THE HARTWELL FOUNDATION

2021 Individual Biomedical Research Award

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Modulation of a Critical Cell Signal Transduction Pathway as a Treatment for Arrhythmic Cardiomyopathy

Arrhythmogenic cardiomyopathy (ACM) is a devastating genetic disease that progressively replaces the heart muscle (myocardium) with fibrous fatty tissue. The transformation reduces the ability of the heart to beat rhythmically and pump blood effectively, leading to life-threatening arrhythmias and often, sudden death heart failure. Although most affected patients have mutations in genes that encode components of cardiac muscle, in 40% the genetic cause remains unknown. Current therapies for ACM only treat symptoms like arrhythmia and fainting, and include medication, implanting a defibrillator, and cardiac tissue ablation. Unfortunately, no intervention is known to reverse or even slow the progress of the disease. In the United States, there are currently about 4000 children who have or will develop ACM; most are diagnosed in the first year of life and between the ages of 12 and 18. Tragically, one in four will die from abnormal heart rhythm before their 21st birthday, and one in two will require a heart transplant. Clearly there is an urgent need for effective therapy; the challenge is an incomplete understanding of the genetic and molecular basis of the disease. More specifically, if a unifying mechanism of ACM development can be identified, then a therapy could be developed to treat any form of the disease regardless of the patient genotype. In this regard, 35–40% of ACM can be accounted for by a mutation in the gene encoding a protein, PKP2, that contributes to maintenance and integrity of cardiac muscle. Several other biomolecular mechanisms, including inflammation, and signaling pathways that cause fibrosis and fat deposition, are known to be involved in ACM, but most are poorly understood. In this regard, I have identified three affected individuals in a single family with a mutation localized in the *TAX1BP3* gene, which encodes a protein in a highly conserved signaling pathway (Wnt) implicated in many biological processes during development and disease. The TAX1BP3 protein is known to be essential for intracellular signaling in certain tissues, but its function in the heart is unknown. In this context, I hypothesize that loss of Wnt signaling may be a "final common pathway" in all genetic examples of ACM; and that modulating the level of critical Wnt signaling may represent a novel approach to treating and reversing ACM, as well as other forms of heart muscle disease. Accordingly, I have developed a first-in-kind inducible genetic mouse model that lacks the *Tax1bp3* gene only in heart tissue. In preliminary experiments, knocking-out the gene caused a phenotype characteristic of ACM, where mice experienced arrythmia, heart failure, and premature death. I propose using this preclinical mouse model to test if stimulation of Wnt signaling with small molecules or gene therapies will act to slow or reverse the observed heart disease. If I am successful, clinical translation of an effective therapy will save the lives of thousands of children affected with this intractable and deadly heart condition.