Trpm4-Linked Isolated Cardiac Conduction Defects
Bad Trafficking Causes Electrical Gridlock

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Cardiac conduction system disease (CCD) is a common medical problem, with about 3 million people worldwide with pacemakers and 600 000 implanted each year. Despite its prevalence, there is little known about the molecular pathogenesis of CCD in the general population. Therefore, investigators have turned to cases of familial conduction system disease to gain insights.

This approach has led to the discovery of several genes involved in syndromic CCD (reviewed by Wolf and Berul). Mutations in the transcription factor NKX2.5 cause atrial septal defects and progressive atrioventricular block (AVB). Defects in another transcription factor, Tbx5, cause Holt-Oram syndrome, characterized by atrial septal defects, progressive AVB, and radial limb deformities. Muscular dystrophies can be associated with AVB as well. Emery-Dreifuss muscular dystrophy, whether caused by defects in Emerin or Lamin A/C, is associated with AVB, and myotonic dystrophy, caused by expansion of a trinucleotide repeat downstream of the DMPK gene, is also associated with progressive AVB. Atrioventricular block is a frequent finding in patients with PRKAG2 mutations who also have accessory atrioventricular connections and glycogen storage cardiomyopathy. Finally, AVB can be seen as part of the Andersen-Tawil syndrome of prolonged QT interval, potassium-sensitive periodic paralysis, ventricular arrhythmias, and dysmorphic features.

What about isolated atrioventricular conduction disease? Until recently, the only gene implicated in human-isolated progressive CCD was the cardiac voltage-gated sodium channel, SCN5a. Thus, there is great interest in the causative gene recently identified in a large South African family with autosomal dominant progressive familial heart block, type I. Likewise, this issue of Circulation: Cardiovascular Genetics reports the identification of the genetic cause of autosomal dominant isolated cardiac conduction block in 3 unrelated families. In all 4 of these families, linkage was found to a mutation in the transient receptor potential cation channel, subfamily M, member 4 gene (TRPM4) at chromosomal locus 19q13.3.

The transient receptor potential (TRP) channels are a large family of ion channels characterized by 6 transmembrane domains and relatively nonselective cation conductance. Originally cloned in the drosophila trp mutant that displays only a transient response to light, the TRP family now has 7 subclasses, including the TRPM class. TRPM4 channels are activated by increases in intracellular calcium and predominantly conduct monovalent cations (mostly Na⁺ and K⁺) with a reversal potential near 0 mV. TRPM4 activation leads to depolarization of the cell that can trigger a number of downstream effects, including feeding back on calcium signaling by decreasing the driving force of calcium entry. TRPM4 is highly expressed in the heart, pancreas, placenta, and prostate and at lower levels in the kidney, skeletal muscle, liver, intestines, thymus, and spleen. TRPM4 has been shown to play a role in the regulation of insulin secretion from β cells, cytokine release from lymphocytes, and cerebral vasoconstriction and has been implicated in the regulation of respiratory rhythm (for review see Guinamard and others).

In the previous report of progressive familial heart block, the authors showed that the TRPM4E7K mutant channels are biophysically similar to wild-type but are constitutively SUMOylated. SUMOylation, a reversible posttranslational protein modification (for review see Geiss-Friedlander and Melchior), has varied regulatory effects on cardiac ion channels, but in the case of the TRPM4 channel appears to impair endocytosis, resulting in enhanced TRPM4 current density caused by increased channel surface density. Thus, the mutation causes a gain of function leading to heart block.

In the present work, the authors show that, similar to the TRPM4E7K mutant, the variants associated with isolated cardiac conduction block also result in channels with unitary properties similar to wild type. These mutants lead to increased surface channel density and thus current density when expressed in HEK cells. Disruption of the dynein endocytic pathway enhanced wild-type current but had no effect on mutant TRPM4 channels. When coexpressed with Ubc9, an enzyme that conjugates SUMO to target proteins, wild-type currents and 2 of the 3 mutant channels displayed increased current density. Together, these data suggest that the mutations result in trafficking defects that ultimately lead to enhanced TRPM4 current. Although the precise mechanism remains to be determined, the authors propose that increased surface TRPM4 channel density would inhibit conduction by increasing the membrane leak conductance. This would presumably depolarize the cellular resting mem-
brane potential, leading to inactivation of sodium channels to the point of conduction failure.

Several other cardiac ion channel subunit mutations cause impaired trafficking and have been linked with proarhythmic syndromes including KCNQ1 (long QT1), the majority of studied KCNH2 mutations (long QT2), the potassium channel KCNJ2 (Andersen-Tawil), SCN5A (CCD and Brugada syndrome), and the hyper-polarization-activated cyclic nucleotide-gated channel 4 gene (sinus node disease). In all of these examples, mutations result in trafficking-deficient proteins that fail to reach the plasma membrane, causing a loss of function. The TRPM4 trafficking defect is unique in leading to a gain of membrane current. Other ion channel gain-of-function mutations, whether in potassium channels leading to the short QT syndromes 1 to 3 or in SCN5A leading to long QT3 syndrome, have not been associated with impaired trafficking or endocytotic activity. This appears to be a novel molecular mechanism for the most recently discovered channelopathy.

These studies raise several important questions. Does TRPM4 play any role in the nonfamilial forms of conduction disease? This could be explored by screening patients with CCD for sequence variants in the TRPM4 gene. Alternately, a genome-wide association study of patients with CCD might demonstrate association at the TRPM4 locus. Absent such a genome-wide association study of patients with CCD for sequence variants in the TRPM4 gene. Alternately, a genome-wide association study of patients with CCD might demonstrate association at the TRPM4 locus. Absent such studies, we could gain insight from genome-wide association studies of the PR interval. Of the several such studies performed to date, no association has been found with TRPM4 or 19q13.3.

Are there any novel therapeutic implications of this work? In contrast to CCD associated with transcription factor mutations that appear to cause impaired conduction system development and hypoplasia of AV conduction structures, the mechanism of bundle-branch and AV block in TRPM4 mutations may be functional. Inhibitors of TRPM4 may be able to restore AV conduction in affected family members. Although there are several compounds used experimentally to inhibit TRPM4, most are poorly selective and inhibit several other ion channels, whereas recently described 9-phenanthrol may be more selective.\textsuperscript{6} Given the role of TRPM4 in such a broad range of biological functions, a cardiac-specific inhibitor might be needed as a realistic therapy.

Partial depolarization of diseased tissue is not new in cardiac arrhythmogenesis. Depolarization of resting membrane potentials in ischemic ventricular myocytes can lead to sodium channel inactivation, conduction slowing, and resulting ventricular arrhythmias. In a novel approach to this problem, investigators recently reported that gene therapy using the skeletal muscle sodium channel SKM1, which operates more effectively at depolarized membrane potentials, improved conduction velocities in ischemic zones and decreased reentrant arrhythmias in an animal model. An approach might also improve conduction in His-Purkinje cells and could obviate the need for pacing in TRPM4-mediated conduction disease.

This study adds to the growing list of genes that have been associated with human CCD. It appears that familial CCD can result from a diverse set of genetic mutations rather than a single unifying cause or pathway. The list of genes includes not only the expected ion channels but transcription factors, a gene encoding a nuclear membrane protein, and a gene encoding a protein kinase subunit. The number of ways that the conduction system may fail speaks to the underlying complexity of this highly specialized tissue that is only now beginning to be unraveled by investigations such as these.

Disclosures

None.

References


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