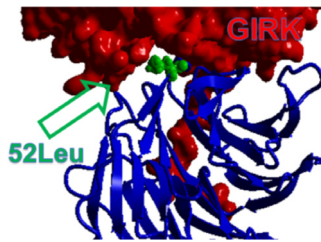


Cardiomyopathy TALEN Knockout Library (p 1561)

Karakikes et al edit genes in induced pluripotent stem cells to examine cardiovascular disease mechanisms.

Although many genetic mutations that cause inherited cardiomyopathies and congenital heart diseases have been identified, the molecular mechanisms underlying these conditions remain poorly understood. However, recent developments in gene editing and the generation of induced pluripotent stem cells (iPSCs) could change that. Karakikes and colleagues have now created a panel of gene editing constructs designed to target and disrupt 88 different genes associated with cardiovascular diseases. Introducing these individual constructs into human iPSCs and then differentiating the cells into cardiomyocytes should enable researchers to observe how a given mutation affects myocardial development. As proof of principle, the team examined iPSCs in which the *TBX5* gene had been homozygously deleted to model Holt-Oram syndrome—a condition characterized by heart defects and limb abnormalities. After cardiomyocyte differentiation, the cells exhibited abnormal action potentials, and the team was able to identify novel genes and pathways targeted by the *TBX5* transcription factor. In separate experiments, the team corrected a mutation associated with dilated cardiomyopathy in iPSCs derived from a patient with the condition.



***GNB2* Is a Disease Gene for Familial SND and AVB (p e33)**

Stallmeyer et al discover a new mutation causing sinus node and atrioventricular conduction dysfunction.

Sinus node dysfunction is characterized by fainting, dizziness and palpitations, and by tachycardia, bradycardia, and impaired or blocked atrioventricular conduction (AVB). The condition is progressive and thus manifests most often in elderly patients, but can also occur early in life, suggesting inheritance of a genetic defect. Although some causative mutations have been identified, in most cases of familial disease, the underlying cause is unknown. Now, from studying 25 members of a family with SND and AVB, Stallmeyer and colleagues have identified a new mutation. Genetic linkage analysis of affected and unaffected family members first narrowed the search to a region on chromosome 7 containing 272 genes. Sequencing of these genes revealed just 1 nucleotide change that both had a predicted functional consequence and was present in all affected family members while being absent from all unaffected members (as well as from 10 000 control individuals). This mutation disrupted a gene encoding a G-protein called *GNB2*, which the team found to be associated with abnormally enhanced activity of the GIRK potassium channel. Taken together, these results suggest that *GNB2* and GIRK play an important regulatory role in the physiology of the sinus and atrioventricular nodes and that these proteins could be potential targets in developing treatments for sinus node dysfunction



Intravenously Delivered Mesenchymal Stem Cells (p 1598)

Intravenous mesenchymal stem cell injections improve outcomes in mice with damaged hearts, report Luger et al.

Excessive inflammation after myocardial infarction (MI) or during chronic cardiomyopathy is associated with poorer outcomes. Such responses, however, could be prevented by mesenchymal stem cells (MSCs), which have been used in cell therapy, and are known to have immunosuppressive effects. While MSC treatments are generally delivered directly to the heart (to maximize local effects), Luger and colleagues argue that if a major benefit of the cells is their anti-inflammatory effect, then the less invasive intravenous delivery might work just as well. To test their concept, the team injected human MSCs into the tail veins of mice 1 day after MI. Three weeks later, the mice had significantly reduced thinning of heart walls and persistent improvement in left ventricle contractility compared with controls. MSC treatment also significantly reduced the abundance of inflammatory cells in the heart, and the team showed that reducing these cells directly (in the absence of MSCs) could improve outcome after MI. MSC injection also significantly improved left ventricle function in ischemic cardiomyopathy model mice. These results indicate that intravenous MSC delivery or other anti-inflammatory approaches deserve further investigation for potential clinical use.

Circulation Research

JOURNAL OF THE AMERICAN HEART ASSOCIATION



In This Issue Ruth Williams

Circ Res. 2017;120:1519

doi: 10.1161/RES.000000000000153

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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