International Society for Heart Research
Southeast Asian Section

Universiti Kebangsaan Malaysia
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Malaysia Truly Asia

2nd Annual Scientific Meeting of the International Society of Heart Research Southeast Asia Section (ISHR-SEA)

Innovation and Collaboration in Cardiovascular Research

April 28th & 29th 2026, Kuala Lumpur, Malaysia

Meeting venue:
Komune Wellness & Living, Cheras,
Kuala Lumpur, Malaysia

Organising committee
ISHR-SEA Section (Malaysia)
Universiti Kebangsaan Malaysia
ISHR-SEA Council

2ND ANNUAL MEETING OF INTERNATIONAL SOCIETY FOR HEART RESEARCH

(SOUTHEAST ASIAN SECTION)

INNOVATION AND COLLABORATION IN CARDIOVASCULAR RESEARCH

Scientific Schedule (Day 1)

TUESDAY | 28.04.2026 | 07:30AM-06:00 PM

07:30 - 08:25	Registration and Poster Set-up
08:30 - 08:40	Doa Recitation
	Welcome and Introductions **Kamisah Yusof** (Chairperson, 2nd ISHR-SEA organising committee)
	Presidential Address **Roger Foo** (Former President, ISHR-SEA section) **Patrick Hsieh** (President, ISHR-SEA section) **Yasuchika Takeishi** (President, ISHR Japanese section)
08:40 – 09:10	**Keynote Lecture 1** Chair: Kamisah Yusof (UKM, Malaysia) Challenging Risk Prediction of CVD with Artificial Intelligence **Sazzli Kasim** Professor of Medicine/Director Cardiovascular Advancement and Research Excellence Institute (CARE Institute), UiTM, Malaysia
09:10 - 10:10	**Scientific Session 1: Ischemic Heart Disease** Chairs: Azizah Ugusman (UKM, Malaysia), Adila Hamid (UKM, Malaysia) 1. Development of an Exercise-Mimetic Gene Therapy for Ischemic Heart Failure Toshiyuki Ko (The University of Tokyo, Japan) 2. Adipokine in Acute Myocardial Infarction Mas Rizky A. A. Syamsunarno (Universitas Padjajaran, Indonesia) 3. Macrophage Polarization during Fibrotic Disease Jacques Behmoaras (DUKE-NUS, Singapore)
10:10 – 10:30	**Tea Break and Poster Viewing**
10:30 – 12:00	**Young Investigator Award Session** Judging panel: Elena Aisha Azizan (Chair, UKM, Malaysia), Roger Foo (NUS

Medicine, Singapore), Patrick Hsieh (Institute of Biomedical Sciences, Taiwan), Yin Hua Zhang (Seoul National University, South Korea), Yasuchika Takeishi (Fukushima Medical University, Japan)

1. Loss of STMP1 Perturbs Mitochondrial Cristae and Drives Cellular Inflammation and Heart Failure
   Francesco Paolo Ruberto (NUS, Singapore)
2. Splenectomy Attenuates Cardiac Inflammation and Diastolic Dysfunction in HFpEF
   Jinyun Zhu (Duke-NUS, Singapore)
3. Identifying Novel Drivers of Cardiac Lineage Specification and Cardiomyocyte Maturation using Paired Short/Long-Read scRNA-seq
   Ryan Fan (NUS Medicine, Singapore)
4. A Translational Mouse Model of Spontaneous Atrial Fibrillation for Therapeutic Development
   Nur Syakirah Othman (National Cerebral and Cardiovascular Center, Japan)
5. Association Between Insulin Resistance and Atrial Fibrillation: Insights from Real-World and Genetic Evidence
   Xiao Liu (Sun Yat-sen Memorial Hospital of Sun Yat-sen University, Guangzhou, China)
6. Resolving the NOS1AP GWAS Signal in Long QT Syndrome Through Isoform-Specific Mechanisms
   Galvin Tang (NUS,Singapore)

12:00 – 13:00 **Mid-Career Open Communication Session**

Chairs: Haojie Yu (NUS-Med, Singapore), Badamkhand Mendsaikhan (Institute of Medical Sciences, Mongolia)

1. Building Better Vessels: From Matrix Integrity to Re-Endothelialisation
   Nadiah Sulaiman (UKM, Malaysia)

2. Smooth Muscle Plasticity in Early Atherosclerosis Revealed by Spatial Multi-omics
   Rijan Gurung (NUS, Singapore)
3. Modulation of Vascular Inflammation by Gynura procumbens: in Vivo and in Vitro Studies
   Norsyahida Mohd Fauzi (UKM, Malaysia)
4. Role of Endoplasmic Reticulum and Mitochondrial Contact Sites in Cardiac Fibrosis
   Jin O-Uchi (University of South Florida, USA)

13:00 – 13:20 **Industrial Talk @Ebony**

Proteomics in Cardiovascular Research: From Biomarker Discovery to Clinical Insight
Jia Kai Lim (Olink Proteomic Sciences)

Premier Integrated Labs: Your Trusted Partner in Diagnostic Excellence
Mr. Bravien Koffman Kiethson (Premier Integrated Labs)

13:20 - 14:10 **Lunch Talk @Oak**
Lunch & Poster Viewing

14:10 - 15:40 **Scientific Session 2: Heart Failure**
Chairs: Bambang Widyantoro (Universitas Indonesia), Amira Hajirah Abd Jamil (UM, Malaysia)

1. Discovery of Novel Therapeutic Targets for Heart Failure Using Human Stem Cell–Derived Cardiomyocytes
   Tomoya Kitani (Kyoto Prefectural University of Medicine, Japan)
2. Non-canonical Effects of Low-Dose Myosin Inhibitor Mavacamten to Facilitate the Relaxation of Myofibrils from the HFpEF Heart
   Lin Ying-Hsi (Alvin) (Duke-NUS, Singapore)
3. Atrial Remodelling and AF Susceptibility in Mouse Models of Hypertrophic Cardiomyopathy
   Lim Wei Wen (NHCS, Singapore)

4. Circulating Profiling and Nanoparticle Delivery of miRNAs Targeting Heart Failure
   Diem My Vu (University of Medicine and Pharmacy, Vietnam)

15:40 - 15:55 **ISHR-SEA Annual General Meeting**

Roger Foo (Former President, ISHR-SEA section)
Patrick Hsieh (President ISHR-SEA)
Derek Hausenloy (Secretary ISHR-SEA)
Haojie Yu (Treasurer ISHR-SEA)

15:55 - 16:10 **Tea Break and Poster Viewing**

16:10 – 16:40 **Keynote Lecture 2**
Chair: Yin Hua Zhang (Seoul National University, South Korea)

Cereblon–TRPC1 Axis Drives ER Stress and Fibrosis in Diabetic Cardiomyopathy through Calcium Signaling Dysfunction
Jin Han
Inje University College of Medicine South Korea

16:40 - 18:00 **Scientific Session 3: Vascular Biology**

Supported by JMCC

Special Issue: Microvessel in the heart
Chairs: Wulan Anggrahini (Universitas Gadjah Mada, Indonesia), Roger Foo (NUS Medicine, Singapore)

1. Targeting Angiogenesis with Navitoclax: Insights from HUVECs toward Stabilizing Atherosclerotic Plaques
   Nur Najmi Mohamad Anuar (UKM, Malaysia)
2. Phosphatidylserine as a Natural Approach to Address Atherosclerotic Plaque Formation
   Elisa Liehn (National Heart Centre Singapore)

	3. The Role of NALCN in Vascular Function and Hypertension Young Min Bae (Konkuk University, South Korea) 4. Endothelial C-type Natriuretic Peptide / Guanylyl Cyclase-B Signaling in Pulmonary Vascular Remodeling Koichiro Kuwahara (Shinshu University, Japan)
18:00 - 19:00	**Moderated Poster Session (Judging session)**
19:00 - 20:30	**Gala Dinner**
20:30 onwards	**Informal ECI/MCI social gathering** Location: Petaling Street, Kuala Lumpur

Scientific Schedule (Day 2)

WEDNESDAY | 29.04.2026 | 8:30AM-6:00 PM

08:30 – 09:00 **Keynote Lecture 3**

Chair: Yibin Wang (DUKE-NUS, Singapore)

Contribution of Insulin Resistance and Mitochondrial Dysfunction to Heart Failure in Diabetes

E. Dale Abel
William S. Adams Distinguished Professor
University of California, Los Angeles, USA

09:00 - 10:20 **Scientific Session 4: Genetics in Cardiovascular Research**

Chairs: Siti Hamimah Sheikh Abdul Kadir (UiTM, Malaysia), Mohd Kaisan Mahadi (UKM, Malaysia)

1. Genetic Landscapes of Cardiomyopathy in Malaysia
   Kee Boon Pin (UM, Malaysia)
2. RNF20 Stabilizes Adult Cardiomyocyte Cell State to Prevent Pathological Dedifferentiation
   Cheng-Fu Kao (Institute of Cellular and Organismic Biology, Academia Sinica, Taiwan)
3. Functional Genomics Analysis Identifies Pleiotropic Genes for Vascular Diseases
   Ye Shu (National University of Singapore)
4. Semaphorin-Plexin-Neuropilin Signaling in Left Ventricular Non-compaction
   Manvendra Singh (DUKE-NUS, Singapore)

10:20 – 10:40 **Tea Break and Poster Viewing**

10:40 – 12:00 **ISHR-SEA Early Career Investigator Rapid Fire Session**

Chairs: Mick Lee (ISHR-SEA ECI rep, Singapore), Yuan Yuan Cheng (ISHR-SEA ECI rep, Taiwan), Diem My Vu (ISHR-SEA ECI rep, Vietnam)

1. The IL-33/ST2 Axis Mediates Macrophage-Driven Inflammation in the Progression of HfpEF
   Zhu Jinyun (Duke-NUS, Singapore)

2. Personalised Arterial-Wall-on-a-Chip Reveals Paracrine Crosstalk Between Diabetic Endothelial and Vascular Smooth Muscle Cells Driving Early Atherogenesis
   Chun-Yi Ng (Nanyang Technological University, Singapore)
3. Intrinsic Cardiac Ketogenesis Maintains Mitochondrial Function
   Yi-Chan Lee (Institute of Biomedical Sciences, Taiwan)
4. Sappanwood (Caesalpinia sappan L.) Attenuates Iron-Overload Induced Cardiac Ferroptosis in Animal Model
   Tanendri Arrizqiyani (Universitas Padjadjaran, Indonesia)
5. Population-Based Analysis of Coronary Artery Disease-Associated SNPs in Malaysian Cohort Compared to ALFA Global Reference Populations
   Nusaibah Sullehuddin (UiTM, Malaysia)
6. Differential Effects of Aldosterone Synthase Inhibition on Adrenal Zona Glomerulosa Remodeling and Cardiac Cellular Turnover in Spontaneously Hypertensive Rats
   Ammani Aminuddin (UKM, Malaysia)
7. The Serine Synthesis Pathway Activation In Early Compensatory Cardiac Hypertrophy
   Nurul Gusti Khatimah (Universitas Indonesia)
8. Prevalence of 22q11 Chromosome Deletion and Immunological Status of Vietnamese Patients with Tetralogy of Fallot
   Phuong Anh Huynh (University of Medicine and Pharmacy, Vietnam)
9. Endothelial and Metabolic Dysfunction in Mongolian Patients with Chronic Coronary Artery Disease
   Anudari Ichinkhorloo (Institute of Medical Sciences of Mongolia, Mongolia)

12:00 – 13:00 **Early-Career Open Communication Session**
Chairs: Satirah Zainalabidin (UKM, Malaysia), Rahayu Zulkapli (UiTM, Malaysia)

1. Bats as Novel Models to Uncover Cardiometabolic Adaptation and Resilience
   Yu Fan (DUKE-NUS, Singapore)
2. SGLT2 Inhibitor: A Novel Cardioprotective Intervention Against Post-Myocardial Infarction in Rats Through Suppression of Myocardial Apoptosis and Mitochondrial Dysfunction
   Chayadom Maneechote (Chiang Mai University, Thailand)
3. Inhibition of Pyroptosis and Apoptosis, but not Ferroptosis, Reduces Cardiac Dysfunction in Prediabetic Rats via Attenuating Mitochondrial Dysfunction, Independent of Metabolic Alterations
   Nattayaporn Apaijai (Chiang Mai University, Thailand)
4. Regulatory and Pathogenic Mechanisms in Aortic Valve Disease
   Yen-Chun Ho (IBMS, Academia Sinica, Taiwan)
5. Targeting Branched-chain Amino Acid Dysregulation to Restore Cardiomyocyte Function in a Human Cellular Model of Diabetic Heart Failure
   Shuo Cong (DUKE-NUS, Singapore)
6. Therapeutic Potential of PDE5 Inhibition in Cardiac Hypertrophy via Akt Signalling
   Nik Aloesnisa Binti Nik Mohd Alwi (USM, Malaysia)

13:00 - 13:10 **Industrial Talk @Ebony**

Climate Change & Autoimmune Disease: The Planetary Health Lens
Amir Hamzah Abdul Latiff (Premier Integrated Labs)

13:10 - 13:20 **Lunch Talk @Oak**
Lunch & Poster Viewing

14:00 - 15:20 **Scientific Session 5: Regenerative Medicine**
Chairs: Derek Hausenloy (NHCS, Singapore), Muhammad Da`in Yazid (UKM, Malaysia)

1. Biomaterials as Platforms for Secretome Therapies in Ischaemic Disease
   David Lundy (Taipei Medical University, Taiwan)
2. Immune-Cardiac Crosstalk via Nfic Regulates Cardiomyocytes Regeneration
   Ben Lai (IBMS, Academia Sinica, Taiwan)

3. Artificial Pacemaker Cell Engineering
   Yu-Feng Hu (Taipei Veteran General Hospital, Taiwan)
4. Direct Cardiac Reprogramming as a Novel Strategy for Heart Failure Treatment
   Taketaro Sadahiro (Keio University, Japan)

15:20 - 15:40 **Tea Break and Poster Viewing**

15:40 - 17:00 **Scientific Session 6: Cardiometabolic Syndrome**

Supported by JMCC

Special Issue JMCC : The Diabetic Heart: Mechanistic Insights Underlying its Phenotype, and Emerging Therapeutic Targets to Limit Diabetic Cardiomyopathy
Chairs: Patrick Hsieh (Institute of Biomedical Sciences, Taiwan), Yibin Wang (Duke-NUS, Singapore)

1. Acetyl-CoA Synthetase 2 Buffers Cytosolic Acetyl-CoA to Sustain Mitochondrial Function in Stressed Myocardium
   Shunsuke Miura (Fukushima Medical University, Japan)
2. Ca^{2+} Homeostasis in Pancreatic Beta-cells and Adipocytes
   Dae-Kyu Song (Keimyung University College of Medicine, South Korea)
3. Targeting Age-related Mechanisms in Cardiovascular-metabolic Disorders
   Ippei Shimizu (National Cerebral and Cardiovascular Center, Japan)
4. Senotherapy as a Novel Strategy for Metabolic Disorders
   So-Young Park (Yeungnam University College of Medicine, South Korea)

17:00 - 18:00 **Closing and Prize Giving Ceremony**

Announcement of the Next Coming 3rd Annual Meeting of ISHR-SEA

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Registration

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Dr. Fatin Farhana Jubaidi
Mrs. Faeezah Abdul Latif

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Assoc. Prof. Dr. Elena Aisha Azizan
Assoc. Prof. Dr. Kamisah Yusof
Mr. Rajasegar Anamalley

Social & Hospitality

Assoc. Prof. Dr. Chin Kok Yong
Mr. Rajasegar Anamalley

Souvenirs and Feedback

Dr. Adila A Hamid
Mrs. Juliana Abdul Hamid

Keynote Speaker

Sazzli Kassim
Director Cardiovascular Advancement and Research
Excellence Institute (CARE Institute), UiTM, Malaysia

Biography

Prof Dr. Sazzli Shahlan Kasim is the Director of the Cardiovascular Research Excellence (CARE) Institute and Professor of Medicine at Universiti Teknologi MARA (UiTM), Malaysia. A consultant cardiologist and digital health innovator, his research spans cardiovascular disease prevention, AI-driven risk prediction, digital cardiac rehabilitation, and EMR data harmonization. His work integrates health informatics, population health, and clinical outcomes which anchored by a strong foundation in health economics from the London School of Economics, in an effort to reduce the burden of cardiac death. He has led and participated in more than 30 clinical trials and has won national and international research and innovation grants. He has published over 100 peer-reviewed articles in journals such as The Lancet, PLOS ONE, Scientific Reports, and BMJ Open, with research translated into national clinical guidelines and digital policy pilots. Under his leadership, UiTM also developed its proprietary EMR (UniMEDS) and pioneering a modular Doctorate in Cardiology program, the first of its kind in Malaysia.

Challenging Risk Prediction of CVD with Artificial Intelligence

Cardiovascular disease (CVD) remains the leading cause of mortality globally and in Malaysia, with an increasing burden among younger populations presenting with acute coronary syndrome (ACS). Premature events are associated with substantial mortality and long-term socioeconomic impact. Despite widespread use, conventional risk scores are largely derived from Western cohorts and fail to accurately capture the heterogeneity of risk in Southeast Asian populations. This highlights a critical gap and the need for localized, population-specific risk prediction models that reflect regional epidemiology and clinical practice. We conducted a multi-phase research program integrating retrospective cohort analyses and prospective implementation studies using Malaysian datasets, including registry and population-based cohorts. Machine learning (ML) models were developed with strict control for data leakage, feature selection, and class imbalance. Model performance was evaluated against conventional risk scores. Parallel efforts focused on embedding the risk prediction tool into electronic medical records (EMR) and digital health platforms to assess real-world usability, clinician adoption, and workflow integration. ML-based models demonstrated improved discrimination and calibration compared to traditional risk scores, particularly in younger and intermediate-risk populations. Key challenges identified included data heterogeneity, limited standardization across EMRs, and barriers to clinical adoption. Implementation revealed the importance of explainability, seamless integration, and behavioral nudging to influence clinician decision-making. Localized AI-driven risk prediction offers significant potential to improve cardiovascular risk stratification in Malaysia. However, successful deployment requires addressing data, system, and behavioral challenges to bridge the gap between predictive performance and real-world impact.

Keynote Speaker

Jin Han
Inje University College of Medicine, South Korea

Biography

Dr. Jin Han, MD, PhD received his MD from College of Medicine, Inje University in Busan and his PhD in Physiology from Seoul National University in Seoul. His PhD focused on myocardial ischemia-reperfusion injury. The focus of Dr. Han's research is energy metabolism in cardiovascular diseases and cancer with physical activity. He is Professor of Physiology at College of Medicine, Inje University where he is Director of Cardiovascular Metabolic Disease Center and of the National Research Laboratory for Mitochondrial Signaling.

Cereblon–TRPC1 Axis Drives ER Stress and Fibrosis in Diabetic Cardiomyopathy through Calcium Signaling Dysfunction

Diabetic cardiomyopathy is a leading cause of heart failure, characterized by metabolic derangement, impaired calcium handling, and chronic endoplasmic reticulum stress. While endoplasmic reticulum stress is a recognized driver of cardiac remodeling, the upstream molecular mechanisms linking calcium dysregulation to maladaptive proteostasis remain incompletely defined. We identify cereblon (CRBN), a substrate receptor of the CUL4–DDB1 E3 ubiquitin ligase complex, as a previously unrecognized regulator of transient receptor potential canonical 1 that modulates endoplasmic reticulum stress and fibrosis in the diabetic heart. Analysis of human heart failure datasets and a diabetic mouse model revealed increased endoplasmic reticulum stress signaling associated with cardiac dysfunction. Genetic ablation of CRBN conferred protection against diabetic cardiomyopathy, as evidenced by preserved ejection fraction, fractional shortening, and stroke volume, alongside reduced cardiac hypertrophy. Mechanistically, CRBN directly interacts with and promotes the degradation of transient receptor potential canonical 1. In the diabetic state, CRBN-mediated suppression of this channel impairs intracellular calcium entry, leading to the activation of stress signaling predominantly through the IRE1α–XBP1–TRAF2 pathway. Conversely, CRBN deficiency or pharmacological inhibition restored channel expression, enhanced calcium transients, and attenuated high glucose-induced stress and myofibroblast transformation. Transcriptomic and histological analyses further demonstrated that the CRBN–transient receptor potential canonical 1 axis regulates pathways governing cardiac contractility and fibrosis in vivo. These findings identify CRBN as a critical regulator of calcium-dependent stress in the diabetic heart. By destabilizing transient receptor potential canonical 1, CRBN impairs adaptive calcium signaling and amplifies mediated stress, promoting fibrosis and cardiac dysfunction. This axis represents a mechanistic link between ion channel dysregulation and proteostatic remodeling, serving as a potential therapeutic target in diabetic heart failure.

Keynote Speaker

E. Dale Abel
William S. Adams Distinguished Professor
University of California, Los Angeles, USA

Biography

Prof. E. Dale Abel is the William S. Adams Distinguished Professor and Chair Department of Medicine, David Geffen School of Medicine and UCLA Health. He completed post-graduate training at Oxford, Northwestern and Harvard Universities. Dr. Abel's research focuses on mitochondrial mechanisms for complications of cardiometabolic disorders, the role of insulin and growth factor signaling in cardiac remodeling and mechanisms by which altered substrate metabolism contributes to heart failure. He has published more than 250 peer reviewed publications. He is the recipient of the Fred Conrad Koch Lifetime Achievement Award of the Endocrine Society and the Keith Reimer Distinguished Lecture Award from the ISHR. He is an elected member of the American Association of Physicians (AAP), the American Society for Clinical Investigation (ASCI), the American Clinical and Climatological Association (ACCA), the National Academy of Medicine (NAM) and the National Academy of Sciences (NAS). He is past President of the Endocrine Society and the Association of Professors of Medicine.

Contribution of Insulin Resistance and Mitochondrial Dysfunction to Heart Failure in Diabetes

Diabetes Mellitus amplifies heart failure risk, which now represents the leading cause of CVD-related hospitalization in patients with the diabetes. The pathophysiology of heart failure in diabetes transcends the increased incidence of coronary atherosclerosis. Generalized insulin resistance which characterizes type 2 diabetes leads to increased lipolysis and increased delivery of fatty acids and triglycerides to the heart, leading to increased utilization of fatty acids as a metabolic substrate. In concert with hyperglycemia, these changes in substrate utilization leads to oxidative stress induced mitochondrial dysfunction characterized by increased mitochondrial uncoupling, decreased cardiac efficiency and reduced mitochondrial ATP production. Reduced mitochondrial oxidative capacity leads to accumulation of toxic lipid and glucose intermediates in cardiomyocytes a phenomenon known as glucolipotoxicity. In addition to mitochondria, targets of these metabolic intermediates include the excitation-contraction (E-C) coupling machinery, and gene expression pathways by epigenetic and transcription-factor mediated pathways. The associated hyperinsulinemia activates growth promoting signaling pathways such as Akt and mTOR that leads to pathological cardiac hypertrophy. Moreover, aberrant insulin signaling downstream of insulin receptor substrates, engages signaling pathways that increase the likelihood of developing cardiac arrhythmias, while accelerating the degradation of cyclic AMP that reduces myocardial contractility .

Toshiyuki Ko
The University of Tokyo, Japan

Biography

Dr. Toshiyuki Ko, MD, PhD, is an Assistant Professor in the Department of Frontier Cardiovascular Science at the University of Tokyo. He received his MD in 2010 and PhD in 2018 from the University of Tokyo. His research spans a broad spectrum from basic science to translational and large-scale epidemiological studies, focusing on heart failure, cardiovascular genetics, and single-cell multiomics analysis. Dr. Ko has received numerous prestigious international awards, including Young Investigator Awards from the European Society of Cardiology, International Society for Heart & Lung Transplantation, International Society for Heart Research, and the American Heart Association.

Development of an Exercise-Mimetic Gene Therapy for Ischemic Heart Failure

Exercise confers cardioprotective effects for ischemic cardiomyopathy. Here, we employed single-nucleus multi-omics to decifer the beneficial effects of exercise on ischemic cardiomyopathy. We employed a 6-week voluntary running protocol in a murine myocardial infarction model, which alleviated the progressive cardiac remodeling. Exercise promoted a reversal of failing cardiomyocyte trajectories, characterized by upregulation of metabolic and sarcomere gene programs and prevention of maladaptive epigenetic remodeling. Notably, we identified robust upregulation of the cardiac mechanosensing gene (Fhx) in exercise-specific cardiomyocyte clusters. *Fhx* overexpression via MyoAAV2A mimicked the cardioprotective effects of exercise on both transcriptome and phenotype levels, whereas its knockdown abolished these effects. Furthermore, exercise perturbed intercellular communication, highlighting upregulation of *Nrg1–Erbb4* signaling between endocardial cells and cardiomyocytes, and *Vegfc–Vegfr3* signaling between epicardial cells and lymphatic endothelial cells. Collectively, these findings provide single-cell resolution insights into exercise-induced cardioprotection and support gene *F*-based gene delivery as a potential exercise-mimetic therapeutic strategy.

Mas Rizky Anggun Adipurna Syamsunarno
Universitas Padjajaran, Indonesia

Biography

Dr. Mas Rizky is an Associate Professor and Head of the Department of Biomedical Sciences, Faculty of Medicine, Universitas Padjadjaran, Indonesia. His research focuses on metabolic processes in cardiovascular disease, particularly adipokines and adipose tissue–derived proteins. He is actively involved in community-based programs within the Academic Health System in West Java to reduce cardiovascular risk factors. He completed his PhD and postdoctoral training in Cardiovascular Medicine at Gunma University, Japan. His work has been published in reputable journals and presented internationally, and he has received awards including recognition from the Government of West Java Province and multiple Investigator Awards.

Adipokine Signatures in Acute Myocardial Infarction

Cardiovascular disease remains the leading cause of mortality worldwide, with acute myocardial infarction (AMI) representing a major clinical manifestation. In recent years, adipose tissue has been increasingly recognized not merely as an energy storage site, but as an active endocrine organ that secretes adipokines involved in the regulation of inflammation and cardiometabolic processes. The phenomenon known as the “obesity paradox,” in which obese patients appear to have lower mortality compared to their non-obese counterparts, raises important questions regarding the underlying biological mechanisms, particularly during acute cardiovascular events. This study aimed to explore adipokine profiles in AMI patients across different body mass index (BMI) categories. Using a cross-sectional approach, serum levels of adipokines were measured using Luminex and ELISA assays, alongside relevant clinical and lipid parameters.The findings suggest that adipokine profiles vary across BMI categories in AMI, offering insights into potential molecular pathways underlying the obesity paradox and emphasizing the role of adipose-derived mediators in shaping cardiometabolic responses during acute events.

Jacques Behmoaras
DUKE-NUS, Singapore

Biography

Prof Jacques has completed his PhD at the Université Paris Cité, where he worked on genetics of cardiovascular disease. He joined Imperial College London in 2005. As a postdoc and Junior Research Fellow at Imperial, he undertook positional cloning studies in chronic kidney disease and secured his PI position in 2010. Using systems genetics approaches and AI, his group revealed the primary role of immune gene and metabolic networks in inflammatory, fibrotic disease and ageing. Dr Behmoaras has recently joined Duke-NUS Medical School as an Associate Professor. He is part of the executive committee of Duke-NUS AI and Medical Sciences Initiative (DAISI) at Duke NUS and Co-director of Quantitative Biology and Medicine PhD Program.

Macrophage Polarization During Fibrotic Disease

We previously identified a monocyte-derived SPP1+ macrophage inflammatory gene signature in multi-organ fibrosis including dilated cardiomyopathy and chronic kidney disease (CKD). Here, we focus on CKD and show that the SPP1+ macrophage signature associates positively with the severity of fibrosis in renal biopsies. Spatial transcriptomics in fibrotic renal disease (CosMx, 452,292 cells, 242 fields) confirmed greater proportion of SPP1+ macrophages when compared to controls. SPP1+ macrophages localize to the glomeruli and as the disease progresses, they show a periglomerular infiltration pattern, a finding that we confirm temporally in a pre-clinical model of CKD. Importantly, ligand-receptor spatial proximity analysis indicated that macrophages near ACTA2+ fibroblasts upregulate SPP1+ and receptors for type-1 interferons, GM-CSF, and TGF-β. When activated sequentially, these ligand-specific signalling pathways potentiate SPP1 expression during healthy human monocyte-to-macrophage differentiation. These findings suggest a spatiotemporal macrophage-fibroblast cooperation enabling SPP1+ macrophage differentiation that is also relevant in fibrotic cardiac disease.

Tomoya Kitani
Kyoto Prefectural University of Medicine, Japan

Biography

Dr. Tomoya Kitani is a physician-scientist and Assistant Professor in the Department of Cardiovascular Medicine at Kyoto Prefectural University of Medicine, Japan. His research focuses on the molecular mechanisms of heart failure, vascular aging, and cardiotoxicity, with particular emphasis on human induced pluripotent stem cell–derived cardiomyocytes. He has received several competitive honors, including the Academic Encouragement Award from the UBE Academic Promotion Foundation, a Young Investigator Award from the Japanese Heart Failure Society, the Best Research Award from the Japanese Onco-cardiology Society, and the Shoren Award from Kyoto Prefectural University of Medicine. He has authored over 20 peer-reviewed publications.

Discovery of Novel Therapeutic Targets for Heart Failure Using Human Stem Cell–Derived Cardiomyocytes

Cardiovascular diseases remain a leading cause of morbidity and mortality worldwide, and limited access to human cardiomyocyte models has hindered direct investigation of cardiomyocyte intrinsic disease mechanisms. Recent advances in pluripotent stem cell technology enable generation of human pluripotent stem cell derived cardiomyocytes (PSC-CMs), providing a powerful platform for translational cardiovascular research. Using PSC-CMs, we previously demonstrated that trastuzumab induced cardiotoxicity is associated with impaired cardiomyocyte energy metabolism, revealing direct drug effects on human cardiomyocytes. In addition, transcriptomic analyses of PSC-CMs derived from patients with congenital heart disease identified disease specific gene expression signatures at the cardiomyocyte level. These studies established PSC-CMs as a human based platform to uncover cardiomyocyte intrinsic pathological mechanisms. Building on this platform, we applied a pooled kinase focused CRISPR Cas9 loss of function screen in human PSC-CMs to identify novel therapeutic targets for heart failure. This screen identified thousand and one amino acid protein kinase 1 (TAOK1) as a critical regulator of cardiomyocyte survival under stress conditions. TAOK1 knockdown significantly improved cardiomyocyte survival under doxorubicin exposure and hypoxic stress, accompanied by attenuation of p38 activation and reduced Caspase-3 cleavage. Furthermore, TAOK1 suppression reduced endothelin-1 induced hypertrophic responses in PSC-CMs with decreased JNK activation. In a mouse model of myocardial infarction, TAOK1 knockdown in the heart improved post infarction survival, preserved cardiac function, and reduced myocardial fibrosis. Together, these results identify TAOK1 as a novel therapeutic target across doxorubicin induced and ischemic cardiomyopathy and highlight the utility of human PSC-CMs for therapeutic target discovery.

Lin Ying-Hsi (Alvin)
DUKE-NUS, Singapore

Biography

I am a cardiac muscle biologist investigating the molecular and biophysical basis of impaired myocardial relaxation in heart failure, with a particular focus on HFpEF. My research focuses on sarcomere-level mechanisms, examining how molecular perturbations propagate through cross-bridge kinetics to shape myofibril mechanics in health and disease. Using integrated platforms spanning murine models, human iPSC-derived cardiomyocytes, and ex vivo myocardial systems, I study mechanisms that enable restoration of myocardial relaxation while preserving systolic performance. Based at Duke-NUS Medical School, my work aims to translate mechanistic insights into targeted, disease-modifying strategies for heart failure.

Non-canonical Effects of Low-Dose Myosin Inhibitor Mavacamten to Facilitate the Relaxation of Myofibrils from the HFpEF Heart

Heart failure with preserved ejection fraction (HFpEF) is now the most prevalent form of heart failure worldwide. Clinically, this syndrome is characterised by impaired myocardial relaxation and increased left ventricular stiffness, yet therapies that directly target this primary myocardial defect remain limited. We are particularly interested in whether relaxation impairment in HFpEF can be corrected by modulating sarcomeric mechanics rather than systemic haemodynamic pathways. Mavacamten (MAVA), a selective cardiac myosin modulator approved for symptomatic obstructive hypertrophic cardiomyopathy (HCM), reduces pathological hypercontractility by inhibiting myosin–actin interactions. However, in non-obstructive HCM and HFpEF, higher doses of MAVA have been associated with reductions in systolic function, limiting its applicability. Given clinical concerns about systolic suppression at higher doses, together with emerging in vitro evidence that relaxation can be accelerated before any detectable loss of force, we tested whether myosin modulation could enhance sarcomeric relaxation independently of contractility. We show that low-dose MAVA consistently accelerates sarcomeric relaxation without reducing contractile force in healthy myocardium and rescues impaired relaxation in a two-hit murine HFpEF model. Mechanistically, this dose normalizes delayed ADP release from myosin in HFpEF myofibrils. Structurally, whereas inhibitory doses of MAVA reduce actin–myosin engagement via OFF/SRX stabilization, sub-inhibitory exposure did not alter myosin–actin proximity but instead produced a less ordered thick-filament structure distinct from the canonical force-suppressive mechanism. Collectively, these findings define a dose-selective, force-preserving lusitropic mechanism of MAVA at the sarcomere level and provide a mechanistic framework for exposure-defined myosin modulation as a disease-modifying strategy for diastolic heart failure.

