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Seminar Title:

Understanding Familial Cardiomyopathies from the Ground Up

Abstract:

Familial cardiomyopathies are leading causes of sudden cardiac death and are major indicators for heart transplant. These diseases are frequently caused by mutations of sarcomeric proteins; however, one of the outstanding challenges in the field has been connecting mutation-induced changes in contractile protein function with the phenotype seen in cardiomyocytes. Many of the cardiomyopathy mutation-induced changes in contractility at the molecular scale are subtle, begging the question of what other factors could link molecular-scale changes in contractile proteins with the cellular phenotype. We hypothesized that disease-causing mutations of sarcomeric proteins would likely affect not only contraction, but also how cardiomyocytes sense and respond to changes in their mechanical environment associated with aging and disease. To test this hypothesis, we studied the molecular and cellular consequences of several cardiomyopathy mutations in troponin-T. We determined the molecular mechanisms of these mutants using biochemical and biophysical tools, and then we used computational modeling to predict the impact of the mutations on sarcomeric contractility. In mutant human stem cell derived cardiomyocytes, we demonstrate that these mutations impact not only contractility, but also the cardiomyocytes' ability to adapt to changes in substrate stiffness (e.g., heart tissue fibrosis that occurs with aging and disease). These results help link the molecular and cellular phenotypes and implicate impaired mechanosensing in cardiomyocytes as an under-appreciated mechanism in the pathogenesis and progression of cardiomyopathies. These results also have important implications for our understanding of multiple heart diseases and the design of precision therapeutics.