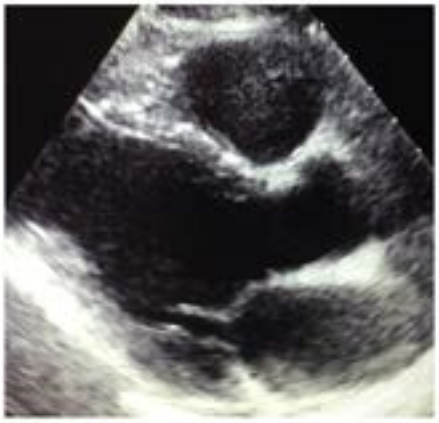
Honoring the memory of CVRI Founder
Dr. Harris J. Granger

Cardiovascular Research Institute
Michael E. DeBakey Institute

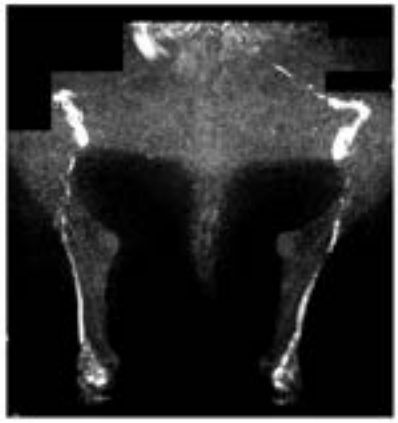
Research Symposium

August 2–3, 2023



Human heart echocardiogram

Rat retinal microcirculation



Dog MR lymphangiogram

In 1981, Professor Harris J. Granger had the vision to start the first TAMUS Board of Regents (BOR) approved institute (May 26, 1981) at TAMU College of Medicine, the Microcirculation Research Institute (MRI) headquartered in the department of Medical Physiology. The following year Dr. Granger became the head of the Department of Medical Physiology and over the course of the next 17 years Dr. Granger grew the MRI at Texas A&M to become the international leader in the microcirculatory field. During that time, the MRI and Department of Medical Physiology expanded to both the College Station and Temple campuses and was a pre-eminent research group in the TAMU College of Medicine. Under his leadership, Dr. Granger recognized the opportunity to broaden the scope of the MRI and include many of the new scientists recruited to the College of Medicine in the cardiovascular field. Thus, on September 25th, 1998, the TAMUS BOR approved the renaming and re-tasking of the MRI to become the CardioVascular Research Institute at TAMU and the CVRI was born. Its mission is to improve our understanding of cardiovascular biology/medicine in structure, function, growth, and development, from the molecular level to the intact organism, for cardiovascular disease prevention and treatment. Since that day almost 25 years ago, the CVRI has grown to include 3 divisions, Vascular Biology, Lymphatic Biology and Cardiac Health and Disease with over 125 members from across 6 TAMU colleges/schools. CVRI members at TAMU have been awarded $>$150 million dollars in funding and published $>$1000 cutting edge research papers. The CVRI sponsors regular seminars, bringing in the most noted scientists in its fields from around the world, as well as hosts the CVRI Research Symposium bringing together CV researchers from across TAMU. Recently the CVRI has coordinated its efforts with that of the Michael E. DeBakey Institute for Comparative Cardiovascular Science & Biomedical Devices headquartered in the Texas A&M School of Veterinary Medicine & Biomedical Sciences. Thus, we are excited to hold the 5th CVRI Research Symposium in conjunction with the Michael E. DeBakey Institute and to honor the visionary leadership started by our founder, Distinguished Professor Harris J. Granger 25 years ago.

David C. Zawieja
Regents Professor and Head
Department of Medical Physiology, Texas A&M Health

Cardiovascular Research Institute
School of Medicine
Texas A&M University

The Cardiovascular Research Institute (CVRI) was established in 1998; yes, this year, 2023 is the silver jubilee anniversary for CVRI! The CVRI is constituted of 3 divisions, Cardiac, Lymphatic and Vascular, with about 125 current members across 7 colleges/schools within Texas A&M University (TAMU) System: School of Medicine, School of Pharmacy, School of Engineering Medicine, School of Veterinary Medicine, College of Engineering, College of Agriculture & Life Sciences and School of Education and Human Development. CVRI scientists have made significant discoveries in the basic physiology of blood vessels, lymphatics, and heart. Other areas of investigation include angiogenesis, lymphangiogenesis, exercise biology, heart failure, atherosclerosis, ischemic heart disease, hypertension, and metabolic diseases. To facilitate research today and for future generations, the CVRI provides an environment for the training of undergraduates, medical students, graduate students, postdoctoral fellows, and residents. The CVRI bestows a platform to foster and share research ideas, and for continuous engagements of activities, such as, seminars, small group meetings, workshop, and symposium, which provide a vibrant environment for trainees and faculty members to build and promote research and education collaborations within TAMU system. Discovery with an emphasis on human health requires basic and clinical research; therefore, our research team consists of basic scientists and physician/scientists from a wide variety of fields and disciplines. The contributions of our faculty to the medical literature can be found on their individual web pages. CVRI investigators' research is funded by the National Institutes of Health, American Heart Association, National Aeronautics and Space Administration, and other agencies.

Mariappan Muthuchamy, Ph.D.
Director

Additional information regarding the CVRI or those affiliated with it is available on the Institute website located at `https://medicine.tamu.edu/centers/cvri.html`

Contents

Lecture and Poster Sessions at School of Medicine
Health Professionals Education Building, LL43A, LL43B, LL44
Texas A&M Health Campus, Bryan, TX
August 2–3, 2023

Wednesday, August 2, 2023

11:00 am Registration and Reception
Lower Level Lobby of the Health Professionals Education Building

12:00 pm **Opening remarks**

Welcome Address
Mariappan Muthuchamy, PhD
Director, Cardiovascular Research Institute, Department of Medical Physiology, School of Medicine, Texas A&M Health

Inaugural Address
Amy L. Waer, MD, FACS
Jean and Tom McMullin Endowed Dean, School of Medicine, Texas A&M Health

Introductory Remarks
Allison C. Rice-Ficht, PhD
Regents Professor, Interim Senior Associate Dean for Research, School of Medicine, Texas A&M Health

Rajesh C. Miranda, PhD
Professor, MSCI Graduate Program Director, School of Medicine, Texas A&M Health

12:30 pm **Honoring the Founder of CVRI Dr. Granger's Memory**

David C. Zawieja, PhD
Executive Director, Cardiovascular Research Institute, Department of Medical Physiology, School of Medicine, Texas A&M Health

Glen Laine, PhD
Director, Michael E. DeBakey Institute, Department of Veterinary Physiology and Pharmacology, School of Veterinary Medicine and Biomedical Sciences, Texas A&M University

Ed W. Childs, MD
Chair and Professor for Trauma and Critical Care, Morehouse School of Medicine, Atlanta, GA

Division of Cardiac Biology Session

Session Chairs:
Carl Tong, MD, PhD and Fadi Khasawneh, PhD, RPh

12:45 pm Keynote Speaker
Douglas Mann, MD
Distinguished Professor of Medicine, Cardiovascular Division, Washington University School of Medicine, St. Louis, MO
Heart failure with an improved left ventricular ejection fraction: mechanisms, models and management

1:30 pm **Sai Sudha Koka, PhD, RPh**
Department of Pharmaceutical Sciences, Irma Lerma Rangel School of Pharmacy, Texas A&M University, Kingsville, TX
The role of gut microbiota-derived metabolites in cardiovascular diseases

1:45 pm **Xu Peng, MD, PhD**
Department of Medical Physiology, School of Medicine, Texas A&M University
Epitranscriptomic regulation in heart failure

2:00 pm **Zhenyu Li, PhD**
Department of Pharmaceutical Sciences, Irma Lerma Rangel School of Pharmacy, Texas A&M University, Kingsville, TX
cGMP regulates platelet activation and thrombosis

2:15 pm Break

2:30 pm **Fadi Khasawneh PhD, RPh**
Department of Pharmaceutical Sciences, Irma Lerma Rangel School of Pharmacy, Texas A&M University, Kingsville, TX
The Impact of Novel Tobacco Products on Platelet Function and Thrombogenesis

2:45 pm **Ravindranath Duggirala, PhD**
Department of Life Sciences, Texas A&M University San Antonio
San Antonio Mexican American Family Studies: Genetics and Genomics of Complex Diseases

3:00 pm **Jacob D. Kuempel**, *METTL14-mediated N6-methyladenosine Modifica9on of mRNA is Required for Maintaining Cardiac Function and Adaptive Hypertrophic Remodeling*

3:10 pm **Tanmay Mukherjee**, *Detection of biomechanical alterations in the left ventricle due to radiation-induced cardiotoxicity*

3:20 pm **Siara K. Rouzer**, *Exposure to cannabinoids and alcohol during the second trimester impairs arterial resistance and increases cardiac stroke volume in fetal cerebral arteries*

3:30 pm *Discussion on Clinical and Translational Research*
Roozbeh Jafari, PhD and Sel Kaan, PhD Department of Electrical and Computer Engineering, Texas A&M University

Kia Parsi, MD
Executive Director, Texas A&M Rural and Community Health Institute

3:45 pm **Group Picture and Poster Session I**

6:30 pm **Dinner at TaD's Louisiana Cooking, College Station**

Thursday, August 3, 2023

7:45 am Registration and Continental Breakfast
Lower Level Lobby of Health Professionals Education Building

Division of Lymphatic Biology Session

Session Chairs:
Sanjukta Chakraborty, PhD and Joseph M. Rutkowski, PhD

8:30 am Keynote Speaker
Timothy Padera, PhD
Associate Professor, Rullo Family MGH Research Scholar, Massachusetts General Hospital, Boston, MA
The lymphatic system in health and disease

9:15 am **Brett M. Mitchell, PhD**
Department of Medical Physiology, School of Medicine, Texas A&M University
Renal Immune Cell Trafficking in Hypertension

9:30 am **Sanjukta Chakraborty, PhD**
Department of Medical Physiology, School of Medicine, Texas A&M University
Inflammatory microenvironment and tumor-lymphatic crosstalk in tumor progression

9:45 am **Keri N. Norman, PhD**
Department of Veterinary Integrative Biosciences, School of Veterinary Medicine and Biomedical Sciences
The Food Safety Concern of Lymph Nodes in the Agricultural Industry

10:00 am Break

10:15 am **Feng Zhao, PhD**
Department of Biomedical Engineering, Texas A&M University
Structured cell-derived extracellular matrix for vascular engineering

10:30 am **Walter E. Cromer, PhD**
Department of Medical Physiology, School of Medicine, Texas A&M University
Evidence for lymphatic transport errors in the GI track during Space flight

10:45 am **Mariappan Muthuchamy, PhD**
Department of Medical Physiology, School of Medicine, Texas A&M University
Lymphatics-inflammation-disease pathogenesis axis in metabolic, neuromuscular diseases and beyond…

11:00 am **Saranya Kannan, PhD,** *Impact of VEGFR-3 signaling on macrophage polarization in kid-ney injury*

11:10 am **Sukanya Roy,** *Inhibition of CXCR2 targets tumor-infiltrating g-MDSCs and T cell exhaustion to suppress immune evasion and lymphangiogenesis in cholangiocarcinoma*

11:20 am **Shedreanna Johnson,** *Pathogenesis of Duchenne Muscular Dystrophy is Associated with Decreased Lymph Transport in Hindlimb and Inflammatory Lymphangiogenesis in Fast-Twitch Skeletal Muscle*

11:30 am **Poster Session II and catered lunch**

Division of Vascular Biology Session

Session Chairs:
Cristine L. Heaps, PhD and Andreea Trache, PhD

1:30 pm Keynote Speaker
Johnathan Tune, PhD
Professor and Chair, University of North Texas Health Science Center, Fort Worth, TX
Disentangling the Gordian Knot of Coronary Microvascular Control in Health and Disease

2:15 pm **Travis Hein, PhD**
Department of Medical Physiology, School of Medicine, Texas A&M Health
Impact of Diabetes and Spaceflight on Vasomotor Function of Ocular Microvessels

2:30 pm **Andreea Trache, PhD**
Department of Medical Physiology, School of Medicine, Texas A&M University
Cellular mechanosensing in vascular aging

2:45 pm **Cristine L. Heaps, PhD**
Department of Veterinary Physiology and Pharmacology, School of Veterinary Medicine and Biomedical Sciences, Texas A&M University
Mechanistic adaptations in vascular resistance of the coronary microcirculation with chronic ischemia and exercise training

3:00 pm Break

3:15 pm **Aaron Morton, PhD**
Department of Kinesiology & Sport Management, School of Education and Human Development, Texas A&M University
Regenerating Soft Tissue in Health and Disease

3:30 pm **Kayla Bayless, PhD**
Department of Cell Biology and Genetics, School of Medicine, Texas A&M Health
New markers of angiogenic sprouting

3:45 pm	**Gladys Ko, PhD** Department of Veterinary Integrative Biosciences, School of Veterinary Medicine and Biomedical Sciences, Texas A&M University *Peptide Lv, a new player in angiogenesis*
4:00 pm	**Reetu Singh**, *Endothelial nitric oxide pathway or calcium-activated potassium channels do not mediate lymphatic responses to short-chain fatty acids*
4:10 pm	**Precious Badejo**, *Paternal exposure to e-hookah increases the risk of thrombotic disorders*
4:20 pm	**Weiming Xu**, *Blood Coagulation Testing Using a Smartphone*
4:30 pm	Break

Awards and Conclusion

4:45 pm	Award Presentations **Farida Sohrabji, PhD and Van G. Wilson, PhD**
5:00 pm	Concluding Remarks **David C. Zawieja, PhD**
5:15 pm	Social

Executive Committee

David C. Zawieja, PhD
Executive Director
Department of Medical Physiology, Texas A&M Health

Mariappan Muthuchamy, PhD
Director
Department of Medical Physiology, Texas A&M Health

Lih Kuo, PhD
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Joseph Rutkowski, PhD
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Department of Medical Physiology, Texas A&M Health

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ad hoc CVRI EC member
Department of Neuroscience & Experimental Therapeutics, Texas A&M Health

Glen Laine, PhD
ad hoc CVRI EC member
Michael E. DeBakey Institute, School of Veterinary Medicine and Biomedical Sciences

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Poster Judges

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Department of Neuroscience & Experimental Therapeutics, Texas A&M Health

Adam Case, PhD
Department of Medical Physiology, Department of Psychiatry, Texas A&M Health

Walter Cromer, PhD
Department of Medical Physiology, School of Medicine, Texas A&M Health

Shannon Glaser, PhD
Department of Medical Physiology, School of Medicine, Texas A&M Health

Travis Hein, PhD
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Xin Wu, PhD
Department of Neuroscience & Experimental Therapeutics, Texas A&M Health

David Zawieja, PhD
Department of Medical Physiology, School of Medicine, Texas A&M Health

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Amelia Rodriguez
Business Coordinator II
Department of Medical Physiology, School of Medicine, Texas A&M Health

Oral Presentation Abstracts

(in alphabetical order by presenter)

New markers of angiogenic sprouting

Colette Abbey[1], Camille Duran[1], Ashley Coffell[1], Gregg Wells[1], Sanjukta Chakraborty[2], and **Kayla Bayless**[1]

[1]Department of Cell Biology and Genetics, and [2]Department of Medical Physiology, Texas A&M School of Medicine

During new blood vessel growth, endothelial cells change dramatically from quiescent cells that form the inner lining of the vascular system and acquire an invasive phenotype. Transcriptional changes are vital for this switch, but a comprehensive genome-wide approach focused exclusively on endothelial cell sprout initiation has not been reported. We developed a method to physically separate invading and non-invading cells initiating the process of new blood vessel formation and then used transcriptomics to analyze multiple independent biological replicates using single-cell RNA sequencing, bulk RNA-sequencing, and single cell cluster analysis of both invading and non-invading populations. When determining genes commonly up-regulated in invasive endothelial cells, we observed a gene signature that was consistent with activation of signal transduction and morphogenesis. Many genes identified have been linked to regulating angiogenesis, including SNAI1, PTGS2 and JUNB. We confirmed upregulation of SNAI1, PTGS2, and JUNB proteins with invasion, and silencing JunB and SNAI1 significantly reduced invasion responses. In addition, we investigated RND3, also known as RhoE, that is known to prevent actin polymerization and promote cell rounding but has not been reported to drive angiogenesis. RND3 knockdown significantly reduced invasion responses. Altogether, these studies confirm that the genes identified are required for sprout initiation and expand the list of genetic markers indicative of endothelial cell sprout initiation. Overall, these studies illuminate molecular changes that coordinate endothelial cell assembly into new vessels.

