations

PP01	**AMPK-DEPENDENT YAP INHIBITION MEDIATES THE PROTECTIVE EFFECT OF METFORMIN AGAINST OBESITY-ASSOCIATED ENDOTHELIAL DYSFUNCTION AND INFLAMMATION** Lijing Kang [1,2,3], Yu Huang[1,2], Li Wang[1] [1] Department of Biomedical Sciences, City University of Hong Kong, Hong Kong, China [2] Hong Kong Center for Cerebro-Cardiovascular Health Engineering, Hong Kong, China [3] School of Biomedical Sciences, The Chinese University of Hong Kong, Hong Kong, China
PP02	**IDENTIFICATION AND FUNCTIONAL VERIFICATION OF CITED2 GENE PROMOTER REGION IN PATIENTS WITH PATENT DUCTUS ARTERIOSUS** Zhuo Chen, Huan-Xin Chen, Hai-Tao Hou, Xiu-Yun Yin, Qin Yang, Guo-Wei He* The Institute of Cardiovascular Diseases & Department Cardiovascular Surgery, TEDA International Cardiovascular Hospital, Tianjin University, No.61, 3rd Ave, TEDA, Tianjin, 300457, China
PP03	**TRIBULUS TERRESTRIS L. EXTRACT AMELIORATES ATHEROSCLEROSIS BY INHIBITION OF VASCULAR SMOOTH MUSCLE CELL PROLIFERATION IN APOE -/- MICE AND A7R5 CELLS VIA SUPPRESSION OF AKT/MEK/ERK SIGNALING** Jing Zhang[a,1], Wai-Rong Zhao[a,1], Wen-Ting Shi[a,1], Jun-Jie Tan[b] , Kai-Yu Zhang[a] , Jing-Yi Tang[a] , XinLin Chen[a,*], Zhong-Yan Zhou[a,**] [a] Longhua Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, China [b] Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai, China
PP04	**METABOLOMICS AND BIOMARKERS FOR PAROXYSMAL AND PERSISTENT ATRIAL FIBRILLATION** Li-Li Zhang$_1$, Wen-Hua Lin[2], Cheng-Ye Di[2], Hai-Tao Hou[3], Huan-Xin Chen[3], Jie Zhou[3], Qin Yang[3], Guo-Wei He[1*] [1]Faculty of Graduate Studies, Chengde Medical University, Chengde, China, & Department of Cardiovascular Surgery & The Institute of Cardiovascular Diseaes, TEDA International Cardiovascular Hospital, Tianjin University & Chinese Academy of Medical Sciences, Tianjin, 300457, China [2]Department of Cardiology & The Institute of Cardiovascular Diseases, TEDA International Cardiovascular Hospital, Tianjin University & Chinese Academy of Medical Science, Tianjin, 300457, China [3]Department of Cardiovascular Surgery & The Institute of Cardiovascular Diseaes, TEDA International Cardiovascular Hospital, Tianjin University & Chinese Academy of Medical Science, Tianjin, 300457, China
PP05	**HIGH SERUM LEVELS OF N-EPSILON-CARBOXYMETHYLLYSINE ARE ASSOCIATED WITH POOR CORONARY COLLATERALIZATION IN TYPE 2 DIABETIC PATIENTS WITH CHRONIC TOTAL OCCLUSION OF CORONARY ARTERY** LY Li, S Chen, FF Li, ZM Wu, Y Shen, FH Ding, XQ Wang, WF Shen, QJ Chen, Y Dai, L Lu Department of Cardiovascular Medicine, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, 197 Rui Jin Road II, Shanghai 200025, People's Republic of China
PP06	**MYOCARDIN REVERSES INSULIN RESISTANCE AND AMELIORATES CARDIOMYOPATHY BY INCREASING IRS-1 EXPRESSION IN A MURINE MODEL OF LIPODYSTROPHY CAUSED BY ADIPOSE DEFICIENCY OF VACUOLAR H+-ATPASE V0D1 SUBUNIT** WL Yuan Department of pathophysiology, Shenzhen University, Shenzhen

Young Investigator Award
Poster Presentations

PP07	**ENDOTHELIAL PPARA ACTIVATION DECREASE VASCULAR INFLAMMATION AND ATHEROGENESIS THROUGH INHIBITION OF YAP/TAZ** Yujie Pu[1,2], Peihua Dong[1], Li Wang[1], Yu Huang[1] [1]Department of Biomedical Science, City University of Hong Kong [2]School of Pharmacy, The Chinese University of Hong Kong
PP08	**CURAXIN CBL0137 INHIBITS ENDOTHELIAL INFLAMMATION AND ATHEROGENESIS VIA SUPPRESSION OF THE SRC-YAP SIGNALLING AXIS** Huanyu DING, Minchun JIANG, Li WANG, Yu HUANG School of Biomedical Sciences, Chinese University of Hong Kong, Hong Kong, China Department of Biomedical Sciences, City University of Hong Kong, Hong Kong, China
PP09	**MICRORNA AND MRNA PROFILING TO STUDY DOXORUBICIN-INDUCED CARDIOTOXICITY** Chloe Ho Yi MA[1], Chun Hin CHEN[1], Hin Shing LAM[1], Binbin WU[1],Ellen Ngar Yun Poon [1, 2*] [1]School of Biomedical Sciences, The Chinese University of Hong Kong, Shatin, Hong Kong, China. [2]Hong Kong Hub of Paediatric Excellence (HK HOPE), The Chinese University of Hong Kong, Kowloon Bay, Hong Kong, China
PP10	**PIEZO1-MEDIATED CA2+ ENTRY IS NEGATIVELY REGULATED BY PROTEIN KINASE G** Zhenchuan LEI, Yunting ZHANG, Jun ZHANG and Xiaoqiang YAO School of Biomedical Sciences, Li Ka Shing Institute of Health Sciences, The Chinese University of Hong Kong, Hong Kong, China
PP11	**THE ROLE OF TGF-B2 IN THE LYMPHATIC DRAINAGE OF INFILTRATING IMMUNE CELLS AFTER MYOCARDIAL INFARCTION** Meng-Yan Wang, Le-Yi Wu, Wen-Juan Liu, Cheng-Lin Zhang[*],and Jie Liu[*] Department of Pathophysiology, Guangdong Key Laboratory of Genome Stability and Human Disease Prevention, Shenzhen University Medical School, Shenzhen 518060, China
PP12	**EVALUATION OF DIFFERENT LIPOCALIN-2 VARIANTS IN A HUMANIZED TRANSGENIC MOUSE MODEL** Haoyun Li, Qiyang Sun, Daniels Konja, Yue Hu, Jingran Zeng, Aimin Xu, Yu Wang The State Key Laboratory of Pharmaceutical Biotechnology, Department of Pharmacology and Pharmacy, and Department of Medicine, The University of Hong Kong, Hong Kong, China
PP13	**MATURED AND PATIENT-SPECIFIC IPSC-CM MODEL FOR THE IDENTIFICATION OF NOVEL DRUGS AGAINST DOXORUBICIN-INDUCED CARDIOTOXICITY** Binbin WU, Chun Hin CHEN, Hin Shing LAM, Chloe Ho Yi MA, Ellen Ngar POON School of Biomedical Sciences, The Chinese University of Hong Kong, Shatin, Hong Kong, China

