ORAL PRESENTATIONS AT VASCULAR BIOLOGY 2024

MECHANISMS OF BLOOD FLOW REGULATION IN THE MICROVASCULATURE

01

Pericyte-mediated cerebrovascular remodeling: Dissecting the contributions of fluid mechanics, oxygenation, and glucose delivery

Hanaa Abdelazim, John Chappell
FBRI at Virginia Tech, Roanoke, Virginia, USA

- Pericytes may constrict a subset of cerebral capillaries during hyperoxia
- Flow-independent constriction of capillaries may be mediated by Endothelin-1
- Pericytes remodel brain vessels during hyperoxia via detachment and reduced vitronectin deposition.

02

Impaired L-type voltage-gated Ca2+ channel function in cerebral arteriolar myocytes from humanized ApoƐ4 knock-in mice

Felipe D Polk BS, Josiane F DaSilva PhD, Paulo W Pires PhD
University of Arizona, Tucson, Arizona, USA

- Cerebral small vessel disease is associated with impaired cerebral blood flow and autoregulation.
- Apolipoprotein Ɛ4 is a genetic risk factor linked to impairments in cerebrovascular function.
- Study shows blunted CaV1.2 activity and vascular contractility in arterioles of ApoƐ4 knock-in mice.

MECHANOTRANSDUCTION IN EMBRYONIC VASCULAR DEVELOPMENT

03

Spatial regulation of actomyosin tension by Heg1/Ccm1 is required to maintain junctional integrity during angiogenic tube formation

Jianmin Yin PhD, Ludovico Maggi MS, Cora Wiesner PhD, Markus Affolter PhD, Heinz-Georg Belting Ph.D
Biozentrum, Basel, Switzerland

- Vascular tube formation requires cell rearrangements driven by junction-based lamellipodia.
- During cell elongation, junctional integrity is maintained by local oscillatory constrictions.
- Anisotropic distribution of junctional myosin-light chain is regulated by Heg1/Ccm1.

04

Novel roles for centriolar protein WDR90 in endothelial cells and cardiac tissue

Sarah Colijn, Amber Stratman
Washington University in St. Louis, St. Louis, MO, USA

- * De novo mutations in centriolar protein WDR90 have been identified as drivers of CHD
- * Zebrafish wdr90 mutants display partial lethality, stenosis, and small hearts
- * Endothelial WDR90 co-localizes with VE-cadherin and the tips of microtubules

VASCULAR SIGNALING AND DISEASES

05

Single-cell RNA sequencing analysis of the aorta of a mouse model of Autosomal Recessive Cutis Laxa type 1B identifies adaptive and maladaptive transcriptional signature in multiple cell types

Wendy Espinoza Camejo BS, Emily Bramel PhD, Leda Restrepo PhD, Elena Gallo MacFarlane PhD
Johns Hopkins University, Baltimore, Maryland, USA

- Aneurysm
- Endothelial cells
- Vascular signaling

06

AVM mural cells initiate endothelial to mesenchymal transition in the adjacent AVM endothelium

Syed J Mehdi[1,2], Haihong Zhang[1,2], Ravi W Sun[1,3], Gresham T Richter[1,2], Graham M Strub[1,2]
[1]Arkansas Children's Research Institute (ACRI), Little rock, Arkansas, USA. [2]Department of Otolaryngology-Head and Neck Surgery, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA. [3]Department of Otolaryngology-Head and Neck Surgery, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA

- Abnormal endothelium in extracranial arteriovenous malformation
- Role of mural cells in eAVM progression
- Role of mural cells in endothelial-to-mesenchymal transition (EndMT) induction in eAVMs

INFLAMMAGING AND AGE-RELATED VASCULAR DISEASES

07

Revealing a crucial role for putrescine in vascular smooth muscle cell differentiation and atherosclerotic plaque stability

Louise Welch BS[1], Theresea Anne Governale BS[1], Shuai Yuan PhD[2], Judith Sluimer PhD[3], Joseph Miano PhD[4], Christopher Pattillo PhD[1], Wayne Orr PhD[1], Arif Yurdagul PhD[1]
[1]LSU Health Shreveport, Shreveport, LA, USA. [2]University of Pittsburgh, Pittsburgh, PA, USA. [3]Maastricht UMC, Maastricht, Netherlands. [4]Augusta University, Augusta, GA, USA

- Reduced putrescine levels drive vSMC dedifferentiation in human and mouse atherosclerosis.
- Putrescine deficiency drives ECM degradation and calcification, promoting plaque instability.
- Targeting putrescine biosynthesis offers a novel strategy to stabilize rupture-prone atheromas.