Inflammatory microenvironment and tumor-lymphatic crosstalk in tumor progression

Sanjukta Chakraborty, PhD
Department of Medical Physiology, School of Medicine, Texas A&M University

The lymphatics have emerged as active players in cancer progression and distant dissemination of tumor cells. Lymph node metastasis is a critical prognostic indicator of tumor progression and often associated with poor patient outcome. Presence of tumor cells in the lymph node is associated with tumor aggressiveness, yet the molecular mechanisms modulating tumor- lymphatic crosstalk remains grossly understudied. Further, expansion of the lymphatic network (or lymphangiogenesis) near a growing tumor plays a significant role in metastatic progression. Research in my lab, is focused on investigating how an inflammatory microenvironment modulates the tumor vasculature, promotes metabolic reprograming, endothelial to mesenchymal transition (EMT) mechanisms and enhances metastasis of tumors to the sentinel tumor draining nodes and to distant metastatic sites. Recent studies from the lab, using a rare hepatobiliary cancer model of cholangiocarcinoma, demonstrate that an active chemokine- cytokine crosstalk modulates lymphatic-tumor crosstalk in the progression of this cancer and is also associated with significant remodeling of the immune microenvironment. Further, alterations in the metastatic tumor draining lymph node helps in establishment of a tumor permissive niche. Our work also demonstrates that cholangiocarcinoma tumor cells exposed to LEC-derived cues acquire vulnerabilities that enable them to show altered sensitivity to different chemotherapeutics and could thus have direct relevance for translational intervention strategies and future drug development targeted to lymph node metastatic cancers.

Evidence for lymphatic transport errors in the GI track during Space flight

Walter E. Cromer, PhD
Department of Medical Physiology, School of Medicine,
Texas A&M University

We have growing evidence over multiple rodent space flight missions that there is in all likelihood a deficit in lymph transport from the gut. In both acute and chronic missions there is apparent accumulation of lipids in the villi of the small bowel and the epithelium of the large bowel suggesting impaired lipid transport. This is accompanied by the lymphatic vessels in the submucosa having a collapsed appearance (no change in perimeter of individual vessels or number of vessels but diameters are reduced) and a reduced lacteal/villus length ratio. There are numerous potential causes for this ranging from changes in the microbiome to radiation induced tissue dysfunction and we are currently addressing several possibilities in ground studies.

San Antonio Mexican American Family Studies: Genetics and Genomics of Complex Diseases

Ravindranath Duggirala, PhD
on behalf of the Public Health Genetics and Genomics Group
Department of Health and Behavioral Sciences, College of Arts and Sciences, Texas A&M University-San Antonio, San Antonio, TX

The major focus of the Public Health Genetics and Genomics group's activities is understanding the genetic and environmental determinants of complex diseases and their related quantitative traits with direct relevance to public health, especially involving the Mexican American community in South Texas. Much of the group's efforts in the past 28 years have been directed towards the detection, localization, and identification of genes influencing complex diseases/traits such as type 2 diabetes (T2D), obesity, metabolic syndrome (MS), childhood obesity, and their related disease conditions (e.g., T2D complications and gallbladder disease [GBD]), using data from large Mexican American families in San Antonio, TX, and omics approaches. As part of our San Antonio Mexican American Family Studies (SAMAFS), several susceptibility genes/loci have been localized for various diseases. To complement the genetic and genomic approaches in understanding the molecular mechanisms underlying complex diseases, we have expertise in dissecting functional mechanisms including genome engineering and iPSC technologies. In addition, our group has expertise in studies focused on gene-by-environment interaction influences on complex traits. As part of this talk, a brief overview of our past and ongoing studies will be presented. In addition, given our background, we are poised to initiate and develop unique Academic and Research Programs at Texas A&M University-San Antonio and develop collaborations with its sister institutions.

Mechanistic adaptations in vascular resistance of the coronary microcirculation with chronic ischemia and exercise training

Cristine L. Heaps, PhD
Department of Veterinary Physiology and Pharmacology,
School of Veterinary Medicine and Biomedical Sciences,Texas A&M University

Ischemic heart disease is a leading cause of death for both men and women and a major public health and economic burden worldwide. Despite numerous advances in prevention and treatment, the number of patients diagnosed with heart disease is projected to rise for the foreseeable future with expected growth of 31% in the U.S. over the years 2025 to 2060. Disturbances in the coronary microcirculation contribute to ischemic heart disease and clinically manifest as diminished coronary flow reserve. Regular physical activity drives adaptations that improve microvascular function and enhance myocardial perfusion in health and disease. Our laboratory has made significant advances in discovery of the fundamental cellular and molecular mechanisms that underlie exercise-induced cardioprotection in the microcirculation of the ischemic heart using a porcine model of chronic coronary artery occlusion and exercise training. Our recent data reveal a significant and beneficial role for reactive oxygen species as critical regulators of microvascular cell signaling after endurance exercise training. Specifically, our data demonstrate that exercise training increases endothelium-derived H_2O_2 levels in coronary arterioles from ischemic hearts and that H_2O_2 is the underlying mediator of significantly enhanced endothelium-dependent dilation after exercise training. Mechanistically, enhanced H_2O_2-mediated dilation after exercise is dependent upon the activation of smooth muscle Kv and BKCa channels and at least in part on the colocalization of BKCa channels and protein kinase A (PKA) with no change in BKCa channel protein levels. Exploration of the role of these mechanisms of vasodilation in vivo has been initiated in this swine model.

Funding: NIH R01 HL139903

Impact of Diabetes and Spaceflight on Vasomotor Function of Ocular Microvessels

Travis W. Hein, PhD
Department of Medical Physiology, School of Medicine, Texas A&M Health

The vasomotor responses (vasoconstriction and vasodilation) of arterioles and venules in the microcirculation help regulate the blood flow supply of oxygen and nutrients to and removal of metabolic wastes from tissues/organs to maintain their normal function. My laboratory's research focuses on identifying the molecular mechanisms involved in vasomotor function of microvessels in health and disease. We are investigating how diabetes impacts vasomotor function of retinal microvessels. Diabetes causes progressive damage of microvessels and neurons in the retina of the eye that can lead to vision loss, and it is the leading cause of blindness in working-age adults. Our studies demonstrate that early diabetes causes abnormal vasomotor regulation of retinal arterioles and venules leading to insufficient blood flow to neural cells for proper function. Because effective therapies are lacking to treat microvascular and neural damage in advanced-stage diabetes, our goal is to identify novel destructive proteins in retinal microvessels that can be targeted for therapy to improve blood flow and consequently retinal function in early diabetes before irreversible damage. We are also working on projects to identify microvascular changes in the eye that may contribute to vision complications in astronauts, known as spaceflight-associated neuro-ocular syndrome (SANS), during long-duration spaceflight missions. The most common ocular change that occurs in microgravity is optic disc edema (swelling of the intraocular portion of the optic nerve), but the underlying pathophysiology remains unclear. Therefore, we are examining whether spaceflight/ microgravity alters vasomotor function of ocular microvessels, which could impact ocular vascular hydrodynamics and promote optic disc edema/SANS.

The Impact of Novel Tobacco Products on Platelet Function and Thrombogenesis

Precious Badejo[1], Fatima Z. Alshbool[2] and **Fadi T. Khasawneh**[1]
[1]Department of Pharmaceutical Sciences, Irma Lerma Rangel School of Pharmacy Texas A&M University, Kingsville, TX, USA. [2]Department of Pharmacy Practice, Irma Lerma Rangel School of Pharmacy Texas A&M University, Kingsville, TX, USA.

Cardiovascular disease (CVD) remains the leading cause of death not only in the United States but also worldwide, with the blood cells known as platelets playing a primary role in the pathogenesis of occlusive/thrombotic form of CVD. To this end, tobacco smoking is known to modulate platelet activation and increase the risk of CVD. However, whether the emerging/novel tobacco products (e.g., electronic-hookah (e-hookah) exert any or similar effects has yet to be investigated. This issue is of critical importance given the increasing popularity of these devices, as well as the misperception regarding their safety. To address this issue, we employed a novel whole-body exposure system and the well-known Beirut exposure protocol, for a one-month duration. The exposure protocol consisted of 171 puffs at 2.6s puff duration and 17s puff interval, and delivered 530 ml volume of the e-liquid. Our results document for the first time that direct exposure of animals to e-hookah does shorten the bleeding time and the occlusion time, in the tail bleeding time and carotid artery injury induced thrombosis models, when compared to the clean air exposed mice. Furthermore, our results show that e-hookah enhnaces platelet aggregation, as well as dense and alpha granule secretion, indicating a state of platelet hyperreactivity. Additionally, and consistet with our findings thus far, our flow cytometry analysis revealed that platelets from the e-hookah exposed mice exhibit enhanced integrin activation and phosphatidylserine exposure. Finally, we also found that the spreading response is enhanced in the exposed platelets relative to the clean-air controls. Collectively, our findings provide evidence for the first time that direct exposue of adult mice to e-hookah for one month increases the risk of thrombosis-based CVD, in part, via modulating platelet function. These data also provide insight into the negative health effects of the novel tobacco product e-hookah.

Peptide Lv, a new player in angiogenesis

Gladys Ko, PhD
Veterinary Integrative Biosciences, School of Veterinary Medicine and Biomedical Sciences

Peptide Lv is a small secretory peptide that is expressed in various organs, tissues, and cell types including the brain, retina, heart, and vascular endothelial cells. Peptide Lv is able to augment the mRNA and protein expressions of L-type voltage-gated calcium channels (LTCCs) in photoreceptors and cardiomyocytes, thus named "Lv". Using co-immunoprecipitation and mass spectrometry analysis, the vascular endothelial growth factor receptor 2 (VEGFR2) was identified as one of multiple binding targets of peptide Lv. Through a series of assays, we found that peptide Lv is able to promote proliferation, migration, and sprouting of vascular endothelial cells in vitro, elicit vasodilation ex vivo, as well as enhance neovascularization in vivo. Experimentally induced pathological neovascularization in mice can be dampened by an antibody specific against peptide Lv (anti-Lv) or genetic deletion of peptide Lv ($PLv^{-/-}$). Thus, peptide Lv's bioactivities are similar to VEGF: enhancing LTCC currents, eliciting vasodilation, and promoting angiogenesis/neovascularization. However, VEGF-elicited vasodilation is completely blocked by a nitric oxide synthase inhibitor, L-NAME, but L-NAME only partially dampens peptide Lv-elicited vasodilation indicating that peptide Lv may have other non-VEGF/VEGFR2 targets that mediate vasodilation and possibly angiogenesis/neovascularization. We recently demonstrated that peptide Lv is able to augment the intermediate conductance calcium-dependent potassium channel (IK_{Ca}; $K_{Ca}3.1$). Endothelial $K_{Ca}3.1$ is essential in VEGF/VEGFR2-dependent or -independent angiogenesis. The story of peptide Lv and angiogenesis has begun and will continue. The success of peptide Lv research thus far has been through crucial collaborations with Drs. Kayla Bayless, Travis Hein, Lih Kuo, and Robert Rosa.

The Role of Gut Microbiota-Derived Metabolites in Cardiovascular Diseases

Sai Sudha Koka, PhD
Department of Pharmaceutical Sciences, Irma Lerma Rangel College of Pharmacy, Texas A&M University, Kingsville, TX

The association between intestinal microbiota and a variety of disease conditions including cardiovascular diseases has been gaining increased attention in recent years. There exists a meta-organismal pathway which involves a complex interplay between dietary nutrients, intestinal microbiota metabolism and host pathogenic pathways. Gut microbiota can significantly influence the metabolism of dietary constituents in mammalian hosts. However, the molecular mechanisms through which intestinal microbiota and their metabolic products alter systemic homoeostasis and promote cardiovascular disease progression are yet beginning to be dissected. In this context, we hypothesized that bioactive gut microbiota-derived metabolites like trimethylamine-N-oxide (TMAO), induce inflammasome formation thereby contributing to endothelial injury and subsequent development of atherosclerosis. Our recent studies demonstrated that gut microbial metabolite TMAO induces the nucleotide oligomerization domain (NOD)-like receptor protein with pryin domain containing 3 (Nlrp3) inflammasome activation, significantly increase caspase-1 activity, IL-1β production and endothelial cell permeability thus contributing to the endothelial dysfunction. We have shown that beyond inflammation, the activated Nlrp3 inflammasomes have direct actions on endothelial cells. TMAO-induced activation of Nlrp3 inflammasomes was associated with both redox regulation and lysosomal dysfunction. Direct infusion of TMAO in mice with partially ligated carotid artery have increased Nlrp3 inflammasome formation, IL-1β production and intimal thickness in the carotid artery of wild type mice but not in Nlrp3 knockout mice. In conclusion, the formation of Nlrp3 inflammasomes by gut microbial metabolites is an important initiating mechanism to turn on the endothelial inflammatory response leading to endothelial and vascular injury associated with the development of atherosclerosis. Our current studies provide new mechanistic insights for targeting inflammasomes and develop novel therapeutic strategies for treating atherosclerosis and the resulting cardiovascular diseases.

cGMP regulates platelet activation and thrombosis

Zhenyu Li, PhD
Department of Pharmaceutical Sciences, Irma Lerma Rangel School of Pharmacy,
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The role of cGMP, an important second messenger, in platelet activation has been investigated for almost five decades. However, its functions in platelets are not fully understood and remain controversial. One major controversy is whether cGMP plays a stimulatory role, an inhibitory role, or both during platelet activation. Early studies in the mid-1970's showed that during platelet activation in response to agonists, such as ADP and collagen, intracellular cGMP concentrations were enhanced significantly, and that exogenous cGMP analogs enhanced platelet aggregation. Therefore, a stimulatory role of cGMP in platelet activation was proposed. This view was soon abandoned in early 1980's because nitric oxide (NO) donors inhibit platelet activation, and dramatically increase intra-platelet cGMP concentrations through its intracellular receptor soluble guanylyl cyclase (sGC). Since then, it has been generally accepted that cGMP plays an inhibitory role in platelet activation. We found that cGMP plays biphasic roles in platelet activation: a stimulatory effect when cGMP is produced endogenously at low concentrations, and an inhibitory effect when cGMP is produced at high concentrations upon induction by NO donors. The biphasic response of platelets to cGMP may be of physiological significance because this response may not only mediate rapid activation of platelets upon vascular injury, but also serve to inhibit the overgrowth of thrombi to prevent the occlusion of blood vessels during normal hemostasis. In support of this conclusion, we found that platelet-specific sGC knockout mice we generated have impaired platelet activation and defective thrombosis and hemostasis in vivo. sGC is believed to be the sole guanylyl cyclase in platelets. Surprisingly, we found that agonist-induced cGMP production is not completely abolished in the sGC deficient platelets. We further identified a membrane-bound guanylyl cyclase, NPRA, a receptor for atrial natriuretic peptide (ANP) and B-type or brain natriuretic peptide (BNP), in platelets. Using NPRA deficient mice, we identified a novel signaling pathway, the BNP/NPRA axis, in platelet activation and thrombosis.

Heart Failure with Improved Left Ventricular Ejection Fraction: Mechanisms, Models and Management

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Reverse left ventricular (LV remodeling and recovery of LV function are associated with improved clinical outcomes in heart failure (HF patients with reduced ejection fraction (HFrEF. A growing body of evidence suggests that even among patients who experience a complete normalization of LVEF, a significant proportion will develop recurrent LV dysfunction accompanied by recurrent HF events. This has led to intense interest in understanding how to manage HF patients with an improved EF (HFimpEF. Because of the lack of a standard definition for HFimpEF, and the paucity of clinical data with respect to the natural history of HFrecEF patients, there have not guidelines on how these patients should be followed and managed until recently. This seminar will review the biology of reverse LV remodeling and the clinical course of HFimpEF patients, as well as provide guidelines for defining, diagnosing and managing HFimpEF patients.

