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RESEARCH NEWS

How a mutation undermines cardiac function

Caitlin Sedwick

JGP paper explores how a mutated troponin T causes cardiac hypertrophy.

Hypertrophic cardiomyopathy (HCM), a common disease of the heart that can cause sudden death, is often linked to mutations in the proteins that make up the contractile unit of cardiac muscle, the sarcomere. In their new paper in *JGP*, Piroddi et al. explore how a mutated version of the regulatory protein troponin T alters heart muscle function (1).

"We're trying to understand the impact of mutations leading to congenital heart disease, and we do that by investigating sarcomere function from human surgical samples," says Corrado Poggesi, a Professor of Physiology at the University of Florence in Italy.

In cardiac muscle sarcomeres, the motor protein myosin produces contractile force by forming cross-bridges with and pulling against actin-based thin filaments. Myosin's access to its actin binding sites is controlled by thin-filament proteins such as tropomyosin, and the troponin subunits C, I, and T. In the absence of calcium, tropomyosin blocks myosin from binding actin. But when calcium floods the cytoplasm after the arrival of an electrochemical action potential at the cell membrane, it binds to troponin C, which undergoes a conformational change that's communicated to tropomyosin by troponin T. This shifts tropomyosin out of the way, allowing myosin to do its work.

Prior studies by Poggesi's laboratory have demonstrated that some mutations in myosin can affect the energetic efficiency of cardiac contraction by changing how the protein binds to actin (2). But recently, as part of the European "Big Heart" research consortium, Poggesi's group had the opportunity to study the heart tissue of a young man with severe HCM caused by a mutation in the C-terminal region of troponin T (3).

Studies by Nicoletta Pirrodi (left), Corrado Poggesi (center), and colleagues (not shown) show that the K280N mutation in troponin T increases the energetic cost of cardiac muscle contraction (see graph) by accelerating cross-bridge kinetics (not shown). Photos courtesy of the authors.

Nicoletta Piroddi, an Assistant Professor working in Poggesi's lab, headed a multicenter effort to understand how this mutation affects cardiac muscle function.

"The impact of mutations associated with HCM on sarcomere function is often difficult to identify in cardiac preparations from humans," notes Poggesi. One reason for this is that most patients are heterozygous for sarcomere protein mutations, so the mutant proteins can be variably expressed throughout the heart. But Piroddi et al. found that this patient was homozygous for mutated troponin T, so they began their studies by isolating myofibrils from the patient's tissue and comparing their mechanical properties with myofibrils from normal donors, from patients with aortic stenosis, and from patients who had HCM but no mutations in sarcomere proteins. "Because we were comparing a single patient with many different controls, it was a challenging statistical problem to determine what the meaningful differences were between the patient and the controls," says Poggesi.

Cardiac tissue can undergo molecular remodeling to try to compensate for impairments in heart function, which can obscure the effect of the mutated protein (4). Piroddi et al. addressed this problem by conducting troponin replacement experiments (5). They studied the mechanics of the patient's myofibrils in which the mutant troponin was replaced with normal protein, and of normal myofibrils where the protein was replaced with the mutant version.

"In the presence of the mutant protein, there was a significant change in cross-bridge kinetics and in the energetic cost of tension generation," says Poggesi. The mutant troponin accelerated both formation and detachment of cross-bridges; the latter resulted in higher energy consumption for muscle contraction. This was accompanied by higher tension in resting myofibrils, suggesting a cellular basis for the diastolic dysfunction observed in HCM disease.

Interestingly, the functional effects of the mutated troponin strongly resemble what has been observed in some myosin mutants, but the underlying molecular mechanism is unknown. This needs more investigation, observes Poggesi.

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sedwick@gmail.com.

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