08

Investigation of cutaneous wound healing in zebrafish

Leah J Greenspan[1], Keith Ameyaw[2], Daniel Castranova[1], Van Pham[1], Gennday Margolin[1], Caleb Mertus[1], Brant Weinstein[1]
[1]National Institutes of Health, Bethesda, MD, USA. [2]Albert Einstein College of Medicine, New York, NY

- Delays in vessel regrowth are a major contributor to defects in wound closure

- Our new rotary tool injury system can be used to study cutaneous wound healing in zebrafish
- Live imaging reveals insights into immune cell and endothelial cell behavior during wound healing

09

Investigating the role of endothelial Nck1 in atherosclerosis

Cyrine Ben Dhaou PhD, Brenna Pearson-Gallion MSC, Elizabeth Denise Cockerham MSC, Wayne Orr
LSU Health Sciences Center, Shreveport, LA, USA

- Global Nck1 deletion significantly reduces atherosclerosis and endothelial inflammation.
- Endothelial-specific Nck1 deletion reduces atherosclerotic plaque formation.
- Nck1-ATF3 signaling regulates flow-induced inflammation in endothelial cells.

10

Conflicting vascular signals in a mouse model of penttinen progeroid syndrome

Longbiao Yao, Hae Ryong Kwon, Alex Rackley, Lorin E Olson PhD
Oklahoma Medical Research Foundation, Oklahoma City, OK, USA

- Penttinen syndrome is caused by point mutations in PDGFRB that result in constitutive activation.
- Penttinen syndrome mice exhibit vascular aging and elevated mTOR and STAT1 signaling.
- Conflicting growth and anti-growth signals may promote premature aging of the vasculature.

MALFORMATIONS

11

MEK signaling represents a viable therapeutic vulnerability of KRAS-driven somatic brain arteriovenous malformations

Carlos Flores Suarez[1], Omar Harb[2], Ariadna Robledo[3], Gabrielle Largoza[2], Peter Kan[3], Sean Marrelli[4], Joshua Wythe[2]
[1]Baylor College of Medicine, Houston, TX, USA. [2]University of Virginia School of Medicine, Charlottesville, VA, USA. [3]University of Texas Medical Branch-Galveston, Galveston, TX, USA. [4]University of Texas Health Sciences Center, Houston, TX, USA

- 3D analysis via micro-CT shows Kras gain of function leads to extensive vascular remodeling.
- While multiple Kras variants induce bAVM formation, they may lead to unique consequences.
- MEK inhibition may stabilize existing bAVMs in mice and humans.

12

Endothelial permeability in GNAQ p.R183Q associated capillary malformations

Sana Nasim PhD[1,2], Mariam Baig BS[1], Jill Wylie-Sears MS[1], Matthew Vivero MD[1,2], Arin K Greene MD[1,2], Joyce Bischoff PhD[1,2]
[1]Boston Children's Hospital, Boston, MA, USA. [2]Harvard Medical School, Boston, MA, USA

- Gαq-R183Q endothelial cells forms significantly reduced barrier comparing to their wild-type cells

- Angiopoietin-2 knockdown and Trametinib offers a therapeutic intervention for capillary malformation
- mTOR inhibitors, currently in clinical trials, had no effect on the compromised barrier function

MECHANOTRANSDUCTION

13

Dissecting YAP/TAZ-dependent mechanotransduction in vascular morphogenesis

Paula Camacho[1], Brendan Tobin[2], Devon E Mason[1], Erin Berlew[1], Javier Abello[3], Jihui Lee[3], Amber N Stratman[3], Levi Wood[2], Joel D Boerckel[1]
[1]University of Pennsylvania, Philadelphia, PA, USA. [2]Georgia Institute of Technology, Atlanta, GA, USA. [3]Washington University in St. Louis, St. Louis, MO, USA

- We dissected pathways regulated by YAP/TAZ mechanotransduction in endothelial cell migration.
- The parallel study design identified analogous transcriptional programs in vitro and in vivo.
- We are exploring how cytoskeletal changes drive identified pathways using optogenetic tools.

