

EDITORIAL COMMENT

Arrhythmias and Dilated Cardiomyopathy

Common Pathogenetic Pathways?*

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Dilated cardiomyopathy (DCM) is the most common cause of heart failure and cardiac transplantation, and is among the most common diagnoses requiring hospitalization in North America. Approximately 4.7 million people in the United States have heart failure, and approximately 550,000 new cases are diagnosed annually (1). The 5-year mortality rate among patients with heart failure is close to 50% (2). Patients with DCM are prone to arrhythmias, and the cause of mortality in these patients is either end-organ dysfunction due to pump failure or arrhythmia-related death (3). The etiology of DCM-associated arrhythmias has been speculated to be the result of a variety of electrical abnormalities, but the primary cause is not well understood. Many believe that the arrhythmogenic substrate results from myocardial fibrosis, leading to an “irritable focus” that is easily triggered. Other hypotheses include high catecholamine levels or stretching of myocardial fibers induced by increased left ventricular end-diastolic volume, leading to an arrhythmic substrate (4). However, we, and others, have shown that the causative genes responsible for various cardiovascular diseases are typically involved in “final common pathways,” and when these pathways are disrupted, the clinical phenotype may occur (5–11).

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In the case of DCM, the disruption of the link between the sarcolemma, the cytoskeleton, and the sarcomere has been shown to be associated with the disease, whereas the “final common pathway” of rhythm disorders is disturbance

of ion channel function (5–8). Therefore, because the majority of dysfunctional ion channels that have been found to cause arrhythmias are typically localized to the sarcolemma, disruption of the sarcolemma-sarcomere link could potentially result in ion channel dysfunction, resulting in the combination of a DCM phenotype and arrhythmias (Fig. 1). Further, it is possible that the opposite may be true, when the function of an ion channel is primarily disturbed, in this case caused by a gene mutation in *SCN5A*. This disturbance may cause dysfunction of cytoskeletal protein binding partners, resulting in a secondary DCM. Another possibility is that the electrical dysfunction caused by the ion channel gene defect leads to mechanical instability, and ultimately to myocardial dysfunction and ventricular dilation. Further, it is possible that the opposite may be true: that primary disruption of an ion channel (through a gene mutation) leads to DCM.

In this issue of the *Journal*, McNair et al. (12) report the screening of the cardiac sodium channel gene *SCN5A* in a cohort of patients and families with DCM. Of the 338 subjects from 289 families studied, 15 mutation carriers were found, including 5 separate mutations (1.7%), 3 being novel (12). In 14 of 15 subjects with mutations (93%), arrhythmias were also notable and included supraventricular arrhythmias (13 of 15), sick sinus syndrome (5 of 15), atrial fibrillation (9 of 15), ventricular tachycardia (5 of 15), and conduction disease (9 of 15). The authors have studied the mechanisms involved in the development of these overlapping phenotypes. In nearly 70% of the *SCN5A* mutations thus far reported to cause DCM, the mutations localize to the highly conserved homologous S3 and S4 transmembrane segments, suggesting a shared mechanism of disruption of the voltage-sensing mechanism of this channel. Hence, the authors intimate a correlation among DCM, arrhythmias, and sodium channel mutations. Unlike the long-QT syndrome subtype (LQT3) caused by *SCN5A* mutations, resulting in a gain of function of the cardiac sodium channel and prolongation of the sodium current during depolarization, Brugada syndrome, another disease caused by *SCN5A* mutations, results from a loss of function (13). In these disease states, variants in *SCN5A* lead to a shift in the voltage dependence of steady-state inactivation in the direction of more positive potentials, accelerating the recovery time from inactivation. In addition, *SCN5A*-induced atrioventricular conduction disease has been shown to be caused by impairing fast inactivation without producing noninactivating currents. Reduction in sodium current density and an enhancement of slower inactivation components resulted in a significant reduction in myocardial conduction velocity leading to atrioventricular block (14). In these reported cases of *SCN5A*-induced DCM, there is a different mechanism resulting in the dilated phenotype, which appears to rely on the location of the channel and a charge change in a critical residue within the channel. The underlying cause of the reported patient's DCM remains