Renal Immune Cell Trafficking in Hypertension

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Renal innate immune cell infiltration and inflammation are hallmarks of hypertension (HTN). An increase in renal macrophages and dendritic cells has been observed in murine salt-sensitive and angiotensin II (Ang II)-induced models of HTN (SSHTN and A2HTN, respectively). We have reported that augmenting renal lymphatics can decrease renal innate immune cells along with blood pressure. However, the activation status, phenotype, and trafficking of these immune cells is less clear. We hypothesized that the hypertensive stimuli salt and Ang II play a direct role in increasing CD38+ macrophages and dendritic cells as CD38+ is an activation marker and cells that express CD38 become pro-inflammatory. There were increased CD38+ macrophages, CD38+ M1 macrophages, and CD38+ dendritic cells in the kidneys of both SSHTN and A2HTN mice compared to controls. Bone marrow derived monocytes (BMDMs) grown in GM-CSF with high salt (190 μm) or Ang II (0.01 μm) had significantly increased numbers of CD38+ macrophages and CD38+ M1 macrophages. Lastly, control BMDMs were labeled with Celltracker and adoptively transferred into mice with established SSHTN or A2HTN. There was a significant increase in renal Celltracker+ cells in the kidneys of both models of HTN compared to normotensive mice receiving these labeled cells. In mice with SSHTN the kidneys exhibited a significant increase in Celltracker+ CD38+ macrophages. Renal Celltracker+ CD38+ dendritic cells were increased significantly in both SSHTN and A2HTN mice. These findings suggest that salt and Ang II increase CD38 expression on macrophages and dendritic cells which hone to the kidney and may contribute to development of HTN. Studies are underway to examine how these cells traffic through the renal and lymphatic vasculature.

Regenerating Soft Tissue in Health and Disease

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Skeletal muscle is comprised of multiple cell types and tissue components that interact with each other during developmental growth and regeneration following injury and disease. As they develop in the embryo, blood vessels and nerves share molecular cues that guide their growth and branching to remote cellular targets, while a subthreshold volumetric muscle loss injury resolves that microvascular growth and perfusion are spatiotemporally dissociated from myogenesis by approximately one week. In addition, nascent myofibers are interwoven and disorganized, as are their associated microvascular networks, indicating loss of local guidance cues during regeneration. In the context of delayed angiogenesis following muscle injury, neuromuscular coupling is delayed, while promoting angiogenesis in muscle dystrophy through incorporation of a timed-release ion matrix enhances vascular endothelial growth factor and muscle function. Taken together, a regulatory crosstalk exists between muscle, vessel, and nerve. As an added dimension to investigating the aforementioned relationships, my laboratory is developing a method to evaluate high resolution mitochondrial morphology in soft tissue, i.e., muscle, blood vessel, and lymphatic vessel to analyze mitochondrial morphology in small volumes of tissue.

This work was supported by an NIH loan repayment award, APS postdoctoral fellowship, and Coulter Biomedical Accelerator Award.

Lymphatics-inflammation-disease pathogenesis axis in metabolic, neuromuscular diseases and beyond…

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The lymphatic system is critical to fluid movement from the interstitial space of the tissue parenchyma and its transport as lymph through the lymphatic vasculature by both extrinsic and intrinsic forces. In the majority of tissues in the body, interstitial fluid is generated by low-level filtrate from the microvasculature and requires an equivalent volume of fluid, as lymph, return to prevent edema. The interconnected network of initial lymphatics, collecting lymphatic vessels, and lymph nodes that comprise the lymphatic system transport fluid and other critical contents including macromolecules, lipids/chylomicron, and antigen-presenting cells/immune cells from the interstitial space back to the circulation. Thus, by doing these tasks, lymph transport plays an essential role in modulating metabolism, immune regulation, and inflammatory status. There is now ample evidence that several disease pathogeneses are associated with inflammation and lymphatic dysfunction. We and others have shown lymphatic function is compromised in the metabolic diseases and is associated with inflammation and immune cell regulation. Our current study is focusing on how lymphatic structure and function respond to neuromuscular diseases, Duchenne muscular dystrophy and Amyotrophic Lateral Sclerosis. Results from our interdisciplinary research group demonstrate that impaired lymphatic network and function are characteristics of disease pathology in ALS and DMD animal models.

The Food Safety Concern of Lymph Nodes in the Agricultural Industry

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Salmonella is one of the top disease-causing foodborne pathogens in the United States and common sources include poultry, pork, and beef products. *Salmonella* has been identified in lymph nodes of healthy cattle and swine. Cattle lymph nodes are embedded in deep layers of fat and are not typically removed during slaughter and can potentially be incorporated into ground beef products. Post-harvest intervention strategies are targeted at removing *Salmonella* from the hide and carcass; however, these post-harvest interventions are ineffective against *Salmonella* in the lymph nodes. Sources of *Salmonella* in lymph nodes remain unclear, though travel of *Salmonella* to the lymphatics is proven to occur via the gastrointestinal tract or transdermal routes. Our research has focused on understanding the role of the host and the environment in relation to *Salmonella* harbored in the lymph nodes. We have also investigated pre-harvest mitigation strategies targeting the environment to reduce *Salmonella* in the lymph nodes. We have found that *Salmonella* serovars in the lymph nodes are similar to those found in both cattle feces and the feedyard environment. While we have found pre-harvest mitigation strategies that may be effective at reducing *Salmonella* on cattle hides, the effect on *Salmonella* in the environment and in cattle lymph nodes requires further investigation.

The lymphatic system in health and disease

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The lymphatic system absorbs interstitial fluid to create lymph and returns it to the blood in order to maintain tissue fluid balance. Lymph is also rich in immune information, so on its journey back to the blood, it passes through lymph nodes to regulate our immune homeostasis. To do its job, the lymphatic system has different types of specialized lymphatic vessels. If these specialized vessels lose their functionality—often through a disease process—then tissue swelling and immune compromised tissue results. Here we will discuss how bacterial infections can impair lymphatic function and some mechanisms involved in lymphatic repair after injury. Finally, we will discuss lymphatic vessel contractility critical to transporting lymph.

Discussion on Clinical and Translational Research

Kia Parsi, MD
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In the US, the prevalence of heart failure (HF) has been increasing, currently affecting 6.7 million Americans with new HF diagnoses (incidence) of 1 million per year. HF progresses in a downward undulating manner over time with multiple hospitalizations and a very high 30-day readmission rate of 24.8%. Since 2000, heart failure mortality has not improved with an overall 5-year mortality of 52.6%. Strikingly, the rural population has a 19% increase of incident HF when compared to urban counterparts, even after adjustment for other known risk factors. Consequently, the rural population has a great need for better HF care. In response, The Texas A&M University Health Science Center is conducting a study to evaluate the effectiveness of remote monitoring of HF patients living in rural communities in the Brazos Valley area. Participants will be recruited from Texas A&M Health Clinics, St. Joseph Regional Hospital, and Central Texas Heart Center. The study will specifically investigate the ability of a new multi-sensor remote monitoring system to improve care of rural HF patients by alerting treating physicians of concerning trends before deterioration into decompensation that require hospitalization. The results will demonstrate a new and more effective method of treating rural HF patients.

Epitranscriptomic regulation in heart failure

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The prevalence of heart failure (HF) has been dramatically increased in the past decades and presently affects around 64 million people worldwide. The m6A modification is the most prevalent epi-transcriptome modification that is deposited through a writer complex, minimally composing of METTL3 and METTL14. Although dysregulation of m6A is involved in numerous human diseases, only sporadic findings implicated a regulatory role of m6A modification in maintaining heart normal structure and functions. This notwithstanding, the bona fide targets of METTL3/METTL14 have not been rigorously validated in heart, and identities of the key targets that contribute to HF and their modes of actions in the heart have been largely unknown. Furthermore, how the METTL3/14 writer complex itself is regulated at a posttranslational level has also been barely studied. To address these questions, we have created novel cardiomyocyte specific Mettl14 knockout and overexpression mouse lines. The inactivation of Mettl14 in cardiomyocytes resulted in mice early lethality with dilated cardiomyopathy. The thickness of left ventriculi wall was decreased in the knockout and increased in Mettl14 overexpression hearts. Importantly, RNA-seq analysis showed that the deletion of Mettl14 caused hundreds of differentially expressed genes that are largely enriched in metabolic pathways, and harbor at least one m6A site in each transcript. Furthermore, we have also identified and experimentally validated that focal adhesion kinase (FAK) could directly interact and phosphorylate METTL14 in the heart. Therefore, we concluded that FAK-regulated METTL14 phosphorylation plays an essential role in the development of heart failure.

Cardiovascular Health Monitoring with Physiology-Driven Sensing Paradigms

Kaan Sel, PhD
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Over the past decade, the concept of real-time sensing has seen unprecedented advances, where a myriad of individuals has now access to wide choices of smart commercial off-the-shelf (COTS wearables that can easily monitor vital biometrics such as heart rate on a continuous basis. Despite these advancements, extracting complex cardiovascular parameters from wearable device measurements for precision medicine remains a challenge, due to several unmet needs; limited availability of advanced sensing paradigms, substantial physiological heterogeneity among individuals, limited access to ground truth data at personalized levels for disease states, the data-intensiveness of artificial intelligence (AI-based modeling of complex input (sensor measurements and output (complex cardiovascular parameters relationships, the disparity between computational model parameters and sensor measurements.

This seminar presents several topics towards developing advances sensors and algorithms coupled with human physiology to enable continuous and unobtrusive monitoring of complex cardiovascular health parameters. We will present simulations on electrical models of biological tissues to drive the design, optimization, and placement of sensors. Additionally, we will discuss novel sensing paradigms utilizing novel form-factors: rings, electronic tattoos, distributed patches, harnessing the deep tissue sensing capabilities of bioimpedance, achieving medical-grade accuracies in blood pressure (BP estimation. Furthermore, we will introduce the concept of physiology-driven AI modeling, which leverages our existing knowledge of human physiology and real-time measurements to uncover hidden and complex BP information, reducing the dependence on ground truth data.

The integration of next-generation wearables and AI will have a significant impact on precision medicine, revolutionizing traditional medical practices that heavily rely on outdated, bulky, and invasive systems. By motivating the use of AI and advanced wearable sensors, in view of human physiology, we aspire to usher in a new era of personalized, effective, and accessible medical care. With this seminar we will cover key challenges of extracting clinical parameters from wearable device measurements and potential solutions through bioimpedance sensors, physiology-driven sensing paradigms, and AI modeling, to provide an understanding of the advancements in cardiovascular health monitoring and the potential for personalized, accessible medical care.

Cellular mechanosensing in vascular aging

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Mechanical forces are important stimuli and determinants of many cell functions including contraction, proliferation, and cell attachment. Relatively little is known about how cells sense and integrate mechanical forces at the molecular level to induce intracellular signaling. Arterial aging is associated with decreased arterial contractility and altered mechanosensitive responses to external stimuli in vascular smooth muscle (VSM) cells. Real-time measurements of mechanosensitive events at sub-cellular level in response to physiologically relevant mechanical stimulation are a critical component in understanding mechanically-induced cellular remodeling. This study investigates the effect of extracellular mechanical signaling (wall stretch and matrix stiffness) on integrin-mediated cell adhesion and actin cytoskeleton in VSM cells isolated from soleus feed arteries from young and old Fischer 344 rats. Structural and functional properties of VSM cell were assessed by using high-resolution fluorescence and atomic force microscopy. 3D-hydrogel tissue-mimic and ex-vivo functional experiments were also used to assess contractility of VSM cell and isolated resistance arteries, respectively. Our data showed that: (i) decreased substrate stiffness restores actin stress fiber formation and integrin β1 recruitment at cell-matrix adhesions in VSM cells from aged arteries; (ii) 2D cyclic stretch or static pressure treatment applied to aged VSM cells on stiffer substrates also restores actin fibers and integrin β1 recruitment; (iii) pre-treatment of isolated aged arteries with an acute, short-duration increase in intraluminal pressure rescues contractility. These findings suggest that discrete VSM cell mechanical properties and their ability to adapt to external mechanical signals are involved in restoring VSM contractility in aging.

Disentangling the Gordian Knot of Coronary Microvascular Control in Health and Disease

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The heart is uniquely responsible for providing its own blood supply through the coronary circulation. Regulation of myocardial perfusion is extremely complex and, after over a century of dedicated research, precisely how coronary microvascular resistance is tightly coupled with myocardial energy requirements persists as the unresolvable "Gordian Knot" of the field. This lecture will highlight current knowledge regarding physiologic regulation of coronary blood flow with emphasis on proposed pathways and the detrimental impact of obesity on mechanisms of coronary control. Such deficits in coronary microvascular reactivity are now understood to be a powerful predictor of major adverse cardiovascular events and associated with the development of overt heart failure. Disentangling the extent to which coronary microvascular dysfunction represents a causal mechanistic link for, versus a patho-physiologic consequence of, underlying disease is accordingly recognized as one of the most pressing questions of cardiovascular medicine today.

Extracellular Matrix for Cardiac and Lymphatic Tissue Engineering and Regeneration

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Natural extracellular matrix (ECM) derived from cultured human cells can recapitulate the chemical and biological motifs of the ECM found in native tissues. Compared with ECM derived from animal tissues, cell-derived ECM avoids the problem of pathogen transfer and host immunological reactions, thereby holding greater potential in tissue engineering. We have previously created a highly aligned ECM scaffold by de-cellularizing fibroblast cell sheets that were grown on synthetic nanogratings. The aligned ECM nanofibers provide directional cues for cell alignment, allowing for the engineering of 3D anisotropic tissue constructs. By combining human mesenchymal stem cells (hMSCs) and endothelial cells on the ECM scaffold, we have fabricated a pre-vascularized hMSC sheet containing highly oriented, dense and mature microvessels, which shows great potential for cardiac and lymphatic tissue regeneration.

Poster Presentation Abstracts

(in alphabetical order by presenter)

Functional characterization of the disease-associated CCL2 rs1024611G-rs13900T haplotype: The role of the RNA-binding protein HuR

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CC-chemokine ligand 2 (CCL2) is involved in the pathogenesis of several diseases associated with monocyte/macrophage recruitment, such as HIV-associated neurocognitive disorder (HAND), tuberculosis, and atherosclerosis. The rs1024611 (alleles: A>G; G is the risk allele) polymorphism in the CCL2 cis-regulatory region is associated with increased CCL2 expression in vitro and ex vivo, leukocyte mobilization in vivo, and deleterious disease outcomes. However, the molecular basis for the rs1024611-associated differential CCL2 expression remains poorly characterized. It is conceivable that genetic variant(s) in linkage disequilibrium (LD) with rs1024611 could mediate such effects. Previously, we used rs13900 (alleles: C>T) in the CCL2 3' untranslated region (3' UTR) that is in perfect LD with rs1024611 to demonstrate allelic expression imbalance (AEI) of CCL2 in heterozygous individuals. Here we tested the hypothesis that the rs13900 could modulate CCL2 expression by altering mRNA turnover and/or translatability. The rs13900 T allele conferred greater stability to the CCL2 transcript when compared to the rs13900 C allele. The rs13900 T allele also had increased binding to Human Antigen R (HuR), an RNA-binding protein, in vitro and ex vivo. The rs13900 alleles imparted differential activity to reporter vectors and influenced the translatability of the reporter transcript. We further demonstrated a role for HuR in mediating allele-specific effects on CCL2 expression in overexpression and silencing studies. Our studies suggest that the differential interactions of HuR with rs13900 could modulate CCL2 expression and explain the interindividual differences in CCL2-mediated disease susceptibility.

Thrombogenicity associated with prenatal THS exposure is mediated by alterations in platelet gene expression profile

Hamdy E. A. Ali, Ahmed B. Alarabi, Ana Carolina Ribeiro Gomes Maia, Fatima Z. Alshbool and Fadi T. Khasawneh

Cigarette smoking is the most preventable risk factor for thrombogenesis-associated disease. To this end, we have previously shown that even when the exposure is indirect, namely thirdhand (THS) in nature, and occurs under prenatal settings, the offspring mice exhibit a higher tendency to develop occlusive thrombosis, through enhancement of several platelet activation functional responses/markers. However, the mechanism underlying prenatal THS-associated prothrombotic phenotype is unknown. In this study, we demonstrated an altered platelet gene expression profile in the prenatal THS exposed mice that is linked to platelet functional responses. Moreover, RNA seq analysis for both mRNA and small RNA revealed distinct changes in both gene expression and microRNA profiles of their circulating platelets. Indeed, 517 coding genes showed significantly altered expression between the two exposure groups, which were accompanied with a concurrent alteration in platelet microRNA profile. In fact, 18 microRNA were found to be differentially expressed between the two groups. Using the same population platelets for generating both mRNA and small RNA libraries for sequencing guaranteed the temporal and spatial co-localization of mRNA and miRNA that's required for the integrative microRNA-miRNA analysis proposed for identification of gene regulatory networks involving miRNA-mRNA pairs. This integrated analysis highlighted 14 of our differentially expressed miRNAs that potentially target 120 of the 517 differentially expressed coding genes in our sequencing dataset. Additionally, the significantly altered coding genes that are potentially targeted by miRNAs that are already altered in the same dataset were functionally enriched into signaling pathways associated with platelet biology, including platelet activation, platelet signaling and aggregation, platelet degranulation, integrin-mediated cell adhesion and cellular response to chemical stimulus. Collectively, we establish that prenatal exposure to THS significantly modifies the platelet transcriptome, prompting elevated functional activation responses that may contribute to THS related thrombogenicity.