Lim Wei Wen
National Heart Centre Singapore, Singapore

Biography

Dr Wei-Wen Lim is a Senior Research Fellow at the National Heart Centre Singapore and Assistant Professor (Research) at Duke-NUS Medical School. He completed his PhD at the University of Adelaide on cardiac remodelling in hypertrophic cardiomyopathy and diabesity in 2016. His postdoctoral work with Professor Stuart Cook at NHCS established interleukin-11 as a key driver of cardiac and vascular fibrosis. He now works with Professor Derek Hausenloy on cardiovascular protection and leads development of the Preclinical Electrophysiology Core at NHRIS. His research integrates human and mouse systems, tissue studies and preclinical models to uncover mechanisms underlying cardiovascular disease.

Atrial Remodelling and AF Susceptibility in Mouse Models of Hypertrophic Cardiomyopathy

Atrial fibrillation (AF) is a major source of morbidity in hypertrophic cardiomyopathy (HCM), yet atrial disease mechanisms remain strikingly understudied compared with the extensive literature on ventricular hypertrophy. Mouse models carrying pathogenic sarcomeric mutations offer a uniquely controlled platform to interrogate atrial pathophysiology, enabling high-resolution structural and electrophysiologic phenotyping that is rarely feasible in patients. Across diverse HCM genotypes—including *Myh7*, *Mybpc3*, *Tnnt2*, and *Tnni3*—atrial remodelling emerges as an early, penetrant, and often pre-ventricular phenotype. Left atrial enlargement, myocyte hypertrophy, interstitial fibrosis, and extracellular matrix expansion reflect a robust fibrotic programme driven by TGF-β signalling and fibroblast activation. Electrophysiologic remodelling is characterised by slowed conduction, increased anisotropy, connexin dysregulation, and a vulnerable substrate for re-entry. Optical mapping consistently reveals heightened AF inducibility, prolonged arrhythmia episodes, and spatially heterogeneous conduction slowing that parallels substrate features observed clinically in HCM patients. Despite AF being one of the most common and morbid complications of HCM, systematic investigation of atrial biology in this disease remains limited. The reproducible atrial phenotypes in HCM mouse models highlight an urgent need to shift mechanistic and therapeutic attention toward the upper chambers. These models provide a powerful testbed for substrate-directed interventions—including antifibrotic strategies, modulators of calcium handling, and haemodynamic unloading approaches—and for defining how sarcomeric mutations prime the atria for arrhythmogenesis. Advancing atrial-focused research in HCM is essential for developing precision therapies that meaningfully reduce AF burden and improve patient outcomes.

Diem My Vu
University of Medicine and Pharmacy, Vietnam

Biography

Dr. Diem My Vu is a Principal Researcher at the Center for Molecular Biomedicine, University of Medicine and Pharmacy at Ho Chi Minh City, Vietnam. She holds a PhD and focuses on advancing cardiovascular science through translational research. Her work centers on heart failure, cardiac regeneration, and the development of RNA- and cell-based therapies aimed at restoring myocardial function. Dr. Vu is particularly interested in innovative molecular approaches that bridge basic science and clinical application, contributing to improved therapeutic strategies for cardiovascular diseases.

Circulating Profiling and Nanoparticle Delivery of miRNAs Targeting Heart Failure

MicroRNAs (miRNAs) are small non-coding RNAs playing crucial roles in regulating gene expression and protein homeostasis. The dysregulation of miRNAs has been reported in numerous studies of heart failure. By profiling the plasma miRNAs, we identified different subsets of dysregulated miRNAs in Vietnamese patients with heart failure. Computational target prediction and subsequent functional investigation identified miR-185-5p as a negative regulator of cardiomyocyte proliferation through modulating *CCND1* and *CDKN2C* expressions. Targeting miR-185-5p for cardiac regeneration, we developed a nanoparticle-based therapy combining poly-L-arginine, chitosan, and polyethylenimine encapsulation that resulted in enhanced stability of miR-185-5p inhibitor.

Nur Najmi Mohamad Anuar
Universiti Kebangsaan Malaysia, Malaysia

Biography

Dr. Nur Najmi Mohamad Anuar is an Associate Professor and Biomedical Scientist at at Universiti Kebangsaan Malaysia (UKM). She completed her PhD in Vascular Pathology at University of Bristol. She is one of the leading researchers in cardiovascular pathology at UKM, specializing in the study of molecular mechanisms underlying cardiovascular diseases such as atherosclerosis and myocardial infarction. She is currently utilising self-isolated umbilical cord–derived endothelial cells as an in vitro model of the disease through the application of various induction methods.. She is also interested on exploring the potential of repurposing anti-cancer drug such as Navitoclax in managing angiogenesis in cardiovascular pathology condition. Her research aims to uncover the complex cellular processes that drive these conditions, with the goal of identifying new biomarkers and therapeutic targets.

Targeting Angiogenesis with Navitoclax: Insights from HUVECs Toward Stabilizing Atherosclerotic Plaques

Intraplaque angiogenesis is increasingly recognized as a key contributor to atherosclerotic plaque instability, a major underlying cause of cardiovascular events. This pathological process shares notable similarities with tumour angiogenesis, including enhanced endothelial cell survival, proliferation, and migration. Given these parallels, anti-cancer agents such as navitoclax, a Bcl-2 family protein inhibitor known for promoting apoptosis in cancer cells suggested to present a novel therapeutic for modulating pathological angiogenesis in cardiovascular disease. The anti-angiogenic potential of navitoclax explored using an in vitro model of human umbilical vein endothelial cells (HUVECs) behaviour that relevant to plaque stability.

Elisa Liehn
National Heart Centre Singapore, Singapore

Biography

Dr. Elisa Liehn is a cardiologist and clinician-scientist at the National Heart Centre Singapore, holding an affiliated professorship at Duke-NUS. Specializedin multimorbid cardiovascular care, she integrates deep clinical insights with extensive expertise in molecular research and preclinical models. With over 140 publications and an h-index of 50, she is a global leader in cardiovascular science, serving as an international grant evaluator and founder of the Discoveries journals. Her mission is to lead interdisciplinary translational research groups that bridge the gap between scientific innovation and improved outcomes for complex patients.

Phosphatidylserine as a Natural Approach to Address Atherosclerotic Plaque Formation

We have investigated the influence of phospholipids on vascular lesion formation following arterial injury. Utilizing murine models, it was observed that phosphatidylserine supplementation did not inhibit lesion development in hyperlipidemic mice, although it contributed to increased neointimal proliferation, likely driven by medial layer growth. Conversely, in ApoE-deficient mice, phosphatidylserine conferred protective effects against lesion formation and was associated with enhanced arterial elasticity, as assessed by echocardiography. These findings underscore significant inter-model differences in plaque composition and pathogenic mechanisms, highlighting the importance of model-specific considerations in cardiovascular research and the development of targeted therapeutic strategies.

Young Min Bae
Konkuk University, South Korea

Biography

Dr. Young Min Bae is a Professor of Physiology at Konkuk University School of Medicine, South Korea, and a Visiting Research Scholar at the University of South Florida. His research centers on ion channel physiology and its role in vascular function and disease, with a focus on mechanisms underlying arterial excitability and hypertension. He has made sustained contributions to the field, including recent work in *Circulation Research* identifying NALCN as a key determinant of vascular tone. In addition, his research extends to mechanotransduction and tactile sensation, exploring how ion channels mediate mechanical signaling in sensory systems. His work bridges fundamental electrophysiology with translational insights into cardiovascular and sensory disorders.

The Role of NALCN in Vascular Function and Hypertension

The regulation of arterial tone is fundamentally governed by membrane potential and ion channel activity in vascular smooth muscle cells. While the roles of K^+ and Ca^{2+} channels are well established, the contribution of background Na^+ conductance to basal excitability has remained largely unexplored. The sodium leak channel, non-selective (NALCN), provides a persistent Na^+ influx that may critically influence resting membrane potential. In our recent study published in *Circulation Research (2025)*, we demonstrate that arterial NALCN knockdown attenuates mineralocorticoid-induced hypertension and reduces vascular hypercontractility. These findings support a model in which NALCN-mediated Na^+ leak contributes to sustained depolarization, thereby facilitating voltage-dependent Ca^{2+} entry and increased contractile tone in hypertension. This work identifies NALCN as a key determinant of vascular excitability and suggests that modulation of background Na^+ conductance represents a novel mechanistic axis in hypertension.

Koichiro Kuwahara
Shinshu University School of Medicine, Japan

Biography

Dr. Koichiro Kuwahara is a Professor of Cardiovascular Medicine at Shinshu University School of Medicine. He obtained M.D. from Kyoto University in 1991 and received Ph.D. from the Graduate School of Medicine, Kyoto University in 2000. He was appointed to Professor of Shinshu University School of Medicine in 2016. He also currently serves as assistant dean of the Shinshu University School of Medicine and vice director of Shinshu University Hospital. He serves as vice president of the Japanese Onco-Cardiology Society and the Society of Cardiovascular Endocrinology and Metabolism, and is president-elect of the International Society for Heart Research Japanese Section.

Endothelial C-type Natriuretic Peptide / Guanylyl Cyclase-B Signaling in Pulmonary Vascular Remodeling

The development of drugs based on novel therapeutic mechanisms is an urgent issue in the treatment of pulmonary arterial hypertension (PAH), which is a life-threatening disease. C-type natriuretic peptide (CNP) is released from endothelial cells and acts as an autocrine/paracrine mediator, regulating systemic blood pressure and vascular remodeling via guanylyl cyclase-B (GC-B) and natriuretic peptide receptor-C. Still, the roles of endothelial cell-derived CNP and its target cell types and receptor-mediated signaling pathways in maintaining pulmonary vascular homeostasis and the development of PAH remained uncertain. In this study, the impact of vascular CNP/GC-B signaling on the development of PAH was investigated. Mice developing pulmonary hypertension (PH) show less pulmonary NPPC and NPR2 expression than mice without PH. Similarly, endothelial cells (EC) from patients with idiopathic PAH exhibit lower NPPC and NPR2 expression than control EC. EC-specific CNP or GC-B conditional knockout (CNP ecKO or GC-B ecKO) mice, but not smooth muscle cell-specific GC-B conditional knockout (GC-B smcKO) mice, show more severe PH and greater expression of Edn1, Il6, Ccl2 and Tgfb1 mRNAs than their genetic controls in PAH models, Mechanistically CNP suppresses hypoxia-induced increases in expression of these mRNAs and restored SMAD2/3-SMAD1/5/9 balance in cultured human pulmonary arterial EC. Furthermore, administration of CNP prevents PH in genetic control and GC-B-smcKO mice but not in GC-B ecKO mice. CNP administration also exerts therapeutic effects against Sugen/hypoxia PAH models and additive benefits with currently established therapies. Thus, endothelial CNP/GC-B signaling exhibits pivotal preventive and therapeutic effects against development of PH.

Kee Boon Pin
University of Malaya, Malaysia

Biography

Dr. Kee Boon Pin is Senior Lecturer and Head of the Department of Biomedical Science at the Faculty of Medicine, Universiti Malaya. He holds a Bachelor of Biomedical Science and a PhD from Universiti Malaya. His research is focused on cardiovascular and molecular genetics, particularly the genetic basis of cardiomyopathy, where he employs genomic and next-generation sequencing approaches to investigate and characterize disease-associated variants in patient cohorts. He also has research expertise in molecular genetics, mitochondrial DNA, and molecular diagnostic technologies.

Genetic Landscapes of Cardiomyopathy in Malaysia

Cardiomyopathy (CMP) is a genetically heterogeneous disease and a leading cause of heart failure globally. While much is known about its genetic basis in Western populations, data from Southeast Asia, particularly Malaysia, remain scarce. In this study, next-generation sequencing approach was conducted on idiopathic cardiomyopathy patients in Malaysia to discover CMP-associated variants. The findings include several reported and novel mutations in CMP-associated genes. These findings underscore the importance of establishing population-specific genetic references to improve diagnosis, risk prediction, and familial counselling. This work contributes essential genomic insight into the underrepresented Southeast Asian context of inherited cardiomyopathies

Cheng-Fu Kao
Institute of Cellular and Organismic Biology, Academia Sinica, Taiwan

Biography

Dr. Cheng-Fu Kao is a researcher in chromatin biology, studying how gene regulation supports cellular function and tissue homeostasis. His work addresses fundamental questions across different biological systems, with a focus on how cells maintain stability under stress. He has contributed to interdisciplinary studies linking basic biology to broader questions in health and disease.

RNF20 Stabilizes Adult Cardiomyocyte Cell State to Prevent Pathological Dedifferentiation

Adult cardiomyocyte (CM) identity requires active maintenance, yet the epigenetic factors preventing pathological reversion remain poorly defined. We identify the E3 ubiquitin ligase RNF20 as an essential guardian of the adult CM cell state. CM-specific RNF20 deletion triggers a rapid transition from a mature transcriptional program to a dedifferentiated state, resulting in lethal dilated cardiomyopathy. Integrated single-nucleus RNA-seq and ATAC-seq reveal that RNF20 loss induces a global chromatin shift, characterized by decreased accessibility at maturity-associated genes and increased accessibility at distal enhancers enriched for AP-1 and TEAD motifs. Notably, this RNF20-null dedifferentiation is uncoupled from proliferation; despite nuclear YAP1 localization, CMs fail to divide. Mechanistically, RNF20 loss upregulates the SWI/SNF subunit Arid1a alongside constrained YAP1-TEAD transcriptional output, identifying an Arid1a-YAP1 axis as a candidate regulator of the non-regenerative dedifferentiation state. Our findings establish RNF20 as a critical epigenetic lock for adult cell identity, the disruption of which induces a compromised, non-regenerative dedifferentiation state.

Shu Ye
National University of Singapore, Singapore

Biography

Prof Shu Ye is a leading cardiovascular researcher with a strong focus on the pathogenesis and treatment of coronary heart disease. His recent work investigates how genetic variants influence cardiovascular disease susceptibility and seeks to identify novel therapeutic targets for improved clinical outcomes. He obtained his MD from Sun Yat-sen University of Medical Sciences, China, in 1992, and completed his PhD at University College London in 1996. He subsequently served as a British Heart Foundation Research Fellow at the University of Oxford, followed by academic roles at the University of Southampton. He later held senior positions at Queen Mary University of London and the University of Leicester. Since 2022, he has been a Research Professor at the National University of Singapore, continuing his contributions to cardiovascular research and innovation.

Functional Genomics Analysis Identifies Pleiotropic Genes for Vascular Diseases

Several vascular diseases including coronary artery disease, hypertension, stroke, and abdominal aortic aneurysm, have significant genetic underpinnings. Genome-wide association studies have unveiled many genetic loci associated with one or more of these diseases. However, the causative genes at most of these loci are yet to be determined, which hampers the translation of the genetic findings into a better understanding of the disease mechanisms and the identification of new therapeutic targets. Here, in an integrative functional genomics analysis of these loci, we identify a panel of likely causal genes, some of which are pleiotropic for more than one of these vascular diseases. Pooled CRISPR knockout screen analyses of these likely causal genes indicate that many of them influence vascular smooth muscle cell behavior, and validation experiments of selected genes confirm that *FES*, *BCAR1*, *CARF* and *SMARCA4* exert such effects. Animal model studies show that *Fes* knockout promotes atherosclerosis and raises blood pressure whilst *Smarca4* knockout reduces atherosclerosis and aortic aneurysm formation. These findings provide an insight into the genetic basis of vascular diseases and inform targets for therapeutic development.

Manvendra Singh
DUKE-NUS, Singapore

Biography

Dr. Manvendra K. Singh is an Associate Professor in the Signature Research Programme in Cardiovascular & Metabolic Disorders at the Duke-NUS Medical School. He also holds an academic appointment at the National Heart Research Institute Singapore, National Heart Centre Singapore. Dr. Singh obtained his M.Sc. in Biotechnology from Madurai Kamaraj University, India, and his Ph.D. in Developmental Biology from Hannover Medical School, Germany. He completed postdoctoral training at Columbia University and University of Pennsylvania, where he specialized in cardiovascular biology. Upon joining Duke-NUS as a faculty member, he was awarded the NRF fellowship to advance his research in cardiovascular science. His research focuses on the molecular mechanisms underlying congenital and adult cardiovascular diseases.

Semaphorin-Plexin-Neuropilin Signaling in Left Ventricular Non-compaction

Left ventricular noncompaction (LVNC) is a common genetic cardiomyopathy marked by excessive trabeculation and failed myocardial compaction during fetal development. Patients face elevated risks of left, right, or biventricular failure. While cardiac chamber development regulators are well known, the role of semaphorin/plexin signaling remains poorly understood. We recently showed that Sema3E/PlexinD1 pathway genes are expressed in the developing heart and essential for trabeculation and compaction. Here, we demonstrate that Neuropilin-1 (Nrp1), a transmembrane co-receptor for Sema-Plexin complexes, is expressed in the developing heart, and its tissue-specific deletion leads to ventricular noncompaction. Nrp1 regulates chamber formation by modulating endocardial–myocardial and epicardial–myocardial interactions, processes critical for myocardial compaction and ventricular remodeling. These findings establish Nrp1 as a key player in LVNC pathogenesis.

David Lundy
Taipei Medical University, Taiwan

Biography

Dr. David J. Lundy received his PhD in Cell Biology from the University of Durham, UK. He then spent four years as a Postdoctoral Research Fellow at Academia Sinica, Taiwan, conducting research on stem cells, biomaterials and drug delivery for ischaemic diseases. Dr. Lundy joined Taipei Medical University as Assistant Professor in 2019, where his lab explores cell-free therapies for ischaemic diseases, with recent work focusing on platelet-derived extracellular vesicles for wound healing and acute ischaemic injuries.

Biomaterials as Platforms for Secretome Therapies in Ischaemic Disease

Ischaemic diseases, including myocardial infarction (MI), remain leading causes of morbidity and mortality. While cell therapy has shown promise in clinical trials, translation has been constrained by poor engraftment and survival of delivered cells, limited retention at the target site, and incomplete understanding of therapeutic mechanisms. A growing body of evidence indicates that much of the benefit arises from the donor-cell secretome, including growth factors, cytokines/chemokines, and extracellular vesicles (EVs). Together, these can promote angiogenesis, reduce parenchymal cell death, and reprogram innate immune responses after injury. Yet secretome-based therapeutics face their own translational barriers, such as low effective dose at the target tissue, short residence time, and scalable manufacturing challenges. In this talk, I will present our biomaterials-enabled strategies to overcome these bottlenecks across multiple ischaemic disease indications. First, I will highlight implantable encapsulation platforms designed to retain therapeutic cells locally while enabling sustained paracrine release. Second, I will discuss our work using platelet-derived EVs as an accessible, cell-free product for cardiac repair, and extend this concept to ongoing studies in kidney ischaemia–reperfusion injury. Finally, I will describe a device-based approach to increase EV isolation yield from conditioned media, supporting more reproducible and scalable secretome production. Collectively, these efforts aim to turn diverse secretomes into practical, durable therapies for ischaemic disease.

Ben Shih-Lei Lai
Institute of Biomedical Sciences, Academia Sinica, Taiwan

Biography

Dr. Ben Lai is an Assistant Research Fellow at Academia Sinica, where he investigates the cellular and molecular mechanisms underlying heart regeneration. His research focuses on immune-cardiac crosstalk, particularly how macrophages coordinate tissue repair, extracellular matrix remodeling, and cardiomyocyte proliferation. Using comparative zebrafish and medaka models and validations in mammalian models, his work uncovers evolutionarily conserved and divergent pathways that govern regenerative capacity. Dr. Lai integrates genetic, imaging, and multi-omics approaches to dissect these processes. His studies aim to translate fundamental insights into therapeutic strategies for cardiovascular disease and have contributed to advancing the emerging field of cardio-immunology.

Immune-Cardiac Crosstalk via Nfic Regulates Cardiomyocyte Regeneration

Myocardial infarction causes irreversible cardiomyocyte loss in mammals, whereas zebrafish regenerate myocardium through cardiomyocyte dedifferentiation and proliferation. Macrophages are essential for this process, yet how immune activation is linked to cardiomyocyte renewal remains unclear. Using single-nucleus ATAC-sequencing of zebrafish hearts before and after cryoinjury, with and without macrophage depletion, we identified a regeneration-associated cardiomyocyte population that expands after injury and is enriched for dedifferentiation markers. Motif analysis revealed selective activation of Nuclear Factor I C, which was lost upon macrophage depletion. Consistently, *nfic* reactivated in dedifferentiated cardiomyocytes at the injury border. Loss of *nfic* impaired cardiomyocyte dedifferentiation and proliferation, resulting in persistent fibrotic scarring, whereas ectopic *nfic* expression in cardiomyocytes promoted proliferation in uninjured adult zebrafish. Notably, Nfic knockdown also impaired proliferation in neonatal mouse cardiomyocytes, indicating evolutionary conservation. Together, these findings identify Nfic as a novel regulator linking immune activation to cardiomyocyte plasticity during heart regeneration.

Yu-Feng Hu
Taipei Veterans General Hospital, Taiwan

Biography

Dr. Yu-Feng Hu is an attending physician at Taipei Veterans General Hospital and Professor at National Yang Ming Chiao Tung University, Taiwan, with a joint research affiliation at Academia Sinica. He obtained his M.D. from National Cheng Kung University, completed cardiology and electrophysiology training in 2008, and earned his Ph.D. in Clinical Medicine, with additional research training at Cedars-Sinai Medical Center, USA. As a physician-scientist, he specializes in cardiac arrhythmias, integrating clinical practice with translational research. His work focuses on sinoatrial node physiology, disease mechanisms, and innovative biological therapies, including pacemaker cardiomyocyte models and stem cell technologies. He also develops artificial intelligence-based ECG analysis and investigates genetic factors underlying arrhythmias. His research has been published in leading journals such as Nature Biomedical Engineering, Circulation Research, and Science Translational Medicine. He has received numerous international awards and is recognized among Stanford University's World's Top 2% Scientists.

Artificial Pacemaker Cell Engineering

Electrical impulses from cardiac pacemaker cardiomyocytes initiate cardiac contraction and blood pumping and maintain life. Abnormal electrical impulses bring patients with low heart rates to cardiac arrest. The current therapy is to implant electronic devices to generate backup electricity. However, complications inherent to electronic devices remain unbearable suffering. Therefore, cardiac biological pacing has been developed as a hardware-free alternative. The approaches to generating biological pacing have evolved recently using cell reprogramming technology to generate pacemaker cardiomyocytes in-vivo or in-vitro. Different from conventional methods by electrical re-engineering, reprogramming-based biological pacing recapitulates various phenotypes of de novo pacemaker cardiomyocytes and is more physiological, efficient, and easy for clinical implementation. We begin with the rationale for this new approach and review its advances in creating a biological pacemaker from rodent to human induced pluripotent stem cell derived cardiomyocyte to treat bradyarrhythmia.

Taketaro Sadahiro
Keio University, Japan

Biography

Dr. Taketaro Sadahiro is a leading researcher in cardiac regeneration and fibrosis, with a focus on direct cellular reprogramming. He earned his PhD in Medicine from Keio University and served as a lecturer at the University of Tsukuba before returning to Keio University, where he is currently an Assistant Professor in the Department of Cardiology at the School of Medicine. Dr. Sadahiro's research explores the mechanisms of cardiac fibrosis, employing cutting-edge methodologies such as single-cell analysis, spatial transcriptomics, and lineage-tracing mouse models. His work has elucidated the characteristics of fibroblasts induced by heart failure and demonstrated the anti-fibrotic potential of direct reprogramming. Recognized with prestigious awards from the Japanese Circulation Society and the International Society for Heart Research (ISHR), Dr. Sadahiro continues to advance innovative therapies for heart failure and fibrosis.

Direct Cardiac Reprogramming as a Novel Strategy for Heart Failure Treatment

Heart failure remains a leading cause of morbidity and mortality worldwide, and effective therapies that directly repair damaged myocardium are still lacking. Because adult cardiomyocytes have limited regenerative capacity, myocardial injury leads to fibroblast activation and fibrosis, contributing to both heart failure with reduced ejection fraction and heart failure with preserved ejection fraction. We investigated whether direct cardiac reprogramming could serve as a therapeutic strategy in established heart failure. Using lineage-tracing mouse models, we induced cardiac reprogramming in chronic myocardial infarction and two-hit heart failure with preserved ejection fraction models. Polycistronic expression of cardiac transcription factors converted resident cardiac fibroblasts into induced cardiomyocyte-like cells in vivo, even in fibrotic hearts. Although reprogramming efficiency was low, cardiac function was significantly improved and fibrosis was markedly reduced in both disease models. Single-cell transcriptomic analyses revealed that reprogramming redirected fibroblasts away from pathological profibrotic states toward more quiescent phenotypes, indicating that normalization of fibroblast states contributes substantially to therapeutic benefit. In heart failure with preserved ejection fraction, where cardiomyocyte loss is limited, anti-fibrotic effects played a dominant role, and GATA4 alone was sufficient to improve cardiac function without inducing cardiomyocyte regeneration. These findings demonstrate that cardiac reprogramming repairs the failing heart through coordinated regenerative and anti-fibrotic mechanisms and support its development as a gene therapy approach for diverse forms of heart failure.

Shunsuke Miura
Fukushima Medical University, Japan

Biography

Dr Shunsuke Miura, MD, PhD, graduated from Fukushima Medical University in 2009 and joined the Department of Cardiovascular Medicine in 2011. He obtained his PhD from the same university in 2017. From 2018 to 2021, he worked as a postdoctoral researcher in the Feinberg Cardiovascular and Renal Institute at Northwestern University (Dr. Hossein Ardehali's laboratory), where he studied T cell metabolism. After returning to Fukushima Medical University, his research has focused on the roles of the cytoskeleton and immune cells in regulating cardiac metabolism.

Acetyl-CoA Synthase 2 Buffers Cytosolic acetyl-CoA to Sustain Mitochondrial Function in Stressed Myocardium

Heart failure is characterized by metabolic remodeling; however, the contribution of compartment-specific acetyl-CoA regulation to mitochondrial dysfunction remains unclear. We investigated the role of acetyl-CoA synthetase 2 (ACSS2) in maintaining cytosolic acetyl-CoA homeostasis under chronic β-adrenergic stress. In a mouse model of isoproterenol-induced heart failure, ACSS2 expression was significantly downregulated, accompanied by a reduction in cytosolic acetyl-CoA without changes in total cellular levels. Similar findings were observed in H9c2 cardiomyoblasts and neonatal rat cardiomyocytes. Inhibition of ACSS2 recapitulated this metabolic disturbance, leading to mitochondrial atrophy and impaired oxidative respiration without altered mitochondrial biogenesis. Prolonged supplementation with butyrate restored mitochondrial respiratory capacity, indicating reversibility of dysfunction. Conversely, cardiomyocyte-specific ACSS2 overexpression preserved cytosolic acetyl-CoA levels, maintained mitochondrial integrity, and improved cardiac function in vivo.These findings identify ACSS2 as a key regulator of cytosolic acetyl-CoA homeostasis and reveal a compartment-specific mechanism underlying mitochondrial dysfunction in heart failure.

Dae-Kyu Song
Keimyung University College of Medicine, South Korea

Biography

Dr Song SE earned a Ph.D. in Physiology from Keimyung University (1989–1992) and has served as a Professor in the Department of Physiology and the Obesity-Mediated Disease Research Center at Keimyung University School of Medicine since 2009. Song also gained international research experience as a Research Scientist at the University of Oxford, United Kingdom (1999–2001). With a strong focus on cellular physiology and metabolic diseases, Song's research explores pancreatic beta-cell function, endoplasmic reticulum stress, and obesity-related mechanisms. Notable publications include studies on the role of cytosolic and endoplasmic reticulum calcium in pancreatic beta cells (Pflugers Archiv, 2024), the protective effects of lupenone against thapsigargin-induced ER stress and apoptosis (Life Sciences, 2023), and the impact of oxidative stress from catalase depletion on adipocyte hyperplasia and hypertrophy contributing to obesity (Redox Biology, 2020).

Ca^{2+} Homeostasis in Pancreatic Beta-cells and Adipocytes

Pancreatic beta cells utilize Ca^{2+} to secrete insulin in response to glucose. The glucose-dependent increase in cytosolic Ca^{2+} concentration ($[Ca^{2+}]_C$) activates a series of insulin secretory machinery in pancreatic beta cells. Therefore, the amount of insulin secreted in response to glucose is determined in a $[Ca^{2+}]_C$-dependent manner. However, the demand for insulin secretion may surpass the capability of beta cells. Abnormal elevation of $[Ca^{2+}]_C$ levels can damage themselves by inducing endoplasmic reticulum (ER) stress and cell death programs. While Ca^{2+} is essential for the insulin secretory functions of beta cells, it could affect their survival at pathologically higher levels. The pathophysiological role of Ca^{2+} is also salient in adipocytes as it is involved in adipocytes differentiation and proliferation as well as the cell survival. Here, we will discuss the clinical significance of Ca^{2+} in beta cells and adipocytes.

Ippei Shimizu
National Cerebral and Cardiovascular Center, Japan

Biography

Dr. Ippei Shimizu is a cardiovascular scientist and physician at the National Cerebral and Cardiovascular Center (NCVC), Japan, where he leads the Department of Cardiovascular Aging. His research focuses on cardiac aging, heart failure and atrial fibrillation, integrating animal models, human tissue analysis, and population-scale studies to redefine atrial fibrillation as an aging-related disease. His work has advanced the understanding of cellular senescence and circulating pro-fibrotic factors as therapeutic targets. He has published in leading cardiovascular journals, and actively promotes international collaborative research. Please see the following for details (https://www.cv-aging.com).

Targeting Age-related Mechanisms in Cardiovascular-metabolic Disorders

Accumulation of senescent cells contributes to the pathogenesis of age-related diseases, including heart failure, atherosclerosis, chronic kidney disease (CKD), and Alzheimer's disease. Senolysis, the selective elimination of senescent cells, has emerged as a promising therapeutic strategy, with both genetic and pharmacological approaches shown to reverse aging phenotypes in rodent models. We recently demonstrated that SGLT2 inhibitors exert senolytic effects and ameliorate aging phenotypes in dietary obesity and progeria models. In addition, we identified a senoantigen and showed that vaccination targeting this molecule improves aging-related phenotypes. Beyond cellular senescence, circulating age-associated factors also play critical roles. We identified a brown adipose tissue-derived pro-fibrotic factor that increases with aging and obesity, contributing to heart failure with preserved ejection fraction (HFpEF), CKD and metabolic dysfunction-associated steatohepatitis (MASH). Based on these findings, we propose a novel concept of "aging fibrotic diseases (A-FiD)", and aim to establish next-generation therapies through combined targeting of senescence and circulating pro-fibrotic factors.

So-Young Park
Yeungnam University College of Medicine, South Korea

Biography

Dr. So-Young Park is a Professor and Director of the Senotherapy-based Metabolic Disease Control Research Center at Yeungnam University College of Medicine. Her research focuses on energy metabolism, with particular emphasis on glucose metabolism and insulin resistance in obesity. Building on evidence that senescent cell accumulation contributes to metabolic dysfunction, her research targets cellular senescence as a therapeutic strategy. Her team develops senotherapeutics that selectively eliminate senescent cells to prevent or attenuate insulin resistance. Through translational and mechanistic studies, her work aims to advance precision therapies for metabolic diseases and promote healthy aging.

Senotherapy as a Novel Strategy for Metabolic Disorders

Cellular senescence is a stress-induced state of permanent growth arrest that contributes to tissue aging and metabolic dysfunction. Senescent cells accumulate due to factors such as telomere attrition and genomic damage, impairing tissue homeostasis through secretion of SASP factors. Adipose tissue is particularly susceptible, where senescence promotes inflammation, fibrosis, and insulin resistance. In this study, a large-scale screen of 2,150 clinically used compounds identified 15 candidates with anti-senescent activity. Among them, Homoharringtonine (HHT) emerged as the lead compound, improving glucose intolerance and reducing senescent cell burden in obese mice. HHT also showed similar effects in aged mice and human adipose tissue. Single-cell analyses revealed attenuation of senescence in adipose progenitor cells and mature adipocytes. Mechanistically, HHT targets the ER chaperone HSPA5, promoting selective clearance of senescent cells. Furthermore, HHT reduced senescence across multiple tissues and extended lifespan, suggesting its potential as a systemic senotherapeutic agent.

