

SNAP29 Restricts Cardiac Arrhythmias by Insulating A Subset of Desmosomal Proteins and Connexin43 from Autophagic Degradation

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Desmosomes are strong cell-cell adhesion junctions that connect the cytoskeleton of one cell to another to maintain the mechanical integrity of tissues under constant stress, such as the heart. Classically, human genetic studies and mouse models have linked mutations/deficiencies in components of the desmosome to arrhythmogenic right ventricular cardiomyopathy (ARVC), an inherited cardiac disease of the desmosome that impacts cardiac structure/morphology. However, growing evidence points to a role for loss of desmosomal integrity in cardiac electrical diseases (eg., Brugada syndrome, long QT, sinus node arrhythmias) that have no impact on cardiac structure/morphology; however, how desmosomal protein loss results in these distinct forms of the cardiac disease remains unclear. We exploited an unbiased yeast-two-hybrid screen using the desmosomal protein, desmoplakin (DSP) as a bait, to uncover novel desmosomal protein-protein interactions that may help further explain the pathobiology (structural versus non-structural) encompassed by desmosomal mutations/loss. Through this screen, we identified the SNARE protein, synaptosomal-associated protein 29 (SNAP29), as a novel DSP-interacting protein. Traditional functions of SNAP29 are to regulate membrane fusion and play a role in autophagy; however, its role at the desmosome and in the heart is undefined. We hypothesized that SNAP29 is a new subcomponent of the cardiac desmosome that regulates desmosomal protein degradation and thus, may have important roles in desmosomal-based diseases. We show that SNAP29 co-localizes with desmoplakin in the adult mouse heart and that adult cardiac-specific DSP deficient mice harbor loss of cardiac SNAP29, validating SNAP29 as a subcomponent of the cardiac desmosome. By generating novel cardiomyocyte-specific SNAP29 knockout (SNAP29-cKO) mice, we show that SNAP29-cKO mouse hearts displayed baseline and pacing-induced ventricular arrhythmias in an age-dependent manner in the absence of cardiac structural and functional deficits. Molecular analyses further revealed that adult SNAP29-cKO hearts displayed a molecular loss of a subset of desmosomal (DSP, plakophilin2) as well as gap junction (connexin43) proteins when compared to controls. These cell-cell junction defects were accompanied by an accumulation of autophagic markers, as well as machinery specifically at the cell-cell junction in SNAP29 deficient cardiomyocytes, which functionally resulted in cardiac arrhythmias. We show that acute blockade of autophagy was sufficient to rescue levels of desmosomal and gap junction proteins as well as arrhythmias in SNAP29 deficient cardiomyocytes. In summary, our data suggest that SNAP29 insulates a subset of desmosomal and gap junction proteins from selective autophagy-mediated degradation to restrict cardiac arrhythmias and that loss of SNAP29-desmosome-gap junction interactome may predispose the heart to desmosomal based diseases of an electrical (non-structural) nature.