Young Investigator Award
Poster Presentations

PP01

AMPK-DEPENDENT YAP INHIBITION MEDIATES THE PROTECTIVE EFFECT OF METFORMIN AGAINST OBESITY-ASSOCIATED ENDOTHELIAL DYSFUNCTION AND INFLAMMATION

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Hyperglycemia is a crucial risk factor for cardiovascular diseases. Chronic inflammation is a central characteristic of obesity, leading to many of its complications. Recent studies have shown that high glucose activates Yes-associated protein 1 (YAP) by suppressing AMPK activity in breast cancer cells. Metformin is a commonly prescribed anti-diabetic drug best known for its AMPK-activating effect. However, the role of YAP in the vasoprotective effect of metformin in diabetic endothelial cell dysfunction is still unknown. The present study aimed to investigate whether YAP activation plays a role in obesity- associated endothelial dysfunction and inflammation and examine whether the vasoprotective effect of metformin is related to YAP inhibition. Reanalysis of the clinical sequencing data revealed YAP signaling, and the YAP target genes CTGF and CYR61 were upregulated in aortic endothelial cells and retinal fibrovascular membranes from diabetic patients. YAP overexpression impaired endothelium-dependent relaxations (EDRs) in isolated mouse aortas and increased the expression of YAP target genes and inflammatory markers in human umbilical vein endothelial cells (HUVECs). High glucose-activated YAP in HUVECs and aortas was accompanied by increased production of oxygen-reactive species. AMPK inhibition was found to induce YAP activation, resulting in increased JNK activity. Metformin activated AMPK and promoted YAP phosphorylation, ultimately improving EDRs and suppressing the JNK activity. Targeting the AMPK–YAP–JNK axis could become a therapeutic strategy for alleviating vascular dysfunction in obesity and diabetes. (supported by HMRF 05161746, RGC-SRFS2021-4S04, 14164817, 14109618, 11103222, and C4024-16W).

PP02

IDENTIFICATION AND FUNCTIONAL VERIFICATION OF CITED2 GENE PROMOTER REGION IN PATIENTS WITH PATENT DUCTUS ARTERIOSUS

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Objective: Patent ductus arteriosus (PDA) is a common congenital heart disease. CITED2 plays an important role in the development of the heart and genetic variants in its coding region are significantly associated with cardiac malformations. However, the role of variants in the promoter region of CITED2 in the development of PDA remains unclear.

Methods: We collected peripheral blood from 646 subjects (including 353 PDA patients and 293 unrelated healthy controls). Total DNA from all subjects was extracted and CITED2 promoter variants were identified by PCR and Sanger sequencing. The luciferase activity of the pGL3 basic-CITED2 promoter (with/without variants) was assayed at the cellular level by a dual luciferase assay. Electrophoretic mobility shift assay (EMSA) was used to detect the effect of CITED2 promoter variants on transcription factor binding sites. The JASPAR database was used to analyze whether the variants altered potential binding sites for transcription factors on the CITED2 promoter.

Results: We identified 13 CITED2 gene promoter variants (including 2 novel heterozygous variants). Ten of these 13 variants were found only in patients with PDA. In cellular level validation, the variants significantly altered the transcriptional activity of the CITED2 gene promoter ($p<0.05$). The results of EMSA suggest that these variants may affect the transcription of the CITED2 gene by influencing the binding capacity of transcription factors. Combined with the JASPAR database analysis, the disruption/creation of transcription factor binding sites due to variants in the promoter region of the CITED2 gene may directly or indirectly affect the binding ability of transcription factors.

Conclusion: Our results for the first time suggest that variants at the CITED2 promoter region may cause low expression of CITED2 protein related to the formation of PDA. These findings may provide a new perspective into the molecular pathogenesis and potential therapeutic insights for patients with PDA.

PP03

TRIBULUS TERRESTRIS L. EXTRACT AMELIORATES ATHEROSCLEROSIS BY INHIBITION OF VASCULAR SMOOTH MUSCLE CELL PROLIFERATION IN APOE -/- MICE AND A7R5 CELLS VIA SUPPRESSION OF AKT/MEK/ERK SIGNALING

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Abstract: Ethnopharmacological relevance: Atherosclerosis (AS) is one of major threatens of death worldwide, and vascular smooth muscle cell (VSMC) proliferation is an important characteristic in the progression of AS. Tribulus terrestris L. is a well-known Chinese Materia Medica for treating skin pruritus, vertigo and cardiovascular diseases in traditional Chinese medicine. However, its anti-AS activity and inhibition effect on VSMC proliferation are not fully elucidated.

Aims: We hypothesize that the furostanol saponins enriched extract (FSEE) of T. terrestris L. presents anti- AS effect by inhibition of VSMC proliferation. The molecular action mechanism underlying the anti-VSMC proliferation effect of FSEE is also investigated.

Methods: In ApoE-/- mice, the amounts of total cholesterol, triglyceride, low density lipoprotein and high density lipoprotein in serum were measured by commercially available kits. The size of atherosclerotic plaque was observed by hematoxylin & eosin staining. The protein expressions of α-smooth muscle actin (α-SMA) and osteopontin (OPN) in the plaque were examined by immunohistochemistry. In A7r5 cells, the cell viability and proliferation were tested by MTT and Real Time Cell Analysis assays. The cell migration was evaluated by wound healing assay. Propidium iodide staining followed by flow cytometry was used to analyze the cell cycle progression. The expression of intracellular total and phosphorylated proteins including protein kinase B (Akt) and mitogen-activated protein kinases (MAPKs), such as mitogen-activated extracellular signal-regulated kinase (MEK), extracellular signal-regulated kinase (ERK) and c-Jun N- terminal kinase (JNK), were detected by western blotting analysis.

Results: FSEE significantly reduced the area of atherosclerotic plaque in high-fat diet-fed ApoE-/- mice. And FSEE increased the protein expression level of α-SMA and decreased the level of OPN in atherosclerotic plaque, which revealed the inhibition of VSMC phenotype switching and proliferation. In A7r5 cells, FSEE suppressed fetal bovine serum (FBS) or oxidized low density lipoprotein (oxLDL)-triggered VSMC proliferation and migration in a concentration dependent manner. FSEE protected against the elevation of cell numbers in S phase induced by FBS or oxLDL and the reduction of cell numbers in G0/G1 phase induced by oxLDL. Moreover, the phosphorylation of Akt and MAPKs including MEK, ERK and JNK could be facilitated by FBS or oxLDL, while co-treatment of FSEE attenuated the phosphorylation of Akt induced by oxLDL as well as the phosphorylation of MEK and ERK induced by FBS. In addition, (25R)- terrestrinin B (JL-6), which was the main ingredient of FSEE, and its potential active pharmaceutical ingredients tigogenin (Tigo) and hecogenin (Heco) also significantly attenuated FBS or oxLDL-induced VSMC proliferation in A7r5 cells.

