



Role of *Hey2* in Transmural Electrical Patterning (p 537)

Veerman et al determine the likely effect of a Brugada syndrome risk allele.

Brugada syndrome is characterized by abnormal electrical signals in the heart and a heightened risk of sudden death. A genome-wide association study (GWAS) has identified a Brugada-linked single nucleotide polymorphism (SNP) at the genetic locus 6q22.31. This SNP lies close to the gene for transcription factor *HEY2*; however, whether *HEY2* contributes to Brugada syndrome is unclear. Veerman and colleagues examined gene expression data from 190 human left ventricle samples and found that, of 8 genes in the 6q22.31 region, only *HEY2* showed significant association—increased expression—with the Brugada risk allele. Further, genome-wide coexpression analyses showed that, of 15617 genes examined, the expression of *KCNIP2*, which encodes an ion channel subunit, was most tightly correlated with the expression of *HEY2*. The team went on to show that myocardial expression of *KCNIP2* was lower in *HEY2*-deficient mice than in wild-type animals, suggesting that *HEY2* regulates *KCNIP2*. Indeed, these *HEY2*-deficient animals exhibited abnormal electrical patterning in the ventricle wall consistent with altered ion channel function. The results indicate that high *HEY2* expression increases the risk of Brugada syndrome and highlight the utility of expression analyses for uncovering potential functions of GWAS identified loci.

Notch and Sick Sinus Syndrome (p 549)

Transient Notch activation causes long-term electrophysiological problems in the heart, say Qiao et al.

Cell-cell signaling via transmembranous Notch proteins is essential for a variety of developmental processes, including the formation and function of several cardiovascular structures and systems. In adult mouse heart cells, Notch signaling is generally quiescent, but after an injury—such as a myocardial infarction—Notch is transiently reactivated, which in turn leads to altered ion channel expression and aberrant electrical properties. Qiao and colleagues have now examined the effects of such transient Notch reactivation in more detail. They found that in mice subjected to transient atrial Notch activation, there was significant heart rate slowing, sinus pausing, and dysregulation of sinus node and atrial conduction factors. Furthermore, these transcriptional and electrophysiological changes were sustained long after Notch signaling had returned to normal. Heart rate, for example, remained low for a year. Because cardiac injuries can predispose patients to atrial arrhythmias, the researchers suggest that a thorough understanding of the long-term cardiac effects of transient, injury-induced Notch activation may reveal pathways and factors that could be targeted for antiarrhythmic interventions.

Inhibition of *Meg3* Prevents Cardiac Remodeling (p 575)

Piccoli and colleagues target a noncoding RNA to prevent cardiac remodeling.

Fibroblasts contribute to myocardial remodeling during pressure overload-induced cardiac hypertrophy. These cells secrete factors that reorganize the extracellular matrix (ECM), creating fibrosis and heart dysfunction. To learn more about the remodeling actions of cardiac fibroblasts, Piccoli and colleagues investigated the array of long noncoding RNAs (lncRNAs) produced by these cells. lncRNAs regulate a variety of cellular processes and certain lncRNAs have been implicated in cardiovascular disease. However, the roles of cardiac fibroblast lncRNAs have not been thoroughly studied. In mice with pressure-induced hypertrophy, the team identified 3 lncRNAs that were specifically dysregulated in cardiac fibroblasts. Of these, one called *Meg3* was the most abundant and has previously been implicated in fibrosis. Functional studies of *Meg3* revealed that the RNA, by binding and activating transcription factor p53, promotes the expression of an ECM enzyme called MMP-2. The team also showed that antisense inhibition of *Meg3* could prevent the pressure-induced increase in MMP-2 as well as the associated fibrosis and hypertrophy in mice. Inhibition of *Meg3* may, therefore, be an effective way to prevent cardiac fibrosis and dysfunction during heart disease, say the authors.

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