EP News: Basic and Translational

Penelope A. Boyden, PhD

From the Department of Pharmacology, Columbia University, New York, New York.

Human pluripotent stem cell–derived cardiomyocytes develop from distinct mesoderm populations

The ability to direct the differentiation of human pluripotent stem cells (hPSCs) to the different cardiomyocyte subtypes is a prerequisite for modeling specific forms of cardiovascular disease in vitro. Lee et al (Cell Stem Cell 2017;21:179, PMID 28777944) investigated the development of the human atrial and ventricular lineages from hPSCs and showed that retinoic acid signaling at the mesoderm stage is required for atrial specification. Analyses of developmental stages revealed that ventricular and atrial cardiomyocytes derive from different mesoderm populations that can be distinguished on the basis of CD235a and RALDH2 expression. Electrophysiological characterization of the derivative cardiomyocytes revealed that the optimal specification of ventricular and atrial cells is dependent on the induction of the appropriate mesoderm. *The authors conclude that insights into the development of the human atrial and ventricular lineages enable the generation of functional cardiomyocyte populations.*

Expression of the rare caveolin-3 variant T78M alters cardiac ion channel function and membrane excitability

Caveolinopathies are a family of genetic disorders that can arise from alterations of the caveolin-3 (cav-3) gene. The T78M cav-3 variant has been associated with both skeletal and cardiac muscle pathologies. Campostrini et al (Cardiovasc Res 2017;113:1256, PMID 28898996) evaluated the T78M cav-3 variant on cardiac ion channel function and excitability by transfecting either the wild type or T78M cav-3 in caveolin-1 knockout mouse embryonic fibroblasts. Using immunofluorescence and electron microscopy, the authors reported that both are expressed at the plasma membrane and form caveolae. While hKv1.5 and hHCN4 interact with T78M cav-3 and reside in lipid rafts, T78M cav-3 causes hKv1.5 channels to activate and inactivate at more hyperpolarized potentials and hHCN4 channels to activate at more depolarized potentials. In silico analysis of 2 cell models confirmed that the T78M-dependent changes are compatible with a proarrhythmic effect. *The authors conclude that the presence of T78M cav-3 can generate a susceptible arrhythmogenic substrate.*

Address reprint requests and correspondence: Dr Penelope A. Boyden, Department of Pharmacology, Columbia University, 630 W 168th St, New York, NY 10032. E-mail address: pab4@columbia.edu.

GJA1-20k arranges actin to guide Cx43 delivery to cardiac intercalated discs

Delivery of connexin 43 (Cx43) to the intercalated disc (ID) is a continuous and rapid process critical for intercellular coupling. Actin provides rest stops for Cx43 forward trafficking, and Cx43 has a 20-kDa internally translated small C-terminus isoform (GJA1-20k) that is required for full-length Cx43 trafficking. Basheer et al (Circ Res 2017;121:1069, PMID 28923791) explored the mechanism by which the GJA1-20k isoform is required for full-length Cx43 forward trafficking to IDs. GJA1-20k markedly increases endogenous myocardial Cx43 gap junction plaque size at IDs. Furthermore, in micropatterned cell pairing systems, exogenous GJA1-20k expression stabilized filamentous actin and complexed with actin and tubulin. Inhibition of actin polymerization with latrunculin A (LatA) disrupted the targeting of microtubules to cell-cell junctions. GJA1-20k protects the actin filament from this LatA disruption. *The authors conclude that the GJA1-20k isoform stabilizes actin filaments that guide growth trajectories of the Cx43 microtubule trafficking machinery, increasing delivery of Cx43 hemichannels to IDs.*

Three-dimensional integrated functional, structural, and computational mapping to define the structural "fingerprints" of heart-specific atrial fibrillation drivers in human heart ex vivo

Structural remodeling of human atria plays a role in sustaining atrial fibrillation (AF), but insufficient quantitative analysis of human atrial structure impedes AF treatment. Zhao et al (J Am Heart Assoc 2017;6, PMID 28862969) developed a novel 3-dimensional (3D) structural and computational simulation analysis tool to reveal the structural contributors to human AF drivers. Epicardial optical mapping of the explanted intact human atria (63-year-old woman, chronic hypertension) was conducted during sinus rhythm and sustained AF maintained by spatially stable reentrant AF left atrial and right atrial drivers. Whole atria were imaged with contrast-enhancement magnetic resonance imaging. 3D human atria were analyzed for wall thickness, myofiber orientations, and transmural fibrosis. Analysis revealed that a specific combination of wall thickness and fibrosis ranges were primarily present in the optically defined AF driver regions vs nondriver tissue. *The authors conclude that this novel 3D computational high-resolution framework may be used to quantitatively analyze structural substrates before AF.*

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