Building Better Vessels: From Matrix Integrity to Re-Endothelialisation

Nadiah Sulaiman

Department of Tissue Engineering and Regenerative Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia

ABSTRACT

Cardiovascular diseases remain a leading cause of morbidity and mortality worldwide. Although autologous saphenous vein grafts are the current standard for coronary artery bypass grafting (CABG), their limited availability and poor long-term patency drive efforts to enhance graft performance and identify alternative sources. This study aims to develop off the-shelf vascular scaffolds that support cell adhesion, proliferation, and tissue remodeling. We explore various decellularised allografts and xenografts, coupled with surface functionalisation strategies to promote endothelialisation. The decellularisation process, including complete denudation of endothelial cells, facilitates host cell integration and enables mechanistic studies of re-endothelialisation for future translational applications.

Smooth Muscle Plasticity in Early Atherosclerosis Revealed by Spatial Multi-omics

Rijan Gurung

Cardiovascular Research Institute (CVRI), Cardiovascular Diseases Translational Research Programme (CVD TRP), National University of Singapore

ABSTRACT

Cardiovascular diseases remain a leading cause of morbidity and mortality worldwide. Although autologous saphenous vein grafts are the current standard for coronary artery bypass grafting (CABG), their limited availability and poor long-term patency drive efforts to enhance graft performance and identify alternative sources. This study aims to develop off the-shelf vascular scaffolds that support cell adhesion, proliferation, and tissue remodeling. We explore various decellularised allografts and xenografts, coupled with surface functionalisation strategies to promote endothelialisation. The decellularisation process, including complete denudation of endothelial cells, facilitates host cell integration and enables mechanistic studies of re-endothelialisation for future translational applications.

Modulation of Vascular Inflammation by Gynura procumbens: in Vivo and in Vitro Studies

Norsyahida Mohd Fauzi

Universiti Kebangsaan Malaysia

ABSTRACT

Vascular inflammation is a key contributor to cardiovascular disease. Gynura procumbens (GP), a medicinal plant, exhibits anti-inflammatory activity relevant to vascular inflammation and endothelial dysfunction. In postmenopausal rats fed repeatedly heated palm oil, standardised GP extract lowered blood pressure, improved vascular reactivity, and reduced systemic inflammatory markers (TNF-α, IL-6, CRP, sICAM-1, sVCAM-1). In vitro, GP extract inhibited monocyte adhesion to TNF-α-activated endothelial cells and downregulated ICAM-1, VCAM-1, MCP-1, and NF-κB signaling. These findings suggest that GP attenuates vascular inflammation by modulating endothelial activation and systemic inflammation, supporting its potential as a natural agent for vascular protection.

Role of Endoplasmic Reticulum and Mitochondria Contact Sites in Cardiac Fibrosis

Jin O-Uchi

Heart Institute, Hypertension and Kidney Research Center, Department of Molecular Pharmacology and Physiology, University of South Florida Morsani College of Medicine, Tampa, FL, USA

ABSTRACT

Severity of right ventricular (RV) fibrosis, and RV dysfunction correlate with the mortality in the patients with pulmonary arterial hypertension (PAH). We previously showed that an oxidative stress-sensitive tyrosine kinase c-Src can phosphorylate mitofusin 2 (Mfn2), a key protein forming tethering structure between endoplasmic reticulum (ER) and mitochondria (Mito), which decreases the ER-Mito distance followed by elevated ER-to-Mito Ca2+ transfer, increased mitochondrial reactive oxygen species (ROS), and the activation of proliferative signalling in adult human cardiac fibroblasts (CFs) from healthy donor. However, it is still not clear whether c-Src has pathological roles in RV under PAH. Tissue samples from human PAH-RVs and a preclinical rat SuHx PAH model (Sugen 5416 injection and 3-week hypoxia followed by 4-week normoxia) were used. Increased c-Src activity and Mfn2 phosphorylation were detectable from CFs, but not from cardiomyocyte area in the human and rat PAH-RVs. RV-CFs from PAH rats exhibited decreased ER-Mito distance, increased ROS, and the activation of proliferative signalling compared to RV-CFs from control animals. The introduction of adeno-associated virus serotype 9 carrying CF-specific promoter hTCF21 and outer mitochondrial membrane-targeted dominant-negative c-Src in PAH rats partially decreased RV fibrosis and recovered RV function compared to those injected with AAV9-hTCF21-luciferase. c-Src-dependent Mfn2 phosphorylation decreases ER-Mito distance, facilitates ER-to-Mito Ca2+ transport, and increases mitochondrial ROS, which promotes CF activation in PAH. CF- and mitochondria-specific inhibition of c-Src may attenuate RV fibrosis and failure in response to PAH.

Bats as Novel Models to Uncover Cardiometabolic Adaptation and Resilience

Yu Fan[a,b]

[a]National Heart Research Institute Singapore, National Heart Centre Singapore, Singapore
[b]Cardiovascular & Metabolic Disorders Programme, Duke-National University of Singapore Medical School, Singapore

ABSTRACT

Bats represent a unique yet underexplored model for cardiovascular research, exhibiting exceptional longevity, preserved cardiac function with aging, and resistance to oxidative stress. As the only mammals capable of powered flight, they sustain high cardiac energy expenditure, providing a valuable system for studying cardiometabolic adaptation and resilience. We investigated the cave nectar bat (*Eonycteris spelaea*) to understand how its heart meets extreme energy demands. Bat and mouse hearts were subjected to RNA-seq and metabolomics. Histology and electron microscopy were performed to assess structural characteristics. Stress echocardiography with dobutamine was conducted to determine cardiac reserve. The effects of angiotensin II (Ang II) were examined in isolated bat and mouse cardiomyocytes. Transcriptomic profiling revealed enrichment of oxidative phosphorylation and fatty acid metabolism pathways in bat hearts relative to mouse hearts. Metabolomics analyses corroborated these findings, showing distinct acylcarnitine profiles and elevated tricarboxylic acid cycle intermediates. Anatomically, bats had relatively larger hearts with increased mitochondrial and vascular densities, and prominent perivascular adipocytes. Echocardiography demonstrated superior cardiac reserve in bats, with enhanced contractile response under dobutamine stress. Notably, isolated bat cardiomyocytes resisted angiotensin II-induced hypertrophy and mitochondrial dysfunction. These integrated adaptations likely support the energetic demands of flight while preserving cardiac function under stress, positioning bats as a powerful model for uncovering evolutionarily optimized cardioprotective mechanisms. Insights from bat cardiovascular physiology may inform innovative strategies for preventing and treating human cardiovascular diseases.

SGLT2 Inhibitor: A Novel Cardioprotective Intervention Against Post-Myocardial Infarction in Rats Through Suppression of Myocardial Apoptosis and Mitochondrial Dysfunction

Chayodom Maneechote[a,b,c]

[a]Cardiac Electrophysiology Research and Training Center, Faculty of Medicine, Chiang Mai University, Thailand
[b]Center of Excellence in Cardiac Electrophysiology Research, Chiang Mai University, Thailand
[c]Office of Research Administration, Chiang Mai University, Thailand

ABSTRACT

Sodium-glucose cotransporter-2 (SGLT2) inhibitors reduce cardiovascular events in heart failure; however, the mechanisms underlying their benefit after myocardial infarction (MI) and their relationship to conventional renin-angiotensin system inhibition remain incompletely defined. Using a rat model of post-MI heart failure, we directly contrasted the effects of the SGLT2 inhibitor dapagliflozin with the angiotensin-converting enzyme inhibitor enalapril. Male Wistar rats underwent left anterior descending coronary artery ligation, and animals with left ventricular ejection fraction <50% received vehicle, dapagliflozin (1 mg/kg/day), or enalapril (10 mg/kg/day) for 10 weeks. Cardiac function was assessed by echocardiography and pressure-volume analysis, followed by comprehensive evaluation of myocardial structure, mitochondrial integrity, cell death pathways, inflammation, and targeted metabolomics. Despite no effects on infarct size, myocardial fibrosis, or cardiomyocyte hypertrophy, both dapagliflozin and enalapril significantly improved cardiac function and reduced myocardial injury. These functional benefits were linked to preservation of mitochondrial function and suppression of cardiomyocyte apoptosis. Notably, targeted metabolomics revealed marked post-MI metabolic reprogramming, characterized by branched-chain amino acid accumulation, L-carnitine depletion, and tricarboxylic acid cycle disruption. Both treatments selectively normalized citrate and isocitrate levels without altering malate or ATP content, identifying TCA cycle modulation as a key mechanism independent of structural remodeling. These findings demonstrate that SGLT2 inhibition confers cardioprotection after MI through mitochondrial preservation and distinct metabolic reprogramming, providing mechanistic insight beyond traditional neurohormonal blockade.

Inhibition of Pyroptosis and Apoptosis, but not Ferroptosis, Reduces Cardiac Dysfunction in Prediabetic Rats via Attenuating Mitochondrial Dysfunction, Independent of Metabolic Alterations

Nattayaporn Apaijai[a,b,c]

[a]Cardiac Electrophysiology Research and Training Center, Faculty of Medicine, Chiang Mai University, Thailand
[b]Center of Excellence in Cardiac Electrophysiology Research, Chiang Mai University, Thailand
[c]Cardiac Electrophysiology Unit, Department of Physiology, Faculty of Medicine, Chiang Mai University, Thailand

ABSTRACT

Programmed cell death has been shown to contribute to the development of cardiac dysfunction in metabolic syndrome. Although inhibition of necroptosis, one of the programmed cell death pathways, was shown previously to exert cardioprotective effects in prediabetic rats, the effects of other programmed cell death inhibitors, including apoptosis, ferroptosis, and pyroptosis, on cardiometabolic profiles of prediabetic rats have never been investigated. Male rats were fed either a high-fat diet (HFD; n=24) or a normal diet (ND; n=6) for 24 weeks. Subsequently, HFD-fed rats were divided into 1) vehicle, 2) apoptosis inhibitor, 3) ferroptosis inhibitor, and 4) pyroptosis inhibitor. Rats were treated with their assigned intervention for an additional 2 weeks. Cardiometabolic profiles and cardiac mitochondrial function were assessed. HFD-fed rats developed prediabetes and cardiac dysfunction, along with impairments of cardiac function and mitochondrial function. Inhibitions of either apoptosis or pyroptosis, but not a ferroptosis, effectively improved left ventricular end-diastolic pressure (LVEDP), cardiac output (CO), and ejection fraction (EF) in prediabetic rats. Moreover, the pyroptosis inhibitor increased CO and EF better than the apoptosis inhibitor. For cardiac mitochondria, mitochondrial oxidative stress was decreased only in prediabetic rats treated with the apoptosis inhibitor, while both apoptosis and pyroptosis inhibitors reduced mitochondrial membrane depolarization and swelling. However, the ferroptosis inhibitor failed to improve mitochondrial function. Metabolic parameters were not altered in any treatments. Pyroptosis and apoptosis inhibitors, but not ferroptosis inhibitor, reduced cardiac dysfunction in prediabetic rats by improving cardiac mitochondrial function without altering the impaired metabolic profiles.

Regulatory and Pathogenic Mechanisms in Aortic Valve Disease

Yen-Chun Ho

Institute of Biomedical Sciences, Academia Sinica 128 Sec. 2, Academia Rd. Nankang, Taipei 115, Taiwan, R.O.C.

ABSTRACT

Aortic valve disease (AVD) is a common cardiovascular condition in senior adults, with its incidence and healthcare impact rising as populations age. AVD, including valve calcification or myxomatous degeneration, is characterized by endothelial dysfunction, abnormal activation of valvular interstitial cells, chronic inflammation, and extracellular matrix (ECM) remodeling. Despite its clinical significance, the molecular mechanisms that initiate and drive AVD progression remain unclear. Emerging evidence indicates that valvular endothelial cells (VECs) actively regulate valve homeostasis and disease. Our recent studies demonstrate that dysregulated endothelial signaling is a key driver of maladaptive remodeling and valve degeneration. Mice with VEC-specific deletion of the transcription factor PROX1 (*Prox1ΔVEC*) develop progressive aortic stenosis, demonstrating a causal role for endothelial dysfunction in disease initiation. Using this model, we identified platelet-derived growth factor-B (PDGF-B) as a VEC-derived pathogenic factor that promotes valve degeneration, highlighting the importance of endothelial–interstitial crosstalk. Additionally, we identified von Willebrand factor (vWF) as another endothelial regulator implicated in valve disease. vWF is crucial for hemostasis and thrombosis. It also contributes to vascular inflammation by promoting endothelial activation and leukocyte recruitment. We found that vWF-deficient mice exhibited enlarged aortic valves and increased endothelial-to-mesenchymal transition, indicating an additional role for endothelial cells in AVD. Together, these findings highlight endothelial dysfunction, inflammatory regulation, and ECM homeostasis as central drivers of AVD initiation and progression and identify endothelial-derived pathways as potential therapeutic targets for heart valve disease.

Targeting Branched-chain Amino Acid Dysregulation to Restore Cardiomyocyte Function in a Human Cellular Model of Diabetic Heart Failure

Shuo Cong

Cardiovascular and Metabolic Disorders Programme, Duke-NUS Medical School, Singapore, Singapore

ABSTRACT

Diabetic patients experience worse heart failure outcomes than those without diabetes, highlighting the need for new treatments. We previously generated a patient-specific induced pluripotent stem cell-derived cardiomyocyte (iPSC-CM) model of D-HF. Here, we investigate whether enhancing branched-chain amino acid (BCAA) catabolism can attenuate the dysfunctional phenotype. Cardiomyocytes were differentiated from iPSCs derived from D-HF patients and healthy controls. Targeted metabolomics and western blots were performed to assess BCAA dysregulation. Genetic and pharmacological inhibitors (BT2 and PF-8254) targeting BCKDK (the kinase that negatively regulated BCAA catabolism) were evaluated by measuring improvements in contractility and bioenergetics. Targeted metabolomics revealed that BCAA levels were unchanged between D-HF and control iPSC-CMs. However, reductions in specific short-chain acylcarnitines (derivatives of BCAA catabolism) indicated impairment of this pathway in D-HF iPSC-CMs. Silencing BCKDK with siRNA improved contractility, ATP production, and mitochondrial respiration in D-HF iPSC-CMs. Notably, pharmacological inhibition of BCKDK produced distinct outcomes. While both BT2 and PF-8254 dose-dependently reduced BCKDHα phosphorylation (a surrogate marker of BCKDK inhibition) and improved contractility, BT2 treatment was accompanied by bioenergetic impairments, including reduced ATP levels, diminished mitochondrial respiration, and cellular hypertrophy. In contrast, these detrimental effects were not observed with PF-8254. Our findings suggest that targeting BCKDK to enhance BCAA catabolism may represent an effective treatment strategy for D-HF. The comparison between BT2 and PF-8254 illustrates how human-based cellular models can serve as robust platforms for preclinical drug screening to identify selective and less toxic therapeutic candidates.

Therapeutic Potential of PDE5 Inhibition in Cardiac Hypertrophy via Akt Signalling

Nik Aloesnisa Nik Mohd Alwi

Universiti Sains Malaysia

ABSTRACT

Phosphodiesterase 5 inhibitors (PDE5i), primarily used for treating erectile dysfunction, have shown promising cardioprotective effects. Using an established hypertrophy model, PDE5 inhibition resulted in elevated intracellular cGMP levels and concomitant suppression of Akt signalling. These changes were accompanied by upregulation of KDM1A and downregulation of TFEB. Such molecular alterations were associated with a significant attenuation of maladaptive cardiac hypertrophy. By modulating interrelated signalling and transcriptional networks involved in hypertrophy, PDE5i may regulate key intracellular pathways involved in cell growth and survival and offer a compelling therapeutic strategy to prevent the progression of cardiac hypertrophy toward heart failure.

YIA 01

Loss of STMP1 Perturbs Mitochondrial Cristae and Drives Cellular Inflammation and Heart Failure

Francesco Paolo Ruberto[a,b], Chang Jie Mick Lee[a,b], Matthew Ackers-Johnson[a,b], Pooja Sridharan[c], Vartika Khanchandani[d], Wu Lik Hang[a], Ling Xuan Goh[b], Tuan Danh Anh Luu[a,b], Leroy Sivappiragasam Pakkiri[a], Isabelle Bonne[f,g], Thong Beng Lu[g], Daniel J. Buss[h], Tell Lovelace[h], Vivek Subramanian[h], Erielle Villanueva[b], Yang Hu[a,b], Prasanna Vidyasekar[a,b], Rijian Gurung[a,b], Jie Min Lee[e], Wai Khang Yong[d,e], Zhe Li[b], Dennis Kappei[d,e,i], Lena Ho[c], Chester Lee Drum[a], and Roger SY Foo[a,b*].

[a]Cardiovascular Metabolic Disease Translational Research Programme, National University Health System, Singapore
[b]Cardiovascular Research Institute, Yong Loo Lin School of Medicine, National University of Singapore
[c]Cardiovascular and Metabolic Disorders Signature Research Programme, Duke-NUS Medical School, Singapore
[d]Department of Biochemistry, Yong Loo Lin School of Medicine, National University of Singapore
[e]Cancer Science Institute of Singapore, National University of Singapore
[f]Department of Microbiology and Immunology, Immunology Translational Research Programme, National University of Singapore.
[g]Electron Microscopy Unit, Microscopy Cluster, National University of Singapore
[h]Materials and Structural Analysis, Thermo Fisher Scientific, Hillsboro, OR, US
[i]NUS Center for Cancer Research, National University of Singapore

ABSTRACT

Background: Heart failure is a predominant cause of morbidity and mortality globally, and even more so in the growing elderly population today. In degenerative ageing and autoimmune diseases, the cytoplasmic leak of mitochondrial DNA (mt-DNA), resulting from mitochondrial cristae compromise, triggers persistent low-grade cellular inflammation through the activation of the cGAS-STING pathway and the type I interferon (IFN-I) response. However, how and whether mitochondrial architectural components and cardiomyocyte inflammation drive cardiac ageing and failure are not yet well understood.

Methods: Here, we investigated the function of STMP1, a 47-amino acid nuclear-encoded mitochondrial-localized peptide, featuring a distinctive GxxxGxxxG glycine zipper domain. A mouse with cardiomyocyte (CM)-specific knockout (KO) of Stmp1 was generated to investigate its role in cardiac function. We profiled the transcriptome, proteome, and metabolome from Stmp1-KO hearts to determine its functional mechanism of action. Electron microscopy was used to assess the impact of STMP1 depletion and functional rescue following AAV9-mediated gene restoration in the KO mouse.

YIA 01

Results: STMP1 is downregulated specifically in CMs, and not other cardiac cell types, in aged mice and humans. Genetic loss of Stmp1 in CMs resulted in heart failure in vivo. STMP1 interacts with components of the cristae organising complexes MICOS and SAM. Consequent to Stmp1 loss, mitochondrial cristae were destabilized, mt-DNA was mislocalized to the cytosol, and the cGAS–STING pathway activated, with ensuing cellular inflammation and CM cell death. Mechanistically, the restoration of wildtype Stmp1 or STING inhibition significantly rescued cardiac function in vivo.

Conclusion: Our work reveals a mechanism connecting the micropeptide STMP1 to mitochondrial cristae architecture and cardiomyocyte cellular inflammation, both of which are present as potential drivers of heart failure and cardiac ageing.

Keywords: Mitochondria, Inflammation, Ageing, Cristae, Cardiomyocytes, Micropeptide

YIA 02

Splenectomy Attenuates Cardiac Inflammation and Diastolic Dysfunction in HFpEF

Jinyun Zhu[a], Hong Jie Tan[a], Meng Wang[a], Yibin Wang[a]

[a]Signature Research Program in Cardiovascular and Metabolic Diseases, Duke-NUS Medical School; National Heart Center of Singapore, Singapore

ABSTRACT

Background: Heart failure with preserved ejection fraction (HFpEF) is a systemic inflammatory disease, yet the contribution of peripheral immune organs remains poorly defined. While the spleen regulates remodeling in ischemic heart disease, its role in HFpEF remains unknown. We investigated whether splenic activation drives systemic inflammation and diastolic dysfunction in a rodent HFpEF model.

Methods: HFpEF was induced in wild-type mice using a high-fat diet and non-selective nitric oxide synthase inhibitor L-NAME. Splenic remodeling was assessed by flow cytometry, immunohistochemistry, and molecular analyses. To establish causality, mice underwent splenectomy (SPX) or sham surgery two-weeks prior to HFpEF induction. Cardiac function and remodeling were evaluated using echocardiography, pressure–volume analysis, immunophenotyping, and histology.

Results: HFpEF mice exhibited pronounced splenic remodeling, characterized by white and red pulp expansion, and immune cell infiltration. Flow cytometry revealed a significant expansion of splenic $Ly6C^+$ monocytes/macrophages and T cells, accompanied by upregulation of pro-inflammatory mediators (IL-1β, TNF-α, CCL2). Further immunohistochemistry confirmed an increased in accumulation of $CD11b^+F4/80^+$ macrophages and $CD3^+$ T cells. Crucially, splenectomy significantly attenuated HFpEF progression. Compared with Sham-HFpEF mice, SPX-HFpEF mice displayed improved glucose tolerance and ameliorated diastolic dysfunction. Furthermore, splenectomy reduced myocardial immune infiltration, fibrosis, and cardiac cytokine expression. Mechanistically, bone marrow–derived macrophages isolated from SPX-HFpEF mice exhibited a blunt inflammatory phenotype with reduced mRNA expression of Il-6, iNos, Il-1β, Tnf-α, and Nf-κb.

Conclusions: Splenic immune activation acts as a critical driver of systemic inflammation and cardiac diastolic dysfunction in HFpEF. These findings identify the spleen–heart axis as a novel therapeutic target for mitigating HFpEF progression.

Keywords: HFpEF, Spleen-Heart Axis, Splenectomy, Macrophage, Inflammation, Diastolic Dysfunction

YIA 03

Identifying Novel Drivers of Cardiac Lineage Specification and Cardiomyocyte Maturation using Paired Short/Long-Read scRNA-seq

Ryan Fan Ruiming[a], Elaine Cao[b], Aneesh[a], Faith Ong[a], Jay W Shin[b], Roger Foo Sik Yin[a,c]

[a]National University of Singapore, Department of Medicine, Singapore
[b]A*STAR, Genome Institute of Singapore, Singapore
[c]A*STAR, Institute of Molecular Cell Biology, Singapore

ABSTRACT

Background: Alternative splicing – the process by which genes encode different isoforms – allows for greater phenotypic diversity at the cellular level. Isoforms are prominent in every aspect of biology, but their complex patterns of regulation have not been comprehensively decoded due to the limitations of short-read sequencing.

Methods: However, the combination of single-cell RNA sequencing (scRNA-seq) with long-read technologies provides a powerful platform, permitting the study of isoform expression patterns whilst decoding cellular heterogeneity and cell state transitions. Leveraging these advantages, we examined the transcriptomes of important stages in cardiomyocyte development using paired short/long-read sequencing to identify novel drivers of cardiac lineage specification and cardiomyocyte maturation.

Results: Here we report the detection of 33,602 genes and 96,816 isoforms across 28,338 single cells representative of different timepoints during directed cardiomyocyte differentiation (D0, D3, D7, D20, D48). Distinct cardiomyocyte cell states were identified, and through integrative analysis with public datasets, we shortlisted novel candidates that may be key modulators or effectors of cardiac specification and maturation. Furthermore, we show remarkable differences between clustering at the gene- and transcript-level that highlights significant epigenetic regulation of cardiac isoforms, and explore differential transcript usage across cardiomyocyte regulatory networks.

Conclusions: Our findings indicate that metabolic maturation generates distinct cardiomyocyte subtypes, and highlights significant epigenetic regulation of cardiac genes at the transcript-level.

Keywords: Cardiomyocyte, development, maturation, transcriptomics, single-cell, long-read

YIA 04

A Translational Mouse Model of Spontaneous Atrial Fibrillation for Therapeutic Development

Nur Syakirah Othman[a], Laurent Bultot[a], Yung-Ting Hsiao[a], Zhihong Li[a], Ippei Shimizua,[b*]

[a]Department of Cardiovascular Aging, National Cerebral and Cardiovascular Center, Osaka, 564-8565, Japan
[b]Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, Osaka, 564-8565, Japan*

ABSTRACT

Background: Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and a major cause of stroke, heart failure, and premature mortality, yet disease-modifying therapies remain limited by the lack of experimental models that recapitulate spontaneous AF and atrial remodelling. Here, we introduce a spontaneous AF transgenic mouse model (AF-Tg) to explore pathogenic mechanisms and therapeutic opportunities.

Methods: We developed an atrial-restricted AF-Tg with a Cre/Lox system to induce spontaneous AF. We analysed the AF-Tg mouse with electrocardiography, echocardiography, optical mapping, electron microscope and multiomics studies. Therapeutic interventions, including antibody-based targeting of senescence-associated signalling and senolytic agents, were tested.

Results: Mice developed spontaneous AF as early as 5 weeks of age, with an AF burden of approximately 70%. Systolic function was preserved, whereas diastolic dysfunction and progressive left atrial fibrosis emerged by 15-16 weeks of age. Ultrastructural analysis revealed early intercellular detachment that preceded fibrosis and arrhythmia. Multiomics studies showed senescence-associated secretory phenotype (SASP) molecules increased in the AF-Tg mouse. Therapeutic targeting of senescence-associated signalling using a neutralizing antibody and senolytic treatment also attenuated disease severity.

Conclusion: This spontaneous AF model reveals previously underappreciated mechanisms of atrial remodelling and provides a powerful platform for identifying disease-modifying therapeutic strategies.

Keywords: Arrhythmia, atrial fibrillation, cellular senescence, fibrosis, senescence-associated secretory phenotype (SASP), transgenic mouse model.

YIA 05

Association between Insulin Resistance and Atrial Fibrillation: Insights from Real-World and Genetic Evidence

Xiao Liu[a,b*], Xiaoyue Zhang[c], Peng Yu[c], Jing Zhang[d], Weiwen Lim[e,f], Chrishan Ramachandra[e,f], Ph.D., Shengjie Lu[e,f], Derek John Hausenloy[e,f,g,h]

[a]Department of Cardiology, Sun Yat-sen Memorial Hospital of Sun Yat-sen University, Guangzhou, China
[b]Cardiovascular and Metabolic Disorders Program, Duke-National University of Singapore Medical School, Singapore, Singapore
[c]Department of Endocrinology and Metabolism, The Second Affiliated Hospital, Jiangxi Medical College, Nanchang University, Nanchang, China
[d]Department of Anesthesiology, The Second Affiliated Hospital, Jiangxi Medical College, Nanchang University, Nanchang, China
[e]National Heart Research Institute Singapore, National Heart Centre Singapore, Singapore 169609, Singapore.
[f]Cardiovascular and Metabolic Disorders Program, Duke-National University of Singapore Medical School, Singapore, Singapore.
[g]Yong Loo Lin School of Medicine, National University Singapore, Singapore
hThe Hatter Cardiovascular Institute, University College London, London, UK

ABSTRACT

Background: Type 2 diabetes mellitus is a well-established risk factor for atrial fibrillation (AF), with insulin resistance (IR) serving as a central pathophysiological factor. However, whether IR is independently associated with AF remains unclear.

Methods: We evaluated the association between IR indices and AF using a prospective cohort of UK Biobank, estimating hazard ratios with 95% confidence intervals (CI). External validity was assessed via a meta-analysis of pooled real-world datasets. The causal effect of genetically predicted IR on AF risk was explored using two-sample Mendelian randomization (MR) analysis.

Results: In this prospective cohort of 422,790 participants without AF, IR related indices (high-density lipoprotein cholesterol, triglyceride-glucose index, metabolic score for insulin resistance, estimated glucose disposal rate, triglycerides) were significantly associated with higher AF incidence (all $P < 0.05$). Significant non-linear dose-response relationships were identified across all indicators except triglycerides (all $P < 0.01$). No significant interaction was found after stratifying by AF polygenic risk score. Pooled evidence of 24 cohorts encompassing 930,862 participants demonstrated that IR was associated with increased risk of new-onset AF (odds ratio [OR]: 1.24), recurrent AF post-radiofrequency ablation (OR: 1.99), and postoperative AF (OR: 5.12). MR analysis revealed that genetically proxied IR was significantly associated with a higher risk of AF (OR: 1.30, 95% CI: 1.14-1.48).

Conclusions: Real-world and genetic evidence confirm IR as a significant and causal contributor of AF. Targeting IR may offer novel prevention strategies for AF. Future research should prioritize developing standardized IR assessment tools to enhance clinical applicability.

Keywords: Diabetes mellitus; atrial fibrillation; polygenic risk score; meta-analysis; metabolomics; mendelian randomization

YIA 06

Resolving the NOS1AP GWAS Signal in Long QT Syndrome Through Isoform-Specific Mechanisms

Galvin Tang[a], Roger Foo[a]

[a]Cardiovascular Research Institute (CVRI), National University of Singapore (NUS), Singapore

ABSTRACT

Background: Genome-wide association studies (GWAS) have repeatedly identified the NOS1AP locus as a major genetic determinant of QT interval duration. Early mechanistic models proposed that NOS1AP influences cardiac repolarization through nitric oxide–dependent regulation of L-type calcium channels (LTCC). However, this paradigm does not fully account for human genetic and transcriptomic data, including limited eQTL support for canonical NOS1AP transcripts and the selective impact of NOS1AP variants on repolarization phenotypes.

Methods & Results: Using long-read RNA sequencing, we identified cN1C1, a novel transcript arising from the NOS1AP locus in cardiomyocytes, and investigated its role in ion channel regulation. Functionally, expression of cN1C1 was associated with alterations in potassium currents consistent with reduced effective channel availability at the cell surface, without gross disruption of total channel expression. Co-immunoprecipitation experiments demonstrated that cN1C1 does not bind NOS1. Furthermore, both NOS1AP and cN1C1 reduced potassium current, supporting a mechanism that is independent of nitric oxide signaling. To further investigate potential pathways, we performed immunoprecipitation followed by mass spectrometry to identify candidate interacting proteins and trafficking regulators in cardiomyocytes, narrowing down potential mechanisms of action.

Conclusions: Together, our findings provide a genetically grounded framework linking the NOS1AP locus to cardiac repolarization through modulation of membrane trafficking, independent of nitric oxide signaling. Ongoing work focuses on defining the molecular machinery underlying this effect.

Keywords: NOS1AP, NOS1, QT interval, LTCC, KCNQ1, Cardiac repolarisation

RAPID 01

The IL-33/ST2 Axis Mediates Macrophage-Driven Inflammation in the Progression of HFpEF

Jinyun Zhu[a], Meng Wang[a], Hong Jie Tan[a], Xuewen Zhang[a], Bin Dong[a], Yunxia Liu[a], Yibin Wang[a]

[a]Signature Research Program in Cardiovascular and Metabolic Diseases, Duke-NUS Medical School and National Heart Center of Singapore, Singapore

ABSTRACT

Background: The IL-33/ST2 axis is a key regulator of immune inflammation and myocardial injury, yet its role in established heart failure with preserved ejection fraction (HFpEF) remains unclear. We tested whether targeting IL-33/ST2 signaling after HFpEF mitigates macrophage-driven inflammation and diastolic dysfunction.

Methods: HFpEF was induced in male C57BL/6 mice using high-fat diet and L-NAME. IL-33 and ST2 expression was characterized by scRNA-seq, flow cytometry, and immunofluorescence. Recombinant IL-33 (rIL-33), macrophage-targeted AAV9-shRNA-ST2, or lipid nanoparticle–formulated siST2 (LNP-siST2) was administered via vein injection. In vitro, RAW264.7 macrophages, bone marrow–derived macrophages (BMDMs), and cardiac fibroblasts were stimulated with palmitic acid and oleic acid.

Results: scRNA-seq revealed IL-33 was predominantly expressed in fibroblasts and endothelial cells, whereas ST2 was enriched in macrophages. These findings were validated by flow cytometry, with immunofluorescence further localizing ST2 mainly to $CD68^+$ cardiac macrophages. ST2 expression was also significantly increased in HFpEF cardiac tissue and BMDM, while cardiac IL-33 protein levels were comparable between HFpEF and control. Metabolic stimulation increased macrophage ST2, IL-1β and TNF-α production, effects that were markedly suppressed by ST2 knockdown. Palmitic acid/oleic acid–stimulated cardiac fibroblasts secreted higher levels of IL-33 and promoted macrophage ST2 expression and migration. In vivo, rIL-33 exacerbated cardiac hypertrophy, fibrosis, and inflammation. In contrast, macrophage-targeted ST2 inhibition using AAV9-shRNA-ST2 or LNP-siST2 improved diastolic function, reduced cardiac IL-1β and TNF-α expression, decreased cardiac hypertrophy and fibrosis.

Conclusions: Metabolic stress promotes HFpEF progression by enhancing fibroblast-macrophage crosstalk through IL-33/ST2 signaling, highlighting ST2 as a therapeutic target.