14

Impact of low shear stress on pulmonary endothelial cells: study of mechanobiological mechanisms in Combined Pre/Post-Capillary Pulmonary Hypertension (Cpc-PH) progression

Tasneem Mustafa BS, Nasim Khorasani BS, Jimmy Nguyen, An Tran, Naomi Chesler PhD
University of California, Irvine, Irvine, CA, USA

- Pulmonary hypertension endothelial dysfunction
- Endothelial glycocalyx mechanosensing
- Endothelial mechanobiology under pulsatile shear stress

15

Distinct smooth muscle cell dysfunction in patients with ascending aortic aneurysms associated with bicuspid aortic valve

Soheila AA Ghavimi PhD[1,2], Lana Vogler[1], Ryan N Martinez MSc[1], Amarri Harrison BSc[1], Hiba Ansari BSc[1], Ashraf Sabe MD[1,2], Marie Billaud PhD[1,2]
[1]Brigham and Women's Hospital, Boston, MA, USA. [2]Harvard Medical School, Boston, MA, USA

- Aortic aneurysms in patients with bicuspid (BAV) vs. trileaflet (TAV) aortic valve are distinct.
- SMCs from TAV patients exhibit reduced levels of contraction, while the BAV group is normal.
- SMC contraction is response to ECM substrates is distinct in BAV vs. TAV groups.

16

Polarized mechanosensitive signaling domains promote endothelial cell resilience

Soon-Gook Hong PhD[1], Julianne W. Ashby[1], John P. Kennelly PhD[1], Meigan Wu[1], Michelle Steel[1], Eesha Chattopadhyay[1], Rob Foreman PhD[1], Peter Tontonoz MD, PhD[1], Elizabeth J. Tarling PhD[1], Patric Turowski PhD[2], Marcus Gallagher-Jones PhD[3], Julia J. Mack PhD[1]
[1]UCLA, Los Angeles, CA, USA. [2]UCL, London, United Kingdom. [3]Rosalind Franklin Institute, Didcot, United Kingdom

- Arterial ECs polarize under high laminar flow by cell body elongation.

- Flow-aligned ECs have mechanosensitive domains that enable localized Ca2+ entry.
- Mechanosensitive signaling via TRPV4 channels protects against vascular inflammation.

VASCULAR MATRICES AND DISEASES

17

Sphingosine kinase 1 plays a key role in defective elastin-induced arterial hypermuscularization

Junichi Saito M.D., Ph.D.[1], Jui M. Dave Ph.D.[1], Eunate Gallardo-Vara Ph.D.[1], Inamul Kabir Ph.D.[1], Timothy Hla Ph.D.[2], Daniel M. Greif M.D.[1]

[1]Yale University, New Haven, CT, USA. [2]Boston Children's Hospital, Boston, MA, USA

- Sphk1 is the most upregulated transcript in Eln(-/-) aortic SMCs prior to morphological differences.
- Human or murine elastin insufficiency increases SPHK1, leading to aortic and DA SMC proliferation.
- Inhibiting SPHK1 reduces aortic disease in elastin mutants and leads to patent DA in wild-type mice.

18

Subendothelial matrix stiffening: a novel regulator of choroidal endothelial cell death in early age-related macular degeneration

Irene Santiago Tierno[1,2], Sathishkumar Chandrakumar[2], Mahesh Agarwal[1,2], Kaustabh Ghosh[1,2]

[1]UCLA, Los Angeles, CA, USA. [2]Doheny Eye Institute, Pasadena, CA, USA

- Early AMD is characterized by stiffening of both choroidal EC and subendothelial matrix.
- Increased stiffening is associated with both endothelial cell death and poor neovascularization.
- Transcriptomic analyses implicate EC mechanobiology as a key driver of early AMD pathogenesis.