Conclusion: FSEE presents potent anti- AS and VSMC proliferation activities and the underlying mechanism is likely to the suppression of Akt/MEK/ERK signaling. The active components of FSEE are JL-6 and its potential active pharmaceutical ingredients Tigo and Heco. So, FSEE and its active compounds may be potential therapeutic drug candidates for AS.

PP04

METABOLOMICS AND BIOMARKERS FOR PAROXYSMAL AND PERSISTENT ATRIAL FIBRILLATION

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Objectives: Atrial fibrillation（AF) is the most common type of arrhythmia worldwide and associated with serious complications. This study investigated the metabolic biomarkers associated with AF and the metabolomics differences and associated metabolic biomarkers between paroxysmal AF (AFPA) and persistent AF (AFPE).

Methods: Plasma samples were prospectively collected from patients with AF and patients in sinus rhythm with negative coronary angiography. The patients were divided into 3 groups: AFPA, AFPE, and sinus rhythm (N =54). Metabolomics (n =36) using ultra-high performance liquid chromatography mass spectrometry was used to detect differential metabolites (DMs) that were validated in a new cohort (n=18). The validated metabolites from the verification phase were further analyzed by ROC.

Results: Among the 36 DMs detected by omics assay and 4 were successfully validated with AUC (area under curve) more than 0.8 ($p<0.05$). Bioinformatics analysis confirmed the enrichment pathways of unsaturated fatty acid biosynthesis, glyoxylate and dicarboxylate metabolism, and carbon metabolism. Arachidonic acid was a potential biomarker of AFPA, glycolic acid and L-serine were biomarkers of AFPA and AFPE, and palmitelaidic acid was a biomarker of AFPA.

Conclusion: In this metabolomics study we detected 36 DMs in AF and 4 were validated with high sensitivity and specificity. These DMs are potential biomarker for diagnosis and monitoring of disease course. This study therefore provides new insights into the precision diagnosis and management of AF.

Young Investigator Award
Poster Presentations

PP05

HIGH SERUM LEVELS OF N-EPSILON-CARBOXYMETHYLLYSINE ARE ASSOCIATED WITH POOR CORONARY COLLATERALIZATION IN TYPE 2 DIABETIC PATIENTS WITH CHRONIC TOTAL OCCLUSION OF CORONARY ARTERY

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Objective: We investigated whether N-epsilon-carboxymethyllysine (CML), a major form of AGEs in vivo, was associated with poor coronary collateral vessel (CCV) formation in patients with type 2 diabetes mellitus (T2DM) and chronic total occlusion (CTO) of coronary artery.

Methods: This study consisted of 242 T2DM patients with coronary angiographically documented CTO. Blood samples were obtained and demographic/clinical characteristics were documented. The coronary collateralization of these patients was defined according to Rentrop or Werner classification. Serum CML levels were evaluated using ELISA assay. Receiver operating characteristic curve and multivariable regression analysis were performed.

Results: 242 patients were categorized into poor CCV group or good CCV group (107 vs. 135 by the Rentrop classification or 193 vs. 49 by the Werner classification, respectively). Serum CML levels were significantly higher in poor CCV than in good CCV group (110.0 ± 83.35 vs. 62.95 ± 58.83 ng/ml by the Rentrop classification and 94.75 ± 78.29 ng/ml vs. 40.37 ± 28.69 ng/ml by Werner classification, both $P < 0.001$). Moreover, CML levels were significantly different across the Rentrop and Werner classification subgroups ($P < 0.001$). In multivariable logistic regression, CML levels ($P < 0.001$) remained independent determinants of poor CCV according to the Rentrop or Werner classification after adjustment of traditional risk factors.

Conclusions: Higher serum CML level is associated with poor collateralization in T2DM patients with CTO.

Odds ratio of poor collateralization in diabetic patients

Rentrop classification			
Tertiles of CML (n, ng/ml)	Poor CCV, n (%)	Crude OR (95% CI)	[a]Adjusted OR (95% CI)
Tertile 1 (n=80, <38.76)	19 (23.75)	1	1
Tertile 2 (n=80, 38.76-95.75)	37 (46.25)	2.763 (1.404-5.437)*	2.556 (1.161-5.624)*
Tertile 3 (n=82, >95.75)	51 (62.20)	5.282 (2.672-10.441)**	6.802 (2.980-15.526)**
Per tertile	/	2.278 (1.626-3.192)**	2.610 (1.729-3.941)**
P value for trend	<0.001	<0.001	<0.001
Werner classification			
Tertiles of CML (n, ng/ml)	Poor CCV, n (%)	Crude OR (95% CI)	[a]Adjusted OR (95% CI)
Tertile 1 (n=80, <38.76)	55 (68.75)	1	1
Tertile 2 (n=80, 38.76-95.75)	62 (77.50)	1.566 (0.773-3.173)	1.399 (0.672-2.914)
Tertile 3 (n=82, >95.75)	78 (95.12)	8.864 (2.920-26.908)**	7.757 (2.511-23.960)**
Per tertile	/	2.511 (1.609-3.918)**	2.336 (1.482-3.682)**
P value for trend	<0.001	<0.001	<0.001

Abbreviations: CCV coronary collateral vessel; CI confidence interval; OR odds ratio.
***P<0.05; ****P<0.001.**

[a]Multiple-adjustment for gender, age, body mass index, hypertension, smoke, HbA1c, estimated glomerular filtration rate, total-to-HDL cholesterol ratio and serum level of high sensitive C reactive protein

PP06

MYOCARDIN REVERSES INSULIN RESISTANCE AND AMELIORATES CARDIOMYOPATHY BY INCREASING IRS-1 EXPRESSION IN A MURINE MODEL OF LIPODYSTROPHY CAUSED BY ADIPOSE DEFICIENCY OF VACUOLAR H+-ATPASE V0D1 SUBUNIT

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Adipose tissue (AT) dysfunction that occurs in both obesity and lipodystrophy is associated with the development of cardiomyopathy. However, it is unclear how dysfunctional AT induces cardiomyopathy due to limited animal models available. We have identified vacuolar H+-ATPase subunit Vod1, encoded by Atp6v0d1, as a master regulator of adipogenesis, and adipose-specific deletion of Atp6v0d1 (Atp6v0d1AKO) in mice caused generalized lipodystrophy and spontaneous cardiomyopathy. Using this unique animal model, we explore the mechanism underlying lipodystrophy-related cardiomyopathy.