Paternal exposure to e-hookah increases the risk of thrombotic disorders

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Introduction: Cardiovascular disease (CVD) is well documented as the leading cause of death worldwide, with smoking being the most preventable cause. Indeed, most smokers die from thrombotic-based diseases, in which platelets play a major role. To this end, because of the proven harm of smoking, other novel tobacco products- including e-hookah- have been gaining popularity even among youth and expecting fathers, partly due to their 'false safety claims'. While many investigators have focused on the negative health effects of direct as well as maternal/in utero exposure of tobacco products on the unborn fetuses, little is known about paternal exposure, which we investigated therein.

Methodology: We employed a whole-body exposure model of e-hookah in which we expose male mice for six-weeks before mating, and throughout the mating period until female mice were visibly pregnant. Experiments were performed on the offspring once they reached 10-12 weeks of age. Exposures took place seven times a week, according to the well-known Beirut protocol, whereas control mice were exposed to clean air. The Beirut exposure protocol- which has been employed in many studies as it mimics real-life scenarios- involves the delivery of 171 puffs of 530 ml volume of the e-liquid at 2.6s puff duration and 17s puff interval.

Results: Our results showed that the paternal e-hookah exposed mice had shortened bleeding and occlusion times when compared to the controls, which indicates a prothrombotic phenotype. Investigation of the mechanism underlying this phenotype showed that e-hookah exposed platelets had enhanced agonist-triggered aggregation and dense granule secretion. Also, flow cytometry analysis of surface markers of platelet activation showed that integrin IIb-IIIa activation was also enhanced in the e-hookah exposed platelets, indicating hyperactivity.

Conclusion: Based on these results, we document for the first time, that paternal e-hookah exposure does exert negative health effects in the context of thrombosis-based CVD, in part, via promoting platelet hyperreactivity. Hence, e-hookah should not be considered a safe alternative to traditional cigarette smoking.

SARS-CoV-2 spike protein triggers endothelial to mesenchymal transition in lymphatic endothelial cells and accelerates pre-mature senescence in liver cancer via the TGFβ-CXCL5-CXCR2 axis

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SARS-COV-2 spike (S1) glycoprotein related cytokine storm, is associated with endothelial dysfunction. However, the precise inflammatory mechanisms activated by the S1 protein is not at all well characterized in the lymphatic endothelium. Further, increasing evidence suggests that in patients with metastatic solid tumors, there is significantly increased risk of susceptibility as well as risk of tumor progression post covid exposure. However, the impact of S1 on tumor-LEC crosstalk also remains completely understudied. We examined the impact of S1 on production of inflammatory mediators by lymphatic endothelial cells (LECs), and its subsequent impact on LEC remodeling. In addition, we also evaluated how factors produced by S1 exposed LECs, impacted proliferation, migration and activation of cellular senescence and cancer stemness in cholangiocarcinoma (CCA), an aggressive biliary cancer characterized by significant lymphangiogenesis. LECs were treated with S1 protein, different pathway specific inhibitors and the activation of lymphangiogenic and tumor promoting mechanisms, proliferation, migration, and metabolic profile were determined. S1 protein increased the cellular proliferation, cellular lactate production, and increased expression of metabolic genes, phosphofructokinase (PFKP) and fatty acid synthase (FASN) in LECs. S1 protein also had a robust impact on lymphatic tube formation and invasion that was associated with enhanced VEGFR3 expression. Interestingly, S1 protein infected LECs produced high levels of TGFβ, a well-known factor for liver fibrosis and cholangiocarcinoma. Our data suggested that high levels of TGFβ induced the ROS production, endothelial to mesenchymal transition (EndMT) and significant induction in levels of CXC motif chemokine ligand 5 (CXCL5), that plays a critical role in immune recruitment and tumor progression. Exposure to S1 protein treated LECs, increased the migratory potential of the CCA cells that overexpress CXCR2 (receptor for CXCL5), with an increase in transcription factors for epithelial to mesenchymal transition (EMT), matrix metalloproteinases, and a significant acceleration of premature cellular senescence. Activation of the TGFb-CXCL5-CXCR2 axis was associated with a concomitant increase in cancer stemness genes that correlate with increased tumor aggressiveness. Taken together, this is the first study to document that LECs directly respond to S1 protein and secrete multiple inflammatory mediators that further augment the inflammatory milieu and cause expansion of the lymphatic network. The factors produced by LECs exposed to S1 can modulate phenotypic and pro-tumorigenic changes in pre-existing tumor cells, thus promoting tumor aggressiveness and growth. The study not only highlights the underexplored impact of S1 on the lymphatic endothelium and effects on tumor remodeling but also underscores the potential role of existing TGF-β inhibitors for the suppression of COVID-19 associated lymphatic inflammatory response.

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Single-cell RNA sequencing identifies response of renal lymphatic endothelial cells to acute kidney injury

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Background: The inflammatory response to acute kidney injury (AKI) likely dictates future renal health. Lymphatic vessels are responsible for maintaining tissue homeostasis through transport and immunomodulatory roles. Due to the relative sparsity of lymphatic endothelial cells (LECs) in the kidney, past sequencing efforts have not characterized these cells and their response to AKI. Methods: Here we characterized murine renal LEC subpopulations by single-cell RNA sequencing and investigated their changes in cisplatin AKI 72 hours post injury. Data was processed using the Seurat package. We validated our findings by qPCR in LECs isolated from both cisplatin-injured and ischemia reperfusion injury, by immunofluorescence, and confirmation in in vitro human LECs.

Results: We have identified renal LECs and their lymphatic vascular roles that have yet to be characterized in previous studies. We report unique gene changes mapped across control and cisplatin injured conditions. Following AKI, renal LECs alter genes involved in endothelial cell apoptosis and vasculogenic processes as well as immunoregulatory signaling and metabolism. Differences between injury models were also identified with renal LECs further demonstrating changed gene expression between cisplatin and ischemia reperfusion injury models, indicating the renal LEC response is both specific to where they lie in the lymphatic vasculature and the renal injury type.

Conclusions: In this study, we uncover lymphatic vessel structural features of captured populations and injury-induced genetic changes. We further determine LEC gene expression is altered between injury models. How LECs respond to AKI may therefore be key in regulating future kidney disease progression.

Blood and angiogenesis-integrated human tumor microenvironment chips enable basic science and drug discovery in cancer

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Angiogenesis is a prime event in tumor microenvironment facilitating its growth and metastasis. However, angiogenesis is not just driven by soluble factors released from the tumor cells but there is growing evidence that platelets play an intensive role in cancer angiogenesis, growth and progression. Tumors are capable of remodeling the blood vessels and the released factors may compromise vessel barrier integrity thereby making way for blood cells such as, platelets to extravasate towards tumor microenvironment. In this study, we have engineered an angiogenic tumor microenvironment-chip (aTME-Chip) that recapitulates the convergence of physiology of angiogenesis and platelet extravasation through the tumor vessels. Since ovarian cancer is one of the most lethal female cancers with known clinical thrombocytosis, we have employed this platform to explore the relative influence of normal vs grade IV ovarian cancer patient platelets on angiogenesis on a variety of ovarian cancer cells co-cultured in the aTME-Chip. Co-culturing of ovarian cancer cells and endothelial cells in the aTME-Chip shows systematic barrier disruption, sprouting and angiogenesis over time in the presence or absence of moving platelets. Quantification of angiogenesis indicated toward three distinct observations with our platform. First, when platelets are introduced, they significantly increase the proangiogenic activity within the tumor microenvironment. Second, the temporal dynamics of angiogenic signaling and tumor vascularization are dependent on ovarian cancer cell type and seeding load. Finally, platelets from cancer patients are typically activated and further fuel the angiogenesis within the aTME-Chip, relative to normal controls. In summary, our aTME chip enables the recapitulation and dissection of angiogenesis due to complex and combinatorial signaling arising from platelets, endothelial and ovarian cancer cells derived from normal human subjects or patients. This engineered model will find potential applications in exploring antiangiogenic targets, combined with antiplatelet and other antimetastatic targets, which adds significant strength over prior *in vivo* and *in vitro* experimental strategies.

Brahma Related Gene-1 (Brg1) Protein Mediates Helpful Compensatory Response To Retard Development Of Heart Failure

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Background: Chromatin remodeling can modulate transcription by changing gene accessibility. Brahma Related Gene-1 (Brg1) protein, which is an adenosine triphosphate catalytic subunit that supports chromatin remodeling, has been implicated in development of hypertrophic cardiomyopathy. However, contribution of Brg1 to the development of heart failure (HF) has not been clearly elucidated.

Hypothesis: We hypothesize that Brg1 mediates compensatory response to cardiac stress; therefore, loss of Brg1 function will accelerate development of HF.

Methods: The myosin light chain-2 Cre/loxP system was used to produce cardiac myocyte specific deletion of Brg1(-/-) mouse model with floxed littermates as control.

Results: At baseline, Brg1(-/-) hearts showed mildly reduced left ventricular ejection fraction (LVEF). Aging to 12 months caused LV dilation and further reduction of LVEF in Brg1(-/-). We used trans-aortic constriction (TAC) for pressure overload challenge and chose similarly severe TAC induced pressure gradients as indicated by similarly fast peak flow velocities across the constriction. At 2-weeks post-TAC, Brg1(-/-) hearts exhibited severely reduced LVEF, severely dilated LV, and decreased ability to thicken LV wall during systole. In contrast, control hearts did not dilate and maintained their LVEF with increased LV wall thickness. Thus, Brg1 deletion greatly diminished the heart's ability to compensate for aging and pressure challenge, thereby accelerating development of heart failure with reduced ejection fraction (HFrEF). Separately, RNA sequence analyses of 12-months aged hearts showed Brg1 deletion caused upregulation of 810 genes including HF associated long noncoding RNA XIST and down regulation of 50 genes, while 3-months old hearts were not significantly different.

Conclusion: Brg1 mediates compensatory responses that are helpful to the heart to prevent development of HF; therefore, it is a potential treatment mechanism for HF.

Genetics of Birth Weight and Its Association with Adult Complex Diseases in Mexican Americans

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Birth weight (BW) is known to be associated with adulthood cardiometabolic traits (CMTs). Recent genome-wide association studies identified a number of common variants influencing variation in BW as well as its correlation with CMTs. However, there is limited knowledge on the functional role of such variants, particularly in minority populations such as Mexican Americans (MAs). Therefore, the purpose of this study is to identify potential functional variants using BW and adulthood phenotypic data (e.g., body mass index [BMI] and type 2 diabetes [T2D]) data and exome-chip-based genotypic data (N = 1,003) obtained from the San Antonio Mexican American Family Studies (SAMAFS) including the San Antonio Family Birth Weight Study (SAFBWS). In addition, we are also examining genetic variants with influences on BW as well as its related CMTs, particularly involving genetic regions that were found by our previous bivariate linkage studies to contain susceptibility loci with pleiotropic influences on BW and several CMTs. Genetic associations were tested using the measured genotype approach as implemented in the computer program SOLAR. We found evidence for loci with both common and rare variants influencing BW after adjusting for covariate effects (i.e., sex, premature birth, and admixture coefficients). For example, a common variant (rs2233369) in ABI3 gene is strongly associated with BW (Minor allele count [MAC] = 471, β = -0.26, p-value = 1.26×10^{-06}), while a rare variant (rs1225090) in ANKAR gene is also strongly associated with BW (MAC = 14, β = 1.20, p-value = 2.5×10^{-05}). We are in the process of identifying potential functional variants associated with both BW and selected CMTs (e.g., BMI and T2D). In sum, our study has great potential to unravel the contribution of common and rare variants impacting BW and its correlated CMTs, which may help us understand the molecular mechanisms underlying the association between birth weight and diseases that occur later in life.

MiRNA-17 Therapeutics for Preeclampsia

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Preeclampsia (PE) is the leading cause of maternal, fetal, and neonatal mortality. Most of the existing biomarkers focus on late gestation or lack sufficient sensitivity or specificity for earlier detection. A successful intervention will require better understanding of disease progression and development of accurate, early biomarkers that appear before clinical symptoms. In a case-control study of healthy and PE women's first trimester blood, we identified several epigenetic biomarkers including DNA methylation, histone modification, and microRNA. To decipher the explicit mechanism of how microRNA regulates PE pathogenesis, we chose to characterize the function of miR-17-5p in placental development. First, we investigated the effect of miR-17-5p on cell invasion through 3D matrix assays. We discovered that a miR-17-5p mimic significantly inhibits human umbilical vein endothelial cells (HUVECs) migration, while a miR-17-5p inhibitor promotes it. We further overexpressed miR-17-5p in the trophoblast layer of blastocysts (E2.5) via lentivirus infection and evaluated the placenta at E16.5. Consistently, we observed severe defects in angiogenesis and other PE-related complications, including placental hemorrhage. To elucidate potential targets of miR-17-5p, we performed RNA-seq analysis in miR-17-5p mimic-transfected and single-cell sequencing analysis in invading and noninvading HUVECs. The results of both analysis were combined to narrow down a list of common genes that are potentially associated with cell invasion, cytoskeletal destabilization, and angiogenesis. We subsequently validated the gene expressions in full-term placenta from PE patients and miR-17-5p overexpressed mouse placenta. In conclusion, miR-17-5p is a predictive marker of PE, and it regulates PE pathogenesis through targeting epigenetic regulations which are essential in placenta development. Future efforts targeting miR-17 inhibition during early pregnancy can provide therapeutic potential for treating PE.

Engineering vessel chips for service in biosafety level 3 facilities

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It is well established that some prominent bacterial and viral infections induce prevalent and threatening cardiovascular diseases. However, commonly used animal research models often do not mimic human physiology sufficiently for understanding the complexities of many vasculopathies. As a result, little is known about many mechanisms of pathogen-induced vascular diseases. Microphysiological systems (MPS) represent a leading candidate technology for advanced in vitro modeling of human diseases and drug response having demonstrated strong representation of physiology. However, there is a significant need for new technologies to translate MPS and similar advanced in vitro technologies for applications in biosafety level 3 (BSL3) research environments. To address these challenges and provide greater opportunities to study the impacts of infectious diseases, we have developed an MPS deployment system integrating five key components – a programmable microcontroller, dual automated three-way control valves, a MPS vascular tissue model (or vessel-chip), a sterile quick disconnect injection coupling, and sealed collection reservoirs. Through a controlled sequence of operation, this system allows perfusion of media or biological fluids and timely introduction of pathogens or other materials of interest while maintaining a sealed closed system in accordance with BSL3 requirements. The built-in automation and operating procedure allow users to operate the platform using standard syringe and pipette techniques that can be performed safely and easily with BSL3-assocated personnel protection equipment (PPE). These components can be packaged with any commercially available pumping instrumentation for easy transportation and increased standardization. The system is also fabricated and packaged such that each component can be easily decontaminated prior to exiting containment. Collectively, this deployment system represents a valuable tool for the future implementation of MPSs in controlled environments for standard research activities, rapid research needs in response to crises, and large-scale drug and therapeutics testing.