TRANSCRIPTIONAL REGULATION OF INFLAMMATION AND RESOLUTION

19

IL-6 induces a non-canonical interferon-like response in endothelial cells

Nina C. Martino B.S., Ramon Bossardi Ramos PhD, Iria Di John Portela B.S., Shuhan Lu B.S., Peter Vincent PhD, Alejandro P. Adam PhD

Albany Medical College, Albany, NY, USA

- IL-6 promotes parallel antiviral and antibacterial responses in the endothelium
- IL-6 induces an interferon-like response via a non-canonical mechanism
- STAT1 and STAT3 drive different transcriptional profiles downstream of IL-6

20

Plasmin and sterile inflammation compromise embryonic liver vascular integrity

Meng-Ling Wu PhD, Courtney T Griffin PhD

Oklahoma Medical Research Foundation, Oklahoma, OK, USA

- Deleting Chd4/Brg1 in ECs reduces plasmin activation and rescues liver bleeding in Chd4 EC mutants.

- A combination of plasminogen deficiency and NSAID treatment rescues lethality in Chd4 mutants.
- CHD4 and BRG1 regulate fetal liver vascular integrity by controlling plasmin and inflammation.

Molecular and Cellular Mechanisms of HHT

21

Somatic mutation of Alk1 in arterial endothelial cells causes vascular bleeding

Xuetao Zhang PhD, Kyle Jacobs BS, Kunal Raygor MD, Sean Li PhD, Jiajun Li, Rong A Wang PhD
UCSF, San Francisco, CA, USA

- Somatic deletion of Alk1 in postnatal arterial ECs leads to spontaneous epistasis, like patients.
- Alk1iΔaEC arteries exhibited disorganized smooth muscle cells and reduced arterial tone.
- This finding question whether HHT-associated bleeding may occur without telangiectasia/AVM

22

Molecular nature and cellular origin of the predominant circulating ALK1 ligand

Teresa L Rosato PhD, Stefanie A Morosky BS, Cynthia S Hinck PhD, Andrew P Hinck PhD, Beth L Roman PhD
University of Pittsburgh, Pittsburgh, PA, USA

- The most abundant ALK1 ligand in human plasma is unprocessed BMP10/processed BMP9 heterodimer
- Hepatic stellate cells are the likely source of this novel ligand
- This new molecular insight may inform development of ligand-based therapeutics for HHT

Emerging Topics in Microcirculation

23

Apolipoprotein M ameliorates microvascular leakage caused by combined acute alcohol intoxication and hemorrhagic shock

Mengmeng Chang MD, PhD, Jerome W Breslin PhD
University of South Florida, Tampa, FL, USA

- Acute alcohol intoxication worsens hemorrhagic shock/resuscitation-induced microvascular leakage.
- Apolipoprotein M (ApoM) enhances endothelial barrier function.
- Fluid resuscitation with ApoM improves microvascular leakage caused by AAI-HSR.

24

Targeting endothelial ERG to mitigate vascular regression and neuronal ischemia in retinopathies

Eric Ma Ph.D.[1], Christopher M Schafer Ph.D.[1], Jun Xie M.D.[1], Anna M Randi M.D., Ph.D.[2], Courtney T Griffin Ph.D.[1,3]
[1]Oklahoma Medical Research Foundation, Oklahoma City, OK, USA. [2]National Heart and Lung Institute, Imperial College London, London, United Kingdom. [3]Department of Cell Biology, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA

- ERG and FLI1 expression are much lower in the eyes of patients with diabetic retinopathy.
- Knockout of endothelial Erg and Fli1 promotes regression of pathological tufts in the OIR model.
- Overexpression of endothelial ERG prevents early-stage retinal vascular regression and ischemia.

25

Identifying transcriptional pathways in the endothelium that contribute to microvascular dysfunction in diabetes-induced heart failure with preserved ejection fraction

Cori Lau[1,2], Kai Ellis[1,3], Rathnakumar Kumaragurubaran[2], Dakota Gustafson[1,2], Lijun Chi[3], Paul Delgado-Olguin[3,1], Ahsan Siraj[2], Mansoor Husain[1,2], Michael D Wilson[1,3], Jason E Fish[1,2]
[1]University of Toronto, Toronto, Ontario, Canada. [2]Toronto General Hospital Research Institute, Toronto, Ontario, Canada. [3]SickKids Hospital, Toronto, Ontario, Canada

- Empagliflozin rescues cardiac microvasculature density in diabetic mice
- Empagliflozin upregulates angiogenic-associated genes and transcription factors in cardiac ECs
- Angiogenesis is a potential therapeutic target to treat microvascular dysfunction in diabetic hearts