Keywords: IL33/ST2, HFpEF, Macrophage, Inflammation.

RAPID 02

Personalised Arterial-Wall-on-a-Chip Reveals Paracrine Crosstalk Between Diabetic Endothelial and Vascular Smooth Muscle Cells Driving Early Atherogenesis

Chun-Yi Ng[a], Hui Min Tay[a], Hong Sheng Cheng[b], Chengxun Su[a], Crespo Avilan Gustavo Enrique[c,e,f,g], Nguan Soon Tan[b,d], Derek Hausenloy[e,f,g,h], Rinkoo Dalan[b,i], and Han Wei Hou[a,b]

[a]School of Mechanical and Aerospace Engineering, Nanyang Technological University, 637460 Singapore
[b]Lee Kong Chian School of Medicine, Nanyang Technological University, 636921 Singapore
[c]Department of Biochemistry, Medical Faculty, Justus Liebig-University, 35392 Giessen, Germany
[d]School of Biological Sciences, Nanyang Technological University, 637551 Singapore
[e]National Heart Research Institute Singapore, National Heart Centre, 169609 Singapore
[f]Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, 117597 Singapore
[g]Cardiovascular & Metabolic Disorders Program, Duke-National University of Singapore Medical School, 169857 Singapore
[h]The Hatter Cardiovascular Institute, University College London, London WC1E 6HX, United Kingdom
[i]Endocrinology Department, Tan Tock Seng Hospital, 308433 Singapore

ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) accelerates atherosclerosis through endothelial cell (EC) dysfunction, yet how diabetic EC signals are transmitted to vascular smooth muscle cells (VSMC) during early disease remain insufficiently resolved. Biomimetic platforms capable of capturing this cell-cell communication are needed to define early atherogenesis.

Methods: An arterial-wall-on-a-chip was established to enable co-culture of healthy or T2DM ECs with healthy VSMCs under controlled physiological conditions. Transcriptomic profiling was used to delineate EC- and VSMC-specific pathway changes. The platform was further engineered to quantify immune cell adhesion, oxidised low-density lipoprotein (oxLDL) uptake, and VSMC migration. Patient-derived extracellular vesicles (EVs) were integrated to personalise the system and probe functional vascular responses.

Results: T2DM ECs exhibited a stable pro-atherogenic transcriptional program characterised by an amplified CXCL/CCL chemokine signalling, which was further upregulated by EC-VSMC interaction. In response, VSMCs underwent distinct transcriptional reprogramming, with enrichment of energy-producing pathways (ketone and fatty acid metabolism) following exposure to the T2DM EC microenvironment. Consistent with these molecular changes, the arterial-wall-on-a-chip recapitulated early atherogenic phenotypes, including an increase in VSMC migration (2- to 4-fold), enhanced immune cell adhesion (3-fold) and oxLDL uptake in T2DM ECs (33% increase). Incorporation of T2DM patient-derived EVs stimulated VSMC migration, which correlated with indices of subclinical atherosclerosis, including pulse wave velocity and carotid intima–media thickness.

RAPID 02

Conclusions: Our study identifies a bi-directional paracrine axis in which diabetic EC signals metabolic reprogramming in VSMCs towards a migratory state. The personalised arterial-wall-on-a-chip provides a human-relevant framework for dissecting early T2DM-associated atherosclerosis and for developing mechanism-informed therapeutic strategies.

Keywords: Endothelial cells; Vascular smooth muscle cells; cell movement; diabetes mellitus; atherosclerosis; lab-on-a-chip devices

RAPID 03

Intrinsic Cardiac Ketogenesis Maintains Mitochondrial Function

Yi-Chan Lee[a,b], Yuan-Yuan Cheng[c], Yu Chieh Chen[a], Ting-Yu Chang[a], Shu-Chian Ruan[a], Po-Ju Lin[a], Pin-Sung Lin[a], Hung-Chih Chen[a], Cheng-Hao Liu[a], Yu-Ting Yan[a], Yeou-Guang Tsay[d], Ruey-Hwa Chen[e], Gabriele G. Schiattarella[f-k], Rong Tian[l], Yibin Wang[m], Timothy J. Kamp[n], Chih-Hao Lee[o], Patrick C.H. Hsieh[a,n,p,q]

[a]Institute of Biomedical Sciences, Academia Sinica; Taipei 115, Taiwan
[b]Molecular Medicine, National Yang Ming Chiao Tung University; Taipei 112, Taiwan
[c]International Ph.D. Program in Cell Therapy and Regenerative Medicine, College of Medicine, Taipei Medical University; Taipei 110, Taiwan
[d]Institute of Biochemistry and Molecular Biology, National Yang Ming Chiao Tung University; Taipei 112, Taiwan
[e]Institute of Biological Chemistry, Academia Sinica; Taipei 115, Taiwan
[f]Deutsches Herzzentrum der Charité, Department of Cardiology, Angiology and Intensive Care Medicine, Max Rubner Center for Cardiovascular Metabolic Renal Research (MRC), Charité-Universitätsmedizin Berlin, Germany, Berlin, Germany.
[g]DZHK (German Centre for Cardiovascular Research), Partner Site Berlin, Berlin, Germany.
[h]Translational Approaches in Heart Failure and Cardiometabolic Disease, Max Delbrück Center for Molecular Medicine in the Helmholtz Association (MDC), Berlin, Germany.
[i]Friede Springer Cardiovascular Prevention Center at Charité – Universitätsmedizin Berlin, Germany.
[j]Experimental and Clinical Research Center (ECRC), a Cooperation of Charité-Universitätsmedizin Berlin and Max Delbruck Center for Molecular Medicine (MDC).
[k]Division of Cardiology, Department of Advanced Biomedical Sciences, Federico II University, Naples, Italy.
[l]Mitochondria and Metabolism Center, Department of Anesthesiology and Pain Medicine and Department of Bioengineering, University of Washington; Seattle, WA 98109, USA
[m]Signature Research Programme in Cardiovascular and Metabolic Disorders, Duke-NUS Medical School; Singapore 169857
[n]Department of Medicine and Stem Cell and Regenerative Medicine Center, University of Wisconsin-Madison; Madison, WI 53705, USA
[o]Genomics Research Center, Academia Sinica; Taipei 115, Taiwan
[p]Institute of Medical Genomics and Proteomics and Institute of Clinical Medicine, National Taiwan University; Taipei 106, Taiwan
[q]Graduate Institute of Medicine, Kaohsiung Medical University; Kaohsiung 807, Taiwan

ABSTRACT

Background: The intersection of aging and metabolic dysregulation is a pivotal frontier in understanding cardiovascular disease. While ketogenic metabolism is known to extend lifespan and promote myocardial repair, the autonomous role of intrinsic cardiac ketone production during aging remains poorly understood. Building on our previous finding that intrinsic cardiac ketogenesis drives remodeling and repair, this study investigates the necessity of this metabolic pathway in the aging heart.

RAPID 03

Methods: We observed that hepatic 3-Hydroxy-3-Methylglutaryl-CoA Synthase 2 (HMGCS2) expression declines with age, while cardiac HMGCS2 paradoxically increases, suggesting a compensatory response in aged heart. To investigate this hypothesis, we generated cardiomyocyte-specific HMGCS2 knockout (CM-HMGCS2-/-) mice.

Results: These CM-HMGCS2-/- mice exhibited reduced survival and premature cardiac aging, including decreased ejection fraction, impaired contractility (dP/dtmax, ESPVR, PRSW etc), and prolonged relaxation (Tau, dP/dtmin etc) (n = 5–8 per group). Histological analysis revealed significant hypertrophy and fibrosis. 13C nuclear magnetic resonance (NMR) spectroscopy and transmission electron microscopy (TEM) showed that HMGCS2 deficiency in cardiomyocytes causes mitochondrial failure, characterized by reduced fatty acid oxidation and disorganized cristae. Mechanistically, cardiac HMGCS2 is essential for sustaining local β-hydroxybutyrate (β-OHB) levels and promoting protein lysine β-hydroxybutyrylation (Kbhb). Proteomic profiling via LC-MS identified numerous mitochondrial metabolic proteins regulated by this HMGCS2-driven post-translational modification.

Conclusions: These findings establish intrinsic cardiac ketogenesis as a critical homeostatic mechanism for preserving mitochondrial function and cardiac performance during aging, highlighting its potential as a therapeutic target for age-related heart failure.

Keywords: Metabolism, Ketogenesis, Cardiac Aging, PTM, Kbhb, and Mitochondria

RAPID 04

Sappanwood (Caesalpinia sappan L.) Attenuates Iron-Overload Induced Cardiac Ferroptosis in Animal Model

Tanendri Arrizqiyani[a,b,c], Yunia Sribudiani[d], Mas Rizky A.A Syamsunarno[b,d], Ratu Safitri[e]

[a]Department of Biotechnology, Postgraduate School, Universitas Padjadjaran, Bandung, Indonesia
[b]Metabolic Medicine Research Group, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia
[c]Medical Laboratory of Technology, Universitas Bakti Tunas Husada, Tasikmalaya, Indonesia
[d]Department of Biomedical Sciences, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia
[e]Department of Biology, Faculty of Mathematics and Natural Sciences, Universitas Padjadjaran, Jatinangor, Sumedang, Indonesia

ABSTRACT

Background: Ferroptosis is an iron-dependent form of programmed cell death characterized by lipid peroxidation, playing a critical role in iron-overload-induced cardiac damage. While Sappanwood (Caesalpinia sappan L.) is known for its potent antioxidant and iron-chelating properties, its specific mechanism in modulating ferroptosis remains elusive. This study investigates the cardioprotective effects of Sappanwood extract against cardiac ferroptosis in an iron-overload rat model.

Methods: Thirty-five male Wistar rats were randomized into seven groups: Normal (N), Iron Dextran (ID; 120 mg/kg BW), Deferiprone (DFP; positive control), and four doses of Sappanwood extract (SC1–SC4: 50, 100, 150, and 200 mg/kg BW). We evaluated cardiac ferroptosis using spectrophotometric analysis of iron deposition, malondialdehyde (MDA), superoxide dismutase (SOD), and glutathione peroxidase 4 (GPx4). Furthermore, the expression of key genes (Ltcc, Slc25a37, Slc25a28, Ftmt, Tnni3, Ckmb, and Bnp) was quantified via qRT-PCR.

Results: Sappanwood extract significantly mitigated iron-induced damage. SC2 achieved the highest reduction in cardiac iron (40.5%) and MDA (62.8%), while enhancing SOD levels by 54.7%. Notably, SC3 markedly elevated GPx4 levels by 191.95%. Molecular analysis revealed that the extract effectively downregulated biomarkers of cardiac injury and iron transport, including Ckmb, Bnp, Tnni3, Ltcc, Slc25a37, Slc25a28, and Ftmt.

Conclusions: Sappanwood extract exerts significant cardioprotective effects by attenuating ferroptosis through iron chelation and the upregulation of antioxidant defenses. These findings suggest its potential as a therapeutic agent for hemochromatosis and iron-overload-related cardiac metabolic disorders.

Keywords: Cardioprotective, Iron chelation, Ferroptosis, Sappanwood extract

RAPID 05

Population-Based Analysis of Coronary Artery Disease-Associated SNPs in Malaysian Cohort Compared to ALFA Global Reference Populations

Nusaibah Sallehuddin[a], Lee Le Jie[b], Chew LeAnn[b], Chua Yung An[a,c], Rahayu Zulkapli[a,d], Mohd Faizal Hafez Hidayat[d], Mohd Yusmiaidil Putra Mohd Yusof[a,d]

[a]Cardiovascular Advancement and Research Excellence Institute, University Teknologi MARA, 47000, Selangor, Malaysia
[b]Prima Nexus Sdn. Bhd., 28-1B, Jalan Puteri ½, Bandar Puteri, 47100, Selangor, Malaysia
[c]Faculty of Medicine, University Teknologi MARA, 47000, Selangor, Malaysia
[d]Faculty of Dentistry, University Teknologi MARA, 47000, Selangor, Malaysia

ABSTRACT

Background: Genome-wide association studies (GWAS) have identified numerous single nucleotide polymorphisms (SNPs) associated with coronary artery diseases (CAD). However, allele frequencies and genetic risk architecture can vary substantially across populations, potentially limiting the transferability of GWAS findings. Thus, this study aimed to compare allele frequencies of selected CAD-associated SNPs in Malaysian population against global reference populations from the Allele Frequency Aggregator database.

Methods: This is a retrospective study using existing microarray genotyping data comprising of 6,824 individuals (MYS) including Malaysian Malay (MYM) (n=1,211), Malaysian Chinese (MYC) (n=5,463), and Malaysian Indian (MYI) (n=150). Allele frequency deviation was calculated and compared using chi-square tests. Alternative allele (ALT) enrichment was quantified using odds ratios and 95% confidence intervals. False discovery rate (FDR) of <0.05 is considered significant.

Results: The ALT frequency heatmap demonstrates clear population stratification, in which MYC clusters with East Asian populations, MYI with South Asian, and MYM and MYS occupy intermediate positions. SNPs including rs2144078, rs4773, and rs10849774 demonstrated strong ALT enrichment, indicating strong candidates for Malaysian-specific CAD risk. Volcano plot showed that the SNPs exceeded -log10(FDR)>100. Forest plot analysis revealed large effect sizes of >10 for MYC (rs2144078), >5 across MYM, MYC, and MYS (rs4773), and 8-10 in MYC and MYS (rs4299376).

Conclusion: In contrary with other homogenous populations, CAD-associated SNPs in multiracial Malaysian population are highly varied and strongly ethnic-dependent. Future functional and downstream analysis on the identified large effect size variants may shed light on the pathogenic mechanism of population-specific mutations underlying CAD in Malaysia.

Keywords: Genome-wide association studies, coronary artery disease, Malaysia, rs2144078, rs4773, rs10849774

RAPID 06

Differential Effects of Aldosterone Synthase Inhibition on Adrenal Zona Glomerulosa Remodeling and Cardiac Cellular Turnover in Spontaneously Hypertensive Rats

Amnani Aminuddin[a,b], Yusof Kamisah[c], Juliana Abdul Hamid[c], Noorzaileen Eileena Zaidi[a,b], Elise Gomez-Sanchez[d,e], Celso Gomez- Sanchez[d,e], Morris J. Brown[f,g], and Elena Aisha Azizan[a,b,g*]

[a]Department of Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia, Jalan Yaacob Latif, Bandar Tun Razak, 56000 Cheras, Kuala Lumpur
[b]Research Centre, Tunku Ampuan Besar Tuanku Aishah Rohani Hospital, Universiti Kebangsaan Malaysia Specialist Children's Hospital, Jalan Yaacob Latif, Bandar Tun Razak, 56000 Cheras, Kuala Lumpur
[c]Department of Pharmacology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Jalan Yaacob Latif, Bandar Tun Razak, 56000 Cheras, Kuala Lumpur
[d]GV (Sonny) Montgomery VA Medical Center, University of Mississippi Medical Center, Jackson, Mississippi, United States of America
[e]Department of Medicine, University of Mississippi Medical Center, Jackson, Mississippi, United States of America
[f]NIHR Barts Biomedical Research Centre, Queen Mary University of London, London, United Kingdom
[g]Centre of Clinical Pharmacology & Precision Medicine, Queen Mary University of London, London, United Kingdom

ABSTRACT

Background: Aldosterone, synthesized in the adrenal zona glomerulosa (zG) by aldosterone synthase (CYP11B2), regulates sodium homeostasis and blood pressure. In primary aldosteronism (PA), autonomous aldosterone excess contributes to hypertension and cardiovascular complications, including myocardial hypertrophy and heart failure. Aldosterone synthase inhibitors (ASIs) are emerging therapeutic agents currently under clinical evaluation for PA and resistant hypertension. While ASIs reduce circulating aldosterone levels, their effects on aldosterone-mediated cardiac injury remain incompletely understood. This study evaluated the impact of ASI treatment on adrenal ZG remodelling and cardiac cellular turnover in spontaneously hypertensive rats (SHR).

Methods: SHRs were treated for 4 weeks with the ASIs osilodrostat phosphate, baxdrostat, or dexfadrostat (n=9), or vehicle controls (n=7). Plasma aldosterone and blood pressure were measured at baseline and study endpoint. Adrenal and cardiac tissues were analyzed by immunohistochemistry for CYP11B2 expression and markers of proliferation (Ki67) and apoptosis (TUNEL).

Results: Compared with vehicle controls, ASI treatment produced variable effects on blood pressure and circulating aldosterone levels; however, all ASI-treated groups demonstrated increased zG thickness (1.27+0.0714-fold vs. 1.00+0.06-fold vehicle control; p=0.01). Across ASI-treated groups, cardiac tissue exhibited reduced Ki67 expression (3.5+0.48 vs. 5.7+0.72; p=0.01), while TUNEL expression showed variable changes between treatments.

Conclusions: CYP11B2 inhibition in SHRs demonstrated differential effects on blood pressure and on apoptotic marker expression, but consistently induced zG remodeling and reduced cardiac proliferative marker expression. These findings suggest that ASI treatment may influence adrenal structural adaptation and modulate cardiac cellular dynamics independently of blood pressure reduction.

Keywords: Primary aldosteronism, Aldosterone synthase inhibitor, Hypertension, Zona glomerulosa remodelling, Cardiac remodelling, Spontaneously hypertensive rat.

RAPID 07

The Serine Synthesis Pathway Activation In Early Compensatory Cardiac Hypertrophy

Nurul Gusti Khatimah[a,b], Chengchen Hu[a], Risa Mukai[a], and Junichi Sadoshima[a]

[a]Department of Cell Biology and Molecular Medicine, Cardiovascular Research Institute, Rutgers – New Jersey Medical School, 185 South Orange Ave, MSB G-609, Newark, New Jersey, 07103, USA
[b]Doctoral Program in Biomedical Sciences, Faculty of Medicine, Salemba Raya 4, Central Jakarta, DKI Jakarta, 10430, Indonesia

ABSTRACT

Background: Heart failure is the end stage of progressive cardiac dysfunction leading to multi-organ failure. In response to early pressure overload, the heart initially undergoes a compensatory phase accompanied by metabolic shifting. During this phase, Yes-associated protein (YAP) is activated leading to serine accumulation. Serine provides one-carbon units essential for supporting cellular function and survival. However, the mechanism by which serine accumulates during compensatory cardiac hypertrophy remains unknown. Here, we investigate the role YAP in mediating the serine synthesis pathway in the heart under acute pressure overload.

Methods: Male C57BL/6J wild-type and cardiac-specific YAP knockout mice at 8-12 weeks of age underwent transaortic constriction (TAC) for 2-3 days, after which hearts were collected to assess serine biosynthesis enzymes. To explore the mechanistic link between YAP and serine biosynthesis, AC16 human cardiomyocytes were transduced with adenovirus carrying LacZ or YAP.

Results: Acute pressure overload induced YAP activation and upregulation of phosphoglycerate dehydrogenase (PHGDH), phosphoserine aminotransferase 1 (PSAT1), and phosphoserine phosphatase (PSPH) in mouse hearts. Overexpression of YAP in AC16 human cardiomyocytes increased the expressions of PHGDH, PSAT1, and PSPH, supporting a cell autonomous effect. Additionally, the expression of serine biosynthesis enzymes was abolished in cardiac-specific YAP knockout mice.

Conclusions: Taken together, these findings indicate that serine synthesis pathway is activated through YAP during early compensatory cardiac hypertrophy, suggesting a mechanistic link between YAP-mediated metabolic shifting and adaptive cardiac response during acute pressure overload.

Keywords: Serine synthesis pathway, Hippo pathway, Yes-associated protein, Pressure overload, Compensatory, Cardiac hypertrophy, Heart failure

RAPID 08

Prevalence of 22q11 Chromosome Deletion and Immunological Status of Vietnamese Patients with Tetralogy of Fallot

Phuong Anh Huynh[a], Nhu Nhat Quynh Nguyen[a], Niem Van Thanh Vo[a], Vy Ngan Tuong Phan[b], Khoi Minh Le[a,c], Diem My Vu[a]

[a]Center for Molecular Biomedicine, University of Medicine and Pharmacy at Ho Chi Minh City (217 Hong Bang, Cho Lon Ward, Ho Chi Minh City), Vietnam
[b]University of Science, Vietnam National University (227 Nguyen Văn Cu, Cho Quan Ward, Ho Chi Minh City), Vietnam
[c]University Medical Center (215 Hong Bang, Cho Lon Ward, Ho Chi Minh City), Vietnam

ABSTRACT

Background: 22q11.2 deletion syndrome (22q11.2DS) is a common chromosomal microdeletion disorder that is frequently observed in patients with Tetralogy of Fallot (TOF). However, considering the conotruncus and thymus arise from the same embryonic origin, immune abnormalities may also be present in TOF patients regardless of 22q11.2 deletion. Our study aimed to investigate 22q11.2 deletion status and its possible association with immunological alterations in TOF patients.

Methods: 22q11.2 deletion was detected by multiplex ligation-dependent probe amplification (MLPA), and cases with confirmed deletions were further assessed using next-generation sequencing to identify other chromosomal copy number variations. Blood lymphocytes were analyzed by flow cytometry.

Results: 210 TOF patients were included in the study. The mean age was 7.16 years and 105 (50%) were male. 22q11.2 deletion was confirmed in 22 cases (10.83%). Most patients (n = 18) had the 2.5 Mb deletion, two cases had the 2.0 Mb deletion, the 1.3 Mb and 0.5 Mb deletion were detected in one case each. Compared with non-deletion cases, TOF patients with 22q11.2 deletion presented a reduction of total T cells, T helper cells, and B lymphocytes; whereas increased proportions of T cytotoxic and NK cells were observed.

Conclusions: Immunological alterations, especially T-cell abnormalities, were commonly presented in TOF patients irrespective of 22q11.2 deletion. These findings emphasize the importance of immune evaluation and 22q11.2 deletion screening in TOF patients.

Keywords: 22q11.2 deletion syndrome, Tetralogy of Fallot, Congenital heart disease, Immunological alterations, Lymphocyte subsets, MLPA

RAPID 9

Endothelial and Metabolic Dysfunction in Mongolian Patients with Chronic Coronary Artery Disease

Anudari Ichinkhorloo[a], Badamkhand Mendsaikhan[a], Buyandelger Jamiyandorj[a], Gansukh Tumurbaatar[a], Myankhai Batkhuyag[a], Yundendash Dashzeveg[a], Batzaya Tsognemeh[b], Byambatsogt Lkhavgasuren[b], Sodgerel Batjargal[a], Chimeglkham Banzrai[a]

[a]Institute of Medical Sciences of Mongolia (BZD - 12 khoroo, Ulaanbaatar 13270)
[b]Third State Central Hospital (Central Clinical Hospital 3., BGD - 5 khoroo, Ulaanbaatar 16081)

ABSTRACT

Background: Metabolic dysfunction and vascular inflammation are central to the pathogenesis of coronary artery disease (CAD). However, whether endothelial and inflammatory biomarkers reflect anatomical coronary burden or earlier vascular dysfunction remains unclear. We investigated the interrelationships between metabolic factors, endothelial dysfunction, vascular inflammation and angiographic coronary artery severity.

Methods: This cross-sectional study included 267 Mongolian patients undergoing coronary angiography. Insulin resistance was estimated using the triglyceride-to-high-density lipoprotein (HDL) cholesterol ratio, and central obesity by waist–hip ratio (WC/HC). Endothelial dysfunction and vascular inflammation were assessed using serum endothelin-1 and Lp-PLA2, respectively. Biomarkers were standardized using z-scores. Biomarkers were standardized as z-scores. Associations were examined using correlation analyses and multivariable regression, with multinomial logistic regression used to assess predictors of angiographic coronary artery severity.

Results: Insulin resistance was associated with central obesity ($\rho=0.28$, $p<0.001$), which in turn correlated with endothelial dysfunction ($\rho=0.22$, $p=0.001$). Endothelin-1 demonstrated a moderate positive correlation with Lp-PLA2 ($\rho=0.38$, $p<0.001$). After multivariable adjustment, WC/HC ($\beta=0.19$, $p=0.01$) and vascular inflammation ($\beta=0.16$, $p=0.03$) remained independently associated with endothelial dysfunction. In contrast, neither endothelin-1 nor Lp-PLA2 independently predicted angiographic coronary artery severity, whereas age was the strongest determinant of multivessel disease.

Conclusions: Metabolic and inflammatory disturbances are closely linked to endothelial dysfunction but do not independently reflect angiographic coronary artery severity. These findings suggest that endothelial and vascular inflammatory biomarkers may represent earlier vascular dysfunction rather than anatomical coronary burden.

Keywords: Vascular inflammation, endothelial dysfunction, insulin resistance, Lp-PLA2, angiographic severity, coronary artery disease

P01

Cardiovascular Burden in Adrenal-Mediated Hypertension: A Comparative Study of Pheochromocytoma and Primary Aldosteronism

Aina Nadheera Abd Rahman[a,c], Haritha Subba Rau[a], Hazim Fadzli[a], Megan Limbang[a], Yue Zhen Lim[a], Adi Syazni Muhammed[b], Norlela Sukor[a] and Elena Aisha Azizan[a,c*]

[a]Department of Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia (UKM), Malaysia
[b]Department of Surgery, Hospital Canselor Tuanku Muhriz UKM, Cheras Kuala Lumpur, Malaysia
[c]Research Centre, Hospital Tunku Ampuan Besar Tuanku Aishah Rohani, UKM Specialist Children's Hospital, Cheras Kuala Lumpur, Malaysia

ABSTRACT

Background: Adrenal-mediated hypertension due to primary aldosteronism (PA) and pheochromocytoma (PCC) arises from distinct hormonal mechanisms. Although cardiovascular complications are well recognized in both conditions, direct comparative data remain limited. This study aimed to compare cardiometabolic profiles and cardiovascular disease (CVD) events among PA subtypes and PCC.

Methods: This retrospective study included patients diagnosed with PA or PCC at Universiti Kebangsaan Malaysia Medical Centre (2015–2025). Comparative analyses of cardiometabolic parameters and CVD events were performed between unilateral PA (uPA), bilateral adrenal hyperplasia (BAH), and PCC using non-parametric and categorical tests (SPSS v26).

Results: The study included 80 patients (uPA, n=33; BAH, n=39; PCC, n=8). CVD prevalence was significantly higher in PCC (87.5%) compared with uPA (39.4%; p=0.015) and BAH (17.9%; p<0.001). Relative to uPA, PCC demonstrated higher rates of left ventricular hypertrophy (50% vs. 12.1%; p=0.015) and higher median glucose (7.20 [5.04–9.37] vs. 5.21 [4.74–5.65] mmol/L; p=0.023). In the BAH-PCC comparison, PCC patients were older at diagnosis (56 [47–60] vs. 38 [31–41] years; p=0.021) but had higher HDL cholesterol (1.42±0.39 vs. 1.18±0.22 mmol/L; p<0.001) and lower diastolic blood pressure (78 [76–94] vs. 90 [84–103] mmHg; p=0.030). Across groups, CVD was associated with smoking (35.7%; p=0.032), older age at diagnosis (53 [44–62] years; p<0.001), and higher glucose level (6.33 [5.57–8.66] mmol/L; p=0.016).

Conclusions: PCC was associated with greater cardiovascular and metabolic burden than uPA or BAH, suggesting subtype-specific cardiovascular phenotypes in adrenal-mediated hypertension. However, the small PCC sample size warrants cautious interpretation. Larger multicentre studies are needed to validate these observations.

Keywords: Primary aldosteronism, Pheochromocytoma, Cardiometabolic profile, Cardiovascular disease, Secondary hypertension, Adrenal gland neoplasms

P02

Recurrent NOTCH4 Mutations Link Adrenal Endothelial Signalling to Aldosterone Overproduction and Cardiovascular Risk

Faeezah Abdul Latif[a*], Nurfatin Syazreen Mohd Rizam[a*], Fatin Athirah Pauzi[a], Munkit Choy[i], Simon Williams[b], Bernard Keavney[b], Amnani Aminuddin[a], Siti Khadijah Syed Mohammed Nazri[a], Xilin Wu[c], Elisabeth Ng[c], Matthew Andrew Ackers-Johnson[d], Roger Foo[d], Troy Puar[e], Norlela Sukor[a,g], Azraai Bahari Nasruddin[f], Morris Jonathan Brown[c,h], Elena Aisha Azizan[a,g]

[a]Department of Medicine, Faculty of Medicine, The National University of Malaysia (UKM) Medical Centre, Malaysia
[b]Division of Cardiovascular Sciences, University of Manchester, United Kingdom
[c]Department of Clinical Pharmacology and Precision Medicine, William Harvey Research Institute, Queen Mary University of London, United Kingdom
[d]Cardiovascular Research Institute, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[e]Department of Endocrinology, Changi General Hospital, Singapore
[f]Department of Endocrinology, Hospital Putrajaya, Putrajaya
[g]Hospital Canselor Tuanku Muhriz, Universiti Kebangsaan Malaysia, Kuala Lumpur
[h]NIHR Barts Biomedical Research Centre, Queen Mary University of London, London, United Kingdom
[i]Department of Life Sciences, Manchester Metropolitan University, UK.
[*]Contributed equally.

ABSTRACT

Background: Primary aldosteronism (PA) is a major cause of secondary hypertension and is strongly associated with myocardial fibrosis, vascular dysfunction, and excess cardiovascular morbidity. While aldosterone excess originates from the adrenal cortex, the contribution of the adrenal endothelium to hormone dysregulation remains poorly understood.

Methods: Germline whole-genome sequencing was performed in 105 Malay patients with bilateral PA. The adrenal-vascular microenvironment was interrogated using single-cell RNA-sequencing-derived datasets and cell-cell communication modelling (CellPhoneDB v4.0, 1,000 permutations, $p<0.05$). Functional validation was conducted using 24-hour co-culture of HAC15 adrenocortical cells with human cardiac (HCMEC) or umbilical vein (HUVEC) endothelial cells. Steroidogenic activity was quantified by CYP11B2 qPCR and aldosterone immunoassay.

Results: Recurrent mutations in NOTCH4 were identified by whole-genome sequencing. Single-cell transcriptomics localized NOTCH4 expression predominantly to adrenal endothelial cells. Cell–cell communication modelling identified an endothelial- and smooth muscle–enriched cluster (Cluster 22) as a dominant signalling hub (n=92 interactions). Co-transfection of a NOTCH4 plasmid with scrambled siRNA increased CYP11B2 expression 2.23±0.38-fold ($p=0.018$) relative to control ($p=0.018$), whereas co-transfection with SiNOTCH4 attenuated this effect (1.37±0.1-fold, $p=0.06$). Co-culture of HCMEC with HAC15 increased aldosterone production 3.15±0.17-fold ($p<0.001$) and CYP11B2 expression 1.82±0.37-fold ($p=0.03$). HUVEC co-culture increased aldosterone production 1.8±0.25-fold ($p=0.007$), with a trend toward increased CYP11B2 expression (1.53±0.49-fold, $p=0.26$).

P02

Conclusions: These findings identify endothelial NOTCH4 signalling as a novel regulator of aldosterone overproduction in PA and reveal a previously underappreciated endothelial–adrenal crosstalk mechanism that may contribute to cardiovascular injury in PA. Targeting endothelial NOTCH4 signalling represents a potential therapeutic strategy to mitigate aldosterone-driven cardiac damage.

Keywords: Adrenal Gland, NOTCH4, Primary Aldosteronism, Secondary Hypertension, Aldosterone, Endothelial

P03

An Odorless Oral Butyrate Nanotherapy Enhances Cardiac Repair After Ischemic Injury

Ming-Yao Chung[a], Yung-Jui Huang[a], Brian Chao[a], Hung-Chih Chen[a], Cheng-Bang Jian[b], Luu Nguyen Ngoc Nguyet[a], Yu-Wen Chen[a], Dennis W.H. Hwang[a], Hsien-Ming Lee[b], Yukio Nagasaki[b,c] and Patrick C.H. Hsieh[a]

[a]Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan
[b]Institute of Chemistry, Academia Sinica, Taipei 115, Taiwan
[c]Graduate School of Pure and Applied Sciences, University of Tsukuba, 1-1-1 Tennodai, Tsukuba 305-8575, Ibaraki, Japan
[d]Center of Applied Nanomedicine, National Cheng Kung University, No. 35, Xiaodong Rd., Tainan 701, Taiwan

ABSTRACT

Background: Ischemic heart injury triggers a robust inflammatory response that critically influences cardiac repair and long-term remodeling. Short-chain fatty acids derived from the gut microbiota, particularly butyrate, have emerged as key regulators of cardiovascular inflammation and tissue repair. However, therapeutic application of butyrate has been limited by poor pharmacokinetics, rapid clearance, and unacceptable odor.

Methods: We developed an odorless, water-soluble butyrate nanoparticle (NanogBA) based on a self-assembling copolymer that functions as an oral butyrate prodrug with controlled intestinal release. NanogBA was administered orally once daily in a murine myocardial ischemia–reperfusion (I/R) injury model. Plasma butyrate levels, cardiac function, myocardial fibrosis, inflammatory responses, and systemic toxicity were evaluated using echocardiography, histological analysis, and plasma biochemical assays.