An Epigenetic Perspective into CVD from a Young Graduate Student

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Epigenetics describes the regulation of gene expression through heritable and reversible alterations to the organization of the genome while leaving the DNA sequence itself undisturbed. It is at this axis that the environment can impose effects that shift the dynamics of this organization to potentially pose risk of disease development. Environmental factors can include exposure to plasticizers, pollution, stress, consumption of a Western diet, and much more. More dire is that the alterations incurred in one generation can consequently be inherited transgenerationally. To be able to address the leading cause of death worldwide, we must investigate the potential epigenetic regulations contributing to the development and progression of cardiovascular disease (CVD). Risk factors such as hypertension, diabetes, obesity, and high low density lipoprotein (LDL) cholesterol bring forth the significant impact that metabolic health can have on the development of CVD. Therefore, consideration for epigenetic regulations in metabolic diseases can provide insight into the CVD scenario. Our lab focuses on the interplay of these epigenetic regulations by evaluating the roles of microRNAs, long noncoding RNAs, histone modifications, and DNA/RNA methylation in various tissues including adipose, liver, bone marrow, placenta, and kidney. In specific, our lab pioneered the discovery of a microRNA biomarker that can permit early detection of preeclampsia before the onset of symptoms. This is highly advantageous in combating a major cardiovascular cause of maternal death worldwide as well as presenting a potential treatment opportunity. Our lab has also demonstrated the effect that a Westernized diet can have on a long noncoding RNA in regulating hepatic metabolism, leading to obesity and metabolic perturbations. Further, we have brought emphasis to how endocrine disrupting chemicals can induce epigenetic dysregulations to exacerbate metabolic diseases including atherosclerosis. These findings are instrumental in discovering methods to mitigate metabolic risk factors towards the development of CVD for there is hope in the reversible nature of epigenetics. We seek not only to elucidate the contributing epigenetic regulations, but to also devise methods of treatments. Current epigenetic therapeutics we are investigating include the application of MSCs, HSCs, iPSCs, and nutraceuticals. Our goal is to identify epigenetic regulations that we can then target with epigenetic interventions to facilitate the prevention and treatment of metabolic diseases and CVD.

Role of a Complex Long Non-coding RNA in Brown Adipose Function: Impact on Cardiometabolic Health

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Brown adipose tissue (BAT) plays a major role in maintaining energy homeostasis. Upon activation, glucose is converted in a multi-step process, ultimately leading to heat production. This phenomenon is especially beneficial in obesity and type 2 diabetes conditions where excess glucose can be converted into heat rather than detrimental fat accumulation. Moreover, recent evidence suggests that brown adipose can regulate cardiometabolic health wherein higher BAT content corelates with lower risk of developing cardiovascular disorders such as hypertension, congestive heart failure, and coronary artery disease emphasizing the importance of identifying novel BAT targets. However, the underlying mechanisms linking these disease characteristics remains unknown. Herein, we hypothesize that a novel but complex long non-coding RNA (lncRNA) with embedded miRNAs and gene cluster, may potentially regulate BAT thermogenesis and metabolic health. Six-week-old lncRNA knockout (KO) mice and the corresponding C57BL/6 wildtype (WT) controls were fed either chow-diet (CD) or high-fat diet (HFD) for 12 weeks. Glucose tolerance and insulin tolerance tests were performed to assess glucose metabolism at 8 and 9 weeks of diet regimen respectively. Further, to assess the BAT function, energy expenditure and activity were estimated using indirect calorimetry and noldus openfield test respectively. From our analysis, we observed that the lncRNA KO mice exhibited significantly higher body weight compared to their age matched WT controls under both CD and HFD conditions. Upon further examination, we also observed an increase especially in the total brown adipose tissue with more beige content ($p<0.05$). In addition, the lncRNA KO mice not only exhibited a significant glucose and insulin intolerance characteristic but also demonstrated significant diminished oxygen consumption, carbon-dioxide release, heat expenditure and total activity. Our overall findings indicate that the lncRNA may be required for the maintenance of metabolic health by regulating brown adipose function. As brown adipose regulation has potential cardiac benefits, we implicate this lncRNA cluster to have a potential role in maintaining cardiometabolic health and is currently under investigation.

Single nuclei transcriptomics of epicardial adipose tissue from female pigs reveals differential effects of endurance exercise on resident innate and adaptive immune cells

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Coronary artery disease (CAD) is a leading cause of mortality. Although exercise mitigates CAD progression, the mechanisms by which exercise impacts epicardial adipose tissue (EAT) are unknown. We hypothesized that exercise modulates EAT to promote an anti-inflammatory microenvironment in the coronary arteries of female pigs. Adult female Yucatan pigs (n=7) were assigned to sedentary or exercise training treatments. EAT was collected for bulk and single nuclei transcriptomic sequencing. Log fold change expression data for bulk RNA seq were analyzed with Ingenuity Pathway Analysis. Microdroplet-based single nuclei transcriptome was analyzed using Seurat pipeline and the cell-cell interactome (CCI) analysis was performed using CellChat. Bulk RNAseq revealed that exercise upregulated G-protein coupled receptor signaling, S100 family signaling, FAK signaling, and glutathione-mediated detoxification pathways. In non-immune cells exercise upregulated genes related to fatty acid synthesis and cellular metabolism. With respect to immune cells, exercise upregulated cell adhesion associated oncogene and downregulated S100 calcium binding protein A9 in B cells. Exercise downregulated genes related to cell-cell adhesion and cellular metabolism in T cells. Although exercise increased macrophage numbers in EAT, genes related to protein folding and trafficking were downregulated in macrophages. All cell types in exercised EAT had increased interactions related to insulin-like growth factor 1 (IGF1) pathway. EAT from sedentary pigs had increased interactions for pathways related to atherosclerosis such as platelet derived growth factor and TGFβ. These results indicate that exercise has differential effects on innate (macrophage) and adaptive (B cells) immune cells in EAT and upregulates the differentiation and lipid storage capacity of EAT via increased cell interactions at IGF1. The precise function of IGF1 in adipose tissue cell types and the role of B cells in adipose tissue are unknown. Therefore, this research uncovers novel insights upon which to discover how exercise impacts these pathways and cell types in EAT.

Pathogenesis of Duchenne Muscular Dystrophy is Associated with Decreased Lymph Transport in Hindlimb and Inflammatory Lymphangiogenesis in Fast-Twitch Skeletal Muscle

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Progressive disability due to Duchenne Muscular Dystrophy (DMD) occurs in 1 of every 5000 males due to the X-linked mutation of the DMD gene. The lack of functional dystrophin results in the immune response remaining activated due to muscular injury during contraction, leading to an excessive and prolonged inflammatory state. This sustained inflammation can result in further tissue damage and contribute to the progression of the disease. Since the lymphatic system plays a crucial role in modulating inflammation at the local tissue and systemic levels, we hypothesized that compromised lymphatic structure and function in skeletal muscle is one of the major determinants contributing to DMD disease progression. We employed the DMD mouse model, D2.*mdx* mice, having the DMD gene mutation in the DBA/2J genetic background and a canine model, golden retriever with muscular dystrophy (GRMD). Results from micro-lymphangiography studies demonstrate that lymph transport was significantly reduced in D2.*mdx* mice when compared with control animals. Gadolinium-enhanced magnetic resonance imaging (MRI) of control and GRMD dogs showed a significant decrease in lymph transport in GRMD dogs comparing to the control group. Lymphatic functional study using isolated mouse flank lymphatic vessels infer that the diastolic diameter, phasic contractile frequency, and ejection fraction were significantly reduced in the 8-week-old D2.*mdx* mice when compared with the control mice. Additionally, inflammatory markers were significantly increased in the gastrocnemius, quadriceps, tibialis anterior, and extensor digitorum longus (EDL) muscles, whereas the soleus muscle was not affected in the D2.*mdx* mice when compared with control mice. Furthermore, the expression of key lymphatic markers was significantly increased in the quadriceps and tibialis anterior muscles and no significant changes were observed in the soleus muscle of 8-week-old D2.*mdx* mice. Immunohistochemical analysis detected the occurrence of pathological lymphangiogenesis within the muscle groups of 8-week-old D2.*mdx* animals. Taken together, our data show the first evidence that: 1) lymph transport function is decreased in both DMD mouse and canine models and 2) an increased inflammatory state in fast-twitch muscle fibers like the gastrocnemius, quadriceps, tibialis anterior, and EDL muscles might have contributed to the increase in the inflammatory lymphangiogenesis in DMD mice.

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Impact of VEGFR-3 signaling on macrophage polarization in kidney injury

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Acute kidney injury (AKI) is associated with increased pro-inflammatory (M1) and decreased anti-inflammatory (M2) renal macrophages. Lymphatic researchers have frequently identified VEGFR-3+ macrophages in their studies of inflammation. Other work suggests that VEGFR-3 signaling may impact macrophage plasticity. Manipulating renal lymphatics has been suggested as a potential therapy, but the impact of targeting VEGFR-3 signaling on macrophage polarization is not clear. We hypothesized that VEGFR-3 activation would increase M1 while its inhibition could increase M2 phenotype. We used a cisplatin (10mg/kg bw,ip) model of AKI in male and female wildtype mice receiving the VEGFR-3 inhibitor (MAZ51) or in KidVD mice (that inducibly express VEGF-D in the kidney) and examined their renal macrophage pools 7 days post-AKI. VEGFR-3+ renal cells were magnetically isolated, and macrophages were immunophenotyped by flow cytometry and were defined as M1 ($CD45^+CD11b^+F4/80^+CD11c^+CD206^-$) or M2 ($CD45^+CD11b^+F4/80^+CD11c^-CD206^+$) macrophages (or neither). Analysis in female mice revealed a significant decrease in M1 macrophages upon injury which is increased in KidVD mice with VEGF-D. Conversely, in males AKI increased M1 macrophages and manipulating VEGFR-3 signaling had no impact on macrophage polarization. Taken together these data suggest that the VEGFR-3+ macrophage response in renal injury varies between males and females improving our understanding of the identified sexual dimorphism in AKI. To further characterize the VEGFR3+ macrophages, we utilized bulk RNA sequencing of VEGFR3+ and R3- macrophages +/- injury. Using Integrated Differential Expression and Pathway analysis we identified the top signaling pathway enrichment significantly upregulated by renal VEGFR3+ macrophages to be immunoregulatory interactions and downregulated to be cellular lipid metabolism and fatty acid metabolism. These findings indicate renal VEGFR3+ macrophages are likely to control immunological outcomes following injury and are polarized towards M1 phenotype by downregulation of fatty acid metabolism.

The First Step into the World of Translational Research: A Tale from the Undergraduates

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As a fundamental step in a young scientist's career, the research laboratory is the birthplace of multigenerational breakthroughs and a place for exploration. Due to the uniqueness of each experiment, study, and group of individuals, the size, style, and classification varies in laboratories across the world. Despite the steep learning curve of working in a laboratory, it is essential for further application of universal techniques and understanding of the scientific field following graduation. Throughout this project, we explored the foundational aspects of participating in a scientific laboratory and its importance in research, and we will now present what we have learned. First, we will outline several ways to get involved in a research lab as undergraduates and begin networking. Next, we will present the safety procedures necessary for limiting contamination and protecting our researchers and their mice, the model organism used in this lab. After that, we will be explaining methods such as western blots and RNA extraction, which are utilized to understand epigenetic machinery and their impacts on gene expression and metabolic diseases. We will walk Biochemistry and Genetics undergraduate students through how to join a lab, learning essential safety protocols, and understanding scientific principles and techniques that will help them further in their research career.

METTL14-mediated N6-methyladenosine Modification of mRNA is Required for Maintaining Cardiac Function and Adaptive Hypertrophic Remodeling

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Background: Post-transcriptional modification of mRNA impacts transcript stability, splicing, and translation. N6-methyladenosine (m6A) is the most abundant mRNA modification in eukaryotic cells and is deposited by the m6A writer protein complex. Although dysregulation of m6A has been observed in many human diseases, only sporadic findings have suggested that m6A modification of cardiac mRNAs is required for normal cardiac function. Furthermore, m6A-dependent and independent mechanistic contributions of methyltransferase-14 (METTL14), a key component of the m6A writer complex, to cardiac structure and function are unknown.

Hypothesis: METTL14-mediated m6A mRNA modification is needed for normal cardiac function and compensatory response to pressure overload stress.

Methods: We used the Cre/loxP system to produce cardiomyocyte-specific *Mettl14* deletion (cm*Mettl14*(-/-)) and *Mettl14* overexpression (cm*Mettl14*(OE)) mouse models. We then conducted a study spanning survival, histological analysis, transthoracic echocardiography, transverse aortic constriction (TAC), mRNA and protein expression analysis, and RNA-seq.

Results: *Mettl14* deletion in cardiomyocytes resulted in 100% mouse mortality by 6 months of age. H&E and Masson's trichrome staining showed disorganized cardiomyocytes and fibrosis in cm*Mettl14*(-/-) mouse hearts. Transthoracic echocardiography revealed that cm*Mettl14*(-/-) mice developed heart failure with reduced ejection fraction (HFrEF) characterized by left ventricular (LV) dilation, reduced LVEF and decreased LV posterior wall thickness. Interestingly, HFrEF exhibited more severe and earlier onset in male cm*Mttl14*(-/-) mice. cm*Mettl*14(-/-) hearts also demonstrated lack of hypertrophy, decreased LVEF, and LV dilation in response to 2 weeks of pressure overload induced by TAC. Conversely, cm*Mettl14*(OE) mouse hearts showed elevated LVEF, decreased LV diameter, and increased LV posterior wall thickness. RNA-seq and follow-up gene ontology analysis revealed down regulation of genes involved in heart contraction and up regulation of pro-inflammatory genes in cm*Mettl14*(-/-) myocardium.

Conclusion: METTL14-mediated m6A modification of cardiac mRNAs and subsequent regulation of cardiac gene expression is required for normal cardiac function and compensatory structural remodeling in response to pressure overload. Therefore, modulating METTL14 and m6A modification of cardiac mRNAs may have therapeutic potential for HFrEF.

Hemadyne: Ultrafast pump recreates clinical hemodynamics and endothelial responses in preclinical human biology-modeling microsystems

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The vascular endothelium, integral to various physiological functions, operates under diverse hemodynamic forces. These forces significantly influence endothelial function, vascular health, and disease progression. However, due to limited flow responsivity, current in-vitro models struggle to mimic clinical hemodynamics accurately and reproducibly.

To address these limitations, we developed a novel tissue perfusion system capable of modelling transient, vessel-specific flow patterns at high temporal resolution. We utilized this system to examine the effect of diastolic flow reversal, a phenomenon associated with sedentary lifestyles and aging, on endothelial function and vascular health. The performance of our system was validated using in-vivo flow waveforms from multiple human vessels obtained via Doppler ultrasound, demonstrating its proficiency in emulating these complex waveforms with high fidelity and thus capturing the nuances of vessel-specific hemodynamics.

Importantly, we applied patient-specific waveforms from the brachial artery, with and without diastolic flow reversal, to endothelialized vessel-chip models. We observed that exposure to the waveform depicting diastolic flow-reversal led to a significant decrease in eNOS production and loss of endothelial barrier integrity, suggesting endothelial dysfunction. Conversely, waveforms without diastolic-reversal preserved barrier integrity and vasodilator function, indicating potential atheroprotective effects.

In conclusion, our novel perfusion system offers a refined in-vitro method for investigating the influences of variable flow patterns on vascular health. This advancement could spur in-depth studies into the progression of vascular diseases such as atherosclerosis, facilitating the identification of potential therapeutic strategies.

Keywords: Vascular Endothelium, Hemodynamic Forces, Tissue Perfusion System, Diastolic Flow Reversal, Doppler Ultrasound, Endothelial Dysfunction, Atherosclerosis.

DECOY PEPTIDE ATTENUATES THE SYNDROME OF PREECLAMPSIA IN A RODENT MODEL

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Background: Preeclampsia (preE) is a serious complication of pregnancy manifested by high blood pressure, proteinuria, and edema. We demonstrated that circulating levels of soluble (pro)renin receptor ((P)RR) were elevated at delivery in patients with preE, and both plasma and placental (pro)renin were found to be elevated in preE patients and in a rat model of preE. Decapeptide based on this handle-region sequence (handle-region peptides or HRP) can block binding of (pro)renin to (P)RR

Objective: The goal of this study is to develop and characterize HRP as an innovative treatment for preE.

Methods and Materials: The human extravillous cytotrophoblast (CTB) cell line Sw-71 used in these studies was derived from first trimester chorionic villous tissue. PRR (2 nM) was incubated in 1.0 mL medium with the receptor-expressing CTB cells for 0, 6, 12, 18, or 24 h, followed by renin activity assay to determine the percent binding and activation of PRR. Female Sprague-Dawley rats (200-250 g, first-time pregnant with confirmation by vaginal plug, Harlan) are randomly assigned to three groups (n=8 per group): 1) NP: normal pregnant rats; 2) PDS: pregnant animals injected initially with 12.5 mg of DOCA in a depot form intraperitoneally, followed by a weekly injection of 6.5 mg, and whose drinking water was replaced with 0.9% saline; 3) PDS-HRP: rats administered DOCA and saline as for Group 2, and also given HRP (10 mg/kg, i.p.) daily from day 10 through day 20 of pregnancy.

