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Modeling Arrhythmogenic Right Ventricular Cardiomyopathy with Human Induced Pluripotent Stem Cells

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Background:

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a primary heart muscle disorder resulting from desmosomal protein mutations; characterized pathologically by fibrofatty infiltration and clinically by arrhythmias and sudden cardiac death. We aimed to establish apatient/disease-specific human induced pluripotent stem cells (hiPSCs) model of ARVC.

Methods and Results:

Dermal fibroblasts were obtained from an ARVC patient with a novel plakophilin-2 (*PKP2*) mutation, reprogrammed to generate hiPSCs, coaxed to differentiate into cardiomyocytes and compared with healthy-control hiPSC-derived cardiomyocytes (hiPSCs-CMs). Real-time PCR showed significant decrease in the expression of*PKP2*in the ARVC-hiPSCs-CMs. Immunostainings revealed reduced densities of*PKP2,* the associated desmosomal protein plakoglobin, and the gap-junction protein connexin-43. Electrophysiological assessment demonstrated prolonged field potential rise time in the ARVC-hiPSCs-CMs. Transmission electron microscopy identified widened and distorted desmosomes in the ARVC-hiPSCs-CMs. Clusters of lipid-droplets were identified in the ARVC-cardiomyocytes that displayed the more severe desmosomal pathology. This finding was associated withupregulation of the pro-adipogenic transcription factorperoxisome proliferator-activated receptor gamma (PPAR-g). Exposure of the cells to apidogenic stimuli augmented lipid accumulation and desmosomal distortion.

Conclusions:

The induced pluripotent stem cell technology can be used to establish an*in-vitro*model of ARVC. The hiPSCs-CMs model can recapitulate the ARVC phenotype in the dish and provide a unique platform to evaluate the early processes participating in disease pathogenesis. Finally, the ARVC-hiPSCs-CMs model may allow identifying novel therapeutic targets for this disease.