26

Integrated multiomic analysis identifies a role for NF-KB pathway in coronary microvascular disease (CMVD)

Marie A Guerraty MD, PhD[1], Tess Cherlin PhD[1], Rasika Venkatesh[1], Nicole Wayne MD[1], Regeneron Genetics Center[2], PennMedicine Biobank[1], Shefali Verma PhD[1]
[1]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA. [2]Regeneron, Tarrytown, NY, USA

- We performed GWAS using Perfusion PET stress testing as a measure of coronary microvascular disease.
- GWAS and downstream analyses identified two loci independently associated with NFKB pathway.
- Transcriptomic and targeted proteomic analysis support a role for NFKB in CMVD.

27

Blood perfusion drives microvessel maturation in engineered microvascular constructs

Angela Zhou HBSc[1,2], Sara S Nunes PhD[1,2,3]
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- Mechanisms of vascular maturation
- Adult neovascularization
- Enhancing cell-replacement therapies

28

Pericyte transition to quiescence: Roles for soluble PDGF receptor-beta and the extracellular matrix in the developing cerebrovasculature

John C Chappell PhD[1], Laura B Payne PhD[1], Hanaa Abdelazim MD[1], James Stupin BS[2]

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- Brain pericytes (PCs) make a soluble isoform of platelet-derived growth factor receptor-beta (sRb).
- Soluble PDGFR-beta may arise from mRNA alternative splicing and likely binds the ECM.
- Soluble PDGFR-beta may influence PC quiescence by modulating PDGF-BB availability and signaling.

VASCULAR PATTERNING AND MECHANOTRANSDUCTION

29

Stiffening of retinal vessels threatens vision in diabetes

Sathishkumar Chandrakumar PhD[1], Irene Santiago Tierno M.S.[2], Mahesh Agarwal PhD[3], Timothy S Kern PhD[4], Kaustabh Ghosh PhD[2]

[1]Doheny Eye Institute, Pasadena, CA, USA. [2]UCLA and Doheny Eye Institute, Los Angeles, CA, USA. [3]UCLA and Doheny Eye Institute, Pasadena, CA, USA. [4]UC Irvine, Irvine, CA, USA

- Diabetes leads to lysyl oxidase (LOX)-mediated retinal capillary stiffening
- Capillary stiffening inhibits mechanosensitive TRPV4 in retinal ECs, which activates RhoA/ROCK
- RhoA/ROCK promotes inflammation via an increase in both ICAM-1 expression and clustering

30

High-throughput quantitative analysis of spatiotemporal endothelial cell dynamics and extracellular matrix remodeling during sprouting angiogenesis

Vincent Vermeulen MSc[1], Ivo van der Bijl PhD[2], Juliette Vleeming BSc[1], Davide Visentin BSc[1], Coert Margadant PhD[1]

[1]Leiden University, Leiden, Netherlands. [2]Sanquin, Amsterdam, Netherlands

- Analysis of spatiotemporal regulation of sprouting angiogenesis is highly important but lacking
- We used hi-throughput quantitative analysis of extracellular matrix remodeling and network formation
- Matrix remodeling, mechanotransduction, and network growth are ordered sequentially in angiogenesis

LEUKOCYTE RECRUITMENT AND INTERACTION WITH THE VASCULATURE

31

Inflammatory signaling in pulmonary endothelial cells regulates tissue response to viral infection

Arnav Sharma BS, Terren K Niethamer PhD

National Cancer Institute, Frederick, MD, USA

- Endothelial response to interferon signaling is essential for the timing of tissue injury response
- A dysplastic endothelial cell state arises after viral lung injury
- Regeneration of the vasculature is essential for tissue repair after lung infection or damage

32

Direct macrophage-smooth muscle cell interactions in the injured arterial wall

Mark C Renton PhD[1], Farwah Iqbal PhD[2], Meghan W Sedovy[3], Adam Hoch[2], Xinyan Leng PhD[1], Kailynn Roberts[1], Melissa Leaf[2], Brant E Isakson PhD[4], Scott R Johnstone PhD[1,2,5]

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- Macrophages accumulate in the blood vessel wall after injury and initiate neointimal formation.
- Macrophage direct contact initiates a proliferative phenotype in vascular smooth muscle cells.
- Macrophages and smooth muscle cells communicate directly through connexin 43 gap junctions.