Results: (Pro)renin was non-proteolytically activated by binding to PRR on the cell membrane of CTB cells, while HRP inhibited binding and attenuated activation of PRR. The HRP decoy peptide normalizes blood pressure, proteinuria, and birth numbers in DOCA model of preE. When HRP was administered following the onset of hypertension, BP, proteinuria, and number of pups were normalized to control normal pregnancy.

Conclusions: HRP inhibits the binding of (pro)renin to PRR. This study in animal model of preE suggests HRP blockade of PRR can attenuate the disease. PRR and (pro)renin levels are elevated in preE patients and in their placenta, as well as in a rat model of preE. These data suggest HRP as a potential therapeutic for intervention in RAS signaling in preE.

The assessment of left ventricle infarct size using strains-percentage of infarct and strains-stiffness of infarct

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Introduction: The size of chronic scar in myocardial infarction (MI) adversely affects cardiac function and is a leading cause of mortality in the US and worldwide. Therefore, an accurate method for measuring infarct size is highly important. We aim to explore the correlation between strain and percentage of infarct and strain and stiffness, with the goal of developing a comprehensive approach for accurately and reproducibly quantifying infarct size in the left ventricle (LV).

Method: An inverse problem was set up for a biventricular finite element (FE) model to estimate active tension and the passive material properties of the infarct, healthy LV, and RV regions. We developed a large database of semi-synthetically FE heart models covering numerous possibilities of MI region location, shape, and stiffness. The endocardium surface was pressurized with a pressure wave of a maximum amplitude of 7.5 mmHg, and Green strains were computed in circumferential, radial, and longitudinal directions at end-systole. Statistical analysis was conducted to elucidate the correlation between the average strains of infarcts and both the percentage of infarct size in the left ventricle, as well as the stiffness of the left ventricle.

Results: The average circumferential and radial strains exhibited positive and negative strains, respectively, in the regions affected by infarction. Both strains in the infarcted areas demonstrated an inverse relationship with those observed in the healthy myocardium as the infarct size increased. Conversely, an increase in stiffness resulted in a decrease in the magnitude of both strains. Both strains showed a significant relationship between the size of the infarct and the stiffness of the affected region.

Conclusion: The statistical analysis showed a strong correlation between strains, infarct size, and stiffness, suggesting that circumferential, radial, and longitudinal strains can serve as predictive indicators for the existence and size of infarction in the left ventricle.

Drop-like nuclear deformation in endothelial cells

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Mechanical stresses from the extracellular environment, such as shear stresses, are propagated to the endothelial nucleus. How the nucleus mechanically responds to these stresses is not well understood. We have recently proposed the "nuclear drop model" for explaining nuclear deformation in cells. Key features of the nuclear drop model are 1) the nucleus deforms at constant surface area and volume, 2) folds/wrinkles in the nuclear lamina allow facile deformation, and 3) the nuclear lamina resists extension by cellular stresses once the folds in the lamina are fully unfolded, resulting in a surface tension in the nuclear drop and a nuclear pressure. Here we tested the nuclear drop model in human umbilical vein endothelial cells (HUVEC). Treating HUVECs with cytochalasin D, to cause the appearance of wrinkles/folds in the lamin B1-labelled nuclear lamina, showed that nuclear surface area and volume were unchanged between these conditions, consistent with the nuclear drop model. Performing an Elliptical Fourier analysis on confocal fluorescent images of the lamin A-stained nucleus to calculate the Elliptical Fourier Coefficient (EFC) ratio demonstrated that the EFC ratio was significantly lower in cytochalasin treated cells compared to control, consistent with the presence of excess area in rounded endothelial nuclei. Treatment with IL-6, an inflammatory cytokine, in HUVECs exposed to shear stress also caused the appearance of folds/wrinkles in some cells. The EFC ratio directly correlated with YAP translocation to the nucleus, consistent with the hypothesis that YAP can translocate to the nucleus upon a development of surface tension in the nuclear lamina. These results collectively suggest that the nucleus undergoes drop-like deformation in endothelial cells.

INCREASED LEVELS OF URINARY ANGIOGENIC FACTORS AND MARINOBUFAGENIN IN PREECLAMPSIA PATEINTS

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Background: Preeclampsia (preE) is a syndrome which occurs in 3-10% of pregnancies and is a leading cause of maternal and fetal morbidity and mortality. The precise etiology (etiologies) of this syndrome remain(s) unknown. There is no single biomarker for detection of the syndrome.

Objective: To measure angiogenic, antiangiogenic factors, and MBG in urine of pregnant patients with and without preE.

Methods: A prospective cohort of patients with normal pregnancies and of those with preE were recruited. sFlt-1, soluble endoglin (sEng), PlGF, TGF-β-1, VEGF, and MBG were assayed using ELISA and results corrected to units per mg creatinine. Patient characteristics were compared using Chi-square tests for proportions, Student's t test for parametric data, and Mann-Whitney U test for nonparametric data. $P < 0.05$ was taken as significant. Variation associated with gestational age was examined using correlations and when appropriate linear regression equations were obtained. Receiver operator curves (ROC) were examined to establish criteria levels for those factors that varied with preeclampsia.

Results: In total, 40 patients with normal pregnancies were sampled between 22 and 39 weeks gestation and 30 patients with preE were sampled between 28 and 39 weeks gestation. As expected, groups differed ($p < 0.02$) for blood pressure, gestational age at delivery, and age. They did not differ for weight ($p = 0.28$), height ($p = 0.38$), and creatinine levels ($p = 0.29$). Groups differed in sEng ($p = 0.016$), PlGF ($p = 0.018$), sFlt-1 ($p = 0.00066$), and MBG ($p < 0.0001$). The PlGF levels were less in preE while sEng, sFlt-1 and MBG levels were increased. TGF-β-1 and VEGF did not differ between groups ($p > 0.14$). Only urinary MBG was found to vary with gestational age in preE ($p = 0.0009$). MBG, sFlt-1, PlGF, and sFlt-1/PlGF ratio had significant ROC area under the curve measures ($p < 0.02$) with criteria for preeclampsia that provided sensitivities between 65 and 88% and specificities between 74 and 96%.

Conclusions: Urinary levels of angiogenic and antiangiogenic factors and MBG as measured in urine demonstrated differences in patients with clinical diagnosis of preE. Urine specimen procurement and assay are less invasive and potentially more acceptable for assessment of preE.

Detection of biomechanical alterations in the left ventricle due to radiation-induced cardiotoxicity

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Cancer-related radiation therapeutics have been associated with the development of radiation-induced cardiotoxicity (RICT), potentially leading to severe cardiac remodeling. The current protocol for diagnosing RICT is performed through organ-level measurements of ejection fraction (EF) in the left ventricle (LV). However, these measures are not adequately sensitive to subclinical ventricular dysfunction in the early stages. Thus, the in-vivo detection of such cardiac remodeling remains largely elusive. We hypothesize that the evaluation of in-vivo cardiac deformation through regional strain analysis will be an effective predictor of RICT. Such analyses are proven sensitive markers to diseases such as hypertrophic cardiomyopathy and myocardial infarction. In addition to calculating anatomical strains, we propose principal strain markers and investigate their sensitivity to RICT and the transmurality of strain distribution. We implement a longitudinal study to characterize the incidence of RICT-related cardiac dysfunction in murine heart models. Two groups subjected to radiation therapy (RT) with varying protocols of 8Gy (n=14) and 24Gy (n=15) whole-heart irradiation were studied. Cardiovascular magnetic resonance (CMR) imaging in conjunction with non-rigid image registration was used to assess the global and regional LV contractility at the baseline, three- and six-months post-RT. Our findings showed the effects of RT in reducing the LV contractile function by around 50% despite relatively unchanged EFs. Regional strain analysis also yielded insights into the decline in endocardial contractility, with principal markers showing promise in capturing the transmurality of strain distribution. Our study highlighted the utility of the proposed strain markers in describing subclinical ventricular dysfunction to improve the early-stage detection of RICT. Such markers can potentially improve risk stratification and ultimately develop individualized therapeutic strategies to improve survival outcomes.

Optimizing Implantable Sleeve Design for Improved Left Ventricular Function Post-Myocardial Infarction: A Computational Approach

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The study focuses on mitigating the adverse remodeling of the left ventricle (LV) following myocardial infarction (MI) by optimizing epicardial sleeve designs, specifically by exploring the potential of auxetic architecture. A computational biventricular (BV) model, reflective of infarcted murine hearts, and a simplified spheroidal model were created. These integrated hyperelastic, transversely isotropic material properties and active force parameters utilizing an inverse model and the Frank-Starling relationship in the simulation framework. The research evaluated various geometries of the epicardial sleeve and the architectural patterns of auxetic surfaces. Preliminary findings suggest that epicardial sleeves effectively reduce end-diastolic volume (EDV), prevent dilation, and normalizes fiber strains compare to MI. While the implementation of epicardial sleeves led to a $\sim$10% increase in ejection fraction (EF), auxetic sleeves showed potential for further enhancements. Optimal outcomes were observed when the sleeve covered the infarct area in acute MI models. These findings underline the potential of personalized epicardial sleeve designs in enhancing cardiac function following MI. It highlights the necessity for tailoring the sleeve design to the unique characteristics of individual infarcted heart models for optimal patient outcomes. The study concludes with a call for future research to focus on patient-specific epicardial sleeve implants, investigating innovative design concepts, materials, and their long-term safety and effectiveness in clinical environments.

Pathogenesis of Amyotrophic Lateral Sclerosis is Associated with Impairment of Lymphatic Function

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Amyotrophic Lateral Sclerosis (ALS) is a fatal neurodegenerative disease caused by a combination of environmental, genetic, and age-related factors. Patients with progressive muscle atrophy and motor neuron degeneration are usually clinically diagnosed with ALS. Unfortunately, there is currently no cure for ALS, and the three FDA-approved drugs, *Rilutek*, *Radicava* and *Relyvrio*, only marginally slow down disease progression. Therefore, there is dire need for extensive research to identify alternative treatment methods for ALS. One of the most common causatives of ALS is a mutation of the Superoxide dismutase 1 gene (*SOD1*), which often results in substitution of Glycine 93 or Aspartic Acid 90 with Alanine (G93A and D90A, respectively) or Alanine 4 with Valine (A4V). These mutations have been studied to be associated with the inflammatory and immune abnormalities occurring in ALS models. Since the lymphatic system plays active roles in both the resolution and progression of inflammation, we hypothesized that lymph transport is compromised in the ALS mice. Firstly, we assessed motor fatigue and coordination of control and ALS mice by subjecting them to an accelerating rotarod test. We then employed micro-lymphangiography to determine hindlimb lymph transport in pre-symptomatic (9-week-old) and symptomatic (16-week-old) SOD1-G93A ALS mice as well as noncarrier control mice. The obtained fluorescence images were analyzed using ImageJ software to determine the lymphatic conductance in control and ALS groups. Additionally, we conducted lymphatic functional studies using isolated flank lymphatics from the control and ALS mice, evaluating parameters of lymphatic contractility by tracing outer diameter changes obtained during systole and diastole. The rotarod test confirmed that the symptomatic group exhibited muscle weakness compared to the control group. Micro-lymphangiography results demonstrated that ALS mice exhibit slower and reduced lymph transport at both pre-symptomatic and symptomatic stages compared to their respective control groups. The 16-week-old ALS mice exhibited a further decrease in lymph transport relative to the 12-week-old group ALS mice. Finally, the isolated vessel functional analysis revealed that lymphatics from ALS mice showed a significant reduction in vessel diameter and phasic contractile frequency which in turn shows reduction in pump function of the vessels. Thus, the findings from our study provide the first evidence that lymphatic transport function is impaired in the ALS mice and could potentially be targeted as a therapeutic strategy.

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Integrated right ventricular-pulmonary artery biomechanics in pulmonary hypertension

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Introduction: Pulmonary hypertension (PH) is defined as an elevation in mean pulmonary arterial pressure and leads to the remodeling of the pulmonary artery (PA) and pulmonary vasculature following the increased resistance in the downstream capillary bed, requiring a larger RV afterload to maintain the flow rate at the capillaries. Despite significant advances in studying RV and PA remodeling, the correlation between RV and PA remodeling remains understudied.

Materials and Methods: Mild model of PH was induced by placing Sprague Dawley (SD) rats (N=6) in a hypoxia (Hx) chamber (10%O2) for 3wks. Severe PH was induced by injecting SU5416 (20mg/kg sc) into Fischer (CDF) (N=6) and placing them in a hypoxia chamber for 3 weeks, followed by 1wk of normoxia (SuHx). The respective controls (N=6 each) were placed in normoxia. RVFW and PA tissues were harvested and subjected to mechanical testing. To analyze the PA remodeling, the pulmonary vasculature was reconstructed from μCT imaging. A 1-D fluid-structure interaction (FSI) model was used to determine the contributions of narrowing and stiffening of the PA on RV afterload.

Results and Discussion: RVFW stiffness increased in both mild and severe PH, with a larger increase in the SuHx rats (SuHx- 264±58 vs 1070±248 kPa; Hx- 231±67 vs 422±82 kPa). The results indicate a strong relationship between RVFW remodeling and RV-PA uncoupling (TAPSE/RVSP). The uniaxial testing of the PA specimen revealed that the PA stiffness increased significantly in the circumferential direction for the SuHx rats (SuHx- 280±215 vs 876±437 kPa; Hx- 296±121 vs 163±54 kPa). Based on the FSI simulations, the combined effect of the remodeling events triples RV afterload.

Conclusions: Results from the study indicate that both the RVFW and pulmonary vasculature undergo significant remodeling due to PH. Distinguishing the contributions of various vascular remodeling events on the function of the RV can provide new insights into risk-stratification markers and aid in identifying optimal therapeutic targets.

Depletion of m6A Stimulates Innate Immune Signaling in the Heart

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Background: Immune system dysfunction and elevated cytokine levels are frequently observed in heart failure patients, and cardiac inflammation has been shown to correlate with adverse left ventricular (LV) remodeling and dysfunction, the cardinal features of heart failure with reduced ejection fraction (HFrEF). Cardiac inflammation can be initiated by the cardiomyocyte, however the molecular mechanisms underlying this phenomenon are not completely understood. N6-methyladenosine (m6A) modification of mRNA is frequently dysregulated in heart failure patients, and depletion of m6A has been shown to activate innate immune signaling pathways in several cell types. However, the impact of m6A depletion on cardiomyocyte-intrinsic innate immune signaling, cardiac inflammation and downstream adverse LV remodeling is unknown.

Methods: We used Cre-Lox recombination to produce genetic deletion of methyltransferase-14 (*Mettl14*), a key regulator of m6A, exclusively in ventricular cardiomyocytes of mice. H&E and Masson's trichrome staining were performed. RNA was isolated from ventricular myocardium using TRIzol, RNA-seq was performed, and mRNA expression was validated using qPCR.

Results: cm*Mettl14*(-/-) mice showed early-onset HF with 100% mortality by 6 months of age. Total m6A levels were decreased in cm*Mettl14*(-/-) mouse hearts. Immune cell accumulation and fibrosis were observed in cm*Mettl14*(-/-) mouse hearts. Gene ontology and gene sets enrichment analysis revealed upregulation of proinflammatory genes and downregulation of genes involved in aerobic metabolism in cm*Mettl14*(-/-) hearts. Follow-up qPCR confirmed increased expression of transcripts that stimulate inflammation (Nlrp3, Il1β) and type-I interferon signaling (Ifnb1, Ifit1, Ifit3, Cxcl10, Zbp1, Oasl1, Oas1a) in cm*Mettl14*(-/-) mouse hearts. qPCR also revealed downregulation of transcripts involved in aerobic ATP synthesis (Aco2, Cs, Dlat, Sdha, Sdhb, Sdhc, Suclg1, and Suclg2) in cm*Mettl14*(-/-) hearts.

Conclusion: Ultimately, these data suggest that depletion of m6A in cardiomyocytes may activate intrinsic innate immune signaling pathways that could disrupt essential cellular processes, promote cardiac inflammation, and accelerate heart failure disease progression. Therefore, restoring m6A in cardiomyocytes could attenuate maladaptive immune system activation and may have therapeutic potential for HFrEF.

