Rhythm Genes Sing More Than One Tune
Noncanonical Functions of Cardiac Ion Channels

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There are 20 to 25,000 genes in the human genome. About 40% have no known function, but cardiac electrophysiologists probably think that they know their slice of the genome well. After all, there have been decades of research on the cardiac action potential and the ion channels that propagate it. A small, but growing number of reports, however, reveal noncanonical functions of ion channels that have nothing to do with the heartbeat. For example, congenital heart defects have been associated with long QT syndrome in rare cases. To investigate the relationship, Duff and colleagues generated a mouse mutant that carried the N629D mutation in the endogenous KCNH2 gene, ie, targeted knock-in. Mutations of KCNH2, also referred to as hERG or mERG in the human or mouse, cause long QT syndrome. The homozygous N629D/N629D mutation is lethal by day 11.5 of gestation (analogous to 7 weeks in humans). On day 9.5, the embryos have an irregular rhythm with pauses and no detectable $I_v$ current. If the overall phenotype were simply explained by the arrhythmia, the result would be reassuringly consistent with what we know about cardiac electrophysiology. The homozygous N629D mutation, however, also disrupted the development of the right ventricle, outflow tract, and vasculature from the aorta to branchial arch artery, which was not as easily explained by the known electrophysiological function of KCNH2.

To determine the mechanism, the authors obtained results that link mERG function to integrin and transforming growth factor-β signaling. Signaling via integrin-β1 has previously been shown to depend on a physical interaction with hERG. The hERG–integrin-β1 interaction is essential for the mechanical response of cells to the extracellular matrix. Here, the authors show that integrin-β1 is downregulated in the mutant, as is the phosphorylation of focal adhesion kinase, which is downstream in the integrin signaling cascade. Transforming growth factor-β is also downregulated in the mutant embryo, and the addition of exogenous transforming growth factor-β to cultured embryoid bodies or embryos partially normalizes the mutant vascular phenotypes. To prove that disruption of the mERG ion channel current causes the mutant phenotype, the authors showed that treatment of wild-type embryos with dofetilide between days 7.5 and 9.5 phenocopied the mutant defects. These and previous results suggest that mutant vasculogenesis phenotype results from a signaling defect as mERG+ cells grow out from the artery and interact with the extracellular matrix.

KCNH2 is among a small but growing number of channelopathy genes that have noncanonical functions with interesting mechanisms of action. Among them, KCNH2 and the Ca$_2$1.2 voltage-gated calcium channel, CACNA1C, illustrate several other emerging themes. Mutations of CACNA1C cause Timothy syndrome. Beside long QT syndrome, affected children have a combination of unusual traits, including baldness at birth, autism, facial dysmorphism, and malaligned dentition, syndactyly, and congenital heart defects. Curiously, the mechanism by which a CACNA1C mutation causes a particular phenotype is not the same in every tissue. In neurons and hair follicles, the pertinent phenotypes are unrelated to disruption of the normal calcium transport activity of the channel. Rather, they are mediated by a conformational change related to channel inactivation and the physical interaction of the channel with other proteins in signaling pathways. In contrast, normal jaw development does depend on the calcium transport function of the channel.

Whether by ion-dependent or ion-independent mechanisms, a clear, noncanonical function of cardiac ion channels is the modulation of diverse signaling pathways in noncardiac tissues. As shown by Teng et al. KCNH2 mediates integrin and transforming growth factor-β signaling. CACNA1C modulates bone morphogenetic protein signaling in the hair follicle, RhoA in neurons, and calcineurin–nuclear factor of activated T-cells in chondrocytes.

It is also clear that the KCNH2 and CACNA1C phenotypes of noncanonical function are not the trivial result of abnormal cardiac contraction or blood flow. This also seems to be true of the ventricular morphogenesis defect associated with Scn5.
mutation and probably of the human nonventricular compaction recently described for Hcn4 mutation. In examples, the mechanisms that produce these latter phenotypes are unknown, but the examples of KCNH2 and CACNA1C suggest general hypotheses for investigation.

Physicians and scientists focus their work and attention to become experts in their field. Cardiac electrophysiologists are no different. Teng et al,2 remind us that the world is larger than the several dozen genes that propagate the cardiac action potential. The world is almost certainly larger than we can imagine because of gene–gene interactions. Consider that all the ion channels in the heart have probably been discovered. Thus, new genes for long QT and other arrhythmia syndromes are now being evaluated based on their interactions with cardiac ion channels. Now, consider that just a few noncanonical functions have been described. There must be many given the number of potential interactions between cardiac ion channels and the 20000 other genes among the estimated 37 trillion cells in the human body.

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References


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