JSPCCS-AHA Joint Session

2026年7月11日(土) 9:10 ~ 10:50 | 第１会場（Conference Hall A）

[AHAJS] JSPCCS-AHA Joint Session（III-AHAJS）

Basic Science in Congenital Heart Disease: Morphology, Genetics & Molecular Mechanisms

Chair:Antonio Cabrera(The Ohio State University,Nationwide Children's Hospital)
Chair:Yoshihide Mitani(Prinatal Care center, Mie University Hospital)

[III-AHAJS-1] AI-Powered Genomics: Accelerating Discovery and Therapeutics in Congenital Heart Disease

○Seema Mital (Hospital for Sick Children, University of Toronto)

[III-AHAJS-2] Notch1 and Bicuspid Aortic Valve Disease: From Human Genetics to Mouse and Cell-based Models

○Vidu Garg (Nationwide Children’s Hospital and The Ohio State University)

[III-AHAJS-3] Deciphering the Pathogenesis of Aortic Dissection Through Vascular-Extravascular Cell Interactions

○Hiromi Yanagisawa (Life Science Center for Survival Dynamics, TARA, University of Tsukuba)

[III-AHAJS-4] Molecular Programs Governing Fetal Differentiation and Postnatal Remodeling of the Ductus Arteriosus

Utako Yokoyama (Tokyo Medical University)

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[III-AHAJS-1] AI-Powered Genomics: Accelerating Discovery and Therapeutics in Congenital Heart Disease

○Seema Mital (Hospital for Sick Children, University of Toronto)

キーワード：Congenital heart disease、genome sequencing、AI models

This talk will show how AI is reshaping genomic discovery in congenital heart disease - revealing hidden causal variants deep in genomes missed by traditional methods. It will highlight how AI-powered integration of multi-omics and clinical data uncovers disease signatures that sharpen risk prediction and outcomes. Finally, it will demonstrate how these insights fuel novel target identification, accelerating drug discovery, paving the way for precision therapies for children with congenital heart disease.

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[III-AHAJS-2] Notch1 and Bicuspid Aortic Valve Disease: From Human Genetics to Mouse and Cell-based Models

○Vidu Garg (Nationwide Children’s Hospital and The Ohio State University)

Bicuspid aortic valve (BAV) is the most common type of cardiac malformation with a prevalence of ~1% in the population. BAV is associated with congenital aortic valve stenosis found in infancy along with later onset aortopathy and calcific aortic valve disease. Pathogenic variants in *NOTCH1* were discovered to be a cause of BAV in humans. Here, we will review evidence supporting the independent roles of Notch1 signaling in aortic valve cells and in smooth muscle cells of the proximal aorta that contribute to the associated diseases of congenital valve stenosis, ascending aortic aneurysms and valve calcification using a combination of mouse and induced pluripotent stem cell models. These findings suggest that genetic contributions to a congenital heart valve malformation are also associated with adult onset cardiovascular diseases.

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[III-AHAJS-3] Deciphering the Pathogenesis of Aortic Dissection Through Vascular-Extravascular Cell Interactions

○Hiromi Yanagisawa (Life Science Center for Survival Dynamics, TARA, University of Tsukuba)

キーワード：Aortic dissection、Fibrillin-1、Hereditary thoracic aortic disease

Aortic dissection (AD) is characterized by the separation of medial layers of the aorta following an intimal tear. AD is a major cause of death in patients with connective tissue disorders such as Marfan syndrome, yet the molecular mechanisms underlying its onset and progression remain incompletely understood. Recently, we established a mouse model of AD based on a novel missense mutation in the fibrillin-1 gene (FBN1) identified in a Japanese male patient with familial AD. The corresponding mutation located in the first hybrid domain of Fbn1 was introduced into mice, and vascular pathology was systematically examined in homozygous animals. Approximately 50% of homozygous mice died within 5 weeks after birth due to aortic rupture. Histological analysis revealed endothelial cell activation preceding the massive accumulation of immune cells in the intima. Single-cell RNA sequencing demonstrated a marked increase in macrophage clusters, including MHC class II–positive pro-inflammatory macrophages (M1) at the onset of dissection and CCR2+ bone marrow-derived macrophages with M1- and M2-like phenotypes as AD progressed. In addition, fibrillin-1 expression was decreased in the aortic media, whereas aberrant subendothelial fibrillin-1 expression was increased during the progression. Notably, TGF-β signaling was downregulated in the AD aortas. This novel mouse model recapitulates key pathological features of human AD and provides a unique opportunity to investigate the early pathological events underlying AD.

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[III-AHAJS-4] Molecular Programs Governing Fetal Differentiation and Postnatal Remodeling of the Ductus Arteriosus

Utako Yokoyama (Tokyo Medical University)

キーワード：ductus arteriosus、vascular remodeling、transcriptional regulation

The ductus arteriosus (DA) is an essential fetal vessel that maintains fetal circulation before birth, and its closure is essential for the transition to postnatal circulation. During fetal development, prostaglandin E2 (PGE_2) signaling through its receptor EP4 plays pivotal roles in establishing DA-specific vascular properties, including smooth muscle cell (SMC) differentiation, intimal thickening, and impaired elastic fiber formation. To clarify the mechanisms controlling DA-specific EP4 expression, we generated EP4 reporter mice and performed transcriptomic and epigenomic analyses, including RNA-seq, ATAC-seq, and CUT&Tag. These studies identified distal regulatory regions upstream of the Ptger4 locus that drive DA-specific EP4 expression during fetal development. Functional disruption of these regions markedly reduced EP4 expression and resulted in PDA-associated neonatal lethality. We also investigated mechanisms underlying postnatal DA remodeling. Single-cell RNA sequencing revealed that SMCs, but not other vascular cell populations, underwent marked transcriptional changes after birth. Among genes induced postnatally in DA SMCs, cyclooxygenase-2 (COX-2) showed prominent upregulation. Oxidative stress and thromboxane signaling increased COX-2 expression in DA SMCs. In vivo experiments further suggested that COX-2-derived PGE2 contributes to postnatal anatomical DA closure via the EP4-Nr4a1 axis. These findings demonstrate that distinct molecular programs regulate fetal DA differentiation and postnatal DA closure.