33

A splice variant of kindlin-3 is functional in β2 integrin activation and neutrophil adhesion

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[1]University of Nevada, Reno, Reno, Nevada, USA. [2]Augusta University, Augusta, Georgia, USA

- FERMT3 encodes a standard kindlin-3 and a longer splicing isoform, kindlin-3-IPRR.
- Kindlin-3-IPRR is fully functional in activating high-affinity β2 integrins.
- Kindlin-3-IPRR rescued the arrest defect of kindlin-3 knockout HL-60 cells.

34

The role of neuroinflammation in the pathogenesis of brain vascular malformations

Eduardo Frias-Anaya PhD[1], Helios Gallego-Gutierrez PhD[1], Brendan Gongol PhD[2], Shantel Weinsheimer PhD[3], Helen Kim PhD[3], Stephan G Anagnostaras PhD[1], Miguel A Lopez-Ramirez PhD[1]

[1]UCSD, San Diego, California, USA. [2]Victor Valley College, Victorville, California, USA. [3]UCSF, San Francisco, California, USA

- Astrocyte-Brain endothelial cell crosstalk triggers recruitment of inflammatory cells into CCMs.
- Environmental and genetic modifiers accelerate CCM disease through neuroinflammation.
- Hypoxia and activated AKT-mTOR pathway boost CCMs by CX3CR1-CX3CL1 pathway.

EMERGING TECHNOLOGIES AND MODELING OF THE VASCULATURE

35

Artificial intelligence and high-content screening identified FDA-approved drugs for the long-term treatment of cerebral cavernous malformation disease

Helios Gallego Gutierrez PhD[1], Eduardo Frias Anaya PhD[1], Bethan Kilpatrick PhD[2], Aaryaman Sawhney[1], Andrea Taddei PhD[2], Miguel A Lopez Ramirez PhD[1]

[1]UCSD, San Diego, CA, USA. [2]BenevolentAI, London, United Kingdom

- AI-driven drug discovery for therapeutic intervention in CCMs
- High-throughput drug screening on CCM disease models.
- AI identified safe and potential long-term use FDA-approved drugs for CCM.

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Integrated 3D mapping and transcriptomic characterization of uterine arterial transformation in human placental development

Mira N Moufarrej PhD, James B Zwierzynski, Lucy Chang, Purnima Iyer, Virginia D Winn, Kristy Red-Horse
Stanford University, Stanford, CA, USA

- 3D whole mount imaging
- Uterine arterial transformation
- Human placental development

SIGNALING IN THE VASCULATURE

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Chemokine regulation of placental vascular development

James B Zwierzynski[1], Mira N Moufarrej PhD[1], Kristy Red-Horse PhD[1,2]
[1]Stanford University, Stanford, CA, USA. [2]Howard Hughes Medical Institute, Stanford, CA, USA

- CXCL12/CXCR4 signaling is highly active in the spiral arteries of the placenta.
- Spiral artery remodeling may modulate CXCL12/CXCR4 signaling in arterial endothelial cells.
- Fetal CXCL12 knockout causes defects in placental development.

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Elevated mitochondrial activity during embryogenesis increases adult cerebrovascular anomalies

Ivan Fan Xia PhD, Anupama Hemalatha PhD, Jared Hintzen PhD, Paola Carneiro PhD candidate, Gabriel Baldissera PhD candidate, Siyuan Cheng PhD, Nicole J. Lake PhD, Valentina Greco PhD, Stefania Nicoli PhD
Yale School of Medicine, New Haven, CT, USA

- Zebrafish lacking miR-125a exhibit incomplete CoW variations, narrowed or absent posterior arteries.
- Incomplete posterior artery formation is heritable and results from endothelial hyper-angiogenesis.
- Inhibiting ppargc1a or modulating mitochondrial activity rescued CoW in miR-125a mutant.