Methods and Results: Atp6v0d1AKO mice developed cardiac hypertrophy at 12 weeks, and progressed to heart failure at 28 weeks. The Atp6v0d1AKO mouse hearts exhibited excessive lipid accumulation and altered lipid and glucose metabolism, which are typical for obesity- and diabetes-related cardiomyopathy. The Atp6v0d1AKO mice developed cardiac insulin resistance evidenced by decreased IRS-1/2 expression in hearts. Meanwhile, the expression of forkhead box O1 (FoxO1), a transcription factor which plays critical roles in regulating cardiac lipid and glucose metabolism, was increased. RNA-seq data and molecular biological assays demonstrated reduced expression of myocardin, a transcription coactivator, in Atp6v0d1AKO mouse hearts. RNA interference (RNAi), luciferase reporter and ChIP-qPCR assays revealed the critical role of myocardin in regulating IRS-1 transcription through the CArG-like element in IRS-1 promoter. Reducing IRS-1 expression with RNAi increased FoxO1 expression, while increasing IRS-1 expression reversed myocardin downregulation-induced FoxO1 upregulation in cardiomyocytes. In vivo, restoring myocardin expression specifically in Atp6v0d1AKO cardiomyocytes increased IRS-1, but decreased FoxO1 expression. As a result, the abnormal expressions of metabolic genes in Atp6v0d1AKO hearts were reversed, and cardiac dysfunctions were ameliorated. Myocardin expression was also reduced in high fat diet-induced diabetic cardiomyopathy and palmitic acid-treated cardiomyocytes. Moreover, increasing systemic insulin resistance with rosiglitazone restored cardiac myocardin expression and improved cardiac functions in Atp6v0d1AKO mice.

Conclusion: Atp6v0d1AKO mice are a novel animal model for studying lipodystrophy- or metabolic dysfunction-related cardiomyopathy. Moreover, myocardin serves as a key regulator of cardiac insulin sensitivity and metabolic homeostasis, highlighting myocardin as a potential therapeutic target for treating lipodystrophy- and diabetes-related cardiomyopathy.

Young Investigator Award
Poster Presentations

PP07

ENDOTHELIAL PPARA ACTIVATION DECREASE VASCULAR INFLAMMATION AND ATHEROGENESIS THROUGH INHIBITION OF YAP/TAZ

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Objectives: Endothelial cell (EC) activation triggers vascular inflammation, leading to atherogenesis. Peroxisome proliferator-activated receptor alpha (PPARα) agonists are commonly prescribed for patients with hypertriglyceridemia, and they exert potential anti-inflammatory and anti-atherosclerotic properties. However, the mechanisms by which PPARα activation works against atherogenesis remain largely unexplored. This study aims to identify the mechanisms of endothelial PPARα against endothelial activation and atherogenesis.

Methods: AAV9-CDH5-Cas9-sgPparα and AAV9-CDH5-Pparα were used to achieve endothelium-specific knockdown and overexpression in apolipoprotein E–deficient (ApoE-/-) mice. A western diet feeding for 10-12 weeks was used to induce an atherosclerotic ApoE-/- mouse model.

Results: The PPARα expression and activation were suppressed in injured human ECs and in atherosclerotic mouse aortic ECs. Endothelium-specific overexpression of PPARα inhibited western diet-induced formation of atherosclerotic plaques and vascular inflammation. Moreover, endothelium-specific PPARα knockdown abolished the inhibitory effect of 14-day oral administration of PPARα agonist pemafibrate on atherosclerosis, indicating endothelial PPARα plays a crucial role in the inhibition of atherogenesis development.

The RNA sequencing data in cultured human ECs with PPARα overexpression enriched Hippo signalling and the heatmap of this pathway show the reduced expression of yes-associated protein/ transcriptional co- activator with PDZ-binding motif (YAP/TAZ) target genes, such as CCN1 (CTGF) and CNN2 (CYR61), which was further confirmed by qPCR in cultured human ECs overexpressed PPARα and in carotid arteries of ApoE-/- mice with endothelium-specific PPARα overexpression. In addition, the phosphorylation of YAP at S127 indicating a nuclear exclusion was increased by PPARα overexpression in cultured human ECs, and by endothelium-specific PPARα overexpression in aortas of ApoE-/- mice. More importantly, overexpression of constitutively active YAP-induced expression of YAP/TAZ target genes and pro-inflammatory genes was reversed by PPARα overexpression and activation in cultured human ECs.

Conclusions: The present study reveals that endothelium-specific PPARα overexpression inhibits atherogenesis while endothelium-specific PPARα knockdown abolishes the beneficial effects of PPARα on inhibition of atherogenesis. PPARα overexpression in endothelial cells inhibits YAP/TAZ activity, and constitutively active YAP overexpression-induced expression of its target genes and pro-inflammatory genes in vivo and in vitro. In summary, endothelial PPARα directly participated in combating vascular inflammation and the formation of atherosclerotic plaques, which is at least partially through inhibition of YAP1 activity, thereby providing scientific support for the use of fibrates in patients with atherosclerotic vascular diseases (Supported by HMRF 07181286 and SRFS2021-4S04).

Young Investigator Award
Poster Presentations

PP08

CURAXIN CBL0137 INHIBITS ENDOTHELIAL INFLAMMATION AND ATHEROGENESIS VIA SUPPRESSION OF THE SRC-YAP SIGNALLING AXIS

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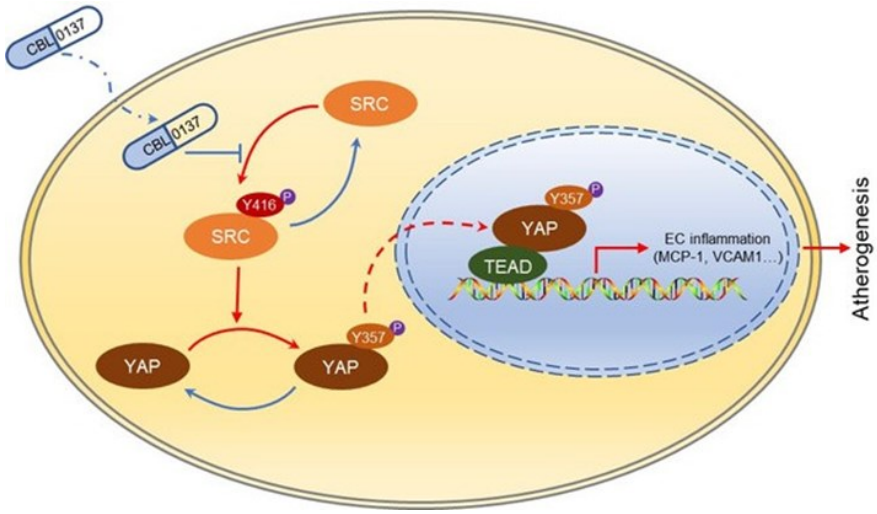
Background: Atherosclerotic vascular disease is the leading cause of mortality and morbidity worldwide. Our previous study uncovered that endothelium-specific knockdown of YAP suppresses atherogenesis, suggesting that YAP is a promising therapeutic target against atherosclerotic vascular disease. We established a drug screening platform, which aimed to identify new YAP inhibitors for antiatherosclerotic treatment.

Method: Drug screening was performed by a luciferase reporter gene assay. RNA sequencing was performed to acquire the transcriptomic profile of CBL0137-treated endothelial cells. We assessed and validated the inhibitory effect of CBL0137 on YAP activity and inflammatory response in HUVECs and HAECs. We evaluated the vasoprotective effect of CBL0137 in vivo against plaque formation in ApoE-/- mice, using both disturbed flow-induced and chronic western diet-induced atherosclerotic models.