NOVEL PEPTIDE B7-33 DEMONSTRATES EFFICACY IN RAT MODELS OF PREECLAMPSIA

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Background: Preeclampsia (PreE) is a hypertensive pregnancy disorder, which occurs in approximately 10% of all gestations. The literature suggests potential therapeutic role of H2 relaxin in PreE. Due to the complex insulin-like structure of relaxin (A- and B- chains, 53 amino acids, 3 disulfide bonds), a novel H2 relaxin B-chain-only peptide variant B7-33 (27 amino acids without any disulfide bonds) has recently been developed.

Objective: This single-chain peptide displayed equivalent efficacy to the natural H2 relaxin in several functional assays both in vitro and in vivo. The Aim of this study is to evaluate whether B7-33 attenuates preE syndrome in rat models of PreE.

Methods: Rat Model 1. The efficacy of B7-33 was evaluated in the Reduction of Uterine Perfusion Pressure (RUPP) model as described previously. RUPP rats are randomly assigned to 4 groups (N=8/group): 1) vehicle, 2) B733; 3) B733-Fc; and 4) B733-HSA. Rats are dosed twice weekly (i.v.) from GD10 to GD 20. Rat Model 2. Timed-pregnant rats are used, and the model is conducted as previously described. DOCA and saline administration begin at approximately GD2. Three groups of animals are studied (n=8 per group). 1) normal pregnant rats; 2) pregnant animals injected (i.p.) initially with 12.5 mg of DOCA, followed by a weekly injection of 6.5 mg, and whose drinking water was replaced with 0.9% saline; 3) rats administered DOCA and saline as for Group 2, and given B733 35 ug i.p. biweekly from GD10-20. BP, proteinuria and inflammatory markers were evaluated. Statistical comparisons were performed using analysis of variance with Duncan's post hoc test.

Results: RUPP rats have increased MAP, plasma TNF-α, and plasma sFlt-1 along with decreased NO index compared to normal pregnancy. Treatment with B733 and B7-33 fusion proteins lowers MAP, TNF-α, and sFlt-1 back to that of normal pregnancy. B7-33 data are consistent with earlier data with serelaxin in the RUPP model. All fusions tested ameliorate hypertension in the RUPP animals. B7-33 normalizes BP and proteinuria in the DOCA rat model of preE.

Conclusion: Both B7-33 and B7-33 fusion proteins attenuate preE syndrome in RUPP and DOCA rat models of PreE. We conclude that B7-33 is an ideal candidate for development as a novel therapeutic in preE.

Impact of lymphangiogenesis on renal phosphate handling following kidney injury

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Overconsumption of inorganic phosphate (Pi) increases kidney dysfunction and renal tubular cell damage, hallmarks of kidney disease. Conversely, acute kidney injury (AKI) and chronic kidney disease (CKD) result in Pi retention and hyperphosphatemia. We hypothesized that damage caused by chronic Pi consumption likely induces lymphangiogenesis in the kidney and by manipulating renal lymphatic density may alter how the kidney handles Pi balance. We first identified increased lymphangiogenesis and elevated levels of lymphangiogenic ligands VEGF-C and VEGF-D in kidneys of mice consuming a 2% Pi diet for 3 weeks or 2 months by immunofluorescence. We utilized "KidVD" mice, a mouse model of kidney-specific inducible expression of VEGF-D, to expand renal lymphatic density and test its impact on Pi handling. Serum Pi, 24-hr urinary Pi excretion, and fractional Pi excretion were equivalent in KidVD mice compared to littermates on chow or high Pi diets. KidVD mice, also, demonstrated significantly higher expression of phosphate related genes *Rgs14* and *Nherf1*. In a Pi-driven CKD model, mice were injured with a single 10 mg/kg cisplatin dose, 2 weeks recovery period, then placed on either chow or 2% Pi diet for 3 weeks with VEGF-D induction. The kidney injury led to Pi retention in all mice. Male KidVD demonstrated significantly increased Pi excretion (total and fractional) compared to their littermates despite reduced glomerular filtration. Injured KidVD also demonstrated significantly higher gene expression of *Rgs14*. Renal VEGF-D overexpression and lymphangiogenesis thus appears to decrease Pi retention following AKI potentially aiding in a future recovery response from CKD.

PRAVASTATIN MITIGATES HYPERGLYCEMIA- INDUCED CYTOTROPHOBLAST DYSFUNCTION

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Objective: Despite advancements in our understanding of preeclampsia (preE), there are currently no effective therapies to prevent the disease. Pravastatin shows promise by attenuating pathophysiologic processes associated with preE such as decreased cytotrophoblast (CTB) migration, aberrant angiogenesis, and increased oxidative stress. This study assesses the effects of pravastatin on hyperglycemia-induced CTB dysfunction and its use as a potential drug for the prevention of preE.

Methods: Human CTB cells were treated with 100, 150, 200, 300, or 400 mg/dL glucose for 48 hours. Some cells were pretreated with pravastatin (1ug/mL), while others were cotreated with pravastatin and glucose. Expression of urokinase plasminogen activator (*uPA*), plasminogen activator inhibitor 1 (*PAI-1*), proliferating cell nuclear antigen (*PCNA*), and *p38 MAPK* phosphorylation were measured by western blot. *uPA* and *PAI-1* mRNA was measured by quantitative PCR. Angiogenic (vascular endothelial growth factor [*VEGF*], placenta growth factor [*PlGF*]) and antiangiogenic factors (soluble fms-like tyrosine kinase-1 [*sFlt-1*], soluble endoglin [*sEng*]) were measured by enzyme-linked immunosorbent assay (ELISA) kits. Statistical comparisons were performed using analysis of variance with Duncan's post-hoc test.

Results: The hyperglycemia-induced downregulation of *uPA* was attenuated in CTB cells pretreated with pravastatin at glucose levels >200 mg/dL, and cotreated at glucose levels >300 mg/dL ($p<0.05$). The hyperglycemia-induced downregulation of *PAI-1*, *PCNA*, *VEGF*, and *PlGF* and the upregulation of *p38* phosphorylation, *sENG*, and *sFlt-1* were also attenuated in both pretreatment and cotreatment samples in all groups regardless of glucose dose ($p<0.05$).

Conclusions: Pravastatin mitigates the CTB cell dysfunction initiated by hyperglycemic conditions by attenuating the glucose-induced down-regulation of *uPA*, *PAI-1*, and *PCNA* expression, up-regulation of *p38* phosphorylation, downregulation of *VEGF* and PlGF, and upregulation of *sFLT-1* and *sEng*, thereby decreasing the stress signaling response that normally leads to abnormal placentation, and is associated with the development of preE in pregnancy.

Key words: Preeclampsia; Hyperglycemia; Cytotrophoblast; Pravastatin; Migration

Exposure to cannabinoids and alcohol during the second trimester impairs arterial resistance and increases cardiac stroke volume in fetal cerebral arteries

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Background: Children prenatally exposed to cannabinoids or alcohol can demonstrate growth deficits and increased expression of neurological disorders, however investigations into the effects of simultaneous alcohol-and-cannabinoid exposure (SAC) on developing neurobiology are currently minimal. During the second trimester, fetal brain vasculature emerges during peak periods of neurogenesis, supporting fetal nutrition, growth, and neural development. Therefore, our research group wanted to investigate whether prenatal polysubstance exposure alters fetal-directed blood during second-trimester exposure.

Methods: We performed high resolution *in vivo* ultrasound imaging in C57Bl/6J pregnant mice. After pregnancy confirmation, dams were assigned to one of four groups: drug-free control, alcohol-exposed, cannabinoid-exposed or SAC-exposed. Drug exposure occurred daily between Gestational Days (G)12-15. For cannabinoid exposure, dams received an i.p injection of cannabinoid agonist CP-55940 (750µg/kg), with controls receiving volume-equivalent saline. For ethanol exposure, dams were placed in ethanol vapor chambers for 30min of inhalation (95% ethanol), and controls were placed in identical chambers without ethanol administration. Dams underwent ultrasound imaging on three days of pregnancy: G11 (pre-exposure), G13.5 (peri-exposure) and G16 (post-exposure).

Results: Compared to controls, only SAC dams experienced a dip in gestational weight gain while undergoing drug exposure. Furthermore, SAC dams demonstrated notably higher (+42mg/dL) blood ethanol concentrations than dams exposed to alcohol-only. Ultrasound analyses of fetuses indicate that both alcohol and cannabinoid exposures reduce blood flow acceleration, a measure of arterial resistance, and Velocity-Time Integral (VTI), a metric of stroke volume, in the middle cerebral and internal carotid arteries on G16, 24hrs after drug exposure has ended. Notably, SAC fetuses exhibit an augmented reduction in VTI within these same arteries. In contrast, drug exposure did not affect umbilical arterial blood flow measurements, and subsequent within-animal analyses indicate fetal blood flow is being directed away from the brain following drug exposure, particularly in cannabinoid-exposed fetuses. Importantly, no group differences in these measures existed prior to drug exposure (G11).

Conclusions: Our results indicate that prenatal drug exposure may lead to persistent reductions in fetal-directed blood flow, which can disrupt normal embryonic growth and neural development, and SAC may augment deficits specifically in cerebral arterial blood flow.

Inhibition of CXCR2 targets tumor-infiltrating g-MDSCs and T cell exhaustion to suppress immune evasion and lymphangiogenesis in cholangiocarcinoma

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Cholangiocarcinoma (CCA) is a highly aggressive cancer of the biliary epithelium with a 5-year survival rate of only 2%. The CCA TME has been characterized as having significantly higher lymphangiogenesis vs angiogenesis, yet tumor-lymphatic interactions have been elusive. Granulocytic myeloid derived suppressor cells (gMDSCs) are highly implicated in causing immune evasion in multiple cancer types. However, their role in CCA in the context of CCA metastasis and lymphangiogenesis remains unexplored. Previously, we have shown that CXCR2 is significantly induced in CCA tumor models and multiple studies show that CXCR2 plays a critical role in recruitment and trafficking of gMDSCs. Hence, we hypothesized that CXCR2 mediated modulation of gMDSCs regulates aggressive LN metastasis of CCA via activation of immunosuppressive pathways. In this study, we report the effects of SB225002, a small molecule inhibitor of the C-X-C receptor 2(CXCR2) both alone as well as synergistically with sorafenib, (protein tyrosine kinase inhibitor of VEGFR that also inhibits gMDSC migration), on MDSC infiltration and the ensuing effects in CCA metastasis and tumorlymphangiogenesis. CXCR2 deficiency prevented CD11b+Ly6Ghi MDSC trafficking to the tumor while also reversing significant T cell exhaustion observed in the tumor bed. CD8+ T cells when treated with CCA gMDSC conditioned media induced expression of several immunosuppressive genes with significantly enhanced expression of lipocalin 2 (LCN2), that is known to be associated with liver injury and tumor progression. Our data also showed that combinatorial treatment of SB225002+Sorafenib showed significant reduction in lymphangiogenesis as determined by Lyve1-CK19 immunofluorescence staining. These findings present a translatable strategy that will have significant implications for future studies using immune checkpoint inhibitors and suppression of CCA growth and progression by preventing trafficking of MDSCs to the tumor site and inhibition of gMDSC and T cell crosstalk.

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High-Fat High-Fructose Diet Elicits Epigenetic Modification in Kidney via miR-21-5p

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Cardiometabolic syndrome is a cluster of several cardiovascular and metabolic dysregulations including type 2 diabetes mellitus, obesity, hypertension, dyslipidemia, and chronic kidney disease; however, the mechanisms mediating these risks remain unclear. Consumption of fructose along with high fat diets has steadily increased over the past 30 years in parallel with the progression of the diabesity epidemic that contributes to renal dysfunction. Here, we hypothesized that the consumption of a high fat-high fructose diet can lead to the progression of chronic kidney disease via epigenetic modifications. Six-week old mice were fed on either low-fat diet (LFD), high-fat diet (HFD), or high-fat high-fructose diet (HFHFD) for 20 weeks. Our group previously published that in HFD and HFHFD fed mice there was significantly increased body weight, fasting glucose levels, and impaired insulin sensitivity compared to LFD fed mice. In the present study, global DNA methylation was significantly downregulated in kidneys from HFD and HFHFD fed mice compared to LFD while liver and adipose tissue DNA methylation were unaltered. Consistent with these results, DNA methyltransferase (DNMT) activity, which is responsible for DNA hypermethylation and the gene expression of methionine adenosyltransferase 2a (MAT2a), which catalyzes the formation of the methyl donor S-adenosylmethionine (SAMe), were significantly decreased in HFHFD mice compared to LFD mice. Interestingly, microRNA-21 that is known to regulate expression of MAT2a and promote the progression of diabetic nephropathy was significantly upregulated in HFHFD fed mice. This led us to consider that the fructose may be the resposible for the above abberations. We then validated the effect of fructose *in vitro* by treating Human Embryonic Kidney (HEK) 293 cells with 100mM fructose for 1h, 2h, 3h, 4h, and 5h. We observed a significant increase in miR-21-5p at 2h of treatment with a concomitant significant decrease in MAT2a expression at 3h which remained significantly decreased until 4h of fructose treatment. Our findings suggest that HFHFD leads to attenuation of MAT2a expression via upregulation of miR-21-5p potentially elicited by fructose. Currently, we are pursuing an in-depth analysis of MAT2a and miR-21-5p in the diet induced diabesity scenario using Ingenuity Pathway Analysis Software. Further investigation into the role of miR-21-5p in kidney dysfunction can pave way for the development of novel therapeutics strategies to address metabolic complications leading to chronic kidney disease.

Endothelial nitric oxide pathway or calcium-activated potassium channels do not mediate lymphatic responses to short-chain fatty acids

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Mesenteric lymphatic vessels are exposed to significantly high concentrations of short-chain fatty acids (SCFAs), the metabolites of the intestinal microbiota. We reported earlier that SCFAs—acetate (AC), propionate (PP), and butyrate (BT) decreased lymphatic pumping in vitro in a concentration-dependent manner, and the blockade of free-fatty acid receptors 2 and 3 (FFAR2 and FFAR3) completely restored pumping. Studies in blood vessels reported that endothelium was essential for SCFA-induced vasodilation, and endothelial nitric oxide (NO) pathway and calcium-activated small (SK) and intermediate (IK) -conductance potassium channels mediated vasodilation. Therefore, in the present study, we evaluated the effects of blocking endothelial NO pathway and SK/IK channels on lymphatic responses to SCFAs. The effects of AC (10 mM), PP (10 mM), and BT (10 mM) were characterized in vitro in separate rat mesenteric lymphatic vessels treated with N(ω)-nitro-L-arginine methyl ester (L-NAME; a NOS blocker; 100 μM) or Apamin (AP, SK blocker, 0.1 μM) + Tram34 (IK blocker, 1 μM). In spontaneously contracting lymphatic vessels, pumping indices were determined at the baseline, after treatment with a blocker, and after treatment with blocker + AC, PP, or BT. Compared to treatment with blocker (L-NAME or AP + Tram34), lymphatic contraction frequency and normalized pump flow were significantly lower after treatment with blocker + AC, PP, or BT. Short-chain fatty acids exert their effects through binding to G protein-coupled receptors FFAR2 and FFAR3 in blood and lymphatic vessels. However, these data suggest that, unlike in blood vessels, endothelial NO pathways or SK/IK channels do not contribute to SCFA signaling in lymphatic vessels.

Hypertensive Stimuli Increase Pro-Inflammatory Bone Marrow Derived Macrophages In Vitro

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Hypertension (HTN) is a leading risk factor for cardiovascular disease and is associated with inflammation. The kidneys are highly sensitive to blood pressure changes and are crucial in regulating blood pressure. Macrophages play a key role in HTN as they are known to infiltrate the kidneys when blood pressure is increased, thereby propagating renal inflammation. In murine angiotensin II-induced and salt-sensitive models of HTN, we and others have identified increased renal activated macrophages (CD45+ CD11b+ F4/80+ CD38+) and pro-inflammatory M1 macrophages (CD45+ CD11b+ F4/80+ CD11c+ CD206-). In this study, we hypothesized that angiotensin II and salt directly induce macrophages to become activated and pro-inflammatory. We exposed bone marrow derived macrophages (BMDMs) grown in GM-CSF to angiotensin II (0.01 μm) and salt (190 μm) and found that there were significant increases in activated macrophages (CD45+ CD11b+ F4/80+ CD38+), pro-inflammatory M1 macrophages (CD45+ CD11b+ F4/80+ CD11c+ CD206-), and activated M1 macrophages (CD45+ CD11b+ F4/80+ CD11c+ CD206- CD38+) as determined by flow cytometry. However, BMDMs grown in M-CSF, the more traditional factor present in culturing BMDMs, did not become activated or pro-inflammatory following angiotensin II or salt treatment. Next, we will identify renal pro-inflammatory cytokines, chemokines, growth factors, and levels of GM-CSF present in these mouse models of HTN. Currently, these findings suggest that GM-CSF increases macrophage responsiveness to HTN stimuli and induces activated and pro-inflammatory macrophages which may contribute to the development and progression of HTN. Targeting activated renal macrophages or renal GM-CSF may provide a new therapeutic option for the treatment of HTN.