ORGAN-SPECIFIC LYMPHATIC DIVERSITY

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Lymphatic endothelial alpha globin regulates cardiac structure and function during cardiometabolic heart failure

Skylar A Loeb M.S.[1], Dennon Hoernig[1], Luke S Dunaway Ph.D.[1], Zhen Li Ph.D.[2], Alexander Young[1], Shruthi Nyshadham[1], Jingshu Chen Ph.D.[3], Smitha Shambhu M.S.[3], Natalie D Gehred B.A.[4], Thomas M Vondriska Ph.D.[4], David Lefer Ph.D.[2], Matthew Wolf M.D., Ph.D.[1], Brant E Isakson Ph.D.[1]
[1]University of Virginia School of Medicine, Charlottesville, VA, USA. [2]Cedars-Sinai Medical Center, Los Angeles, CA, USA. [3]Gordian Biotechnology, South San Francisco, CA, USA. [4]University of California Los Angeles, Los Angeless, CA, USA

- Hbα is upregulated in human HFpEF hearts and in cardiac lymphatic endothelium in rats with HFpEF
- Lymphatic endothelial Hbα regulates heart structure and function during heart failure
- Lymphatic endothelial Hbα regulates cardiac immune landscape during heart failure

40

Adipose tissue expansion is dependent on a Piezo2-Vegfr3 signaling axis that regulates lymphangiogenesis

Zuzanna J Juskiewicz M.S.[1,2], Luke S Dunaway PhD[1], Melissa A Luse PhD[1,2], Skylar A Loeb M.S.[1,2], Brant E Isakson PhD[1,2]

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- Piezo2 is highly expressed in lymphatic capillary endothelium.
- Genetic loss of Piezo2 in mouse and humans is strongly correlated with redistribution of fat mass.
- Vegfr3 expression is Piezo2 dependent, possibly working through Klf2.

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Advanced glycation end products induce lymphatic dysfunction in metabolic syndrome

Mengmeng Chang MD, PhD[1], Laurelis Santiago MS[1], Chris Katnik PhD[1], Min Zhang PhD[1], Bi Zhao PhD[1], Nien-Wen Hu[2], Walter L Murfee PhD[2], Jerome W Breslin PhD[1]

[1]University of South Florida, Tampa, FL, USA. [2]University of Florida, Gainesville, FL, USA

- Metabolic syndrome causes impaired lymphatic pumping.
- snRNA-Seq analysis shows AGE-RAGE signaling is enriched in obese Zucker rat mesentery.
- AGE-BSA reduces lymphatic contraction frequency and promotes lymphatic network remodeling.

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Osteopathy in complex lymphatic anomalies

Ernesto Solorzano PhD[1], Jalal Jwayyed[1], Gabrielle T Robinson[1], Mitchell W Bailey[1], Dean Spyres[1], Emily Kunz[1], Michael Kay[1], Shahabeddin Yazdanpanah[1], Trinity A Kronk[1], Kennedy Nkachukwu[1], Bryce Pember[1], Alex P Powell[1], Andrea L Solorzano[1], Rama Safadi[1], Jared Hinton[1], Michael Kelly MD, PhD[2], Fayez F Safadi PhD[1]

[1]NEOMED, Rootstown, Ohio, USA. [2]Cleveland Clinic, Cleveland, Ohio, USA

- Lymhpatic vessel invasion in bone leads to bone resorption
- Mouse model for Gorham Stout Disease
- Identification of a novel diseases regulator for Complex Lymphatic Anomalies

CEREBRAL MICROVASCULAR FUNCTION IN HEALTH AND DISEASE

43

InCITE-seq analysis links disruption of core blood brain barrier pathways in neurodegeneration to the nuclear depletion of TDP-43 in endothelial cells

Omar Moustafa Fathy Omar MS, Amy Kimble MS, Patrick Murphy PhD
University of Connecticut Health Center, Farmington, CT, USA

- Novel nuclear isolation techniques reveal distinct endothelial cell signatures in neurodegeneration
- TDP-43 loss in brain EC alters signaling pathways involved in blood-brain barrier maintenance
- Endothelial TDP-43 dysfunction may drive barrier breakdown in neurodegeneration

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Whole-brain irradiation alters mitochondrial bioenergetics in the microvascular endothelium

Olha Koval PhD, Kyle J Westhoff, Vikram Subramanian PhD, Isabella M Grumbach MD, PhD
University of Iowa, Iowa City, IA, USA

- Whole-brain radiation reduces mtDNA copy number and increases mtDNA damage
- Whole-brain radiation decreases basal mitochondrial respiration in isolated microvessels
- Cultured endothelial cells from irradiated microvessels fail to form an intact monolayer

45

Brain microvascular pericyte pathology links Alzheimer's Disease to Type II Diabetes

Kareem El-Ghazawi, Ukpong B Eyo PhD, Shayn M Peirce PhD
University of Virginia, Charlottesville, VA, USA

- T2D is a risk factor for AD and AD patients have high rates of T2D, but no one knows why.
- Microvascular impairments are evident in both AD and T2D.
- Pericytes constrict capillaries in T2D in a similar manner to what's been shown in AD.