Results: We identified CBL0137 as a novel YAP inhibitor from an FDA drug library. CBL0137 inhibited YAP activity by restraining its phosphorylation at Y357. CBL0137 inhibited YAP activity to repress endothelial inflammation. Mechanistically, CBL0137 suppressed YAP phosphorylation at Y357 via the tyrosine-protein kinase Src. Furthermore, administration of CBL0137 ameliorated endothelial inflammation and the atherogenesis induced by disturbed flow and consumption of an atherogenic diet in ApoE-/- mice.

Conclusion: To our knowledge, this is the first study to identify CBL0137 as a novel YAP inhibitor. We have demonstrated that pharmacologically targeting YAP by CBL0137 inhibits atherogenesis. The present results suggest that CBL0137 holds promise as a new drug for the treatment of atherosclerotic vascular disease.



PP09

MICRORNA AND MRNA PROFILING TO STUDY DOXORUBICIN-INDUCED CARDIOTOXICITY

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Background: Anthracyclines such as doxorubicin (DOX) are commonly used for the treatment of malignant tumors, but it can induce progressive and potentially lethal cardiac complications. Consequently, early detection of cardiac injury is critical to prevent irreversible damages to the heart. miRNAs are small non- coding RNAs that can negatively regulate gene expression. During the last decade, microRNA have emerged as promising biomarkers of different cardiac disorders due to their stability in the blood stream and their abilities to reflect cellular dysfunction. Secreted miRNAs can also act as autocrine or paracrine messengers to affect disease pathogenesis.

Objective:
1.To identify miRNAs which can act as biomarkers for DOX-induced cardiotoxicity
2.To predict autocrine and paracrine effects of secreted miRNAs via integrated miRNA/mRNA profiling

Method: We utilized human pluripotent stem cell derived cardiomyocytes (hPSC-CMs) from patients with DOX induced cardiotoxicity. The hPSC-CMs were subjected to low dose DOX treatment. We collected secreted microRNAs from cell supernatant, as well as mRNA from cell lysate. microRNA and mRNA were then subjected to small RNA and mRNA sequencing, and bioinformatics analysis.

Results: Differential gene expression analysis revealed that genes involved in cardiac fibrosis, hypertrophy, and necrosis were significantly enriched in DOX-treated group compared to the control group. The top five activated regulators were components of the p53 signalling pathway, which is highly consistent with the persistent DNA damage and p21CDKN1A staining, implicating p53 is a central mediator of the DOX-induced cardiotoxicity. We have also identified microRNAs which were upregulated by DOX, and are now investigating the interactions between microRNA and mRNA profiles.

Conclusion: Upon the completion of study, we anticipate our results will facilitate better diagnosis of DOX-induced cardiotoxicity, and our bioinformatics analysis will yield new insights into the aetiology of cardiotoxicity.

PP10

PIEZO1-MEDIATED CA2+ ENTRY IS NEGATIVELY REGULATED BY PROTEIN KINASE G

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Flow shear force activates mechanosensitive ion channels to induce Ca2+ rise in vascular endothelial cells, consequently regulating nitric oxide release and modulating vascular tone. This Ca2+ rise is finely regulated. One well-known regulatory mechanism is negative feedback inhibition of Ca2+ entry channel by nitric oxide-cyclic GMP and protein kinase G (NO-cGMP-PKG) signaling axis, which could prevent Ca2+ overload. Piezo1 is major flow-activated ion channels in vascular endothelial cells. However, it is unclear whether Piezo1 activity is regulated by NO-cGMP-PKG signaling axis. In the present study, we found that Yoda1-activated Ca2+ rise and flow-activated Ca2+ rise in endothelial cells are inhibited by cGMP, the effect of which was reversed by specific PKG inhibitors KT5823 and DT3. Point mutations were made at putative PKG phosphorylation sites. We expressed different Piezo1 mutants in PKG-overexpressing HEK293 cells. The results showed that mutation at Thr-1896 or Ser-1945 substantially reduced the cGMP- PKG inhibition on Piezo1-mediated Ca2+ rise, while mutation at Thr-351 had much smaller effect, suggesting that PKG mainly phosphorylate on Thr-1896 or Ser-1945 to inhibit Piezo1 activity. Patch clamp recording of piezo1 current further verified these findings. Taken together, the present study uncovered a novel Piezo1 regulatory mechanism, namely NO-cGMP-PKG inhibition on Piezo1. This mechanism may serve to protect endothelial cells from Ca2+ overload, and may also have anti-hypertensive and anti-atherosclerotic roles.

PP11

THE ROLE OF TGF-B2 IN THE LYMPHATIC DRAINAGE OF INFILTRATING IMMUNE CELLS AFTER MYOCARDIAL INFARCTION

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Objective: To investigate the role of transforming growth factor-β2 (TGF-β2) on immune cell infiltration and pathological ventricular remodeling in the late stage of myocardial infarction (MI).

Methods: The mouse model of MI was established by ligation of the left anterior descending coronary artery, and cardiac function was assessed by echocardiography. WB and qPCR were used to measure the expression of related molecules. Tissue transparency and immunofluorescence were used to measure immune cell infiltration and localization.

Results: TGF-β2 was expressed in various cell types such as lymphatic endothelium, fibroblasts, and macrophages in the mouse heart. After MI, the upregulation of TGF-β2 was faster and of higher amplitude than that of TGF-β1. RNA-seq data from human lymphatic endothelial cells suggested that lymphatic endothelial cell receptor-1 (LYVE-1) was one of the most significantly downregulated genes by TGF-β2. Administration of TGF-β2 neutralizing antibody can significantly attenuate immune cell infiltration, ventricular remodeling and improve cardiac systolic function after MI. Mechanistically, TGF-β2 increased nuclear translocation of YAP. Inhibition of YAP attenuated the inhibitory effect of TGF-β2 on LYVE-1.

Conclusions: Lymphatic endothelial cell TGF-β2 inhibits immune cell clearance by inhibiting LYVE-1 expression, resulting in the continuous deterioration of cardiac function after MI in mice. TGF-β2 may be a novel target for the treatment of myocardial infarction.

Young Investigator Award
Poster Presentations

PP12

EVALUATION OF DIFFERENT LIPOCALIN-2 VARIANTS IN A HUMANIZED TRANSGENIC MOUSE MODEL

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Objectives: Lipocalin-2 is a pro-inflammatory adipokine implicated in obesity-related cardiorenal syndrome (CRS) pathogenesis. Different protein variants, hLcn2, C87A and R81E, of human lipocalin-2 possess distinct structures and functions. This study aims to evaluate the potential of different lipocalin-2 variants as biomarkers and drug targets for cardiovascular (CVD) diseases and chronic kidney disease (CKD).

