Determination of Mutant JUP Localization in an iPSC Model of ARVC: Implications for Diagnosis and Pathogenesis

Dincer, Ethan (School: Saint Paul Academy and Summit School)

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) is an inheritable myocardial disease characterized by fibrofatty replacement of cardiomyocytes and is the leading cause of sudden cardiac death in young athletes. Mutations in junctional plakoglobin (JUP), a key protein in maintaining structural integrity of the desmosome, have been found to contribute to ARVC through JUP detaching from the desmosome. However, research has not been focused on mutant JUP localization after detaching from the desmosome, providing insight into subcellular JUP interactions. The experiment was carried out by inducing Pluripotent Stem Cells (iPSC's) into cardiomyocytes followed by subsequent immunohistochemical analysis and immunofluorescence confocal microscopy to determine subcellular location of JUP. Mutant JUP was found to largely translocate to the nucleus, implying a connection between JUP and it's paralog protein, ß-catenin, in the Wnt signaling pathway. Mutant JUP was also found to overtake ß-catenin in Wnt signaling, activating the TCF/LEF target transcription factors without ß-catenin present. A deeper understanding of the pathogenesis of ARVC allows for a thorough review of modern ARVC diagnosis practices, and the methods used in this experiment provide insight to a more effective way to diagnose the often elusive disease. Keywords: Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC), sudden cardiac death, junctional plakoglobin (JUP), ß-catenin, Wnt signaling pathway, immunofluorescence confocal microscopy, desmosome.