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Molecular mechanisms in the pathogenesis of arrhythmogenic cardiomyopathy

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ABSTRACT

The article is based on work presented in the Distinguished Achievement Award lecture at the Society for Cardiovascular Pathology meeting in Seattle, WA, in March 2016. It reviews our current understanding of mechanisms responsible for a highly arrhythmogenic, nonischemic cardiomyopathy. It highlights the armamentarium of powerful methods available to the experimental pathologist in efforts to define how complex cardiovascular diseases work. It concludes with acknowledgment of the need for a far more detailed approach as to how we categorize human disease, a task for which pathologists are especially well positioned.

Contents

1. Introduction

Arrhythmogenic cardiomyopathy (ACM) is a familial nonischemic cardiomyopathy first described clinically [1] and pathologically [2] in the 1980s. It is a leading cause of sudden death in the young and especially in athletes [2–6]. It has a dramatic and complex clinical and pathologic phenotype. Arrhythmias occur early in the disease, during the so-called concealed phase, before the onset of ventricular remodeling and contractile dysfunction. With time, progressive myocardial degeneration ensues with replacement by fibro-fatty scar tissue [1–4]. The disease typically affects the right ventricle most severely, but both ventricles usually exhibit pathological abnormalities [3,4]. The right ventricular preponderance is likely related to different biomechanical responses of the ventricles to exercise [5,6].

ACM is caused, in most cases, by mutations in genes that encode desmosomal proteins [3,4,7]. Mutations in all known desmosomal genes (encoding the desmosomal cadherins desmocollin-2 and desmoglein-2, and intracellular linker proteins plakophilin-2, plakoglobin, and desmoplakin) have been implicated in ACM [3,4,7]. Mutations in other genes including some previously linked to dilated cardiomyopathy (DCM), such as phospholamban [8], or hypertrophic cardiomyopathy, such as titin [9], have also been reported in subjects who fulfill

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diagnostic criteria for ACM. This likely reflects the increasing recognition of clinicopathological overlap among the nonischemic cardiomyoapthies as well as persistent challenges in clinical diagnosis in this complex spectrum of heart muscle diseases.

In most cases, ACM is inherited as an autosomal dominant trait with variable penetrance [3,4,7]. Digenic, compound heterozygous and recessive forms have been reported and are typically associated with more severe clinical phenotypes [10–12]. Still, ACM is generally regarded as a "monogenic" cardiomyopathy in which the disease can be reasonably attributed to specific pathologic variants within single genes. Desmosomal proteins have traditionally been thought to fulfill structural roles in cell–cell adhesion, but they also interact with diverse cell signaling pathways [13]. Thus, disease alleles in ACM likely exert deleterious effects through multiple mechanisms. The fact that arrhythmias arise during the concealed phase implicates mechanisms such as may be at play in the ion channelopathies, but the progressive development of myocardial damage, fibro-fatty scarring, and inflammation points to mechanisms of cardiac myocyte injury that go beyond those of the ion channelopathies. Also, the fact that exercise increases disease penetrance and risk of adverse events [5,6] strongly suggests that mechanical stimuli somehow interact with genetic factors to determine disease expression.

The overarching goal of our work is to explain how mutations in desmosomal genes cause ACM. Ultimately, we want to help develop truly mechanism-based therapies to prevent sudden death and myocardial damage in this lethal human heart disease. As detailed in this review, we have found that glycogen synthase kinase-3β (GSK3β) plays a role in the pathogenesis of ACM [14]. We have also identified a small molecule, annotated as an inhibitor of GSK3β [15], that has a remarkable ability to prevent and/or reverse the full disease phenotype (arrhythmias, exercise-induced sudden death, ventricular myocyte injury and apoptosis, inflammation, and contractile dysfunction) in various experimental models of ACM, and in human iPSC-cardiac myocytes derived from patients with ACM [14,16]. Although much of our work and several representative figures included in this review involve models based on expression of a mutant form of plakoglobin (an allele implicated in only a small minority of ACM patients), the basic disease pathway involving GSK3β has been observed consistently in diverse models including those involving expression of mutant plakophilin-2 and desmoglein-2, as well as in cardiac myocytes derived from iPSCs from ACM patients with plakophilin-2 mutations [14,16]. The ACM disease mechanism appears to include a defect in forward trafficking of ion channel proteins to the intercalated disk in ventricular myocytes that may be responsible for establishing conditions conducive to abnormal impulse propagation and arrhythmias [14,16]. Whether abnormal protein trafficking also contributes to myocyte injury is unknown, but the fact that a single small molecule is able to prevent both the arrhythmia and myocardial injury features of the ACM phenotype suggests a mechanistic connection.