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Hemoglobin-Induced transcriptomic changes in human cerebral arteries

Shafeeque C Mohammedali PhD, Arif O Harmanci PhD, Devin W McBride PhD, Peeyush T Kumar PhD, Spiros L Blackburn MD
UTHealth, Houston, TX, USA

- Effect of subarachnoid blood and Hemoglobin on cerebral arteries to understand SAH pathophysiology
- Hb alters iron regulation, angiogenesis, barrier function, activates oxidative stress & ferroptosis
- Provides a translational reference to understand vascular injury following hemorrhagic events

VASCULAR CROSS TALK

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Human genetics evidence for Tetraspanin 14-mediated signaling in the vascular endothelium

Vivian Lee Ph.D.
UT Southwestern, Dallas, TX, USA

- Using genome-wide association studies to identify and functionally validate causal variants.
- The role of adaptor proteins in regulating vascular signaling.
- Noncoding variants in common disease.

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Downregulation of coronary thromboxane A2 receptor signaling in postpartum swine

Selina M Tucker BS[1], Cooper M Warne MS[1], Salman I Essajee MS[1], Styliani Goulopoulou PhD[2], Gregory M Dick PhD[1], Johnathan D Tune PhD[1]
[1]UNT Health Science Center, Fort Worth, Texas, USA. [2]Loma Linda University, Loma Linda, California, USA

- Thromboxane-mediated contraction is altered in coronary arteries from postpartum swine
- Postpartum vascular reactivity is augmented in the coronary circulation
- Postpartum coronary flow not impacted by Thromboxane A2 memetic U46619

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Crk/Crkl are required for embryonic and postnatal angiogenesis in mammals

Lijie Shi[1], Hansoo Song[1], Gloria Stoyanova[1], Bin Zhou[2], Bernice Morrow[1]
[1]Albert Einstein College of Medicine, Bronx, NY, USA. [2]The University of Chicago, Chicago, IL, USA

- Crk/Crkl are required for embryonic angiogenesis in mammals
- Crk/Crkl are required for postnatal angiogenesis in mammals
- Crk/Crkl may regulate NOTCH signaling during angiogenesis

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In-vivo investigation of the mechanisms driving venous malformation downstream of mutant TIE2

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- A novel mouse model of mutant TIE2-driven venous malformation recapitulates patients' phenotypes
- Lesion development in mice is associated with increased endothelial cell size and proliferation
- Treatment of mutant mice with rapamycin reduces growth of venous malformation lesions

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Hepatic autophagy negatively regulates ANGPTL4 biosynthesis and this contributes to hypertensive vascular dysfunction

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- Hypertension has reduced hepatic autophagy
- Autophagy negatively regulates ANGPTL4
- EL/LPL activation influences vascular contractility

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Characterizing and modeling the pericyte-to-fibroblast transition in pancreatic ductal adenocarcinoma

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- Iterative indirect immunofluorescence imaging allows the identification of pericyte-derived iCAFs.
- Agent-based modeling simulates dynamic cell transitions in response to heterogeneous signals.
- Lineage-traced pericytes-to-fibroblast transition can be observed in the tumor microenvironment.

METABOLISM

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KRAS-dependent metabolic reprogramming in brain arteriovenous malformations

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- Metabolic Rewiring in Brain Arteriovenous Malformations
- Mutant KRAS Signaling Drives Glycolytic Changes in Endothelial Cells
- Endothelial Glycolysis Contributes to Abnormal Vascular Remodeling

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Mitochondrial respiration in smooth muscle cell proliferation, migration, and vascular remodeling

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- Metabolisms/Mitochondrial respiration in vascular smooth muscle cells plasticity
- The link between mitochondrial Complex I and mitochondrial dynamic in smooth muscle cells
- The link between mitochondrial respiration and Atherosclerosis