INVESTIGATION OF THE IMPACT OF IN UTERO THIRDHAND E-CIGARETTE EXPOSURE ON PLATELET FUNCTION

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Cardiovascular disease (CVD) is the leading cause of death worldwide, with many deaths being due to heart attacks and stroke. To this end, platelets are key players in maintaining and regulating "hemostasis" in the cardiovascular system. However, a disruption in the platelet function (hyperactivity) can promote the genesis of occlusive (thrombosis-based) CVD. Though there are many known risk factors for CVD, the number one preventable risk factor is exposure to tobacco or tobacco related products. Interestingly, the use of emerging tobacco products, specifically e-cigarettes (e-cigs) has been on the rise, achieving unprecedented levels, due to the misconception that they are a safe(r) alternative to traditional cigarette smoking, especially amongst pregnant women or women of childbearing age. Therefore, there has been efforts- including by our laboratory- to characterize the negative effects of smoking on the CV system. To this end, we have previously shown that direct exposure to e-cigs increases the risk of occlusive CVD. However, the effects of indirect exposure to e-cigs, namely thirdhand exposure, which is formed from toxicants "produced" by e-cig vapor that accumulate on surfaces such as upholstery, curtains, car seats, carpet etc., are still unknown, including under *in utero* settings. To this end, the present studies aim to characterize the impact that in utero thirdhand e-cig (IUTHEC) exposure exerts on platelet function and the CV system and examine the mechanism of these effects. Utilizing a custom e-cig vape system mice were housed with clean air or e-cig-exposed material for one week prior to mating and for the duration of their pregnancy. Using this approach to mimic a real life exposure scenario, our preliminary results indicate that IUTHEC exposed pups exhibited a shortened bleeding and thrombus occlusion times, in two widely used hemostasis and thrombosis models. In terms of the mechanism of this prothrombotic phenotype, it was found that platelet aggregation, as well as dense and alpha granule secretion were potentiated in the IUTHEC exposed mice in response to agonist stimulation. Furthermore, integrin activation and phosphatidylserine exposure, additional markers of platelet function, were also found to be enhanced. These data together demonstrate for the first time that IUTHEC increases the risk of thrombotic CVD in part via modulation of platelet activation. Moreover, our findings highlight the negative health effects of exposure to IUTHEC, which is an underappreciated threat to human health.

AI-enabled vascularized biological systems: Evaluation of oxygen transport from microscopic images

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Microfluidic models of human tissues fenestrated with microvascular networks, called vascularized microphysiological systems (MPS), have gained increasing attention for their applications in drug discovery, toxicity screening, and disease modeling. A critical limitation in determining the vascular network quality and health of these systems, however, is a reliance on morphological analysis. Since 2D microscopic images are routinely and easily acquired during the course of biological analysis within MPS, they may serve as a dataset on which artificial intelligence models can be developed that predict physiologically-relevant biological function of these vascularized biosystems. To leverage this, we first developed an in silico computational platform, called AngioMT, which models the oxygen transport dynamics through confocal images of vascular networks formed in MPS. This software was validated against in vivo measurements. Next, we used this as ground truth to train machine learning models to serve as a diagnostic measure of the health of vascularized MPS. We created a database of over 500 images of microvascular networks on-chip, performed an exploratory data analysis to short-list several AI/ML architectures, and tested these using contemporary data science practices. We found that regression models and random forest algorithms can integrate several morphological metrics of vascularized metrics and together. However, while they may reasonably correlate to oxygen transport, they imposed high collinearity. Therefore, we also designed a novel, chained neural network architecture that predicted oxygen transport dynamics to the highest degree. The predicted transport, outputting a single metric called the Vascular Network Quality Index, is more representative of oxygen transport dynamics, and thus vascular quality, compared to the previously-used vascular morphological metrics. In summary, we offer a biologically inspired, evaluative pipeline for scoring vascular networks in organoids, organ-on-chips and other biology model systems that might be adopted in future standardization and/or regulatory efforts.

Investigating the feasibility of predicting myocardial fiber architecture using cardiac strains

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Myofiber architecture is designed to provide optimal contractile behavior in a healthy state, and architectural remodeling in diseased hearts impairs contractile motion. In-vivo quantification of myo-architecture provides a higher-fidelity tissue remodeling marker, promising to improve several cardiac diseases' early diagnosis and prognosis. The study of the cardiac structure using diffusion-tensor magnetic resonance imaging (DT-MRI) has accelerated the relationship between cardiac architecture and function in health and disease. However, despite recent advances in in-vivo cardiac DT-MRI, the need for additional sequencing and complex motion compensation processing to eliminate artifacts, a low spatial resolution, and poor accessibility have severely limited the application of cardiac DT-MRI in the clinical setting. We propose estimating myofiber orientation from cardiac strains for which cine sequences have already been established and standardized in humans and small animals.

In-silico heart models with synthetic fiber orientation were constructed by defining the fiber angles in the epicardial and endocardial layers with linear helicity variation across the thickness. MRI scans of four healthy male murine hearts were used to generate strain vs. orientation correlations. Strains were calculated on four representative slices, and LV thickness was divided into six layers. Both forward and inverse problems were conducted. Torsion was also calculated in terms of twist angle. Correlation analysis between fiber orientation and cardiac strains (and their ratios) indicated a strong association at various short-axis ventricle slices. The inverse problem approach, used to estimate architectural metrics, was able to accurately predict both fiber range and regional fiber angles from cardiac strains. The next step is to use CMR-measured cardiac strains in mice and humans and compare the predicted fiber orientation against ground truth (histology or DTI) for the same subject.

Butyl Benzyl Phthalate Exposure Exacerbates Progression of Atherosclerosis in High Fat High Cholesterol-fed LDLR$^{-/-}$ and ApoE$^{-/-}$ Mice Models

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Cardiovascular disease (CVD) continues to be a major global health concern, contributing to substantial morbidity and mortality rates worldwide. Atherosclerosis, the leading cause of CVD is a chronic inflammatory disease, characterized by the accumulation of lipid-rich plaques within arterial walls. Although proven risk factors for CVD and atherosclerosis development include smoking, hypertension, and hyperlipidemia, recent research indicates that environmental factors, such as exposure to endocrine-disrupting chemicals (EDCs) interfere with the cardiac endocrine signaling mechanisms. Benzyl butyl phthalate (BBP), a well-known EDC is a widely used plasticizer found in various consumer products, has gathered attention due to its potential adverse effects on human health. Here, we hypothesize that acute exposure to BBP in the background of western diet can accelerate pro-inflammatory response leading to atherosclerosis in Low-density lipoprotein receptor knock-out (LDLR$^{-/-}$) and Apolipoprotein E knock-out (ApoE$^{-/-}$) mice. Eight-week-old LDLR$^{-/-}$ and ApoE$^{-/-}$ male mice were fed on high-fat high-cholesterol diet (HFHCD) with or without variable doses of 4 µg/kg/day(BBP1), 169 µg/kg/day(BBP2), and 3 mg/kg/day (BBP3) mixed in HFHCD for 5 and 10 weeks. BBP treated group in LDLR$^{-/-}$ as well as ApoE$^{-/-}$ mice exhibited marginal increase in serum lipid profile when compared to the control group with no change in body weight and glycemic condition. Interestingly, BBP induced a pro-inflammatory response by exhibiting a significant increase in serum TNF-α ($P < 0.01$ for BBP2, and $P < 0.001$ for BBP3), IFN-γ ($P < 0.01$ for BBP3), and GM-CSF ($P < 0.001$ for BBP3) in a dose-dependent manner only in LDLR$^{-/-}$ mice. In addition, the atherosclerotic lesion (plaque) area measurement in the aortic root revealed that both BBP2 ($P < 0.05$) and BBP3 ($P < 0.01$) contributed to a significant increase in plaque area in the 5 week regimen group compared to the control. Furthermore, the pro-inflammatory genes; IL-6 and VCAM-1 were significantly ($P < 0.05$) upregulated in the aorta of 5 weeks BBP3 treated ApoE$^{-/-}$ mice. On the other hand, NRF2 (protects cells from oxidative stress) expression in the aorta of 5 weeks BBP3 treated LDLR$^{-/-}$ mice was significantly ($P < 0.05$) downregulated. Currently, we are pursuing an in-depth analysis of gene regulatory systems involved in CVD through BBP exposure using Ingenuity Pathway Analysis Software. We are also investigating if the mixture of phthalates can induce similar gene regulations via miRNA-lncRNA epigenetic pathway. In conclusion, further research is warranted to investigate the underlying mechanism for the acceleration of atherosclerotic lesions formation by BBP exposure and to understand the potential strategies for intervention and prevention.

Dietary supplementation with L-leucine reduces nitric-oxide synthesis by endothelial cells of rats

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This study tested the hypothesis that elevated L-leucine concentrations in plasma reduce nitric oxide (NO) synthesis by endothelial cells (ECs) and affects adiposity in obese rats. Beginning at 4 weeks of age, male Sprague-Dawley rats were fed a casein-based low-fat (LF) or high-fat (HF) diet for 15 weeks. Thereafter, rats in the LF and HF groups were assigned randomly into one of two sub-groups (n=8/sub-group) and received drinking water containing either 1.02% L-alanine (isonitrogenous control) or 1.5% L-leucine for 12 weeks. The energy expenditure of the rats was determined at weeks 0, 6 and 11 of the supplementation period. At the end of the study, an oral glucose tolerance test was performed on all the rats immediately before being euthanized for the collection of tissues. HF feeding reduced ($P < 0.001$) NO synthesis in ECs by 21% and whole-body insulin sensitivity by 19%, but increased ($P < 0.001$) glutamine:fructose-6-phosphate transaminase (GFAT) activity in ECs by 42%. Oral administration of L-leucine decreased ($P < 0.05$) NO synthesis in ECs by 14%, increased ($P < 0.05$) GFAT activity in ECs by 35%, and reduced ($P < 0.05$) whole-body insulin sensitivity by 14% in rats fed the LF diet, but had no effect ($P < 0.05$) on these variables in rats fed the HF diet. L-Leucine supplementation did not affect ($P > 0.05$) weight gain, tissue masses (including white adipose tissue, brown adipose tissue, and skeletal muscle), or antioxidative capacity (indicated by ratios of glutathione/glutathione disulfide) in rats fed the LF or HF diet, and did not worsen ($P > 0.05$) adiposity, whole-body insulin sensitivity, or metabolic profiles in plasma from obese rats. These results indicate that high concentrations of L-leucine promote glucosamine synthesis and impair NO production by ECs, possibly contributing to an increased risk for cardiovascular disease in diet-induced obese rats. This work was supported by grants from American Heart Association–TX (No. 0755024Y and 10GRNT4480020).

Key words: Amino acids, energy expenditure, leucine, nitric oxide, obesity, vascular function

INACTIVATION OF METTL14 IN CARDIOMYOCYTES RESULTED IN DILATED CARDIOMYOPATHY AND HEART FAILURE

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Heart failure is a world-wide debilitating disease that imposes a growing clinical and economic burden. Recent studies have highlighted the role of RNA modification in governing mRNA fate, suggesting that RNA modification serves as an additional layer of regulatory mechanisms in the context of heart failure. Among various RNA modifications, the methylation of adenosine at the N6-position (m6A) emerges as the most prevalent internal modification in eukaryotic mRNA. The installation of m6A modification is orchestrated by a protein complex consisting of Mettl3, Mettl14, WTAP, and others. Mettl14 acts as an adaptor protein that facilitates Mettl3-induced m6A installation. Notably, inactivation of Mettl14 in mammalian cells leads to a more than 90% reduction in m6A levels in mRNA. However, the precise involvement of Mettl14-mediated m6A modification in the development of heart failure remains largely unexplored. To address this crucial question, we generated a cardiomyocyte-specific knockout mouse line by crossing Mettl14 flox mice with Mlc2vKICre mice. Our preliminary data indicate that the inactivation of Mettl14 in cardiomyocytes results in early lethality in mice due to severe cardiac failure. Histological analysis reveals disorganized cardiomyocytes and fibrosis in the hearts of knockout mice. Furthermore, RNA-seq analysis demonstrates that several pathways critical for heart function, such as heart contraction and the tricarboxylic acid (TCA) cycle, are downregulated upon the loss of Mettl14. Additionally, the ablation of Mettl14 leads to a significant increase in transcripts associated with inflammation. Collectively, these findings suggest that METTL14 plays an essential role in preventing heart failure, potentially through an m6A-dependent mechanism. Moreover, we have also identified and experimentally validated that focal adhesion kinase (FAK) could directly interact and phosphorylate METTL14 in the heart. Therefore, we concluded that METTL14-mediated m6A modification of mRNA regulates the expression of key metabolic enzymes to maintain proper cardiac function. Furthermore, this process can be fine-tuned through the alternation of phosphorylation status of METTL14.

Blood Coagulation Testing Using a Smartphone

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Cardiovascular diseases (CVDs) resulting from blood clotting affect millions of people worldwide. Warfarin, a commonly prescribed anticoagulant, requires dosage adjustments based on the patient's diet to effectively thin the blood. International normalized ratio (INR) indicates the blood coagulation level, and its regular testing in current practice requires hospital visits and an expert to perform the measurement and interpretation. Here, we present an affordable, portable point-of-care device that utilizes smartphones for INR testing. Our device consists of two primary components: a 3D printed platform and custom microfluidic cartridges. The 3D printed platform incorporates backlight modules with light-emitting diodes (LEDs) to ensure uniform illumination of samples for video recording. The platform features a foldable design that enables easy transportation. Its smartphone holder is tilted at a 30-degree angle, accommodating both transparent samples (e.g., serum) and colored samples (e.g., whole blood). We prepared custom-developed video processing algorithms that facilitate to process of sample videos and obtain the INR result at the point of care. This handheld platform costs less than $8, excluding the smartphone. To test and validate its performance, we conducted tests using both commercially available control samples and 47 clinical human blood samples at different INR levels. The results demonstrated over 90% accuracy. This smartphone-based INR device provides a convenient and affordable alternative for monitoring blood coagulation at the point of care.

Cardiac specific Tet deficiency impedes normal systemic energy homeostasis in adult mice

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Increasing obesity prevalence is one of the key public health issues in the United States. Obesity is a multifactorial disease with various deleterious outcomes, including high blood pressure and increased risk of cardiovascular diseases. Heart is a high energy demanding organ and consumes a large number of metabolites, including fatty acids, glucose, lactate, and ketones. Therefore, there is a mutual influence between obesity and myocardium dysfunction. We report herein abnormal systemic energy homeostasis and obesity phenotypes in adult mice upon disrupting DNA methylation and demethylation balance in heart tissues. Tet enzymes belong to the dioxygenase family that successively oxidize 5-methylcytosine (5mC) to yield 5-hydroxymethylcytosine (5hmC) and ultimate cause active DNA demethylation in the eukaryotic genome. To investigate the function of Tet-mediated DNA demethylation in adult heart, we generated a myocardium specific Tet-triple (Tet1/2/3) knockout (TKO) mouse model. We observed that myocardium-specific Tet deletion had minor effects on heart size, structure, and function. By contrast, Tet ablation in heart resulted in increased whole-body weight, accompanied with higher blood glucose and lipid levels. In parallel, Tet-TKO mice exhibited increased glucose intolerance, insulin insensitivity and body fat, which mimicked the obesity phenotype. Molecular analysis using purified myocardium is under the way to further dissect the underlying mechanism. In summary, our study unveils a previously-unrecognized role of the TET family of epigenetic enzymes in cardiac tissues that might contribute to systemic metabolic rewiring and obesity in adult mice.

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