2. Why is ACM so arrhythmogenic?

There is something inherently arrhythmogenic about the basic disease mechanism in ACM. Whereas overall survival free of cardiac death or transplantation is better in patients with ACM compared with DCM, the proportion of sudden deaths is much greater in ACM (>80%) than DCM (~30%) patients [17]. Moreover, arrhythmias in the hypertrophic and dilated cardiomyopathies arise in hearts that exhibit significant structural remodeling (myocyte injury/death and fibrosis) [17]. By contrast, arrhythmias in ACM typically occur as an early manifestation of disease in hearts that show no apparent gross or microscopic features of remodeling [3,4]. While there has not been a previous report of a desmosomal mutation in a sudden death victim with a normal heart at autopsy, molecular autopsies have only recently included analysis of desmosomal genes. Thus, it remains an open question whether ACM can cause sudden death in a structurally normal heart.

We have gained insights into mechanisms responsible for the early arrhythmogenic clinical phenotype in ACM through study of patient

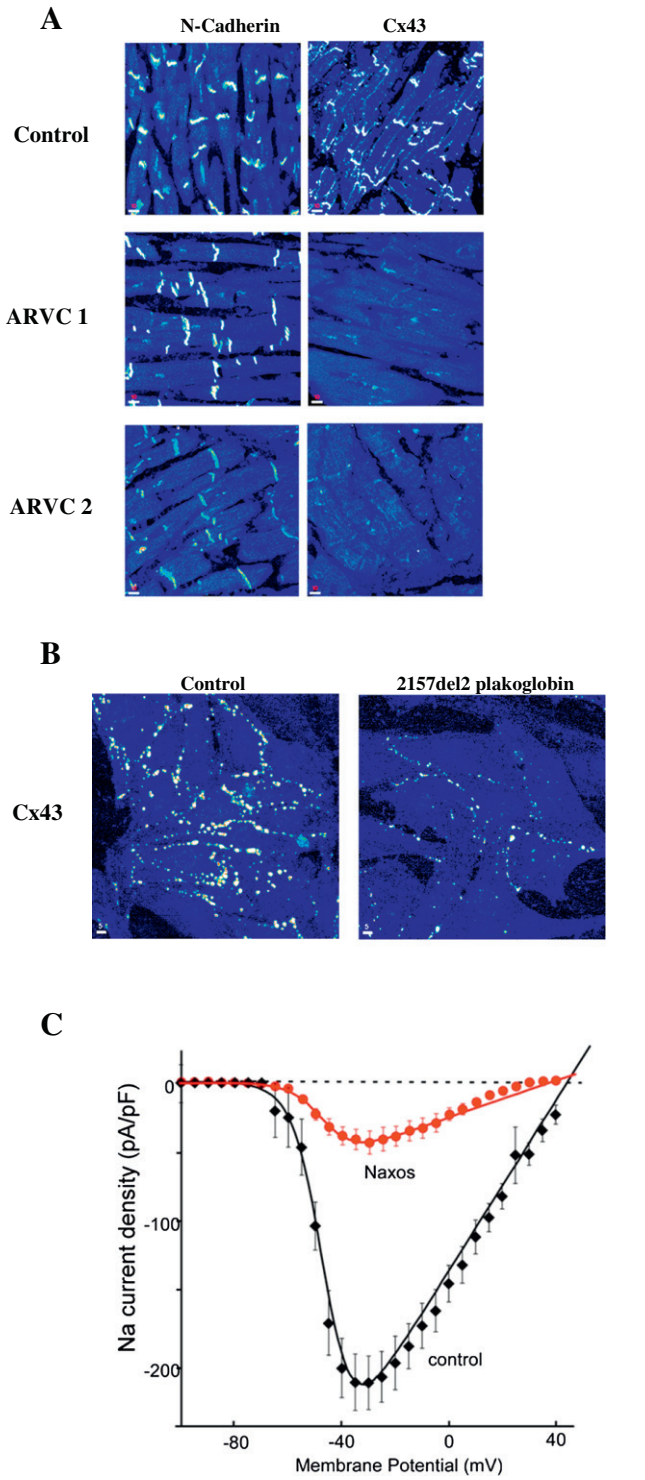

Fig. 1. (A and B) Immunohistochemical staining of human myocardium (A) and cultured neonatal rat ventricular myocytes (B). In panel A, abundant immunoreactive signals for the adhesion molecule N-cadherin and the major ventricular gap junction protein Cx43 localize to intercalated disks in a normal control heart (upper panels), whereas signal for Cx43 is greatly reduced at cell–cell junctions in hearts from representative ACM patients (middle and lower panels). In panel B, Cx43 signal in control myocytes is seen as numerous punctate clusters at cell–cell junctions, but is greatly reduced in myocytes expressing 2157del2 plakoglobin which causes ACM in patients with Naxos disease. (C) Reduced sodium current in ventricular myocytes isolated from zebrafish expressing 2157del2 plakoglobin (Naxos) compared to control myocytes. Panel A is reproduced from Asimaki et al. [18]; panels B and C are reproduced from Asimaki et al. [16].