Methods: Male mice with human lipocalin-2 expression (TG-hLcn2), lacking the endogenous murine Lcn2 alleles, were generated and subjected to a six-week treatment with aldosterone and high salt (ANS) after uninephrectomy and subsequently treated with specific Lcn2 antibodies respectively. The body weight and composition and blood pressure were monitored for comparison biweekly. The heart function was also evaluated by echography every two weeks. The levels of lipocalin-2 variants in the serum were measured by immunoassay and the inflammatory and cardiac injury biomarkers in the heart tissue were detected at the endpoint of the experiment.

Results: Body weight, fat mass, and systolic blood pressure (SBP) were higher in ANS mice versus the sham mice. Circulating Lcn2 variant concentrations were also higher in ANS TG mice than in their sham controls. Among the three different types of antibodies, anti-C87A exhibited the most potent protective effects on ANS-induced diastolic dysfunction, cardiac abnormalities, and inflammatory injuries. Anti-hLcn2 and anti- R81E treatment also performed a protective effect on ANS-induced heart and kidney dysfunction.

Conclusion: Targeting the pathological forms of lipocalin-2 represents a promising strategy for alleviating the progression of cardiorenal dysfunction.

Other Poster Presentations

PP14	**ENDOTHELIAL TRANSCRIPTION FACTOR EB ALLEVIATES PULMONARY HYPERTENSION RELATED VASCULAR DYSFUNCTION BY INDUCING ENOS DIMERIZATION** Qinghua Chen, Cheng-lin Zhang, Lei He, Yu Huang Department of Biomedical Sciences, City University of Hong Kong, Hong Kong
PP15	**CENTROSOME ASSEMBLY AS THE KEY TO PROMOTE CARDIOMYOCYTES PROLIFERATION** HS Lam[1], D Zebrowski[2], EN Poon[1,3] [1]School of Biomedical Sciences, The Chinese University of Hong Kong, Shatin, Hong Kong, China [2]GenKardia Inc [3]Hong Kong Hub of Pediatric Excellence (HK HOPE), The Chinese University of Hong Kong, Kowloon Bay, Hong Kong, China
PP16	**ACTIVE IMMUNIZATION USING TRPM2 PEPTIDE VACCINE ATTENUATES ATHEROSCLEROTIC PROGRESSION IN A MOUSE MODEL OF ATHEROSCLEROSIS** Fan Ying, Yunting Zhang, Zhaoyue Meng, Xiao Li, Jingxuan Li, Chun-yin Lo, Xiaoqiang Yao* School of Biomedical Sciences, The Chinese University of Hong Kong, Hong Kong

Other Poster Presentations

PP13

MATURED AND PATIENT-SPECIFIC IPSC-CM MODEL FOR THE IDENTIFICATION OF NOVEL DRUGS AGAINST DOXORUBICIN-INDUCED CARDIOTOXICITY

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Background: Doxorubicin (DOX) is an effective chemotherapeutic agent for the treatment of cancer but it causes irreversible and life-threatening cardiotoxicity. Human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) are of great values for cardiotoxicity evaluations with the ability to recapitulate key traits of human cardiomyocytes, including spontaneous contraction, cardiac-specific gene expression and physiology. However, conventional hiPSC-CMs phenotypes resemble embryonic CMs, and fail to respond to dexrazoxane, the only cardioprotective drug currently approved by the FDA for preventing doxorubicin-induced cardiotoxicity (DCT) in cancer patients. We previously identified CD36 as a surface marker of maturation of hiPSC-CMs and CD36high-CMs uniquely recapitulate the effects of both DOX and dexrazoxane treatment.

Objective: To identify potential treatment for DCT using CD36high-CMs.

Methods: We utlised adult-like hPSC-CD36high-CMs derived from patients who developed DCT. A panel of compounds were chosen based on their abilities to protect CMs in animal experiments. We performed viability experiments to identify compound(s) that best alleviated the cardiotoxicity induced by DOX, without protecting cancer cells. We then investigated the cellular and molecular mechanisms of the chosen compound.

Results: Our patient derived-CD36high-CMs correctly responded to dexrazoxane, consistent with clinical reports, showing our model is suitable for investigations of DCT. Using this validated model, we showed that compound A improved mitochondrial morphology and function, and also alleviated both non- mitochondrial damage induced by DOX. Unlike its effects in CMs, compound A did not protect against DOX in tumor cells.

Conclusions: Our results support on-going animal studies and future clinical trials to confirm the cardioprotective effects of compound A.

PP14

ENDOTHELIAL TRANSCRIPTION FACTOR EB ALLEVIATES PULMONARY HYPERTENSION RELATED VASCULAR DYSFUNCTION BY INDUCING ENOS DIMERIZATION

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Background: Pulmonary hypertension (PAH) is a life-threatening disease, characterized by persistent increase of pulmonary artery (PA) resistance and vascular remodeling, leading to right heart failure and death. One of the critical factors in the development of PH is endothelial cell (EC) dysfunction. Transcription factor EB (TFEB), known as the master regulator of autophagy and lysosomal biogenesis. Our previous study showed that TFEB is highly expressed in ECs and diminished TFEB plays a crucial role in regulating endothelial dysfunction in diabetic mice. However, whether altered TFEB is also associated with the pathogenesis of PH is yet to be studied.

Methods: EC-enhanced AAV9-mediated Tfeb-sgRNA was used to inject Cdh5Cre Cas9fl/fl mice to obtain EC-specific TFEB knockdown mice. sgTFEB mice receiving SU5416 (20 mg/kg) were kept under a hypoxic condition (10% O2) for 1 week to induce an early stage of PH. Overexpression of TFEB by adenovirus in C57BL/6 mice after receiving SU5416 (20mg/kg) and subjected to hypoxia chamber (10% O2) for 3 weeks. To identify the PH phenotypes and vascular remodeling, hemodynamics and histological staining were performed. Relaxation and contraction of pulmonary arteries were measured by wire myograph. A hypoxia incubator (1% O2) was used to mimic hypoxic situation in vitro. The mRNA and protein levels of TFEB and its target genes have been determined by Western blot and qPCR. In vitro, overexpression of TFEB was achieved using adenovirus and lentivirus, respectively.

Results: TFEB is majorly expresses in ECs in the pulmonary artery. The expression of TFEB and eNOS were reduced under hypoxia condition in human umbilical vein endothelial cells (HUVECs) and human pulmonary artery endothelial cells (PAECs). Overexpression of TFEB significantly increased eNOS expression and dimerization. Overexpression of TFEB also ameliorated PH in mice models by reducing right ventricular systolic pressure (RVSP) and right ventricular hypertrophy index (RVHI). Pulmonary vascular remodeling caused by hypoxia was also inhibited by TFEB overexpression. Relaxation of PA impaired by hypoxia has been partially rescued by TFEB. And sgTFEB mice exhibited an exaggerated PH reflected by the increases of RVSP and PA contraction and decrease of pulmonary artery relaxation.