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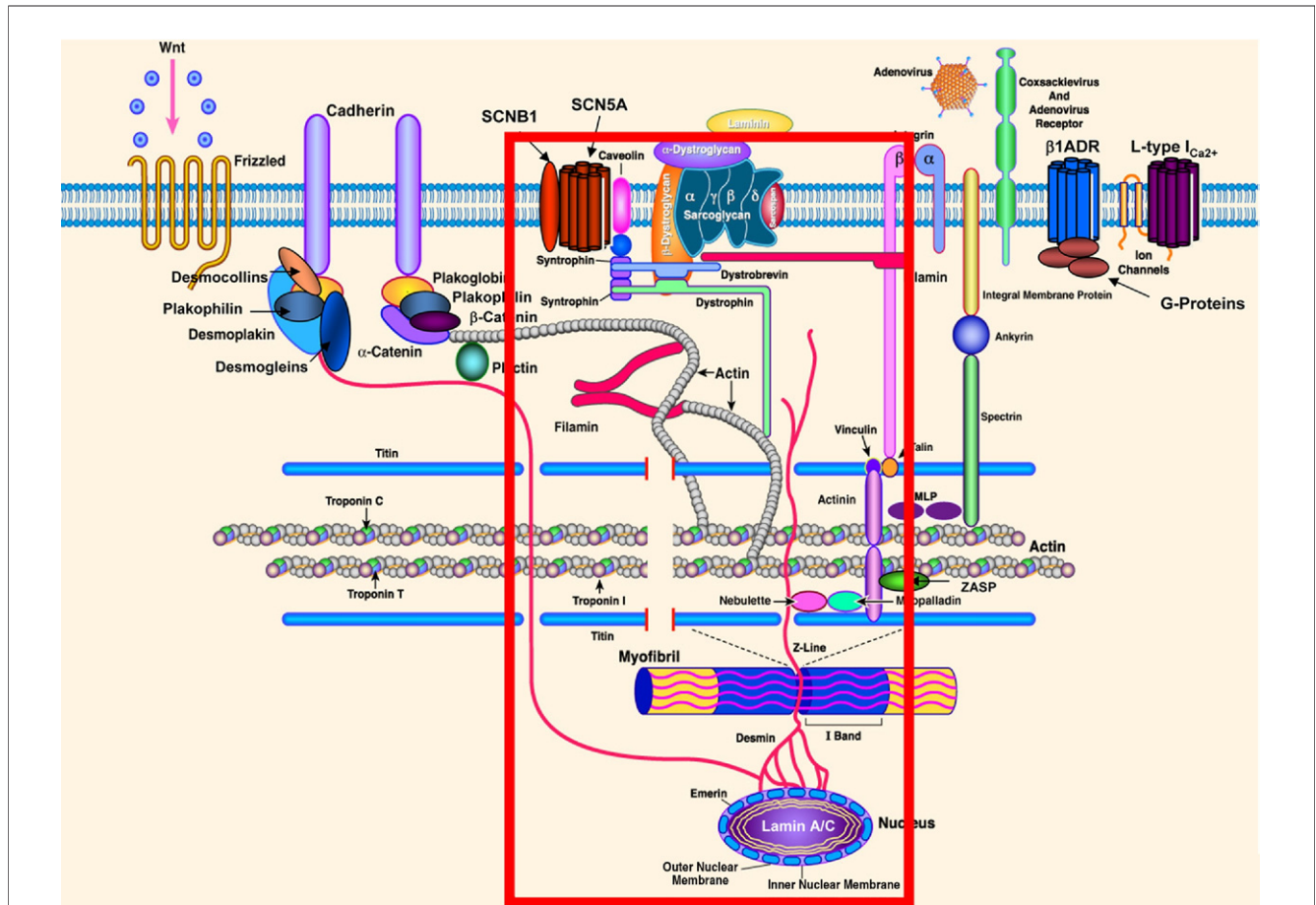


