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Policing Cell-Cell Connections: A Novel Role for the COP9 Signalosome in Mechanisms Underlying Arrhythmogenic Heart Disease and Sudden Death

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Arrhythmogenic right ventricular cardiomyopathy is a genetic based cardiomyopathy, characterized by ventricular dysfunction,fibrofatty replacement of the ventricle and ventricular arrhythmias leading to sudden cardiac death in young people. ARVC is termed a "disease of the desmosome"; however, limited information exists on how desmosomal protein dysregulation/loss triggers ARVC. To identify novel protein targets that impact desmosomal biology and the desmosomal disease, ARVC, we performed a yeast two hybrid screen using the desmosomal gene, desmoplakin (DSP) as bait to screen an adult human heart cDNA library. We identified CSN6, subunit 6 of the COP9 signalosome, as a novel cardiac desmosomal interacting protein (via desmoplakin, DSP). Traditional functions of the CSN complex (composed of subunits 1-8) are to inhibit protein degradation by "turning off" ubiquitinatin-mediated protein degradation via deneddlylation; however, the role of CSN6 in the heart is undefined. We show that CSN6 uniquely protects the cardiac desmosome and its loss accelerates desmosome destruction as (i) CSN6 co-localizes to desmosomal junctions, (ii) CSN6 co-immunoprecipitates with desmosomal proteins and (iii) hearts from novel cardiac-specific CSN6 knockout (CSN6-cKO) mice display selective loss of desmosomal protein levels (and its primary target, connexin43). CSN6 loss is a trigger for ARVC as CSN6-cKO mice exhibit sudden death and cardiac disease features associated with a biventricular form of ARVC, similar to our cardiac-specific DSP knockout mice (DSP-cKO) that is a classic biventricular model of ARVC. CSN6 and DSP-cKO hearts both selectively display underlying hyper-accumulation of protein degradation machinery at the cell junction, specifically linking CSN6 pathways to the desmosome. CSN6 pathways are relevant to human ARVC as (i) CSN6 levels are down-regulated in ARVC hiPSC-derived cardiac cells that exhibit striking desmosomal defects and arrhythmogenic behavior and (ii) CSN6 localization is lost from cell junctions in a cardiac biopsy from an ARVC patient harboring desmosomal (DSP (R315C) and plakophilin-2 (PKP2 IVS10-1 G>C) mutations. Yeast and *in silico* modeling assays reveal that this DSP R315C mutation is sufficient to abrogate DSP binding to CSN6. We highlight the importance of CSN6 at the cardiac desmosome in maintaining desmosomal protein turnover ("desmophagy"), and suggest that loss of CSN6 and desmosomal protein turnover as new underlying mechanisms driving ARVC and sudden death.

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