Conclusion: Collectively, our study shows that TFEB is involved in pulmonary artery function. The present results imply that medications that might boost TFEB expression and activity may be useful in improving pulmonary artery function in PH. (This study is supported by GRF 14100121 and SRFS2021-4S04)

PP15

CENTROSOME ASSEMBLY AS THE KEY TO PROMOTE CARDIOMYOCYTES PROLIFERATION

HS Lam[1], D Zebrowski[2], EN Poon[1,3]

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Objectives: Cardiomyocytes have limited regenerative capacity. The loss of cardiomyocytes can therefore irreparably injure the heart. Replenishing cardiomyocytes by promoting cardiomyocyte proliferation is an important avenue for cardiac repair. A preliminary small molecule library screen was performed using human pluripotent stem cells-derived cardiomyocytes (hPSC-CMs) and demonstrated that verapamil, an FDA- approved L-type Calcium channel blocker, could promote cardiomyocyte proliferation in vitro, but the mechanism is unclear. The centrosome is an organelle associated with cell cycle progression and proliferation. Here we aim to validate our preliminary results and to test if verapamil induced proliferation by promoting centrosome assembly.

Methods: Verapamil treated hPSC-CMs were assayed for proliferation. Centrosome status was examined using established markers. The effect of treatment was evaluated using immunostaining and metabolic assays.

Results: We confirmed using multiple assays that co-treatment of verapamil with serum induced proliferation at clinically relevant concentrations. Such cotreatment also rendered hPSC-CMs more fetal-like in terms of their phenotype. Using centrosome satellite marker PCM1, we found that proliferation was associated with centrosome assembly.

Conclusions: Our results indicate that verapamil promotes proliferation of hPSC-CMs, and renders the latter more immature. We also revealed the important role of centrosome assembly in hPSC-CM proliferation, which may inform future strategies to regenerate the heart.

Other Poster Presentations

PP16

ACTIVE IMMUNIZATION USING TRPM2 PEPTIDE VACCINE ATTENUATES ATHEROSCLEROTIC PROGRESSION IN A MOUSE MODEL OF ATHEROSCLEROSIS

Fan Ying, Yunting Zhang, Zhaoyue Meng, Xiao Li, Jingxuan Li, Chun-yin Lo1, Xiaoqiang Yao*

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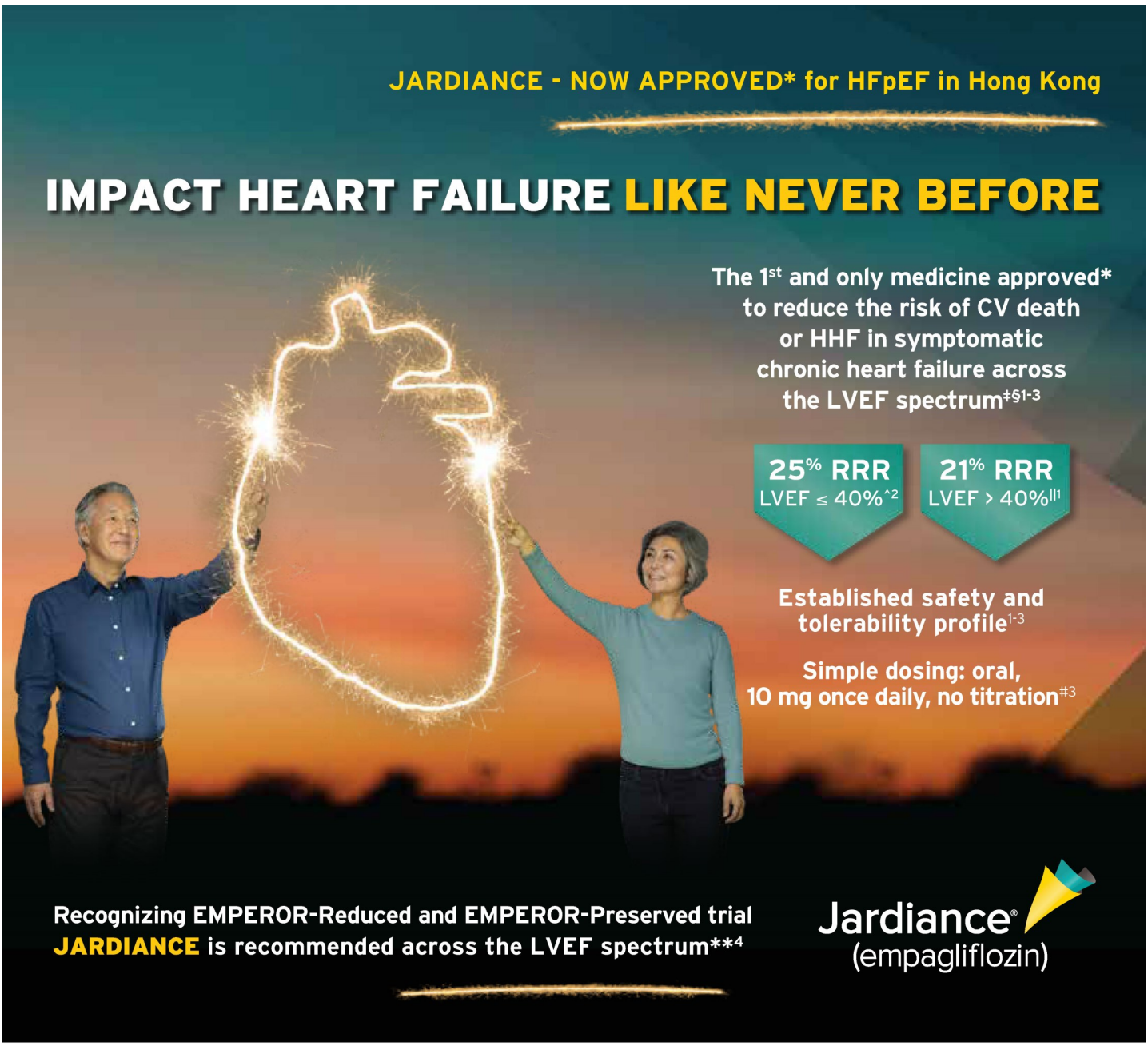
Atherosclerosis is one of the leading causes of cardiovascular diseases and mortality around the world. One exciting strategy for atherosclerosis treatment is immunotherapy, especially active immunization. Active immunization relies on the delivery of antigens in a vaccine platform to introduce humoral and cellular immunity alleviating atherosclerotic progression TRPM2 is an ROS-activated Ca2+- permeable ion channel that can promote atherosclerosis via stimulating vascular inflammation. In the present study, we developed a strategy of active immunization with TRPM2 E3 domain peptide in a vaccine platform, aiming to induce endogenous production of anti-TRPM2 blocking antibody in mice in vivo, consequently inhibiting TRPM2 channel activity to alleviate atherosclerotic progression. The results show that immunization with a pig TRPM2 E3 region-based peptide (P1) could effectively alleviate high cholesterol diet-induced atherosclerosis in ApoE-/- mice. We worked out the best vaccine formulation for most effective atheroprotection, namely P1 at the dose of 67.5µg per mouse (2.5mg/kg body weight) with aluminium salts as adjuvant. The present study laid the foundation for future clinical trials using TRPM2 E3 vaccine for potential therapeutic option against atherosclerosis.