Results: Oral administration of NanogBA significantly increased systemic butyrate exposure. In a mouse ischemia-reperfusion injury model, NanogBA markedly improved cardiac function and reduced adverse myocardial remodeling, including fibrosis. Importantly, comprehensive plasma biochemistry and multi-organ histological analyses demonstrated no detectable systemic toxicity. Mechanistic analyses revealed that NanogBA attenuated post-ischemic inflammatory signaling and shifted myocardial macrophage populations toward an anti-inflammatory, reparative phenotype, consistent with enhanced immune-mediated cardiac repair.

Conclusions: These findings identify oral NanogBA as a novel, microbiota-inspired nanotherapy that overcomes key translational barriers of butyrate delivery, modulates post-ischemic inflammation, and promotes functional cardiac repair, highlighting its therapeutic potential for ischemic heart disease.

Keywords: Ischemic heart, Short-chain fatty acids, Nanotherapy, Butyrate, Oral gavage, Cardiac repair

P04

Roselle Polyphenol-Rich Extract Mitigates Diabetic Cardiomyopathy by Attenuating NADPH Oxidase-Mediated Oxidative Stress

Fatin Farhana Jubaidi[a], Nur Liyana Mohammed Yusof[b], Satirah Zainalabidin[c], Izatus Shima Taib[d], Zariyantey Abd Hamid[d] and Siti Balkis Budin[d]

[a]Department of Physiology, Faculty of Medicine, Universiti Kebangsaan Malaysia, 56000 Cheras, Kuala Lumpur, Malaysia
[b]Department of Pharmacology, Faculty of Medicine, Universiti Kebangsaan Malaysia, 56000 Cheras, Kuala Lumpur, Malaysia
[c]Center for Toxicology and Health Risk Studies (CORE), Faculty of Health Sciences, Universiti Kebangsaan Malaysia, 50300 Kuala Lumpur, Malaysia
[d]Center for Diagnostic, Therapeutic and Investigative Studies (CODTIS), Faculty of Health Sciences, Universiti Kebangsaan Malaysia, 50300 Kuala Lumpur, Malaysia

ABSTRACT

Background: Roselle polyphenol-rich extract (HPE) has previously demonstrated cardioprotective properties; however, its specific role in modulating the NOX-dependent oxidative environment in diabetic cardiomyopathy (DCM) condition remains to be fully elucidated. This study investigated the protective mechanisms of HPE in mitigating DCM progression in a rat model, specifically focusing on the modulation of the NADPH oxidase complex.

Methods: Male Sprague-Dawley rats were induced with type 1 diabetes via a single injection of streptozotocin (55 mg/kg) and left untreated for four weeks to allow for the development of DCM. The rats were then randomized into five groups: untreated normal control (NDM), untreated diabetic control (DM), diabetic rats treated with metformin (DMM; 150 mg/kg), and diabetic rats supplemented with low-dose (DMRL; 100 mg/kg) or high-dose (DMRH; 200 mg/kg) HPE for four weeks.

Results: Molecular analysis of the cardiac tissue revealed that HPE supplementation significantly suppressed the protein expression of the NADPH oxidase subunits NOX2, p47phox, p67phox, and gp91phox. This inhibition of NADPH oxidase activation was associated with a marked reduction in cardiac oxidative stress markers and a concomitant increase in antioxidant status. Furthermore, the attenuation of oxidative damage by HPE led to a significant impediment of cardiac remodeling, characterized by reduced myocardial fibrosis and cardiomyocyte hypertrophy. These structural improvements resulted in the prevention of both systolic and diastolic dysfunction in HPE-treated diabetic rats.

Conclusions: HPE supplementation effectively mitigates the progression of DCM by inhibiting the NADPH oxidase pathway, thereby reducing oxidative stress and preserving cardiac structural and functional integrity.

Keywords: Hibiscus sabdariffa, Roselle polyphenol-rich extract, Diabetic cardiomyopathy, NADPH oxidase, Oxidative stress, Cardiac remodeling

P05

Mapping Stress Response QTLs using an iPSC-Cardiomyocyte Cell Village Platform for Heart Failure

Brandon Tan[a], Lin Zi Hao[a], Wei Qiang Seow[a] and Roger Foo[a]

[a]National University of Singapore, Yong Loo Lin School of Medicine, Singapore

ABSTRACT

Background: Heart failure (HF) with preserved ejection fraction (HFpEF) is a growing global epidemic with limited therapeutic options. Human induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) are a powerful resource to investigate how genetic variation shapes cardiomyocyte responses in stress and disease.

Methods: We employed a cell-village approach, pooling iPSCs from 120 PICMAN study participants (ASCVD risk >5%), differentiating them into CMs, and exposing them to a metabolic-inflammatory cocktail that mimics HFpEF risk factors such as hyperglycaemia and hyperlipidaemia. This perturbation was designed to induce cellular metabolic and diastolic dysfunction characteristic to HFpEF. Single-cell droplet-based indexing, combined with donor whole-genome sequences, enabled demultiplexing of 96 individuals to resolve donor-specific transcriptomic profiles.

Results: Transcriptomic profiling of stressed and control iPSC-CMs enabled the mapping of baseline and response expression quantitative trait loci (beQTLs & reQTLs), identifying 75 (baseline) genetic variants associated with gene loci (eGENEs) that modulate transcriptional responses to HFpEF-like stress. Both baseline and response QTLs were colocalised with HF GWAS datasets, refining 3 causal candidate genes contributing to HF pathophysiology.

Conclusions: Our current findings support the use of an iPSC-CM cell village platform to link human genetic variation to cell-type specific responses both at baseline and when perturbed. This work establishes a scalable, cost-effective framework of nominating novel genetic pathways for further mechanistic interrogation contributing to more personalised therapeutic targeting for heart failure.

Keywords: iPSC, Cardiomyocyte, QTL, Heart, Failure, Preserved

P06

Comparative Analysis of circRNA Expression Profiles in PAH-CHD: Geographic Heterogeneity between Indonesian and Chinese Studies

Fajri Marindra Siregar[a,b], Sofia Mubarika Haryana[c], Dyah Wulan Anggrahini[d], Lucia Kris Dinarti[d] and Anggoro Budi Hartopo[d]

[a]Doctorate Program, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia
[b]Department of Biochemistry, Faculty of Medicine, Universitas.Riau, Pekanbaru, Indonesia
[c]Department of Histology.and Cell Biology, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia
[d]Department.of.Cardiology.and.Vascular.Medicine, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada–Dr.Sardjito Hospital, Yogyakarta, Indonesia

ABSTRACT

Background: Circular RNAs (circRNAs) are stable epigenetic regulators and potential biomarkers in pulmonary arterial hypertension associated with congenital heart disease (PAH-CHD). This study synthesizes and compares differentially expressed circRNAs (DECs) from independent analyses to identify robust biomarkers and evaluate population-specific expression patterns.

Methods: A meta-synthesis of 92 DECs identified from three independent analyses involving Indonesian and Chinese populations was conducted. Bioinformatics nomenclature was normalized to ensure accurate cross-study comparison of circRNA identifiers and expression directions.

Results: The differentially expressed circRNAs identified across all three studies were predominantly downregulated. In the Chinese studies, a robust signature of six circRNAs (hsa_circ_0001334, hsa_circ_0003416, hsa_circ_0008882, hsa_circ_0089761, hsa_circ_0089762, and hsa_circ_0089763) was consistently downregulated. Despite this shared trend, the Indonesian analysis revealed a distinct profile with no overlapping circRNAs compared to the Chinese data.

Conclusions: A consistent, predominantly downregulated circRNA signature for PAH-CHD was identified in Chinese populations, which was absent in the Indonesian population. This pronounced geographic and ethnic heterogeneity indicates that the epigenetic landscape of PAH-CHD is population-dependent. These findings highlight the need for region-specific genomic research in Southeast Asia to develop accurate diagnostic strategies for local populations.

Keywords: Biomarkers, circRNA, Microarray, Geographic heterogeneity, Non-coding RNA, PAH-CHD

P07

Hyperglycemia-Driven Hepatic Immune Dysfunction Facilitates Microbial Dissemination Post-Myocardial Infarction

Tony W.H. Tang[a], Sumi Nani Novita Pasaribu[a], Hung-Chih Chen[a], Po-Ju Lin[a], Shu-Chian Ruan[a], Emily Wissel[a], Chiung-Wen Kuo[b], Peilin Chen[b], Yen-Chun Ho[a], Yi-Cheng Chang[a,c] and Patrick C.H. Hsieh[a,c*]

[a]Institute of Biomedical Sciences, Academia Sinica, Taipei 115, Taiwan
[b]Research Center for Applied Sciences, Academia Sinica, Taipei 115, Taiwan
[c]Institute of Medical Genomics and Proteomics and Institute of Clinical Medicine, National Taiwan University College of Medicine, Taipei 100, Taiwan

ABSTRACT

Background: The gut microbiome is intimately connected to cardiovascular health through the gut-heart axis and plays a pivotal role in maintaining homeostasis. Myocardial infarction (MI) disrupts this homeostatic balance, leading to widespread adverse effects. Hyperglycemia, a hallmark of metabolic dysfunction, further exacerbates these disruptions, emphasizing the need to understand the underlying mechanisms to develop effective therapeutic strategies for mitigating the cascading complications along the gut-heart axis. This study aims to elucidate the dynamics of gut barrier disruption during MI, and explore the liver's function as an immune sentinel in this process, with a focus on the impact of hyperglycemia on microbial dissemination, systemic inflammation, and liver immune function.

Methods: A murine MI model was used to evaluate gut permeability, bacterial translocation, and hepatic immune responses. MI was induced via permanent left anterior descending artery ligation. Hyperglycemia was established through streptozotocin injections and a high-fat, high-sugar diet. Gut barrier integrity was assessed using FITC-dextran assays, and microbial translocation was tracked through intravital imaging and anaerobic bacterial cultures from multiple organs. Hepatic immune function was analyzed via flow cytometry, cytokine profiling, and phagocytosis assays. 16S rRNA sequencing characterized the composition of translocated bacteria.

Results: MI significantly increased intestinal permeability, with hyperglycemia further exacerbating gut barrier dysfunction. Intravital imaging revealed bacterial translocation through the portal vein to the liver, highlighting the liver's role in microbial interception. Hyperglycemia impaired hepatic macrophage function by activating NLRP3 inflammasome signaling, reducing bacterial clearance and promoting persistent liver colonization. Systemic inflammatory cytokines, particularly TNF-α, were elevated, further facilitating microbial dissemination. 16S rRNA sequencing demonstrated host-dependent stochastic variability in translocated bacterial composition.

Conclusions: The liver serves as a key immune regulator in the gut-liver-heart axis but is functionally compromised under hyperglycemia, exacerbating systemic inflammation and microbial dissemination post-MI. Targeting NLRP3 signaling and restoring gut barrier integrity may mitigate post-MI complications, particularly in hyperglycemic conditions. These findings underscore the need for integrated therapeutic strategies incorporating metabolic control and microbiome-targeted interventions to improve post-MI outcomes.

P08

Subclinical Cardiac Functional Alterations in Young Adults with Dyslipidemia

Amilia Aminuddin[a], Nur Akilah Ismail[a], Azizah Ugusman[a], Norliana Masbah[b], Beh Boon Chong[c]

[a]Department of Physiology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Jalan Yaacob Latif, Bandar Tun Razak, Cheras, Kuala Lumpur
[b]Department of Pharmacology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Jalan Yaacob Latif, Bandar Tun Razak, Cheras, Kuala Lumpur
[c]Cardiology Unit, Department of Medicine, Hospital Canselor Tuanku Muhriz, Jalan Yaacob Latif, Bandar Tun Razak, Cheras, Kuala Lumpur

ABSTRACT

Background: Dyslipidemia is a key risk factor for cardiovascular diseases, yet its association with cardiac functional changes in young adults remains unclear. This study aimed to examine early myocardial functional alterations in apparently healthy young adult males with dyslipidemia using echocardiography.

Methods: A total of 87 participants aged 20-40 underwent lipid profiling and echocardiographic assessment. Dyslipidemia was defined as low-density lipoprotein cholesterol (LDL-C) ≥3.4 mmol/L. Cardiac function was assessed using systolic and diastolic indices, including left ventricular ejection fraction (LVEF), transmitral early-to-late diastolic velocity ratio (E/A ratio), and deceleration time (DT). Group comparisons were performed using independent t-tests or Mann-Whitney U tests, and associations with lipid components were explored using bivariate correlation analyses.

Results: The E/A ratio was significantly lower in dyslipidemic participants compared with normal controls [median (IQR): 1.355 (1.2375–1.5925) vs 1.5250 (1.3050–1.9000), p=0.047]. A significant negative correlation was observed between E/A ratio and LDL-C (Spearman's ρ= -0.270, p=0.018). No significant differences were observed between groups in LVEF (dyslipidemic: 65.84±5.052 % vs normal: 66.16±5.284 %) and DT (dyslipidemic: 192.88±34.844 ms vs normal: 197.11±40.509 ms).

Conclusions: Elevated LDL-C is associated with subtle alterations in diastolic function, as indicated by a reduced E/A ratio despite preserved systolic function. These findings suggest that lipid abnormalities in young adults may be linked to early subclinical diastolic changes before the development of overt cardiac dysfunction.

Keywords: Dyslipidemia, Cardiac function, Young adults, Cardiovascular, E/A ratio, Echocardiogram

P09

Untargeted Whole Blood Metabolomics Reveals Distinct Metabolic Profiles in Sudden Cardiac Death Post-Mortem Subjects

Ammar Hariz Ahmad Razmy[a], Normala Abdul Latip[b], Razuin Rahimi[c,d], Wan Mohammad Hafiz Wan Razali[d], Nur Fatimah Ahmad Zairin[d], Kunasilan Subramaniam[e], Fatin Faizah Mohamed Isa[e], Sharaniza Abdul Rahim[c] and Siti Hamimah Sheikh Abdul Kadir[a,c]

[a]Cardiovascular Advancement and Research Excellence Institute (CARE Institute), Level 4, Academic Building, Universiti Teknologi MARA (UiTM) Sungai Buloh Campus, 47000 Sungai Buloh, Selangor, Malaysia
[b]Integrative Pharmacogenomics Institute (iPROMISE), Level 7, FF3 Building, UiTM Puncak Alam Campus, 42300 Puncak Alam, Selangor, Malaysia
[c]Faculty of Medicine, Universiti Teknologi MARA (UiTM) Sungai Buloh Campus, 47000 Sungai Buloh, Selangor, Malaysia
[d]Department of Forensic Pathology, Hospital Al-Sultan Abdullah, Universiti Teknologi MARA (UiTM) Puncak Alam Campus, 42300 Puncak Alam, Selangor, Malaysia
[e]National Institute of Forensic Medicine (IPFN), Hospital Kuala Lumpur, 50586 Kuala Lumpur, W.P. Kuala Lumpur, Malaysia

ABSTRACT

Background: Sudden cardiac death (SCD) results from various aetiologies, including coronary artery disease (CAD), hypertrophic cardiomyopathy (HCM) and inherited channelopathies. Determining the cause of SCD in forensics remains a diagnostic challenge, especially when autopsy findings are inconclusive. Metabolomics has become a robust methodology for delineating metabolic profiles in cardiovascular diseases. Consequently, this study aims to compare the metabolomic profiles of SCD and non-SCD cases.

Methods: Whole blood samples from SCD (CAD, n=5; HCM, n=3; other cardiac etiologies, n=2) and controls (non-SCD n=14) were collected from two tertiary hospitals in the Klang Valley, Malaysia. Untargeted liquid chromatography-mass spectrometry (LC-MS) profiling was performed. Peak features were pre-processed, filtered and normalised prior to analysis. Pairwise comparisons, principal component analysis (PCA) and multigroup ANOVA were performed. Significant metabolites were evaluated using partial least squares-determinant analysis (PLS-DA), false discovery rate (FDR) correction and pathway enrichment analysis (MetaboAnalyst 6.0).

Results: A total of 1,847 metabolites were detected. Multigroup analyses demonstrated distinct clustering of groups across principal components. CAD-associated SCD demonstrated significant disruption of glycerophospholipid metabolism (FDR <0.05), with phosphatidylcholine species mapping to four significant pathways in comparison to controls. Fold-change (FC) analysis revealed a predominant downregulation of membrane glycerophospholipids in CAD versus controls, whereas HCM exhibited relative upregulation of acylcarnitines.

Conclusion: Our findings demonstrated SCD possesses distinct metabolic pathways to non-SCD. CAD-related SCD is characterised by metabolic signatures consistent with membrane phospholipid breakdown and acute ischemic ATP depletion, whereas HCM-associated SCD reflects mitochondrial fatty acid remodelling.

Keywords: Sudden cardiac death, Metabolomics, Liquid chromatography-mass spectrometry, Post-mortem analysis, Glycerophospholipids, Acylcarnitines,

P10

Unlocking Ghrelin as a Novel Modulator of Hemodynamic Unloading and Ventricular Coupling in Heart Failure Reduce Ejection Fraction : A Systematic Review, Meta-Analysis & Correlation Analysis

Bima Diokta Alparisi[a,b], Mas Rizky A.A. Syamsunarno[b,c], Rosmaliana[d], Irwan[d], Samira Amanda[e], and Dewa Ngakan Nyoman Karyana[f]

[a]Clinical Clerkship, RSUD Arifin Achmad, Faculty of Medicine, Riau University, Pekanbaru, Indonesia
[b]Cardiometabolic Working Group Study, Faculty of Medicine, Padjadjaran University, Bandung, West Java, Indonesia
[c]Department of Biomedical Sciences, Faculty of Medicine, Padjadjaran University, Bandung, West Java, Indonesia
[d]Department of Cardiology and Vascular Medicine, RSUD Arifin Achmad, Faculty of Medicine, Riau University, Pekanbaru, Indonesia
[e]Medical Education Program, Faculty of Medicine, Riau University, Pekanbaru, Indonesia
[f]Medical Education Program, Faculty of Medicine, Mataram University, Lombok, Indonesia

ABSTRACT

Background: Heart failure with reduced ejection fraction (HFrEF) is marked by systolic dysfunction, adverse ventricular remodeling, and increased afterload. Ghrelin, a gut-derived cardiometabolic hormone, has vasodilatory and anti-remodeling properties that may counter these mechanisms. This study evaluated the effects of ghrelin modulation on ventricular function, structural remodeling, and hemodynamics in HFrEF.

Methods: A PRISMA-guided systematic review and meta-analysis of controlled HFrEF studies was performed. Risk of bias was assessed using the Cochrane Risk of Bias tool and the Joanna Briggs Institute checklist. Pooled mean differences (MDs) with 95% confidence intervals were calculated using a random-effects model, with exploratory correlation analyses assessing interactions between structural and functional parameters.

Results: Ghrelin significantly improved systolic function, reflected by increased LVEF (MD +8.14%; p=0.0098), cardiac output (MD:+0.94 L/min; p=0.016), and TAPSE (MD +3.78 mm; p=0.0005). These improvements were accompanied by significant afterload reduction, with decreases in SBP (MD −21.95 mmHg; p<0.000001) and DBP (MD −7.30 mmHg; p=0.031). Structural changes were observed in LVEDV (MD +20.78 mL; p=0.031), LVESV (MD +13.88 mL; p=0.0012), and PWT (MD −0.44 mm; p=0.018). Correlation analyses demonstrated that SBP reduction was associated with CO augmentation, ΔLVEF paralleled ΔTAPSE improvement indicating LV–RV coupling, and ΔLVEDV inversely correlated with ΔPWT, consistent with eccentric remodeling under reduced afterload.

Conclusion: Ghrelin promotes coordinated hemodynamic unloading and coupled ventricular remodeling in HFrEF, highlighting its potential as a mechanistically integrated therapeutic strategy.

Keywords: Cardiac remodelling, HFrEF, Hemodynamic unloading, Left ventricular function, Ventricular coupling

P11

A Scaffold-Free Human 4-Cell-Type Cardiac Microtissue Model for Investigating Metabolic Stress-Induced Heart Failure

Khe Ying Chong[a], Chang Jie Mick Lee[a,b] and Roger S.-Y. Foo[a,b]

[a]Cardiovascular & Metabolic Disease Translational Research Programme, Centre for Translational Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore
[b]Institute of Molecular and Cell Biology, Agency for Science Technology and Research, Singapore, Singapore

ABSTRACT

Background: Heart failure (HF) is a leading cause of morbidity and mortality worldwide and presents as a heterogeneous clinical syndrome. In Asia, nearly two-thirds of HF patients have multimorbidities, including obesity, hypertension, and diabetes. However, the mechanisms underlying metabolic stress–induced HF remain poorly defined, and there is a lack of human-based experimental models that accurately recapitulate disease pathology and enable mechanistic investigations and drug discovery.

Methods: In this study, we refined an established cardiac microtissue platform by incorporating macrophages, thereby introducing an immune dimension to HF pathophysiology modeling. The resulting four-cell-type cardiac microtissue (4CT-MT) comprises isogenic cardiomyocytes, endothelial cells, cardiac fibroblasts, and macrophages derived from a single human stem cell line. To mimic metabolic stress, the 4CT-MTs were exposed for one week to a high-fat, high-sugar, pro-inflammatory cocktail containing glucose, palmitic acid, oleic acid, interferon-γ, and angiotensin II.

Results: The metabolic stress–treated 4CT-MTs exhibited several key hallmarks of heart failure with preserved ejection fraction, including cardiomyocyte hypertrophy, heightened inflammatory signaling, and macrophage polarization toward a pro-inflammatory phenotype. Functional assessments revealed reduced ATP production and oxygen consumption rate, indicating compromised bioenergetics. Additionally, insulin resistance, marked by elevated IRS1-Ser307 phosphorylation and impaired relaxation, was observed, suggesting metabolic derangement and diastolic dysfunction. Bulk RNA sequencing analysis demonstrated downregulation of oxidative phosphorylation and cardiac contractility pathways, along with upregulation of immune gene networks.

Conclusion: Collectively, this physiologically relevant in vitro metabolic stress model recapitulates immune–metabolic interactions that drive HF progression and offers a versatile platform to investigate crosstalk between myocytes and non-myocytes in the failing heart.

Keywords: Cardiac microtissue, Metabolic stress, Immune crosstalk, Multicellular model, Disease modeling, HFpEF

P12

Interplay between Epicardial Adiposity and Left Ventricular Function in a Multiethnic Malaysian T2DM Cohort with CAD

Yiaw En Chung[a], Wan Ahmad Syazani Mohamed[b], Azilleo Kristo Mozihim[c], Hasniza Zaman Huri[d], Ahmad Syadi Mahmood Zuhdi[e] and Amira Hajirah Abd Jamil[a]

[a]Department of Pharmaceutical Life Sciences, Faculty of Pharmacy, Universiti Malaya, 50603 Kuala Lumpur, Malaysia
[b]Nutrition Unit, Nutrition, Metabolic and Cardiovascular Research Centre (NMCRC), Institute for Medical Research (IMR), National Institutes of Health (NIH), Ministry of Health (MOH), Malaysia
[c]Department of Pharmacology, Faculty of Medicine, University of Malaya, Kuala Lumpur 50603, Malaysia
[d]Department of Clinical Pharmacy and Pharmacy Practice, Faculty of Pharmacy, Universiti Malaya, 50603 Kuala Lumpur, Malaysia
[e]Cardiology Unit, University Malaya Medical Centre, Faculty of Medicine, Universiti Malaya, 50603 Kuala Lumpur, Malaysia

ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is associated with premature mortality, predominantly driven by cardiovascular complications. Epicardial adipose tissue (EAT), a metabolically active visceral fat depot, has been implicated in cardiometabolic risk and adverse cardiac remodeling. Ethnic variation influences EAT accumulation, however data from Southeast Asian populations remain scarce. This study investigated the association between EAT thickness and left ventricular (LV) function in the multiracial Malaysian T2DM patients with coronary artery diseases (CAD).

Methods: A total of 376 patients (123 Chinese, 127 Malay, 126 Indian) were recruited from Universiti Malaya Medical Centre. Demographic, anthropometric, and biochemical data were collected. Transthoracic echocardiography was performed, with EAT thickness measured at the right ventricular free wall and LV function parameters assessed.

Results: The median EAT thickness was 4.8mm, which was correlated with body mass index (BMI; $r=0.142$, $p=0.011$) and waist-to-hip ratio ($r=0.162$, $p=0.003$), but not with glycemic or lipid parameters. Increased EAT was associated with adverse LV function, with strongest association observed for LV mass ($r=0.228$, $p<0.001$). Chinese patients exhibited greater EAT thickness (median 5.2mm) despite lower BMI and demonstrated more pronounced LV remodeling. In multivariable analyses, Chinese ethnicity is independently associated with greater LV mass, together with EAT thickness and male sex, after adjustment for age, BMI, HbA1c, total cholesterol and medication use.

Conclusions: In Malaysian T2DM patients with CAD, increased EAT thickness is associated with anthropometric parameters and adverse LV remodeling. Chinese ethnicity is independently associated with greater LV structural changes beyond conventional risk factors, suggesting a potential ethnicity-specific vulnerability to EAT-mediated cardiovascular risk.

Keywords: Epicardial adipose tissue, Type 2 diabetes mellitus, Coronary artery disease, Left ventricular remodeling, Ethnicity, Echocardiography

P13

Role of EPPK1 Expression in Cardiorenal Syndrome: A Retrospective Study

Uma Nahar Saikia[a], Anchal Dhiman[b], Sahil Verma[b], Abhi Dutta[b], Ajay Bahl[c], Vivek Kumar[d], and Anupam Mittal[b*]

[b]Department of Translational and Regenerative Medicine, PGIMER, Chandigarh, India
[c]Department of Cardiology, PGIMER, Chandigarh, India
[d]Department of Nephrology, PGIMER, Chandigarh, India

ABSTRACT

Background: Cardiorenal syndrome (CRS) encompasses disorders with dysfunction of either heart or kidney with their dysfunction leading to disease progression and mortality. Epiplakin 1 (EPPK1), a cytolinker protein is a cellular stress responses and cytoskeletal stabilization, linked to tissue remodelling and damage, upregulated in various inflammatory conditions. Its clinicopathological importance in CRS is yet unknown. Hence we aimed to evaluate EPPK1 expression pattern and its clinical role in heart and kidney of CRS.

Methods: Retrospective study included 12 CRS, 6 chronic heart failure (CHF),10 chronic kidney disease (CKD) and, 5 controls from 2017 - 2019. The hematoxylin and eosin stained slides used for histopathological evaluation. The expression of EPPK1 in heart and kidney was evaluated by immunohistochemical examination.

Results: Immunohistochemistry revealed significant upregulation of EPPK1 (both membranous and cytoplasmic) in CRS heart and kidney compared with normal. The staining intensity of EPPK1 in heart of CRS subjects were 1+ in 1 (8.3%), 2+ in 3 (25%), and 3+ in 7 (58.3%). The staining intensity of EPPK1 in kidney of CRS subjects were 1+ in 3 (25%) and 2+ in 5 (41.6%). The control tissue showed 0 to 1+ positivity. The overall relative mean expression was 72.5 and 65 in heart and kidney of CRS. The degree of structural damage and clinical characteristics were associated with increased expression levels.

Conclusions: EPPK1 is dysregulated in kidney and heart of CRS patients tissue suggesting kidney-heart crosstalk in CRS may be mechanistically mediated by EPPK1. Further function studies are necessary to explore its prognostic and therapeutic potential.

Keywords: CRS, EPPK1,IHC, Kidney, Heart

P14

Determining the Optimal Age Threshold for Mortality Risk in Malaysian Men with Acute Coronary Syndrome

Dinesh Veerapatrana[b], Amilia Aminuddin[a], Azizah Ugusman[a], Azimatun Noor Binti Aizuddin[c], Beh Boon Cong[d] and Kalaivani Chellappan[e]

[a]Department of Physiology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Jalan Yaacob Latif, Bandar Tun Razak, 56000 Kuala Lumpur, Malaysia
[b]School of Medicine, IMU University, No. 126, Jalan Jalil Perkasa 19, Bukit Jalil, 57000 Kuala Lumpur
[c]Department of Community Health, Faculty of Medicine, Universiti Kebangsaan Malaysia, Jalan Yaacob Latif, Bandar Tun Razak, 56000 Kuala Lumpur, Malaysia
[d]Department of Cardiology, Hospital Canselor Tuanku Muhriz, Universiti Kebangsaan Malaysia Medical Centre, Jalan Yaacob Latif, Bandar Tun Razak, 56000 Kuala Lumpur, Malaysia
[e]Department of Electrical, Electronic and Systems Engineering, Faculty of Engineering and Built Environment, Universiti Kebangsaan Malaysia, 43600 Bangi, Selangor, Malaysia

ABSTRACT

Background: Age is a major determinant of mortality in acute coronary syndrome (ACS). However, data-driven age thresholds for Southeast Asian male populations remain underexplored. This study aimed to identify a statistically and clinically relevant age cut-off associated with 30-day and 1-year mortality in a multiethnic Malaysian male cohort.

Methods: Data from 45,916 male STEMI/NSTEMI patients in the Malaysian NCVD registry (2014–2021) were retrospectively retrieved and analysed. Age was treated as a continuous predictor. Restricted cubic splines were used to assess linearity and identify inflection points. ROC analysis and the Youden Index were applied to determine optimal cut-offs. Multivariable logistic regression, adjusting for cardiovascular risk factors and ACS severity markers, was performed to validate the threshold.

Results: Age showed a significant non-linear association with both 30-day and 1-year mortality (non-linearity $p = 0.0004$ and <0.001). Spline curves demonstrated a sharp rise in 30-day and 1-year mortality risk beginning around 58–60 years. ROC analysis yielded AUCs of 0.660 (30-day) and 0.675 (1-year), with optimal thresholds at 59–59.5 years. For clinical applicability, this was rounded to 60 years. In adjusted models, age ≥60 remained a strong independent mortality predictor (adjusted OR 2.182; 95% CI 1.963–2.426; $p <0.001$), showing better model performance than alternative specifications.

Conclusions: In conclusion, ≥60 years is a significant data-driven mortality threshold for Malaysian male ACS patients. It provides an early foundation for refining regional age-based risk stratification, but further external validation across multi-centre Southeast Asian cohorts is required.

Keywords: Acute coronary syndrome (ACS), STEMI/NSTEMI, Cardiovascular mortality, Age-related risk, Risk stratification, Prognostic factors

P15

lncRNA Miat Regulates Ribosome Biogenesis and Protein Translation to Drive Cardiac Hypertrophy

Gaizhen Liu[a,b], Zhiru Huangfu[b], Yifan Wang[b], and Yibin Wang[b]

[a]Department of Cardiology, Second Hospital of Shanxi Medical University, Taiyuan, China
[b]Cardiovascular & Metabolic Disorders Program, Duke-NUS Medical School, Singapore

ABSTRACT

Background: Pathological cardiac hypertrophy requires rapid protein synthesis, yet mechanisms coordinating translational control remain poorly defined. The long non-coding RNA MIAT has been implicated in cardiovascular disease, but its role in translational regulation during hypertrophic remodeling is unknown.

Methods: Cardiac hypertrophy was induced using phenylephrine (PE) stimulation in vitro and transverse aortic constriction (TAC) in mice. Protein synthesis was evaluated using puromycin incorporation and translatome profiling. Ribosome biogenesis and nucleolar dynamics were examined by molecular and imaging approaches. Cardiomyocyte-specific translatome analysis was performed using translating ribosome affinity purification sequencing (TRAP-seq). Therapeutic potential was evaluated using antisense oligonucleotide (Miat-ASO) treatment following PE stimulation in vitro and TAC in vivo.

Results: MIAT expression increased during hypertrophic stress. MIAT deficiency blunted cardiomyocyte growth and suppressed global protein synthesis in vitro and in vivo. MIAT deficiency disrupted ribosome biogenesis and prevented the translational reprogramming required for hypertrophic growth. Mechanistically, MIAT interacted with nucleolin and was required for proper rRNA processing, and ribosome biogenesis. Importantly, systemic administration of Miat-ASO attenuated TAC-induced cardiac hypertrophy and improved cardiac remodeling.

Conclusions: MIAT is a critical regulator of translational control in cardiac hypertrophy by maintaining ribosome biogenesis and protein synthesis. Targeting MIAT with antisense therapy may represent a promising translational approach for attenuating pathological hypertrophic remodeling.