Figure 1 The Cardiomyocyte

In this illustration of the cardiomyocyte, the extracellular matrix (in which laminin is shown), sarcolemma (in which SCN5A is shown), sarcomere (in which the troponins are shown), and nucleus (in which lamin A/C is shown) are shown along with a variety of interactive proteins within each area of the cardiomyocyte. The cardiac sodium channel, SCN5A, is shown in the sarcolemma and interacts with its β -subunit SCN1B in the sarcolemma, as well as dystrophin, syntrophin, and caveolin, among other proteins (note red rectangular box denoting this pathway). As can be seen, disturbance of any of these interacting proteins can disrupt the function of the others that interact directly or downstream, thereby resulting in dysfunction and a clinical cardiac phenotype such as dilated cardiomyopathy or arrhythmias, or both. nNOS = neuronal nitric oxide synthase.

unclear, however. Unfortunately, the authors have not studied the myocardium of any of the *SCN5A* mutant cases for the cellular biological changes within the heart. Interestingly, heterozygous *SCN5A*-knockout mice have extensive myocardial fibrosis and up-regulation of hypertrophic markers as they age (15). It may be insightful to look closer at the myocardium of the patients with *SCN5A* mutations that exhibit the dilated phenotype with more advanced imaging such as magnetic resonance imaging with delayed enhancement to evaluate for fibrosis. From a molecular standpoint, studies of binding partners of *SCN5A* could help us to understand whether the protein make-up of the heart is intact and whether functional abnormalities in the sarcolemma, cytoskeleton, or sarcomere occur secondarily to the *SCN5A* mutations. There is precedence for these considerations. For instance, we have shown that mutations in caveolin-3 (*Cav3*) (16) and syntrophin α -1 (*SNTA1*) (17) both cause a long-QT syndrome phenotype with a gain of

function in *SCN5A* and that this occurs through disturbed binding of each of these proteins with *SCN5A*. Therefore, we called these proteins “channel-interacting proteins” (ChIPs). In a similar manner, ChIPs could be disrupted that interact with *SCN5A* and are more involved in structure and mechanical function. For instance, dystrophin is another binding partner of *SCN5A* (Fig. 1). Gene mutations leading to abnormalities in the dystrophin protein result in the X-linked neuromuscular diseases Duchenne muscular dystrophy and Becker muscular dystrophy. Boys with Duchenne and Becker muscular dystrophies have DCM and often have arrhythmias. In addition, dystrophin mutations can result in X-linked dilated cardiomyopathy, a severe form of DCM commonly associated with arrhythmias as well (18). Dystrophin is also disrupted in coxsackie myocarditis due to protease 2A cleavage, resulting in myocardial inflammation, necrosis, and subsequently, fibrosis (19). Patients with coxsackie myocarditis can have features consistent with

a DCM phenotype and frequently have arrhythmias. The involvement of dystrophin in the development of the DCM phenotype has been shown in idiopathic DCM and other genetic forms of DCM (20), but can only be speculated as potentially playing a role here, and therefore should be evaluated. In addition, desmosomal and other intercalated disk proteins interact with and bind to *SCN5A* and could also play a role in these phenotypes that result from *SCN5A* mutations. Again, cellular biology and proteomic analysis could be helpful in distinguishing the mechanisms responsible for the overlapping phenotype.

The study by McNair et al. (12) is an excellent first step in defining the association of DCM and arrhythmias caused by *SCN5A* mutations. Future studies focused on the mechanisms responsible for arrhythmias and DCM will better define the full extent of these overlapping phenotypes and perhaps clarify why some patients have DCM alone, arrhythmias alone, or the combination of DCM and arrhythmias. We predict that the answers lie in the proteins functioning in electrical and mechanical roles and that disturbance of these overlapping “final common pathways” will shed light on this long-standing mystery.

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