* Approved = Jardiance 10mg is indicated in adults for the treatment of symptomatic chronic heart failure in Hong Kong

‡ Adult patients with chronic heart failure (NYHA class II, III, or IV) and reduced ejection fraction (LVEF ≤ 40%). Adult patients with chronic heart failure (NYHA class II, III, or IV) and preserved ejection fraction (LVEF > 40%).[1,2]

§ In the EMPEROR-Preserved trial, a randomised, double-blind, parallel-group, placebo-controlled study of 5988 patients with HFpEF, the efficacy and safety of JARDIANCE 10 mg (n=2997) were evaluated vs placebo (n=2991). The primary endpoint in the EMPEROR-Preserved trial was a composite of CV death or HHF, analysed as time to the first event. Patients treated with JARDIANCE experienced a 21% RRR in this endpoint (HR=0.79; 95% CI: 0.69, 0.90; p<0.001). In the EMPEROR-Reduced trial, a randomised, double-blind, parallel-group, placebo-controlled study of 3730 patients with HFrEF, the efficacy and safety of JARDIANCE 10 mg (n=1863) were evaluated vs placebo (n=1867). The primary endpoint in the EMPEROR-Reduced trial was a composite of CV death or HHF, analysed as time to the first event. Patients treated with JARDIANCE experienced a 25% RRR in this endpoint (HR=0.75; 95% CI: 0.65, 0.86; p<0.001).[1,2]

^ In the EMPEROR-Reduced trial, a randomised, double-blind, parallel-group, placebo-controlled study of 3730 patients with HFrEF, the efficacy and safety of JARDIANCE 10 mg (n=1863) were evaluated vs placebo (n=1867). The primary composite endpoint in the EMPEROR-Reduced trial was a composite of CV death or HHF, analysed as time to the first event. Patients treated with JARDIANCE experienced a 25% RRR in this endpoint (HR=0.75; 95% CI: 0.65, 0.86; p<0.001).[2]

|| In the EMPEROR-Preserved trial, a randomised, double-blind, parallel-group, placebo-controlled study of 5988 patients with HFpEF, the efficacy and safety of JARDIANCE 10 mg (n=2997) were evaluated vs placebo (n=2991). The primary composite endpoint in the EMPEROR-Preserved trial was a composite of CV death or HHF, analysed as time to the first event. Patients treated with JARDIANCE experienced a 21% RRR in this endpoint (HR=0.79; 95% CI: 0.69, 0.90; p<0.001).[1]

When Jardiance is used in combination with a sulphonylurea or with insulin, a lower dose of the sulphonylurea or insulin may be considered to reduce risk of hypoglycaemia.[3]

** The SGLT2i class, such as Jardiance, has gained a 1A recommendation for HFrEF and a 2a-B-R recommendation for HFmrEF and HFpEF.[4]

CI=confidence interval; CV=cardiovascular; HFpEF=heart failure with preserved ejection fraction; HFrEF=heart failure with reduced ejection fraction; HFmrEF=heart failure with mid range ejection fraction; HHF=hospitalisation for heart failure; HR=hazard ratio; LVEF=left ventricular ejection fraction; NYHA=New York Heart Association; RRR=relative risk reduction; SGLT2i=sodium-glucose cotransporter 2 inhibitor

JARDIANCE® Abbreviated Prescribing Information (aPI-JARD-02)

Presentation: Empagliflozin. Film-coated tablets 10 mg; 25 mg. **Indications: 10 mg and 25 mg:** Indicated in the treatment of type 2 diabetes mellitus to improve glycaemic control in adults as: monotherapy when diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance; and as add-on combination therapy with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control. Indicated in patients with type 2 diabetes mellitus and established cardiovascular disease to reduce the risk of cardiovascular death. **10 mg:** Jardiance is indicated in adults for the treatment of symptomatic chronic heart failure. **Dosage and administration: Type 2 diabetes mellitus:** 10 mg once daily. In patients tolerating 10 mg once daily and requiring additional glycaemic control, the dose can be increased to 25 mg once daily. Can be taken with or without food. No dose adjustment is required for patients with eGFR ≥ 30 mL/min/1.73m^2 or with hepatic impairment, or for elderly patients. **Heart Failure:** 10 mg once daily. Can be taken with or without food. In HF patients with or without T2DM, 10 mg may be initiated or continued down to an eGFR of 20 ml/min/1.73m^2 or CrCl of 20 ml/min. **Contraindication:** Hypersensitivity to empagliflozin or any of the excipients. For the treatment of Type 2 diabetes, JARDIANCE should not be used in patients with severe renal impairment (eGFR <30 mL/min/1.73m^2), end-stage renal disease and patients on dialysis, as glycaemic efficacy depends on renal function. **Special warnings and precautions:** Should not be used in patients with type 1 diabetes or for treatment of ketoacidosis. Discontinue immediately when ketoacidosis is suspected or diagnosed. Treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses, and may be restarted once the patient's condition has stabilised. For type 2 diabetes mellitus, should not be used in patients with severe renal impairment (eGFR <30 mL/min/1.73m^2), end-stage renal disease and patients on dialysis. For HF, not recommended for use when eGFR < 20 mL/min/1.73m^2. Discontinue in cases of recurrent UTI. Due to a risk of modest decrease in blood pressure, caution should be exercised in patients with known cardiovascular disease, patients on diuretics, patients with history of hypotension or patients aged 75 years and older. Monitoring of volume status and electrolytes is recommended. Regularly examine the feet and counsel patients on routine preventative footcare. Caution is advised in patients at increased risk of genital infections. Avoid use during pregnancy and breast-feeding. Safety and effectiveness in children under 18 years of age have not been established. Initiation is not recommended in patients aged 85 years and older. Urine will test positive for glucose while patients are taking JARDIANCE. **Interactions:** Risk of dehydration and hypotension may increase when used in combination with thiazide and loop diuretics. Lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycemia when used in combination with JARDIANCE. **Adverse reactions:** Hypoglycaemia (depends on type of background therapy of patients); Urinary tract infection, vaginal moniliasis, vulvovaginitis, balanitis and other genital infection; Increased urination, dysuria; Pruritus; Volume depletion; Thirst; Glomerular filtration rate decreased, blood creatinine increased, haematocrit increased, serum lipids increased. Post-marketing experience: Ketoacidosis, complicated urinary tract infections, necrotising fasciitis of the perineum (Fournier's gangrene), allergic skin reaction, angioedema. **Storage condition:** Please refer to outer packaging for special precautions for storage. **Note:** Before prescribing, please consult full prescribing information.

References: 1. Anker SD, Butler J, Filippatos G, et al; EMPEROR-Preserved Trial Investigators. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med. 2021;385(16):1451-1461. (EMPEROR-Preserved results and the publication's Supplementary Appendix.) **2.** Packer M, Anker SD, Butler J, et al; EMPEROR-Reduced Trial Investigators. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med. 2020;383(15):1413-1424. (EMPEROR-Reduced results and the publication's Supplementary Appendix.) **3.** Jardiance Hong Kong Prescribing Information. **4.** Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines [Epub ahead of print]. J Am Coll Cardiol. 2022. doi:10.1016/j.jacc.2021.12.011

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