Keywords: lncRNA, MIAT, ribosome biogenesis, protein translation, cardiac hypertrophy, hypertrophy

P16

Targeting Residual Inflammatory Risk in Diabetic Atherosclerosis: An In Silico Comparison of Seaweed-Derived Bioactives with Atorvastatin Against IRAK4 and NLRP3

Iman Nabilah Abd Rahim[a], Opik Taupiqurrohman[b] and Mohd Yusmiaidil Putera Mohd Yusof[a,c]

[a]Faculty of Dentistry, Universiti Teknologi MARA, 47000 Sungai Buloh, Selangor, Malaysia
[b]Graduate School, Universitas Padjadjaran, Bandung, West Java, Indonesia
[c]Cardiovascular Advancement and Research Excellence Institute, Universiti Teknologi MARA, 47000 Sungai Buloh, Selangor, Malaysia

ABSTRACT

Background: Despite optimal lipid-lowering therapy with statins, many patients with diabetes mellitus remain at high risk of atherosclerotic cardiovascular events due to persistent vascular inflammation, a phenomenon termed residual inflammatory risk. The IRAK4–NF-κB–NLRP3 signaling axis plays a pivotal role in inflammatory priming and inflammasome activation, contributing to plaque instability and progression. Targeting both upstream kinase signaling and downstream inflammasome activation may represent a complementary strategy to current lipid-focused therapies. This study aimed to evaluate the molecular interactions of seaweed-derived bioactives against IRAK4 and NLRP3 in comparison with atorvastatin.

Methods: Molecular docking analysis was performed using validated human IRAK4 kinase and NLRP3 protein structures. Fucoxanthin and fucosterol were evaluated as candidate ligands, with atorvastatin included as a clinical comparator. Binding energies and interaction profiles were analyzed using Discovery Studio.

Results: Fucosterol demonstrated stronger binding affinity than atorvastatin toward both IRAK4 and NLRP3. For IRAK4, binding energies were –9.7 kcal/mol for fucosterol, –9.1 kcal/mol for atorvastatin, and –6.4 kcal/mol for fucoxanthin. For NLRP3, fucosterol exhibited the highest affinity (–11.6 kcal/mol), compared with –9.3 kcal/mol for atorvastatin and –6.7 kcal/mol for fucoxanthin. Interaction analysis revealed stable hydrophobic anchoring of fucosterol within both kinase and inflammasome domains, suggesting potential modulation of inflammatory priming and inflammasome activation.

Conclusions: Fucosterol demonstrated consistent in silico affinity toward IRAK4 and NLRP3. These findings support further experimental and clinical investigations to evaluate seaweed-derived bioactives as potential adjunct strategies targeting vascular inflammation in diabetic cardiovascular disease.

Keywords: Diabetic atherosclerosis, Residual inflammatory risk, IRAK4, NLRP3 inflammasome, Fucosterol, Molecular docking

P17

GLIS3 as a Potential Regulator of Heart Failure

Xi Yei[1], Mick Lee[1], Tuan Danh Anh Luu[1], Matthew Ackers-Johnson[1], Eddie Keng[2], Wei Leong Chew[2] and Roger Foo[1]

[1]Yong Loo Lin School of Medicine, National University of Singapore, Singapore 117599
[2]Genome Institute of Singapore, Agency of Science, Technology and Research, Singapore

ABSTRACT

Background: Cardiovascular disease (CVD) accounts for ~32% of all mortality, and heart failure (HF) is a major final common pathway to all CVD. To identify disease drivers of HF, a genome-wide association study (GWAS) was conducted in the Asian Network for Translational Research and Cardiovascular Trials (ATTRaCT) cohort of patients with HF in Singapore. Using BOLT-LMM analysis, we identified the GLIS family Zinc Finger 3 (GLIS3) as a candidate gene of interest. Glis3 is known to be an important transcription factor in islet β-cells, where human GLIS3 mutations are directly causal to neonatal diabetes. Interestingly, Glis3 is also upregulated in cardiac fibroblasts of human adult failing hearts, and the knockdown of Glis3 is likely to drive fibroblast activation, further implicating the role of Glis3 in cardiac fibroblasts. However, the molecular mechanisms of action for GLIS3 in heart failure remains to be elucidated.

Methods: In vivo murine models (n=8) were used to knock down GLIS3 via an Adeno-Associated Virus (AAV) system of targeted serotypes for efficient cardiac cell-type specific transgene delivery, and the respective echocardiography data and tissues were collected for downstream data analysis.

Results: From the in vivo knockdown experiments, we observe that C57NTAC mice generally have a poorer prognosis, where there was an acute reduction in ejection fraction and a sharp increase in the number of fibroblasts. Interestingly, there was no increase in the amount of fibrosis based on Sirius Red staining, suggesting a metabolic stress gene response. Surprisingly, upon isolation of the cardiac fibroblasts from mice, knockdown was observed in circGlis3, instead of linear Glis3, suggesting an isoform-dependent role of Glis3.

Conclusion: Human genetic analysis and murine validation experiments suggest that both candidate genes play a role in augmenting the pathophysiological state of the diseased hearts, however, the mechanistic understanding behind both genes in heart failure remain to be understood.

Keywords: Cardiac Fibroblasts, Adeno-Associated Virus, Mouse Models, GWAS, ATTRaCT, circRNA

P18

Oral Supplementation of Indole-3-Propionic Acid Preserves Cardiac Function in Ischemic and Doxorubicin-Induced Cardiomyopathy

Muthu Kumaraswamy Shanmugama[b,c], Lik Hang Wua[b,d], Pakkiri Leroy Sivappiragasam[a,b], Lim Poh Leong[a,b], Jielin Yang[a,b], Amudha Deivasigamani[a,b], Amandine Mahieux[a,b], Elisa Anamaria Liehn[f,g], Roshni R. Singaraja[a,b] and Chester Lee Drum[a,b,e]

[a]Cardiovascular Research Institute, National University Health System, 117599, Singapore
[b]Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, 119228, Singapore
[c]Department of Pharmacology, National University of Singapore, 117600, Singapore
[d]Department of Data Science, Kitasato University, Sagamihara, Kanagawa, Japan
[e]Department of Cardiology, National University Heart Centre, 119074, Singapore
[f]Institute for Molecular Medicine, University of Southern Denmark, Odense 5000, Denmark.
[g]Institute for Innovation and eHealth, University of Medicine and Farmacy "Carol Davila", Bucharest 010451, Romania

ABSTRACT

Background: Heart failure and metabolic disease are major, age-associated health burdens. Growing evidence suggests that alterations in gut microbiome profoundly impact cardiovascular health, with protective microbial metabolites often depleted in aging and heart failure. Indole-3-Propionic Acid (IPA)—produced from dietary tryptophan by specific intestinal microbes—has recently emerged as a powerful natural antioxidant and anti-inflammatory molecule. This study investigates cardioprotective potential of IPA against two common forms of severe cardiac injury: acute myocardial infarction (AMI), driven by ischemic hypoxia, and doxorubicin (DOX)-induced cardiomyopathy, characterized by iron-catalysed oxidative stress and DNA damage.

Methods: We demonstrate that oral supplementation of IPA in mice (20 mg/kg and 40 mg/kg) confers significant cardioprotection, preventing the decline of left ventricular ejection fraction and inhibiting aberrant cardiac remodelling in both DOX- and AMI-induced injury models.

Results: Mechanistically, exogenous IPA mitigated ferroptosis-associated injury by modulating the labile iron pool and regulating key iron transport and homeostasis proteins, including SLC25A37 (a mitochondrial iron regulator), transferrin receptor, FTL, and FTH. To further define the metabolic rescue provided by IPA, we utilized LC/MS/MS targeted metabolic profiling. Micromolar concentrations of IPA were detected in murine plasma and in heart tissue. IPA uniquely rescued pathways involving tryptophan, indole, kynurenine, and other key metabolites and upregulated inhibitors of nitric oxide synthase while modulating the flux of acylcarnitines and amino acids.

Conclusions: Together, these results demonstrate that IPA counteracts injury-associated metabolic shifts in both heart tissue and plasma. The gut-derived IPA mirrors protective patterns observed with FDA-approved cardioprotectors in ferroptosis-associated injury settings.

Keywords: Indole-3-propionic acid, Cardiotoxicity, Doxorubicin, Cardioprotection, Acute myocardial infarction, iron homeostasis

P19

Distribution of RYR2 in Heart Tissue of Malaysian Post-Mortem Subjects

Nur Aqasyah Amran[a], Noorul Izzati Hanafi[a], Afiqq Aiman Abd Ghapor[a], Ammar Hariz Ahmad Razmy[a], Razuin Rahimi[b,c], Wan Mohammad Hafiz Wan Razali[b], Nur Fatimah Ahmad Zairin[b], Alyaa Rajih Mahmood Al-Khateeb[c], Mardiana Abdul Aziz[c] and Siti Hamimah Sheikh Abdul Kadir[a,c]

[a]Cardiovascular Advancement and Research Excellence Institute (CARE Institute), Level 4, Academic Building, UiTM Kampus Sungai Buloh, Jalan Hospital, 47000 Sungai Buloh, Selangor, MALAYSIA
[b]Department of Forensic Pathology, Hospital Al-Sultan Abdullah, Universiti Teknologi MARA (UiTM) Puncak Alam Campus, 42300 Puncak Alam, Selangor, Malaysia
[c]Faculty of Medicine, Universiti Teknologi MARA (UiTM) Sungai Buloh Campus, Jalan Hospital, 47000 Sungai Buloh, Selangor, Malaysia

ABSTRACT

Background: Ryanodine receptor 2 (RYR2) is a key calcium-release channel in cardiomyocytes and plays an essential role in cardiac excitation–contraction coupling. Altered RYR2 expression has been associated with sudden cardiac death (SCD). However, RYR2 distribution in post-mortem heart tissue remains limited. This study aimed to characterise the distribution and relative abundance of RYR2 in Malaysian post-mortem cardiac specimens.

Methods: Cardiac tissues (n = 5) were obtained from the Department of Forensic Pathology, UiTM Hospital Al-Sultan Abdullah (HASA), encompassing cases of SCD and non-SCD (e.g., motor vehicle accidents). Formalin-fixed, paraffin-embedded sections were examined using hematoxylin and eosin (H&E) staining for histomorphological assessment. Immunohistochemistry (IHC) was done to determine RYR2 expression. Digital micrographs were analysed using ImageJ software to quantify the RYR2 immunopositive area as a percentage of the total myocardial tissue area.

Results: Histological analysis demonstrated preserved myocardial architecture with no clear evidence of ischaemia in the analysed sections. RYR2 immunoreactivity was predominantly localised within the cytoplasm of cardiomyocytes, which is consistent with sarcoplasmic reticulum distribution. Quantitative analysis showed a mean RYR2-positive area of 2.84 ± 2.18%, with a median of 3.86% and a range of 0.30–4.37%, indicating relatively low overall tissue area positivity.

Conclusions: RYR2 is detectable in Malaysian post-mortem ventricular tissue with low overall percentage area expression by IHC. These findings provide an insight into RYR2 distribution in SCD cardiac tissues and may support future investigations into its role in arrhythmia-related cardiac pathology.

Keywords: Sudden cardiac death, Post-mortem cardiac tissue, Ventricular myocardium, Histopathology, Immunohistochemistry, RYR2

P20

The Potential Of Patient-Specific Multicellular Spheroids In Vascular Biology

Mei Shan Ong[a], Umamaheswari Muniasamy[a], Xiao Yun Linb, Hao Wu[b], Dorajoo Rajkumar[c] and Sorokin Vitaly[a,b]

[a]Department of Surgery, Yong Loo Lin School of Medicine, National University of Singapore, Singapore (10 Medical Dr, Singapore 117597)
[b]Department of Cardiac, Thoracic and Vascular Surgery, National University Hospital, National University Health System, Singapore (5 Lower Kent Ridge Rd, Singapore 119074)
[c]Genome Institute of Singapore, Agency for Science, Technology and Research (A*STAR), Singapore (60 Biopolis St, Singapore 138672)

ABSTRACT

Background: Three-dimensional (3D) culture has gradually gained importance in the field of cardiovascular research with its potential in precision medicine and disease modelling. In the most ideal scenario, the 3D system should mimic the disease pathophysiological features and microenvironment, which then enables its usage in functional and therapeutic studies.

Methods: In our study, we have generated multicellular spheroids using patient-derived vascular smooth muscle cells (VSMC), endothelial cells (EC) and Macrophage to investigate their potential in disease modelling and understanding vascular biology interactions.

Results: Our earlier data showed that 3D spheroids can recapitulate gene signatures identified in patients comparing low and high syntax score signatures, and in diabetic and non-diabetic conditions, indicating the potential of cells in 3D spheroids in retaining patient biological signals. To better understand these spheroids, we carried out scRNA-seq analysis and identified that patient-derived 3D spheroids generated from different patient-derived VSMC, with the same patient-derived macrophage and EC, exhibited differential 2D UMAP profile and VSMC phenotypic modulation pattern, indicative of specificity retained from original tissue. Moreover, different patient-derived 3D spheroids were also observed to have different degrees of responsiveness in inflammatory status with high cholesterol and colchicine treatment. Several proatherogenic and proinflammatory interactions including IL1, IL6 and CXCL signalling were identified in the microenvironment, suggesting the possibility of these spheroids in inflammation-driven disease modelling.

Conclusion: As patient-specific 3D spheroids can retain features of disease profile and patient-specificity, it could contribute to the study of disease progression in modelling cellular and metabolic changes and pharmacological prediction in a patient-specific manner.

Keywords: 3D multicellular spheroids, Vascular smooth muscle cell phenotypic modulation, Patient-derived model, Intercellular crosstalk, Cardiovascular disease modelling, Personalized medicine

P21

Antihypertensive Drugs for the Prevention of Heart Failure: A Drug Target Mendelian Randomization Study

Chenhao Ouyang[a], Jiawei Wang[b] and Xinyi Zhang[b]

[a]Department of Anesthesiology, the Second Affiliated Hospital of Nanchang University, Nanchang, China
[b]Department of Metabolism and Endocrinology, the Second Affiliated Hospital of Nanchang University, Nanchang, China

ABSTRACT

Background: Hypertension is a major risk factor for heart failure (HF), yet causal effects of antihypertensive drug classes on HF remain unclear. We aimed to evaluate the causal impact of 12 major drug classes on HF risk.

Methods: A two-sample Mendelian randomization (MR) analysis was performed to investigate 12 antihypertensive drug classes (adrenergic neuron blockers, alpha-adrenoceptor blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta-adrenoceptor blockers, calcium channel blockers, centrally acting agents, loop diuretics, potassium-sparing diuretics and mineralocorticoid receptor antagonists, renin inhibitors, thiazide and related diuretics, and vasodilators). Genetic proxies for pharmacological targets (DrugBank) were derived from GTEx eQTL data intersected with systolic blood pressure GWAS. HF's statistics were obtained from FinnGen. The inverse variance weighted method served as the primary estimate, complemented by sensitivity and Bayesian co-localization analyses.

Results: MR analyses indicated that a genetically predicted 10-mm Hg reduction in systolic blood pressure via calcium channel blockers (67 SNPs; OR, 0.9965; 95% CI, 0.9943–0.9988). Specifically, the KCNJ11 target was identified as a protective factor (4 SNPs; OR, 0.9906; 95% CI, 0.9848–0.9964). No statistically significant associations were observed for the remaining 11 drug classes or the combined analysis after Bonferroni correction. Findings were robust in sensitivity analyses. Bayesian colocalization did not support a shared causal variant for KCNJ11 (PP.H4 = 10.7%).

Conclusions: Genetic evidence supports a potential causal benefit of calcium channel blocker-related pathways in reducing HF risk. The lack of colocalization support for KCNJ11 necessitates cautious interpretation. Pathway-specific modulation may offer distinct advantages in HF prevention.

Keywords: Mendelian randomization, Antihypertensive drugs, Calcium channel blockers, Systolic blood pressure, Heart failure, KCNJ11 gene

P22

In Vivo Therapeutic Platform of Novel Engineered Structured RNA Molecules

Permeen Yusoff[a], Daniel Yim Guo Rong[a], Annadory Lavenniah[a], Erica M. Wee[b], Bhav Harshad Parikh[c], Xinyi Su[c] and Roger Foo SY[a]

[a]Cardiovascular Metabolic Disease Translational Research Programme, National University of Singapore
[b]Singapore 2AI Singapore NUS
[c]Institute of Molecular and Cell Biology (IMCB), Agency for Science, Technology and Research (A*STAR), Singapore

ABSTRACT

Background: RNA-based therapeutics is one of the most exciting frontiers in biopharma currently. New RNA targeting approaches breach the barrier of "undruggable" targets in the pharma sphere. This therapeutics market is projected to reach $25.12 billion by 2030, according to Allied Market Research. An RNA based platform addresses incurable diseases that include noncommunicable diseases (NCDs). Data from a WHO report shows cardiovascular diseases account for a large majority of NCD deaths, 17.9 million people annually, followed by cancer (9.3 million), chronic respiratory diseases (4.1 million), and diabetes (2.0 million including kidney disease deaths caused by diabetes).

Methods: We will describe a strategy to overcome the limitations of using unmodified sfRNA in our study by incorporating chemically modified nucleotides during in vitro transcription. Our RNA-based platform technology builds upon long iterative experimental experience and datasets, comprising of designed structured small RNA molecules, with defined physicochemical and physiological properties.

Results: Modified NTPs incorporated into sfRNA exert distinct functional affects that depend on the sfRNA's structure and sequence, particularly when targeting specific miRNAs. Among the modifications tested, combination of 5mCTP with Ψ-UTP or with Ψ-UTP are the most favourable for reducing immunogenicity while preserving functional activity.

Conclusions: Incorporating modified nucleotides during transcription can improve RNA performance, enhance RNA stability and reduce recognition by immune sensors. Modified sfRNA may reduce technical barriers in epithelial-mesenchymal transition (EMT) programme studies, this approach enhances mRNA therapeutics and can improve millions of patients' quality of life.

Keywords: RNA therapeutics, Modified nucleotides

P23

Integrated Hemodynamic and Structural Indices Define Diastolic Dysfunction in a Murine HFpEF Model

Po-Ju Lin[a], Theodore Steward[a,b], Shu-Chian Ruan[a], Patrick C.H Hsieh[a,b*]

[a]Division of Cardiovascular and Metabolic Diseases, Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan
[b]Taiwan International Graduate Program in Molecular Medicine, National Yang Ming Chiao Tung University and Academia Sinica, Taipei, Taiwan

ABSTRACT

Background: Heart failure with preserved ejection fraction (HFpEF) constitutes more than half of all heart failure cases and currently lacks targeted therapies. Preclinical models are critical for elucidating underlying mechanisms; however, diagnostic criteria frequently depend on limited echocardiographic surrogates. This study aimed to characterize a two-hit murine HFpEF model through integrated echocardiographic and invasive hemodynamic assessments.

Methods: A total of 188 male C57BL/6J mice were studied across 10 cohorts. Of these, 111 mice received a high-fat diet combined with L-NAME, while 77 mice were maintained on standard chow as controls. Transthoracic echocardiography was conducted at week 16, followed by invasive pressure–volume analysis at week 20. Echocardiographic parameters assessed included ejection fraction (EF), E/E′, isovolumic relaxation time (IVRT), and left atrial area. Invasive assessments measured relaxation, chamber stiffness, contractility, and ventricular–arterial coupling.

Results: Both groups maintained preserved EF, consistent with an HFpEF phenotype. Mice in the HFpEF group developed elevated filling pressures, as indicated by increased E/E′, and exhibited left atrial enlargement, supporting structural evidence of chronic diastolic burden. No significant difference in IVRT was observed between groups, highlighting the necessity for multiparametric evaluation. To further support these findings, invasive hemodynamic assessment showed marked diastolic dysfunction in HFpEF mice. This was evidenced by reduced active relaxation (prolonged Tau) and increased ventricular stiffness (steeper EDPVR). Additionally, HFpEF mice exhibited greater energetic demand (steeper PVA–EDV slope) and increased PRSW, indicating a compensatory yet inefficient augmentation of systolic performance in response to impaired ventricular–arterial coupling

Conclusions: The two-hit murine HFpEF model replicates key features of human disease, including preserved EF, diastolic dysfunction, atrial remodeling, and maladaptive energetic responses. These results underscore the value of integrating structural and hemodynamic indices for rigorous phenotyping in preclinical HFpEF investigation.

P24

Inflammatory Crosstalk between Periodontitis and Atherosclerotic Cardiovascular Disease: A Network-Based Transcriptomic Analysis

Rahayu Zulkapli[a], Adriana Hamiera Zainol Anuar[b], Muhammad Nazirul Mubin Aziz[c], and Mohd Yusmiaidil Putera Mohd Yusof[d]

[a]Faculty of Dentistry, UiTM Sungai Buloh Campus, Selangor, Malaysia.
[b]Cardiovascular Advancement and Research Excellence Institute (CARE Institute), Universiti Teknologi MARA, Selangor, Malaysia.
[c]Faculty of Dentistry, AIMST University, Kedah, Malaysia

ABSTRACT

Background: Periodontitis and atherosclerotic cardiovascular disease are chronic inflammatory disorders with a consistent epidemiological association. However, the shared molecular drivers underlying this relationship remain incompletely understood. This study aimed to identify common hub genes and signaling pathways that mechanistically connect periodontitis and coronary artery disease.

Methods: Thirty-two consensus hub genes common to both conditions were analyzed using STRING (version 12.0) to construct a protein–protein interaction network. Functional enrichment analyses were performed to determine significantly associated biological processes and signaling pathways.

Results: Functional enrichment revealed significant involvement in leukocyte migration, cytokine–cytokine receptor interaction, and chemokine signaling. KEGG analysis demonstrated strong enrichment in NF-κB, TNF, and NOD-like receptor signaling pathways (false discovery rate = 8.1×10^{-12}). The protein–protein interaction network showed high connectivity ($p < 1.0 \times 10^{-16}$), suggesting robust molecular interaction among shared genes. Key inflammatory mediators identified included IL1B, IL6, TNF, ICAM1, ITGAM, LCK, and HCK, with NF-κB signaling emerging as a central regulatory node integrating periodontal bacterial challenge with vascular inflammation.

Conclusions: The LPS–TLR/NOD–NF-κB–TNF axis represents a critical mechanistic bridge between periodontal infection and atherosclerotic vascular injury, highlighting potential transcriptomic biomarkers and therapeutic targets for integrated cardio-periodontal management.

Keywords: Periodontitis, Atherosclerotic cardiovascular disease, Coronary artery disease, Transcriptomic studies, RNA-seq, Differential expression genes

P25

Determinants of Ischaemic Heart Disease Among Patients with Type 2 Diabetes Mellitus: A Registry-Based Analysis from Johor, Malaysia

Muhammad Muzzammil Mohamad Salleh[a], Sazzli Shahlan Kasim[b], Tajul Rosli Razak[c], Nazar Mohd Azahar[d], Norzaher Ismail[e], Mohamad Zuhair Mohamed Yusoff[a], Muhammad Hariz 'Ammar Khebir[a], Muhammad Muaz Shahriman Teruna[a], Nur Adilla Che Rameli[a], Muhammad Irfan Mohd Sallehhuddin[a], Muhammad Syazni Mohamad Asraff[a], Mohamad Rodi Isa[a*]

[a]Department of Public Health, Faculty of Medicine, Universiti Teknologi MARA, 47000 Sungai Buloh, Selangor, Malaysia
[b]Cardiovascular Advancement and Research Excellence Institute (CARE Institute), Universiti Teknologi MARA, 47000 Sungai Buloh, Selangor, Malaysia
[c]Faculty of Computer and Mathematical Sciences, Universiti Teknologi MARA, 40450 Shah Alam, Selangor, Malaysia
[d]Department of Medical Laboratory Technology, Faculty of Health Sciences, Universiti Teknologi MARA (UiTM) Cawangan Pulau Pinang, Kampus Bertam, 13200 Kepala Batas, Pulau Pinang, Malaysia
[e]Johor State Health Department, Jalan Persiaran Permai, Kempas Baru, 81200 Johor Bahru, Johor

ABSTRACT

Background: Ischaemic heart disease (IHD) remains a major cardiovascular complication among individuals with type 2 diabetes mellitus (T2DM). Local data describing its determinants and predictive performance are still limited. This study aimed to determine the prevalence, associated factors, and model discrimination for IHD among T2DM patients in Johor.

Methods: A cross-sectional analysis was conducted using secondary data from 11,082 T2DM patients in the National Diabetes Registry (2019–2021). Multivariable logistic regression identified independent predictors, and model discrimination was assessed using receiver operating characteristic (ROC) analysis.

Results: IHD prevalence was 10.4%. Independent predictors included age ≥60 years (aOR 1.57), male sex (aOR 1.46), Chinese ethnicity (aOR 1.60), hypertension (aOR 1.86), dyslipidaemia (aOR 1.47), longer diabetes duration (5–10 years: aOR 1.22 and >10 years: aOR 1.35), and diabetic retinopathy (aOR 1.52). Higher odds were also observed in patients not receiving calcium channel blockers (aOR 1.52) and those prescribed glitazones (aOR 10.46). The model showed good discrimination (Area under ROC (AUROC) of 0.797 with $p<0.001$).

Conclusions: IHD among T2DM patients is driven by multiple demographic and clinical factors. The model showed good discriminatory ability, supporting its potential utility for cardiovascular risk stratification in Malaysian primary care settings.

Keywords: Diabetes mellitus, Myocardial ischaemia, Risk factors, Registries, Logistic models, Malaysia.

P27

Inflammation Mediates Sex-Specific Associations between Insulin Resistance and Cardiovascular Reactivity: the MIDUS Cohort

Xiao Liu[a,b], Sitong Chen[c], Lihan Zhu[d], Yinhua Zhang[d,e]

[a]Department of Cardiology, Sun Yat-sen Memorial Hospital of Sun Yat-sen University, Guangzhou, China
[b]Cardiovascular and Metabolic Disorders Program, Duke-National University of Singapore Medical School, Singapore, Singapore
[c]Department of Endocrinology and Metabolism, the Second Affiliated Hospital, Jiangxi Medical College, Nanchang University, Nanchang, Jiangxi, China
[d]Department of Physiology & Biomedical Sciences, Ischemic/Hypoxic Disease Institute, Seoul National University College of Medicine, Seoul, Republic of Korea
[e]Yanbian University Hospital, Yanji, China

ABSTRACT

Background: The triglyceride-glucose (TyG) index is a marker of insulin resistance linked to cardiovascular disease, but its physiological role in cardiovascular reactivity (CVR) and potential sex differences remains unclear.

Methods: CVR was assessed by the reactivity of systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) in Midlife in the United States cohort. TyG index was calculated as ln [fasting triglycerides × fasting glucose /2]. Mediation analyses evaluated inflammatory pathways, and machine learning models assessed diagnostic performance.

Results: Among 1,009 participants (mean age: 53 years; 44% female), the TyG index demonstrated an inverted U-shaped association with lower odds of SBP reactivity (T1&T3: OR < 0.71, P < 0.05) and an inverse linear relationship with HR reactivity (T1: OR = 1.64, P < 0.001; T3: OR = 0.90, P = 0.569). No significant association was found for DBP reactivity (T1&T3: OR > 0.89, P > 0.449). Sex-stratified analyses highlighted distinct patterns that the inverted U-shaped TyG-SBP association was specific to women, whereas the inverse TyG-HR relationship was observed in both sexes. Furthermore, mediation analyses indicated sex-dependent pathways, with fibrinogen (8.05%) driving the association in men and E-selectin (15.64%) in women. Finally, machine learning models predicting SBP, DBP, and HR reactivity achieved area under the AUCs of 0.692, 0.662, and 0.611, respectively.

Conclusion: The TyG index is linked to autonomic stress responses with sex-specific differences, indicating insulin resistance increases cardiovascular risk through the stress responses dysregulation, particularly in women.

Keywords: Triglyceride-glucose index, Sex difference, Insulin resistance, Cardiovascular reactivity, Machine learning

P28

Interrogating Cell-to-Cell Interactions under Cardiometabolic Stress Conditions through Human PSC-derived Heart Organoid

Yuanhe Ma[a], Wei Qiang Seow[a], and Roger Foo[a,b]

[a]Cardiovascular Metabolic Disease Translational Research Programme, NUS Yong Loo Lin School of Medicine, Singapore
[b]Institute of Molecular Cell Biology (IMCB), A*STAR, Singapore

ABSTRACT

Background: Heart failure with preserved ejection fraction (HFpEF) is one of the major challenges in cardiovascular medicine today. The progression of HFpEF is a dynamic process involving interactions between multiple cardiac cell types, such as cardiomyocytes (CMs), endothelial cells (ECs), fibroblasts, and immune cells. However, the contribution of intra- and inter-cell-type interactions to disease progression remains underexplored. 3D cardiac organoids have emerged as a powerful tool to study cell-to-cell interactions (CTI) in disease models. We generate 3-cell-type cardiac organoids (3CT) from a cardiovascular disease-risk cohort (n=120), integrate quantitative trait locus (QTL) mapping with GWAS colocalization and clinical traits to identify the genetic architecture and drivers for metabolic stress-driven cardiac disease.

Methods: We generate human pluripotent stem cell (hPSC)-derived heart organoids comprising three cell types: CMs, ECs and fibroblasts. In separate experimental groups, individual cell-types are pre-conditioned in a high metabolic stress environment (high glucose, high insulin and other stress factors) before organoid assembly, while other cell types remain unstressed. Thereafter, CMs are isolated from organoids and bulk RNA sequencing was performed to assess for transcriptomic changes induced by metabolically stressed non-cardiomyocytes.

Results: Metabolically stressed ECs and fibroblasts are able to induce disease phenotypes in CMs that recapitulate key clinical features of HF with preserved ejection fraction (HFpEF), such as oxidative stress and pro-inflammatory responses.

Conclusions: Our three cell types hPSC-derived heart organoid model provides a platform to interrogate how stressed cell types affect CMs. This approach is expected to yield insights on CTI under cardiometabolic stress and the progression of CVD.

Keywords: HFpEF, Cell-to-cell interactions, Cardiac organoid, Cardiometabolic stress, Cell village, Cardiomyocyte genetics

P29

Early Glucocorticoid Use and Mortality in Acute Myocardial Infarction without Revascularization: A Multicenter Cohort Study using Machine Learning-Based Early Severity Stratification

Xin Yi[a,c], Weijing Sun[b], Razif Abas[c], Raja Abdul Wafy Raja Muhammad Rooshdi[a], Jie Yan[b], Chongshuang Yang[e], Canzhang Liu[b] and Ummi Nadira Daut[a*]

[a]Department of Internal Medicine, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400, Serdang, Selangor, Malaysia
[b]Department of Nursing, Faculty of Medicine and Health Sciences, University Putra Malaysia, 43400, Serdang, Selangor, Malaysia.
[c]Department 1 of Cardiovasology, North China University of Science and Technology Affiliated Hospital, 063000, Tangshan City, Hebei Province, China
[d]Department of Human Anatomy, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400, Serdang, Selangor, Malaysia
[e]Department of Radiology, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia,43400 UPM Serdang, Selangor, Malaysia

ABSTRACT

Background: Acute myocardial infarction (AMI) remains highly lethal among critically ill patients who do not undergo coronary revascularization. Glucocorticoids (GCs) are frequently administered early in intensive care unit (ICU) for their anti-inflammatory and hemodynamic effects, yet their benefit in this population is uncertain. Whether the association between early GC use and mortality varies by organ failure severity remains unclear.

Methods: We conducted a multicenter retrospective cohort study using MIMIC-IV database with external validation in the eICU Collaborative Research Database. Critically ill AMI patients without revascularization were included. Early GC exposure was defined as administration within 24 hours of ICU admission. Patients were stratified by observed maximum Sequential Organ Failure Assessment (SOFA) scores and by machine learning (ML) model predicting severe organ failure risk at admission. Mortality was evaluated using Kaplan–Meier analysis and multivariable Cox regression.

Results: Among 3,159 patients in MIMIC-IV, early GC use was not associated with in-hospital mortality but was linked to increased 28-day, 90-day, and 1-year mortality. Effect heterogeneity was evident: excess long-term mortality was confined to patients with lower organ failure severity, defined by either maximum SOFA or low-risk ML predictions. In low-risk patients, early GC use was associated with more than twofold increase in long-term mortality, whereas no significant association was observed in high-severity patients. Findings were consistent in validation cohort.

Conclusions: Early GC use is associated with increased long-term mortality in non-revascularized critically ill AMI patients, particularly those with relatively preserved organ function. ML-based early risk stratification may support more individualized treatment decisions.

Keywords: Acute myocardial infarction, Intensive care unit, Percutaneous coronary intervention, Machine learning, In-hospital mortality, Glucocorticoids

P30

Synergistic Impact of the Novel TyG-Sarcopenia Index on Cardiovascular and All-Cause Mortality: A Prospective Cohort Study and Machine Learning

Jiang Cheng[a], Zeqian Mei[b], Jing Zhang[a], Peng Yu[c], and **Xiao Liu**[d,e]

[a]Department of Anesthesiology, the Second Affiliated Hospital of Nanchang University, Nanchang, China
[b]Department of Plastic Surgery, The Second Affiliated Hospital of Dalian Medical University, Dalian, Liaoning Province, China
[c]Department of Anesthesiology, the Second Affiliated Hospital of Nanchang University, Nanchang, China
[d]Department of Cardiology, Sun Yat-sen Memorial Hospital of Sun Yat-sen University, Guangzhou, China
[e]Cardiovascular and Metabolic Disorders Program, Duke-National University of Singapore Medical School, Singapore, Singapore

ABSTRACT

Background: The triglyceride-glucose (TyG) index is a recognized surrogate marker of insulin resistance, while sarcopenia, characterized by loss of skeletal muscle mass, is an independent risk factor for adverse cardiovascular outcomes. However, prognostic value of a mathematically integrated metric capturing the synergistic burden of both conditions remains unclear.

Methods: This prospective cohort study included 14,314 adults from the National Health and Nutrition Examination Survey (1999-2006, 2011-2018). TyG-Sarcopenia index was constructed by integrating TyG index with the reciprocal of appendicular lean mass-to-body mass index ratio. Mortality outcomes were tracked through linkage with National Death Index records until December 31, 2019. Weighted Cox models, restricted cubic splines, mediation analysis, and machine learning algorithms were employed for analysis.

Results: Over a median follow-up of 133.7 months, the highest index tertile was associated with a 1.98-fold increased risk of cardiovascular mortality (HR 1.984, 95% CI 1.194-3.298) and a 1.71-fold increased risk of all-cause mortality (HR 1.706, 95% CI 1.343-2.167), showing a J-shaped relationship. Mediation analysis indicated that C-reactive protein (18.8%) and neutrophils (16.6%) were significant mediators. Machine learning validation demonstrated the index's superior predictive performance (AUC 0.886) and identified it as a top modifiable risk factor.

Conclusions: The novel TyG-Sarcopenia index is a strong, independent predictor of cardiovascular and all-cause mortality, reflecting synergistic risk of insulin resistance and muscle depletion. It offers incremental value for risk stratification and holds promise as a practical tool for identifying high-risk individuals in clinical practice.

Keywords: TyG index, Sarcopenia, Cardiovascular mortality, Machine learning, National health and nutrition examination survey, Insulin resistance

P31

Schwarzinicine A Attenuates Vasoconstriction and Lowers Blood Pressure in Spontaneously Hypertensive Rats via TRPC3/6 Modulation

Shobana Kumar[a], Kayatri Govindaraju[b] and Baharudin Ibrahim[c]

[a]Department of Pharmaceutical Life Sciences, Faculty of Pharmacy, Universiti Malaya, Kuala Lumpur, Malaysia
[b]Department of Pharmaceutical Life Sciences, Faculty of Pharmacy, Universiti Malaya, Kuala Lumpur, Malaysia
[c]Department of Clinical Pharmacy and Pharmacy Practice, Faculty of Pharmacy, Universiti Malaya, Kuala Lumpur, Malaysia

ABSTRACT

Background: Resistant hypertension remains inadequately controlled despite multi-drug therapy. Transient receptor potential canonical (TRPC) 3 and 6 channels regulate vascular calcium influx and contribute to enhanced vasoconstriction. Schwarzinicine A (Sch A), a phenylethylamine alkaloid, has demonstrated in vitro TRPC3/6 inhibition; however, its in vivo safety and antihypertensive effects remain uncharacterised.

Methods: Acute oral toxicity was evaluated in Sprague Dawley rats following OECD 425 guidelines. Antihypertensive efficacy was assessed in spontaneously hypertensive rats (SHR) treated with Sch A (10 or 30 mg/kg, intraperitoneal) for 10 days. Systolic blood pressure was measured using tail-cuff plethysmography. Vascular reactivity was examined in isolated thoracic aortic rings using cumulative concentration–response curves to phenylephrine (PE) and carbachol (CCh).

Results: Sch A exhibited a favourable acute safety profile, with no mortality observed at doses up to 2000 mg/kg. In SHR, Sch A significantly reduced systolic blood pressure, with the 30 mg/kg dose demonstrating the greatest effect. Ex vivo studies revealed dose-dependent attenuation of PE-induced vasoconstriction without abolishing maximal contractile capacity. Endothelium-dependent relaxation to CCh was preserved and showed a tendency toward enhancement.

Conclusions: Sch A lowers blood pressure and modulates vascular reactivity in SHR while maintaining endothelial function. These findings support TRPC3/6 inhibition as a promising mechanism-based strategy for resistant hypertension and justify further mechanistic investigation.

Keywords: Schwarzinicine A, TRPC3/6 channels, Resistant hypertension, Spontaneously hypertensive rats, Vascular reactivity, Calcium signalling

P32

MOTS-c and its Relationship with Physical Activity, VO2 max and Muscle Mass in Adolescents

Nellysha Namela Muhammad Abdul Kadar[a,b], Zainal Arifin[a], Kistina Mohamed[b], Eileen Wong[a], Mohd. Faizal bin Madrim[c] and Dayang Maryama Awang Daud[b,c*]

[a]Health Through Exercise and Active Living (HEAL) Research Unit, Faculty of Medicine and Health Sciences, Universiti Malaysia Sabah, Kota Kinabalu, 88400, Sabah, Malaysia.Department of Biomedical Sciences, Faculty of Medicine and Health Sciences, Universiti Malaysia Sabah, Kota Kinabalu, 88400, Sabah, Malaysia.
[b]Department of Biomedical Sciences, Faculty of Medicine and Health Sciences, Universiti Malaysia Sabah, Kota Kinabalu, 88400, Sabah, Malaysia.
[c]Department of Public Health, Faculty of Medicine and Health Sciences, Universiti Malaysia Sabah, Kota Kinabalu, 88400, Sabah, Malaysia.

ABSTRACT

Background: Mitochondrial open reading frame of the 12S rRNA-c (MOTS-c), is a mitochondrial derived peptide (MDP) that has been researched to have promising effect on athletic performance. Evidence suggests that MOTS-c influences energy homeostasis and mitochondrial function which are critical for exercise capacity. This study aims to explore the connection between athleticism, cardiorespiratory fitness, physical activeness and muscle mass with circulating MOTS-c level at rest.

Methods: Data were collected from 117 teens (16.2 ± o.6 years old) comprising athletes (n=79) and non-athletes (n=38). Seurm MOTS-c level at rest, estimated VO2 max (ml/kg/min), muscle mass (kg) and physical activity scores were taken. Results of MOTS-c, VO2 max and muscle mass were compared according to participants athlete status and physical activity score.

Results: Independent t-tests showed athletes had lower resting MOTS-c level compared to non-athletes ($p<0.05$). In this cohort, athletes showed significantly higher VO2 max compared to non-athletes ($p<0.01$). Muscle mass showed no significant difference between the athlete and non-athlete groups. One-way ANOVA showed significant difference in VO2 max between IPAQ groups ($p<0.01$). However, no significant difference was found between physical activity groups for MOTS-c level and muscle mass difference. Multiple regression analysis showed significant results ($p<0.05$) with muscle mass contributing significantly to the model.

Conclusions: This study suggests that athletes and those with moderate and high physical activity scores have significantly lower serum MOTS-c levels compared to non-athletes and low physical activity scored individuals.

Keywords: Mitochondrial derived peptide, Teens, Athletes, Physical activity, Muscle mass, VO2 max

P33

Explainable Machine Learning for Post-PCI Mortality Risk Stratification in a Hospital-Based Cardiovascular Cohort

Johannes Dedi Kanchau[a], Nur Auni Khaliesa Khairuddin[a,b], Nashuha Omar[a], Norhasmira Mohammad[c], Suraya Abdul Razak[a], Sazzli Shahlan Kasim[a]

[a]Cardiovascular Advancement and Research Excellence Institute (CARE Institute), Universiti Teknologi MARA, Selangor, Malaysia.
[b]Faculty Defence Science and Technology, Universiti Pertahanan Nasional Malaysia, Kem Sungai Besi, 57000 Kuala Lumpur, Malaysia.
[c]Faculty of Cognitive Sciences and Human Development, University of Malaysia Sarawak (UNIMAS)

ABSTRACT

Background: Accurate risk stratification following percutaneous coronary intervention (PCI) remains central to improving cardiovascular outcomes. Although machine learning (ML) models show promise in mortality prediction, concerns regarding data leakage, extreme class imbalance, and limited interpretability hinder clinical adoption. We aimed to develop a leakage-controlled, explainable ML framework for post-PCI mortality prediction using hospital-based real-world cardiovascular data.

Methods: A retrospective hospital PCI cohort (n = 2,859) was curated following deduplication and structured preprocessing. Leakage-prone features were explicitly excluded prior to model development. The dataset was stratified into (70/30) of training (n = 2,001) and testing (n = 858) sets, preserving the observed mortality rate (~1.5%). Missing data across 19 numerical variables were imputed using both median and Multiple Imputation by Chained Equations (MICE). Severe class imbalance was addressed using Synthetic Minority Over-sampling Technique (SMOTE). Recursive Feature Elimination reduced 138 candidate predictors to 15 key features. Five machine learning models (Logistic Regression, Support Vector Machine, Random Forest, Decision Tree, and Neural Network) were trained with hyperparameter tuning using 5-fold cross-validation. Model interpretability was assessed using SHAP (SHapley Additive exPlanations).

Results: Across all preprocessing pipelines, models demonstrated excellent discrimination, with Random Forest and Neural Network models achieving near-perfect performance (Accuracy, F1-score, ROC-AUC ≈ 1.00) on the independent test set, despite removal of leakage features. SHAP analysis consistently identified cardiovascular pharmacotherapy variables as dominant predictors of mortality risk, particularly: mACE (ACE inhibitors, mBB (Beta-blockers, mClopid (Clopidogrel and mStatin (Statins). These medication-related variables exhibited the highest contribution to model output across both ensemble and neural network architectures.

Conclusions: In a hospital-based PCI cohort, leakage-controlled explainable machine learning achieved robust post-PCI mortality prediction using a compact set of clinically meaningful predictors. Cardiovascular pharmacotherapy emerged as a dominant risk signal, underscoring the prognostic importance of guideline-directed therapy. External validation is warranted to confirm generalizability. This study highlights the translational potential of explainable artificial intelligence in advancing cardiovascular risk stratification.

Keywords: Percutaneous coronary intervention, Machine learning, Cardiovascular risk prediction, Explainable artificial intelligence, SHAP, Mortality prediction, Real-world data, Pharmacotherapy, Risk stratification

P34

Characterising the Role of DNAJC18

Vicky Lai[a], Mick Lee[a], Rijan Gurung[a], Francesco Rubero[a], Matias Autio, Shu Ye[a], Alexander Bershadsky[b] and Roger SY Foo[a]

[a]Cardiovascular Research Institute, National University of Singapore, Singapore
[b]Mechanobiology Institute, National University of Singapore, Singapore

ABSTRACT

Background: Genome-wide association studies have identified the DNAJC18 locus in dilated cardiomyopathy, yet its cardiovascular function remains unknown. DNAJC18 encodes a poorly characterized HSP40 family member enriched in endothelial cells and under stress. Given the central role of endothelial proteostasis in vascular remodelling and cardiac disease, we investigated the role of DNAJC18 in endothelial function.

Methods: CRISPR-Cas9 knockout and rescue models of DNAJC18 were generated in human induced pluripotent stem cell-derived endothelial cells. Angiogenic function was assessed using Matrigel network formation assays. Cytoskeletal architecture and focal adhesions were examined by immunofluorescence. Global transcriptional changes were analysed by RNA sequencing. Protein interaction networks were characterized by mass spectrometry. Protein abundance, phosphorylation, and ubiquitination were assessed by immunoblotting and immunoprecipitation under basal and proteasome-inhibited conditions.

Results: Loss of DNAJC18 significantly impaired endothelial network formation and disrupted actin cytoskeletal organization, accompanied by increased actomyosin contractility. Transcriptomic profiling revealed coordinated downregulation of angiogenic and cytoskeleton-associated gene programs, alongside activation of stress-related pathways. Proteomic analysis identified enrichment of cytoskeletal and stress granule-associated binding partners, suggesting altered protein quality control networks. DNAJC18 deficiency increased ubiquitinated protein accumulation under proteasome inhibition, consistent with impaired proteostasis control. Re-expression of DNAJC18 partially restored angiogenic capacity and cytoskeletal organization.

Conclusions: DNAJC18 maintains endothelial angiogenic capacity by preserving cytoskeletal homeostasis and suggests stabilizing Yes-associated protein signalling. These findings identify DNAJC18 as a previously unrecognized regulator of endothelial proteostasis and mechano-transduction with potential relevance to cardiovascular disease.

P35

Weight Loss and the Risk of Atrial Fibrillation: A Dose-Response Meta-Analysis from Longitudinal Studies with 178,003 Individuals

Xiao Liu[a,b], Zexuan Wang[c], Jinzhu Hu[d], Peng Yu[e] and Jing Zhang[f]

[a]Department of Cardiology, Sun Yat-sen Memorial Hospital of Sun Yat-sen University, Guangzhou, China
[b]Cardiovascular and Metabolic Disorders Program, Duke-National University of Singapore Medical School, Singapore, Singapore
[c]School of Basic Medical Sciences, Heilongjiang University of Chinese Medicine, Harbin, Heilongjiang Province, China
[d]Department of Cardiology, The Second Affiliated Hospital, Jiangxi Medical College, Nanchang University, Nanchang, China
[e]Department of Endocrinology and Metabolism, The Second Affiliated Hospital, Jiangxi Medical College, Nanchang University, Nanchang, China
[f]Xiangya School of Pharmaceutical Sciences, Central South University, Changsha, Hunan, China

ABSTRACT

Background: Obesity is a major risk factor for atrial fibrillation (AF). Although clinical guidelines recommend intentional weight loss for obese patients to reduce the risk of AF, the specific dose-response relationship and the preventative efficacy of different weight loss strategies in the general population remain unclear.

Methods: We conducted a dose-response meta-analysis of longitudinal studies searched from Cochrane Library, Embase, and PubMed up to October 1, 2025. Random effects models were used to pool estimate effects, and restricted cubic splines were employed to analyze the non-linear dose-response relationship between weight reduction and AF incidence.

Results: We included 11 cohorts (5 prospective and 6 retrospective) comprising 178,003 individuals. In the primary analysis, weight loss was not significantly associated with a reduced incidence of AF (hazard ratio [HR]: 0.80, 95% confidence interval [CI] 0.63-1.01, I2 = 85%). Similarly, a 5% reduction in body weight did not yield a statistically significant benefit (HR [95%CI] = 1.07 [0.86-1.35], I2 = 93%). However, subgroup analysis revealed that weight loss achieved through bariatric surgery was significantly associated with a lower risk of AF (HR [95%CI] = 0.72 [0.58-0.88], I2 = 86%). A potential inverse dose-response trend was observed in the fitting curve, though it did not reach statistical significance for nonlinearity (p = 0.70).

Conclusions: While general weight loss showed a non-significant trend toward risk reduction of AF, metabolic surgery was significantly associated with a lower incidence of atrial AF. This finding needs to be confirmed by large prospective studies.

P36

Association between Proton Pump Inhibitors and Myocardial Infarction: Insights from Real-World and Genetic Evidence

Xiaoyue Zhang[a], Peng Yu[a], Jing Zhang[b]

[a]Department of Endocrinology and Metabolism, The Second Affiliated Hospital, Jiangxi Medical College, Nanchang University, Nanchang, China
[b]Xiangya School of Pharmaceutical Sciences, Central South University, Changsha, Hunan, China

ABSTRACT

Background: Proton pump inhibitors (PPIs) are widely prescribed, yet the association between long-term PPI use and myocardial infarction (MI) remains debated. This study aimed to evaluate the causal relationship between PPI monotherapy and MI by integrating genetic analysis with real-world evidence.

Methods: We conducted a two-sample Mendelian randomization (MR) analysis using genome-wide association study data from the UK Biobank and FinnGen to assess the causal effects of five genetically proxied PPIs (esomeprazole, omeprazole, lansoprazole, pantoprazole and rabeprazole) on MI. Furthermore, we analyzed real-world observational data from the National Health and Nutrition Examination Survey 1999–2018 by employing weighted multivariable logistic regression models to examine associations between self-reported PPI use and MI.

Results: MR analysis indicated that genetically proxied omeprazole was significantly associated with a higher risk of MI (odds ratio [OR] = 4.20, 95% confidence interval [95% CI] = 1.87-9.43). Consistent with these findings, the real-world analysis of 30,493 adults revealed that overall PPI use was associated with increased odds of MI (OR [95% CI] = 1.48 [1.22-1.80]). Subgroup analysis confirmed this elevated risk specifically among omeprazole users (OR [95% CI] = 1.47 [1.13-1.93]), whereas other agents (esomeprazole, lansoprazole, pantoprazole, and rabeprazole) showed no significant association. The inverse probability of treatment weighting and propensity score matching showed results consistent with the primary analysis.

Conclusions: Both genetic and observational evidence link omeprazole therapy to a higher risk of MI in the general population. Further research is warranted to confirm the effects of long-term PPI use on MI risk.

Keywords: Proton pump inhibitors, Omeprazole, Myocardial infarction, Mendelian randomization, Real-world evidence, Cardiovascular risk

P37

Sex-Age Difference in the Global Burden of Underlying Causes, and Prediction Study of Heart Failure, 1990-2035

Jie Bai[a], Jiang Chen[a], Jing Zhang[b], Peng Yu[a] and Xiao Liu[a,c]

[a]Department of Endocrinology Medicine, the Second Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, China
[b]Department of Anesthesiology, the Second Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, China
[c]Cardiovascular & Metabolic Disorders Program, Duke-National University of Singapore Medical School, Singapore

ABSTRACT

Background: Heart failure (HF) presents a significant prevalence burden globally.

Methods: Extracting data from the Global Burden of Disease Study, we calculated the global prevalent case number and age-standardized prevalent rate (ASPR) of HF from 1990 to 2021. Examination of temporal patterns involved the determination of the average annual percentage change (AAPC) from 1990 to 2021.

Results: In 2021, global HF prevalent cases were 28,586,051 (95% uncertainty interval [UI] 25,341,999-32,821,121) in males and 26,911,782 (95% UI 23,711,028-30,981,333) in females, with ASPR of 760.78 per 100,000 population (95% UI 673.19-874.71) and 604.00 (95% UI 534.95-692.29), and AAPC of 0.15% (95% confidence interval [CI] 0.10-0.20%) and 0.18% (95% CI 0.15-0.2%) from 1990 to 2021. Prevalent cases increased with age after age 25, peaking at 65-89. The ASPR of HF also rose with age in both sexes, with steeper increases in the 60-64 and 80-84 age groups. Generally, the prevalent cases of both males and females showed an upward trend and the ASPR of males showed a slight downward trend, while that of females showed a slight upward trend. Middle sociodemographic index regions had the highest prevalent cases, while high sociodemographic index regions (especially high-income countries North America and Central Europe) had the highest ASPR. Ischemic and hypertensive heart diseases were the leading causes of HF in both sexes.

Conclusions: HF remains a major global health issue, with sex-, age-, regional and sociodemographic index-differences. Prevention and treatment of primary diseases like ischemic and hypertensive heart diseases are crucial for controlling HF prevalence burden.

Keywords: Heart failure, Global burden of disease, Age-standardized prevalence rate, Sex disparity, Temporal trend, Socio-demographic index

P38

In Vivo Vascular Protection by Lignosus Rhinocerus TM02®: ACE/Ang II/AT1R-NO Axis in SHR

Dharmani Devi Murugan[a], Yi En Wong[a], Muhammad Fazril Mohamad Razif[b], Ng Chyan Leong[c], Rafidah Ahmad[c], Szu Ting Ng[d], Chon Seng Tan[d], Shin Yee Fung[b]

[a]Department of Pharmacology, Faculty of Medicine, Universiti Malaya, 50603 Kuala Lumpur, Malaysia
[b]Medicinal Mushroom Research Group (MMRG), Department of Molecular Medicine, Faculty of Medicine, Universiti Malaya, 50603, Kuala Lumpur, Malaysia
[c]Institute of Systems Biology (INBIOSIS), Universiti Kebangsaan Malaysia, 43600 Bangi, Selangor, Malaysia
[d]LiGNO Biotech Sdn. Bhd, 43300, Balakong Jaya, Selangor, Malaysia

ABSTRACT

Background: Hypertension is associated with vascular dysfunction, partly via dysregulation of the renin–angiotensin (Ang) system, particularly angiotensin-converting enzyme (ACE) signaling. Lignosus rhinocerus, commonly referred to as Tiger Milk mushroom (TMM), shows anti-inflammatory, antioxidative and immunomodulatory properties. Recently, in silico and in vitro studies demonstrated that L. rhinocerus TM02® exhibited ACE inhibitory activity. However, its in vivo ACE inhibitory activity and systemic metabolite profile for vascular protection remain unexplored. This study investigated the effect of L. rhinocerus TM02® on ACE inhibition and Ang II signaling in spontaneously hypertensive rats (SHR).

Methods: SHR received oral Milli-Q® water (vehicle control), L. rhinocerus TM02® sclerotia (100 mg/kg and 300 mg/kg) and captopril (100 mg/kg) for 8 weeks. Vascular function was assessed via organ bath. Vascular ACE inhibition and Ang II signaling were measured by using fluorescence staining, biochemical kits, Western blot and histology.

Results: In vivo treatment with L. rhinocerus TM02® significantly reversed endothelial dysfunction in SHR, upregulated vascular nitric oxide (NO) bioavailability and release. It also inhibited vascular oxidative stress, inflammation, aortic ACE activity and AT1R protein expression and reduced vascular remodeling.

Conclusion: These findings demonstrate that L. rhinocerus TM02® sclerotia protects against hypertension-induced vascular dysfunction via ACE/Ang II/AT1R–NO axis modulation, resulting in reduced oxidative stress and inflammation.

Keywords: Angiotensin-converting enzyme, Endothelial dysfunction, L. rhinocerus TM02®, Oxidative stress, Nitric oxide, Vascular remodeling

P39

A Technical Experience of the Multi-Electrode Array for Electrophysiology and Pacing studies in Langendorff-Perfused Mouse Hearts

Wei-Wen Lim[1,2], Yu-Ning Liu[1], Loo Sze Jie[2], Sauri Hernandez-Resendiz[1], Derek J Hausenloy[1,2,3,4]

[1]Cardiovascular and Metabolic Disorders Program, Duke-National University of Singapore Medical School, Singapore
[2]National Heart Research Institute Singapore, National Heart Centre Singapore, Singapore.
[3]Yong Loo Lin School of Medicine, National University Singapore (NUS), Singapore 117597, Singapore
[4]The Hatter Cardiovascular Institute, University College London, London, UK

ABSTRACT

Background: Cardiac arrhythmias disrupt the heart's normal conduction leading to inefficient heart pumping, reduced organ perfusion and potentially life-threatening conditions. Atrial fibrillation (AF) is the most common arrhythmia representing a global health burden, whereas ventricular fibrillation is the most catastrophic and life-threatening arrhythmia. We established a platform for studying conduction properties in the isolated heart.

Methods: An electrical mapping platform (EMS128, MappingLab) was used to simultaneously record the left atrium (LA) and ventricle (LV) in the isolated heart. Adult C57BL/6J mouse hearts (6- to 8-month-old; n=11) were Langendorff-perfused with Krebs-Henseleit solution bubbled with 95% O2/5% CO2, with two penMEAs (64-ch, 8x8 grid; electrode diameter: 0.1mm, interelectrode distance: 0.22mm (LA) and 0.29mm (LV)). Pacing was delivered at twice the diastolic threshold to the right atrium. Sinus node recovery time (SNRT) was determined following a 15s pacing train (100ms cycle-length), and atrial effective refractory period (AERP) assessed via standard S1-S2 decremental protocol. In episodes of atrial and ventricular arrhythmias, we characterize the time-progression of irregular conduction.

Results: All analyses were conducted on EMapScope 5 (MappingLab). We report on normal readings (in mean±SEM) in mice: SNRT (294.3±33.14 ms), AERP (25.71±2.97 ms). Normal conduction velocities (CV) and heterogeneity index (CHI) in mice atria and ventricles were 0.639±0.044 vs. 0.875±0.093 m/s, and 1.93±0.11 vs. 2.12±0.30 respectively.

Conclusions: We established baseline electrophysiology characteristics in isolated mouse hearts. This technique allows for detailed electrical phenotyping for studying cardiac arrhythmias with future applications in genetic and acquired models and investigative therapies.

Keywords: Arrhythmia, Cardiac conduction, Isolated heart preparation, Epicardial mapping, Multi-electrode array, Mice

P40

Intensity-Dependent Myocardial Transcriptional Remodeling in Response to Aerobic Treadmill Training: Pro-Repair and Anti-Fibrotic Signatures

Putri Karisa[a], Shafira Sepriana[b], Nova Sylviana[c,d,e], Mas Rizky Anggun Adipurna Syamsunarno[c,d,e], Setiawan Setiawan[c,d,e]

[a]Doctoral Program in Medical Science, Faculty of Medicine, Universitas Padjadjaran, Bandung, West Java, Indonesia
[b]Master of Biomedical Science, Faculty of Medicine, Universitas Padjadjaran, Bandung, West Java, Indonesia
[c]Department of Biomedical Science, Faculty of Medicine, Universitas Padjadjaran, Bandung, West Java, Indonesia
[d]Physiology Division, Biology Activation Laboratory, Central Laboratory, Universitas Padjadjaran, Sumedang, Indonesia
[e]Cardiovascular and Metabolic Medicine Working Group, Faculty of Medicine, Universitas Padjadjaran, Sumedang, Indonesia

ABSTRACT

Background: Aerobic exercise is widely prescribed to induce beneficial cardiac adaptations. However, the optimal molecular "dose" of exercise intensity that maximizes favorable myocardial remodeling remains unclear. This study aimed to determine how varying levels of treadmill training intensity regulate cardiac repair and anti-fibrotic processes in the myocardium.

Methods: Male Wistar rats were randomized into four groups (n=5/group): sedentary, low-intensity (10 m/min), moderate-intensity (20 m/min), and high-intensity (30 m/min). Exercise intensity was prescribed relative to the lactate threshold. Rats were trained 30 minutes/day, 5 days/week for 8 weeks. Body weight and heart weight were recorded post-intervention to calculate the heart-to-body weight ratio. Left ventricular mRNA expression of FGF-1, FSTL-1, CITED4, Cyclin D1, CDK4, TGF-β, and p27 was quantified by qPCR and normalized to β-actin.

Results: Exercise elicited a robust, intensity-dependent transcriptional response in the myocardium. FGF-1 expression increased progressively with intensity ($p<0.01$). FSTL-1 and CITED4 were markedly upregulated at high intensity, indicating threshold-dependent activation ($p<0.05$). Anti-fibrotic signaling was evidenced by a gradual decrease in TGF-β expression with increasing intensity ($p<0.01$). The cell-cycle inhibitor p27 was reduced primarily at moderate to high intensities, while Cyclin D1 and CDK4 showed modest increases. Body weight differed between groups, whereas the heart-to-body weight ratio remained unchanged.

Conclusions: Aerobic training induces distinct intensity-dependent myocardial transcriptional programs: low intensity primes repair, moderate intensity consolidates anti-fibrotic and growth-permissive signaling, and high intensity activates key pro-repair pathways. These findings provide mechanistic insight into a molecular framework for precision exercise prescription.

Keywords: Aerobic exercise, Exercise intensity, Myocardial remodeling, Cardiac hypertrophy, Fibrosis, Gene expression

P41

Association and Metabolic Significance of Visfatin in Obese Patients with Acute Myocardial Infarction: A Cross-Sectional Study

Bima Diokta Alparisi[a,b], Sunita Sunita[b,c], Nova Sylviana[b,e], Mohammad Rizki Akbar[b,d], Mohammad Ghozali[b,e], Tri Hanggono Achmad[b,e], Mas Rizky A. A. Syamsunarno[b,e]

[a]Clinical Clerkship, RSUD Arifin Achmad, Faculty of Medicine Riau University, Pekanbaru, Indonesia
[b]Cardiometabolic Working Group Study, Faculty of Medicine Universitas Padjadjaran, Bandung, West Java, Indonesia
[c]Doctoral Program, Faculty of Medicine Universitas Padjadjaran, Bandung, West Java, Indonesia
[d]Department of Biomedical Sciences, Faculty of Medicine Universitas Padjadjaran, Bandung, West Java, Indonesia
[e]Department of Cardiology and Vascular Medicine, Hasan Sadikin General Hospital-Faculty of Medicine Universitas Padjadjaran, Bandung, West Java, Indonesia

ABSTRACT

Background: Obesity increases the risk of acute myocardial infarction (AMI) through adipose tissue dysfunction and inflammatory adipokines. Visfatin has emerged as a promising biomarker for cardiometabolic risk due to its association with visceral adiposity and lipid abnormalities. This study examined the diagnostic performance of visfatin in acute myocardial infarction patients according to body mass index (BMI) classification.

Methods: This cross-sectional study enrolled 80 patients with confirmed acute myocardial infarction at Hasan Sadikin Hospital, Indonesia, classified as normoweight (BMI 18.5–24.9 kg/m²) or obese (BMI ≥30.0 kg/m²). Serum visfatin levels were measured at the time of AMI presentation using ELISA and analyzed according to obesity status using regression, receiver operating characteristic (ROC), and correlation analyses.

Results: Among patients with acute myocardial infarction, visfatin showed a consistent and robust association with obesity. Median visfatin levels were higher in obese than in normoweight patients (0.150 vs 0.075 ng/mL), with a moderate effect size (0.27; 95%CI 0.03–0.47). Elevated visfatin was strongly associated with obesity (OR 18.6; 95%CI 2.59–235.0; p=0.011). Visfatin demonstrated moderate discrimination (AUC 0.654) but very high sensitivity (100%) with low specificity (33%). Visfatin correlated positively with LDL cholesterol across all AMI patients (r=0.246; p=0.028), with a stronger correlation in obese patients (r=0.410; p=0.009).

Conclusions: Elevated visfatin levels are strongly associated with obesity and adverse lipid profiles in AMI patients. Despite limited specificity, its high sensitivity and robust metabolic associations underscore visfatin's potential screening biomarker for obesity-related AMI risk.

Keywords: Acute myocardial infarction, Adipokines, Biomarker, Cardiometabolic risk, Obesity, Visfatin

P42

Dynamic Culture of Denuded Human Umbilical Artery Reveals Limited Intimal Hyperplasia and Transient MCP-1-Enhanced PBMC Recruitment

Siti Sarah Azman[a,b], Muhammad Dain Yazid[a,c], Nur Azurah Abdul Ghani[d], Nadiah Sulaiman[a,c]

[a]Department of Tissue Engineering and Regenerative Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia, Cheras, Kuala Lumpur 56000, Malaysia
[b]Faculty of Applied Sciences, Universiti Teknologi MARA, Perak Branch, Tapah Campus, Perak, Malaysia
[c]Cardiovascular and Pulmonary (CardioResp) Research Group, Universiti Kebangsaan Malaysia, 43600 Bangi, Selangor, Malaysia
[d]Department of Obstetrics and Gynaecology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Cheras, Malaysia.

ABSTRACT

Background: Endothelial denudation is a key-initiating event in vascular remodelling and intimal hyperplasia (IH), yet controlled human ex vivo models to study early repair responses remain limited. Adaptive vascular repair and maladaptive remodelling arise from similar injury signals, but their downstream outcomes diverge depending on the repair environment.

Methods: This study evaluated structural remodelling and peripheral blood mononuclear cells (PBMC) recruitment in an enzymatically denuded human umbilical artery (hUA) model under prolonged rocking culture. Denuded hUA segments were cultured under gentle rocking for 21 days and intima-media thickness and proliferation activity was assessed. To evaluate behaviour in a remodelled environment, PBMC adhesion assays were performed on day-14 vessels with and without monocyte chemoattractant protein-1 (MCP-1) supplementation (20 ng/mL).

Results: A modest but non-significant increase in intima-media thickness was observed between day 7 and day 14, followed by a plateau by day 21 in six denuded hUA samples, indicating adaptive remodelling without progressive IH. EdU incorporation demonstrated low and spatially restricted proliferative activity, supporting a limited hyperplastic response. PBMC attachment occurred under all conditions (n = 3 per group), confirming retained luminal permissiveness. MCP-1 supplementation significantly enhanced PBMC recruitment at 2 hours, but not at 8 or 24 hours, indicating a transient, early-phase recruitment effect.

Conclusions: These findings suggest that enzymatically denuded hUA under dynamic culture supports early remodelling without robust IH, while remaining permissive for circulating cell attachment. MCP-1 primarily enhances early PBMC adhesion, highlighting the importance of temporally regulated chemokine signalling. This model provides a controlled platform to investigate early recruitment dynamics and supports optimisation of MCP-1 timing or delivery as a potential strategy to enhance PBMC-mediated re-endothelialisation.

Keywords: Human umbilical artery (HUA), Re-endothelialisation, Vascular remodelling, Cell recruitment, MCP-1 (CCL2), Peripheral blood mononuclear cells (PBMC)

P43

Integrative Functional Assessment of TGF-β1-induced EndMT in Human Coronary Artery Endothelial Cells

Nur Ain Syahirah Ismadi[a], Ahmad Hafiz Murtadha[a], Muhammad Dain Yazid[a,b], Sarah J. George[c], Nadiah Sulaiman[a,b,c]

[a]Department of Tissue Engineering and Regenerative Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia, Jalan Yaacob Latif, Bandar Tun Razak, 56000 Cheras, Wilayah Persekutuan Kuala Lumpur, Malaysia.
[b]Cardiovascular and Pulmonary (CardioResp) Research Group, Universiti Kebangsaan Malaysia, 43600 Bangi, Selangor, Malaysia
[c]Translational Health Sciences, Bristol Medical School, Faculty of Health and Life Sciences, University of Bristol, Bristol BS2 8HW, United Kingdom

ABSTRACT

Background: Endothelial to mesenchymal transition (EndMT) plays an important role in vascular remodelling and endothelial dysfunction, during which endothelial cells lose their identity and acquire mesenchymal-like characteristics. Transforming growth factor-beta 1 (TGF-β1) is a major inducer of EndMT, but its effects on endothelial function and behaviour remain unclear.

Methods: Human coronary artery endothelial cells (HCAEC) were treated with 0, 20, and 50 ng/mL TGF-β1 for 72 hours. EndMT was evaluated using immunocytochemistry for endothelial markers (CD31, CD34, and von Willebrand factor) and mesenchymal markers (CD105, CD73, and CD90). Cellular behavioural and functional alterations were assessed using WST-1 and EdU assays (viability and proliferation), low-density lipoprotein (LDL) uptake, scratch wound migration, and tube formation assays.

Results: TGF-β1 treatment reduced endothelial marker expression, LDL update, and metabolic activity, while increasing mesenchymal marker expression; however, these changes were not statistically significant ($p > 0.05$, $n = 3$). Notably, TGF-β1 significantly enhanced cell viability and migratory ($p < 0.05$, $n = 3$), consistent with a shift toward a more motile mesenchymal-like phenotype.

Conclusions: These findings demonstrate that TGF-β1 robustly induces EndMT in HCAECs, resulting in pronounced phenotypic switching accompanied by functional remodelling.

Keywords: Endothelial to mesenchymal transition (EndMT), Transforming growth factor-beta 1 (TGF-β1), Human coronary artery endothelial cells (HCAEC), Endothelial dysfunction, Vascular remodelling, angiogenesis.

P44

Cardioprotective Potential of S-Allyl-L-Cysteine Against Myocardial Infarction via Activation of the Nrf2 Pathway in an Ovariectomized Rat Model

Muhamad Adib Abdul Ghani[a], Izatus Shima Taib[b], Kaisan Mohd Mahadi[c], Norliza Muhammad[d], Satirah Zainalabidin[a]

[a]Programme of Biomedical Sciences, Centre of Toxicology and Health Risk Study, Faculty of Health Sciences, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia
[b]Programme of Biomedical Science, School of Diagnostic and Applied Health Sciences, Faculty of Health Sciences, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia
[c]Centre for Drug Herbal and Development, Faculty of Pharmacy, Universiti Kebangsaan Malaysia, Jalan Raja Muda Abdul Aziz, Kuala Lumpur 50300, Malaysia
[d]Department of Pharmacology, Faculty of Medicine, Universiti Kebangsaan Malaysia Medical Centre, Cheras, Malaysia

ABSTRACT

Background: Menopause constitutes a fundamental risk factor for ischemic heart disease, as estrogen deficiency disrupts lipid and glucose metabolism, and promotes vascular dysfunction, which leads to eventual myocardial ischemic event. While percutaneous coronary intervention remains the gold standard for restoring blood flow to ischemic regions, reperfusion can paradoxically exacerbate tissue damage, resulting in Myocardial Ischemia-Reperfusion Injury (MIRI). Currently, no pharmacological intervention specifically targets MIRI. S-allyl-L-cysteine (SAC), a bioactive compound derived from aged garlic, is known as a potent antioxidant due to its ability to enhance endogenous antioxidant defences through activation of the Nrf2 pathway. This study evaluated SAC's pharmacological impact on IRI-induced myocardial infarction in ovariectomized (OVX) rats.

Methods: Thirty-two female Wistar rats were randomly divided into four groups: Sham, OVX-IR, OVX-IR-SAC, and OVX-IR-DL-Propargylglycine (PAG)-SAC. Bilateral ovariectomy was performed through a ventral incision. MIRI was induced by temporarily occluding the left anterior descending coronary artery for 30 minutes, followed by 2 hours of reperfusion. SAC (25 mg/kg) or PAG (50 mg/kg) was given intravenously through the right carotid artery at the onset of reperfusion.

Results: SAC significantly increased serum H_2S production and enhanced endogenous antioxidants, including glutathione and superoxide dismutase, through Nrf2 upregulation compared to OVX-IR. SAC treatment significantly reduced troponin-T levels and myocardial infarct size by modulating key inflammatory (TNF-α, IL-10, IL-6) and apoptotic (Caspase-3) markers, indicating a cardioprotective effect.

Conclusions: This study demonstrates that SAC, as a promising nutritional intervention, confers cardioprotection against MIRI in ovariectomized rats by boosting antioxidant defences through H_2S-mediated activation of the Nrf2 signaling pathway.

Keywords: S-Allyl-L-cysteine, Cardioprotection, Myocardial-ischemia reperfusion injury, Ischemic heart diseases, Ovariectomy, Nrf2

P45

From Blood to Beating Cardiomyocytes. A Human Platform for Cardiotoxicity and Regenerative Medicine.

Nurul Ain Nasim Mohd Yusof[a], Khairul Akmal Abdul Rahman[a], Tan Wee Nee[b], Ulfatul Khusna Samuri[a], Shaik Ahmad Kamal Shaik Fakiruddin[a], Nurrul Izzah Mohd Pauzi[a], Zulaiha Muda[b], Tan Jun Jie[c], Adiratna Mat Ripen[d], Yuslina Mat Yusoff[a]

[a]Hematology Unit, Cancer Research Centre, Institute for Medical Research, National Institutes of Health (NIH) Malaysia, Setia Alam, Shah Alam, Selangor, Malaysia
[b]Tunku Azizah Hospital, Jalan Pahang, Wilayah Persekutuan Kuala Lumpur, Malaysia
[c]Zhejiang Tianyuan Biotechnology Co., LTD., Ningbo, Zhejiang, China
[d]Cancer Research Centre, Institute for Medical Research, National Institutes of Health (NIH) Malaysia, Setia Alam, 40170 Shah Alam, Selangor, Malaysia

ABSTRACT

Background: Anthracycline-associated cardiotoxicity remains a significant contributor to long-term cardiovascular dysfunction in cancer survivors. Progress in understanding the cellular mechanisms underlying cardiomyocyte injury and regenerative responses has been limited by the lack of human-relevant cardiac models. Human induced pluripotent stem cell–derived cardiomyocytes (iPSC-CMs) provide a robust basic science platform to investigate patient-specific cardiac phenotypes and molecular pathways relevant to regenerative medicine.

Methods: Peripheral blood mononuclear cells were obtained using a minimally invasive approach and reprogrammed into iPSCs using non-integrating episomal vectors. iPSC lines were expanded under feeder-free conditions and differentiated into cardiomyocytes using chemically defined protocols. Pluripotency, genomic integrity, and cardiac lineage commitment were assessed.

Results: Stable patient-specific iPSC lines were successfully established and maintained, with pluripotent characteristics and preserved genomic integrity. Directed differentiation yielded iPSC-derived cardiomyocytes exhibiting spontaneous contractility. The workflow demonstrated reproducibility and scalability, supporting its suitability for mechanistic studies of cardiomyocyte injury, cellular stress responses, and regenerative capacity in a human cellular context.

Conclusions: This study establishes a scalable and minimally invasive iPSC-derived cardiomyocyte platform in Malaysia. This patient-in-a-dish model provides a strong foundation for basic science investigations into cardiotoxicity mechanisms and cardiac regeneration. Importantly, it enables population-specific cardiovascular research, contributing to the understanding of human cardiac biology within the Southeast Asian context.

Keywords: Cardiotoxicity, Induced Pluripotent Stem Cells, Cardiomyocytes, Disease Models, Regenerative Medicine

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Perfluorooctanesulfonic Acid (PFOS) Disrupts Adult Rat Ventricular Cardiomyocytes Structural Integrity and Calcium Efficiency

Noorul Izzati Hanafi[a], Nur Aqasyah Amran, Ammar Hariz Ahmad Razmy[a], Afiqq Aiman Abd Ghapor[a], Nur Zawani Mazlan[a], Noor Alicezah Mohd Kasih[a,b], Thuhairah Basrah Abdul Rahman[a,b] and Siti Hamimah Sheikh Abdul Kadir[a,c]

[a]Cardiovascular Advancement and Research Excellence Institute (CARE Institute), Universiti Teknologi MARA (UiTM) Sungai Buloh Campus, Jalan Hospital, 47000 Sungai Buloh, Selangor, Malaysia
[b]Hospital Al-Sultan Abdullah, Universiti Teknologi MARA (UiTM) Puncak Alam Campus, 42300 Puncak Alam, Selangor, Malaysia
[c]Department of Biochemistry and Molecular Medicine, Faculty of Medicine, Universiti Teknologi MARA (UiTM) Sungai Buloh Campus, Jalan Hospital, 47000 Sungai Buloh, Selangor, Malaysia

ABSTRACT

Background: Perfluorooctanesulfonic acid (PFOS) is a persistent organic pollutant and its exposure has been associated with cardiovascular diseases. However, its effect on cardiomyocyte structure and function remains unclear.

Methods: Adult rat ventricular cardiomyocytes were divided into 1.PFOS exposed 2.angiotensin II (pro-hypertrophic hormone) 3. Combined. Surface structural organization was assessed using scanning ion conductance microscopy (SICM). Calcium handling [calcium time to peak (TTP90), time to baseline (TTB90), normalized force (F/F_0)] and contractile function (sarcomere shortening, and contraction-relaxation kinetics) were evaluated with the Cytocypher® system.

Results: SICM showed disrupted cardiomyocyte surface architecture in PFOS exposure and the combined group compared to control. PFOS exposure significantly reduced calcium transient amplitude (F/F_0) compared with control (0.7407 ± 0.0297 vs 0.8021 ± 0.0297, $p = 0.0482$), indicating impaired calcium release. In contrast, calcium decay and recovery kinetics were not significantly altered by PFOS, unchanged calcium TTP90 ($p = 0.0667$) and calcium TTB90 ($p = 0.25$). Despite preserved calcium relaxation, PFOS significantly increased sarcomere shortening compared with control ($4.44 \pm 0.86\%$ vs $2.36 \pm 0.86\%$, $p = 0.0468$). For sarcomere relaxation dynamics, PFOS showed shortening sarcomere TTB90 relative to control ($p < 0.05$, compared to control), and the combined group showed markedly prolonged sarcomere TTP90 and TTB90 compared to other groups ($p < 0.0001$).

Conclusions: In conclusion, PFOS may disrupt excitation-contraction coupling predominantly through altered myofilament mechanics rather than impaired calcium reuptake.

Keywords: PFOS, SICM, CVDs, Cardiomyocytes, Structural integrity, Calcium deficiency

P47

Effect of Palm Oil Tocotrienols on Metabolic Syndrome: The Role of FXR in High-Fat Diet-Induced Male Rats

Qairunnisyah Mohd Noor[a,b], Effendi Ibrahim[b] and Siti Hamimah Sheikh Abdul Kadir[c,d]

[a]Institute of Medical Molecular Biotechnology (IMMB), Faculty of Medicine, Sungai Buloh Campus, Universiti Teknologi MARA, Jalan Hospital, 47000, Sungai Buloh, Selangor, Malaysia
[b]Department of Physiology, Faculty of Medicine, Sungai Buloh Campus, Universiti Teknologi MARA, Jalan Hospital, 47000, Sungai Buloh, Selangor, Malaysia
[c]Department of Biochemistry, Faculty of Medicine, Sungai Buloh Campus, Universiti Teknologi MARA, Jalan Hospital, 47000, Sungai Buloh, Selangor, Malaysia
[d]Cardiovascular Advancement and Research Excellence Institute (CARE Institute), Sungai Buloh Campus, Universiti Teknologi MARA, Jalan Hospital, 47000, Sungai Buloh, Selangor, Malaysia

ABSTRACT

Background: Tocotrienol-rich fraction (TRF) has been widely reported to attenuate components of metabolic syndrome in animal studies. The key bile acid receptor, farnesoid X receptor (fxr), has been shown to reduce cardiac injury in obese- and diabetic- cardiomyopathy animal models. Recently, our finding demonstrated that TRF supplementation upregulates cardiac fxr expression in high-fat diet (HFD)-fed mice Thus, here we aimed to determine whether the metabolic effects of TRF are mediated by fxr.

Methods: Male Sprague-Dawley rats were grouped into (n=5 per group), 1) age-matched. (control), 2) HFD + corn oil vehicle (HFD), 3) HFD + TRF (TRF), 4) HFD + TRF + z-gugglsterone (fxr inhibitor) and 5) HFD + z-guggulsterone. Body weight, waist circumference, and blood pressure were measured weekly for 12 weeks, while blood glucose levels were assessed at the end of 12 weeks intervention.

Results: Compared to the HFD group, TRF group showed significantly lower weight gain (54.15 ± 2.93% vs. 74.61 ± 3.54%, $p < 0.05$), waist circumference (26.97 ± 0.8247% vs. 46.84 ± 0.7123%, $p < 0.0001$) and blood glucose level (-15.24 ± 3.192% vs. 11.42 ± 1.979%, $p < 0.0001$). Meanwhile, in comparison to TRF group, fxr inhibitor group showed significantly higher weight gain (60.12 ± 3.785% vs. 54.15 ± 2.928%), waist circumference (38.55 ± 1.985% vs. 26.97 ± 0.8247%) and blood glucose level (-5.988 ± 1.246% vs. -15.24 ± 3.192%) with $p < 0.05$.

Conclusions: TRF ameliorates HFD-induced metabolic disturbances, however, fxr inhibition reduces its effect suggesting the involvement of fxr signaling.

Keywords: Tocotrienol-rich fraction, Farnesoid X receptor, Fxr signaling, High-fat diet, Metabolic syndrome, Metabolic dysfunction

P48

Protecting the Diabetic Heart from Acute Myocardial Ischemia-Reperfusion Injury to Prevent Heart Failure

Linh Chi Dam[a,b], Sze Jie Loo[a,b], Devika Menon[c], Gustavo E. Crespo-Avilan[a,b], Jianhong Ching[a], Shengjie Lu[a,b], Sonia Chothani[c], Wei-Wen Lim[a,b], Sauri Hernandez-Resendiz[a,b], Derek J. Hausenloy[a,b,d,e]

[a]Duke-NUS Medical School, Cardiovascular and Metabolic Disorders Programme, Singapore, Singapore
[b]National Heart Centre Singapore, National Heart Research Institute Singapore, Singapore, Singapore
[c]Genome Institute of Singapore, A*STAR, Singapore
[d]University College London, The Hatter Cardiovascular Institute, London, United Kingdom
[e]National University of Singapore, Yong Loo Lin School of Medicine, Singapore

ABSTRACT

Background: Acute myocardial infarction (AMI) and heart failure (HF) are more severe in obese, type 2 diabetic (T2D) patients. Mitochondrial abnormalities are hallmark of T2D myocardium, with Mitofusin-2 (Mfn2) playing central role. We demonstrated 45% decrease in cardiac Mfn2 in Western-diet mouse model of obese-T2D. Because ischemia-reperfusion (I/R) further lowers Mfn2, T2D heart with already reduced Mfn2 is predicted to be more vulnerable to mitochondrial damage and cell death. Our study aims to determine (1) cardiac basal role of Mfn2, (2) its response to T2D and I/R, (3) if pharmacological activation of Mfn2 confers cardioprotection in obese-T2D heart.

Methods: Cardiomyocyte-specific Mfn2 knockout (Myh6-Cre; Mfn2^fl/fl) mouse model (cKO Mfn2) was used to validate basal Mfn2 functions. Additionally, male C57BL/6J mice were fed Western diet or chow diet (control) for six weeks. Mice underwent LAD ischemia-reperfusion, with ECG, cardiac function, infarct size, molecular/omics analyses to assess Mfn2-related changes.

Results: cKO Mfn2 heart developed early hypertrophy, systolic dysfunction, mitochondrial fragmentation. Meanwhile, six-week Western-diet induced glucose intolerance, hyperglycaemia, obesity, preserved EF; 45% lower Mfn2 expression, 50% lower respiratory capacities. Transcriptomics indicated upregulated FA oxidation, disrupted TCA/glycolysis. Despite the remodelling, infarct size was similar in untreated Western-diet and control mice. Mfn2 activator CPR1-B was non-cytotoxic (1nM–10μM), but neutral for infarct size when dosed at reperfusion in control heart.

Conclusions: Evidences showed Mfn2 is critical determinant of cardiac and mitochondrial health. We hypothesize neutral effect of CPR1-B in control heart suggests Mfn2 activation may exert cardioprotection only under disease conditions where Mfn2 is suppressed (T2D).

Keywords: Mitochondria, Mitofusin-2, Ischemia-reperfusion injury, Obesity, Diabetes mellitus, Cardioprotection.

P49

Arterial Wall Tissue Gene Expression Identifies Distinct Coronary Artery Disease Pathogenesis Pathways Associated with Telomere Length Attritions

Zhi Chng Lau[a,b,c], Arshia Naaz[a], Umamaheswari Muniasamy[b], Xiao Yun Lim[d], Resham Lal Gurung[e,f], Gokce Oguz[a], Adaikalavan Ramasamy[a], Woon-Puay Koh[c,g], Vitaly A.Sorokin[b,d] and Rajkumar Dorajoo[a,h]

[a]Genome Institute of Singapore (GIS), Agency for Science, Technology and Research (A*STAR), 60 Biopolis Street, Genome, Singapore 138672, Singapore
[b]Department of Surgery, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[c]Healthy Longevity Translational Research Programme, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[d]Department of Cardiac, Thoracic and Vascular Surgery, National University Hospital, National University Health System, Singapore
[e]Clinical Research Unit, Khoo Teck Puat Hospital, Singapore
[f]Cardiovascular and Metabolic Disorders Signature Research Program, Duke-NUS Medical School, Singapore
[g]A*STAR Institute for Human Development and Potential (A*STAR IHDP), 30 Medical Drive, Brenner Centre for Molecular Medicine, Singapore 117609, Singapore
[h]Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore, Singapore 119228, Singapore

ABSTRACT

Background: Shortened telomere length (TL) in blood cells is an ageing biomarker and has been associated with atherosclerotic coronary artery disease (CAD). However, mechanistic pathways underlying TL attrition in arterial walls of patients with CAD remain unclear. We evaluated the association of arterial wall gene expression with TL in arterial walls and granulocytes from CAD patients.

Methods: TL was measured using quantitative polymerase chain reaction in blood granulocytes and matched arterial walls from 155 Chinese men with CAD. RNA sequencing was performed in 34 patients to profile the arterial wall transcriptome. These patients were dichotomized according to the median TL of either arterial walls or granulocytes, and differential gene expression was examined with respect to TL.

Results: No significant correlation was observed between TLs of arterial walls and granulocytes (R=0.107, p=0.19). We identified 10 significant differentially expressed genes (DEGs) associated with TL attrition in arterial walls (false discovery rate [FDR] < 0.045), including upregulation of ADRA2A (FDR=0.043), a gene encoding an adrenergic receptor implicated in vasoconstriction of atherosclerotic coronary arteries. Gene-set enrichment analysis also revealed positive enrichment of the vasoconstriction pathway (FDR=0.012) in association with TL attrition at the arterial wall. However, these 10 DEGs were not associated with TL attrition in granulocytes. Instead, TL attrition in granulocytes was linked to negative enrichment of ATP synthesis pathways, potentially reflecting mitochondrial dysfunction.

Conclusions: Our findings suggest that distinct pathway dysfunctions may underlie TL attrition in atherosclerotic arterial walls versus granulocytes, potentially contributing to CAD pathogenesis through different mechanisms.

Keywords: Telomere; Ageing; Gene Expression; mRNA sequencing; Coronary arteries; Coronary artery disease

P50

Salvianolic Acid A Targets Glutamic-Oxaloacetic Transaminase 2 to Ameliorate Doxorubicin-Induced Myocardial Oxidative Injury by Activating Malate-Aspartate NADH Shuttle

Yao-lei Ma[a], Xiao-wei Huo[a], Colin Wong[a], Feng-jie Zhou[a], Shan-ze Li[a], Han Zhang[a], **Wei Lei**[a]

[a]State Key Laboratory of Chinese Medicine Modernization, Tianjin University of Traditional Chinese Medicine, Tianjin 301617, China

ABSTRACT

Background: Although doxorubicin (DOX) is a highly efficient antineoplastic chemotherapeutic drug, it greatly increases the risk of heart damage. Salvianolic acid A (SAA), a water-soluble penolic acid, exerts various cardioprotective effects. In the current study, we aimed to evaluate the effects of SAA in protecting DOX-induced cardiotoxicity (DIC), and then to uncover its potential mechanisms.

Methods: We established DIC mice to evaluate the cardioprotective effects of SAA by pharmacodynamics, myocardial metabolomic and proteomics analysis. Multiple protein-small molecule interaction strategies including surface plasmon resonance, microscale thermophoresis and cellular thermal shift assay, combined with target depleted cell and animal models were applied for identifying potential targets of SAA. For clinical translation, we also investigated cardioprotective activities of SAA in DOX-treated Lewis lung carcinoma-bearing mice.

Results: SAA significantly alleviated cardiomyocyte apoptosis and oxidative damage, and improved echocardiographic parameters in DIC mice. In addition, multiple-omics analysis revealed that SAA preserved hearts by modulating l-Glutamic acid, l-Aspartic acid, citrate and isocitrate. GOT2 was identified as the target of SAA with a dissociation constant of 1.712 μM. SAA ameliorated DOX-induced mitochondrial injuries, which were validated in GOT2 knockdown H9C2 cells. In GOT2-depleted zebrafish, SAA did not display a protective effect against DIC, while in lewis lung carcinoma-bearing mice, SAA not only improved DIC, but also exerted combined anti-tumor effects with DOX.

Conclusion: SAA targets GOT2 to alleviate myocardial oxidative stress, thereby protecting against DIC. Our findings highlighted the therapeutic potential of activating GOT2 in mitigating DIC and the possibility of SAA and DOX-based combination therapy.

Keywords: Salvianolic acid A, Doxorubicin, Cardiotoxicity, Glutamic-oxaloacetic transaminase 2, Oxidative stress, Cardio-oncology

P51

Post-Mortem Whole Exome Sequencing Reveals Frequent ZNF717 Variants in Sudden Cardiac Death Cases

Afiqq Aiman Abd Ghapor[a], Ammar Hariz Ahmad Razmy[b], Nur Aqasyah Amran[b], Noorul Izzati Hanafi[b], Razuin Rahimi[b,c], Wan Mohammad Hafiz Wan Razali[c], Nur Raihan Che Mohd Roslan[c], Alyaa Rajih Mahmood Al-Khateeb[b,d], Chua Yung An[b,d] and Siti Hamimah Sheikh Abdul Kadir[b,d]

[a]Faculty of Health and Life Sciences, INTI International University, Nilai, Negeri Sembilan, Malaysia
[b]Cardiovascular Advancement and Research Excellence Institute (CARE Institute), Universiti Teknologi MARA (UiTM), Sungai Buloh, Selangor, Malaysia
[c]Department of Forensic Pathology, Hospital Al-Sultan Abdullah, Universiti Teknologi MARA (UiTM), Puncak Alam, Selangor, Malaysia.
[d]Department of Biochemistry and Molecular Medicine, Faculty of Medicine, Universiti Teknologi MARA (UiTM), Sungai Buloh, Selangor, Malaysia

ABSTRACT

Background: Sudden cardiac death (SCD) remains a major cause of unexpected mortality which often occurs without prior warning. Genetic predisposition is increasingly recognized as a key contributor when conventional autopsy results are inconclusive.This study aimed to identify possible genetic variants associated with SCD using post-mortem genomic analysis.

Methods: Six SCD post-mortem cases were included in this study; heart tissue was harvested during post-mortem investigations, followed by whole exome sequencing (WES) analysis. Annotation of gene variants was done using prediction tools such as ClinVar and VarSome.

Results: A total of 18 pathogenic variants (PV) were detected in all subjects. The detected variants were synonymous single-nucleotide variants (6/18, 33.3%), followed by nonsynonymous SNVs (5/18, 27.8%), stop-gain mutations (4/18, 22.2%), and frameshift insertions (3/18, 16.7%), indicating that single-nucleotide substitutions represent the predominant mutation type in this cohort. Among all PVs, zinc finger protein ZNF171 was detected in all 6 samples. ZNF171 encodes a Krüppel-associated box (KRAB– zinc-finger transcription factor, a class of proteins that generally bind DNA and repress gene expression. Although most ZNF171 showed synonymous mutation, there is a possibility it affects gene function by altering mRNA splicing, stability, or translational efficiency.

Conclusions: Post-mortem WESidentified multiple pathogenic variants across all SCD cases, highlighting the important contribution of genetic factors when autopsy findings are inconclusive. These findings underscore the value of genomic analysis in uncovering potential molecular contributors to sudden cardiac death and guiding future investigations into its underlying mechanisms.

Keywords: Sudden cardiac death, autopsy, whole exone sequencing, ZNF717, sudden unexplained death

P52

Association of Adipokines with Major Adverse Cardiovascular Events in Acute Myocardial Infarction: A Systematic Review and Meta-Analysis

Auda Nadira[a,b], Sunita Sunita[c], Bima Diokta Alparisi[b,d], Amanda Cheryl Fayza[b,e], Nur Syifa Rahmatika[a,b], Putri Karisa[b,f], Nova Sylviana[b,g], Mas Rizky A.A. Syamsunarno[b,g]

[a]Master Study Program of Biomedical Sciences, Faculty of Medicine Universitas Padjadjaran, Bandung, West Java, Indonesia
[b]Cardiometabolic Working Group Study, Faculty of Medicine Universitas Padjadjaran, Bandung, West Java, Indonesia
[c]Department of Medical Laboratory Technology, Poltekkes Kemenkes Bengkulu, Bengkulu, Indonesia
[d]Clinical Professional Program, RSUD Arifin Achmad, Faculty of Medicine Universitas Riau, Pekanbaru, Riau, Indonesia
[e]Bachelor Study Program, Faculty of Medicine Universitas Padjadjaran, Bandung, West Java, Indonesia
[f]Doctoral Program, Faculty of Medicine Universitas Padjadjaran, Bandung, West Java, Indonesia
[g]Department of Biomedical Sciences, Faculty of Medicine Universitas Padjadjaran, Bandung, West Java, Indonesia

ABSTRACT

Background: Major adverse cardiovascular event (MACE) remain a leading cause of poor prognosis following acute myocardial infarction (AMI). Emerging evidence suggests that adipose tissue-derived adipokines may better reflect cardiometabolic risk than conventional anthropometric measures. This systematic review and meta-analysis aimed to evaluate the association between circulating adipokines, specifically adiponectin and visfatin, and the occurrence of MACE in patients with AMI.

Methods: A systematic search of PubMed/MEDLINE, Scopus, and the Cochrane Library was performed from inception to identify cohort studies reporting adiponectin or visfatin levels in adult AMI patients with and without MACE during follow-up. Pooled mean differences (MD) with 95% confidence intervals (CI) were calculated.

Results: Five cohort studies (n = 707 AMI patients) conducted in China, Taiwan, Japan, and Poland with follow-up durations ranging from 2 to 43 months were included. Adiponectin levels were significantly lower in MACE patients (MD = -2.85 [95% CI -5.42 to -0.27, p = 0.03]; I2 = 94%), while visfatin levels were significantly higher in the MACE group (MD = 2.99 [95% CI 1.51 to 4.47, p < 0.0001]; I2 = 0%).

Conclusions: Lower adiponectin and higher visfatin levels are associated with MACE occurrence in AMI patients, whereas BMI did not demonstrate significant discriminatory value.

Keywords: Acute myocardial infarction, Adipose tissue, Adipokine, Adiponectin, Visfatin, Major adverse cardiovascular events

P53

Circulating miR-106b-5p and miR-185-5p Expressions and Their Functional Analysis in Chronic Heart Failure Patients

Bao-Quoc Vu[a], Phuong Anh Huynh[a], and Diem My Vu[a]

[a]Center for Molecular Biomedicine, University of Medicine and Pharmacy at Ho Chi Minh City, 217 Hong Bang, Cho Lon Ward, Ho Chi Minh City 70000, Vietnam

ABSTRACT

Background: Heart failure (HF) is one of the largest contributors to disease burden and healthcare expenditure worldwide. Countless studies have shown that microRNAs (miRNAs) are pivotal regulators of heart homeostasis and promising biomarkers for the diagnosis and management of HF. Among the reported miRNAs, miR-106b-5p and miR-185-5p were implicated in various cardiovascular diseases through involvement in cardiac injury, fibrosis, and cell survival pathways. Although cellular functions of miR-106b-5p and miR-185-5p have been investigated intensively, their circulating levels remain largely elusive in patients with HF.

Methods: This study examined expression levels of plasma miR-106b-5p and miR-185-5p by quantitative reverse transcription PCR (RT-qPCR) in a study cohort comprising 41 chronic HF patients and 41 matched, non-HF subjects. Bioinformatic analysis was conducted for miR-106b-5p and miR-185-5p to identify their potential target genes, biological functions, and association with cardiovascular-related clinical phenotypes.

Results: Chronic HF patients presented a significant increase in plasma miR-106b-5p and miR-185-5p levels. Diverse expressive patterns of miR-106b-5p and miR-185-5p were observed in different types and functional classes of HF. A positive correlation of plasma miR-106b-5p and miR-185-5p was also identified. In silico analysis suggested that many genes related to cell proliferation and metabolic pathways were shared targets of miR-106b-5p and miR-185-5p.

Conclusions: Our study reveals the dysregulation of plasma miR-106b-5p and miR-185-5p in patients with chronic HF that may contribute to the pathological course of this disease.

Keywords: Biomarkers, Circulating microRNAs, Plasma miR-106b-5p, Plasma miR-185-5p, Heart Failure, RT-qPCR.

P54

Mfn2 as a Novel Mitochondrial Target to Prevent Diabetic Heart Failure

Yitong Zeng[1], Shuo Cong[1], Fan Yu[1], Marie MyuMaiJa KP[2], Sze Jie Loo[2], Chen Xie[2], Chrishan Julian Ramachandra[1,2], Ying-Hsi Lin[1], Gerald W. Dorn II[3], Derek J Hausenloy[1,2]

[1]Duke NUS Medical School, Singapore
[2]National Heart Research Institute Singapore, National Heart Centre Singapore, Singapore
[3]Medical University of South Carolina, United States

ABSTRACT

Background: Diabetes mellitus (DM) is an independent risk factor for heart failure, with heart failure with preserved ejection fraction (HFpEF) representing the predominant and therapeutically challenging phenotype. Emerging evidence implicates impaired mitochondrial dynamics (fusion and fission), together with impaired mitochondrial function, as key mechanisms underlying DM HFpEF, with excessive mitochondrial fission as a major contributing factor. However, existing strategies to modulate mitochondrial dynamics largely rely on genetic manipulation or indirect regulation of upstream signaling pathways, limiting translational applicability. We investigated whether pharmacological activation of mitochondrial fusion using a small-molecule Mitofusin-2 (Mfn2) activator could improve myocardial relaxation by restoring mitochondrial dynamics and function in DM HFpEF.

Methods: We employed 8015-P2, a bioavailable small-molecule Mfn2 activator suitable for in vivo studies, to interrogate the role of mitochondrial network integrity in myocardial physiology using two complementary models: (i) adult mouse cardiomyocytes exposed to high-glucose and high-fat (HG/HF) conditions to assess cardiomyocyte-intrinsic mechanisms, (ii) the two-hit HFpEF mouse model to evaluate in vivo cardiac function.

Results: Across both in vitro and in vivo models, DM HFpEF was associated with downregulation of Mfn2 and imbalanced mitochondrial dynamics. In HG/HF-treated cardiomyocytes, pharmacological activation of Mfn2 improved impaired contractile relaxation, reduced mitochondrial fragmentation, and partially restored mitochondrial respiratory capacity. Consistently, Mfn2 activation improved diastolic function and attenuated adverse cardiac remodeling in the two-hit DM HFpEF mouse model.

Conclusions: Pharmacological activation of Mfn2 restores mitochondrial organization and improves diastolic function in preclinical models of DM HFpEF, supporting Mfn2 as a promising and translationally relevant therapeutic target.

Keywords: Mitochondrial, Mitofusin-2, Small-molecule activator, DM HFpEF, Two-hit model, Cardiomyocytes

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