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Throttling back the heart's molecular motor:

A small molecule inhibits mutated forms of myosin that cause cardiac hypertrophy

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A young athlete collapses and dies during competition. Autopsy reveals an enlarged heart with thickened walls in which the cardiac muscle cells are in disarray and surrounded by fibrotic tissue. Until 1990, the cause of such sudden death was unknown. This devastating condition, called familial hypertrophic cardiomyopathy (HCM), was eventually linked to a mutation in myosin (1), the heart's molecular motor. Today, more than 300 separate HCM-causing mutations have been identified throughout the myosin molecule. On page 617 of this issue, Green *et al.* (2) describe a small molecule that binds to myosin and inhibits its activity, delaying the onset and progression of the disease in a mouse model. The study offers hope that a "simple" remedy for HCM may be possible.

Myosin is an adenosine triphosphatase (ATPase) enzyme that cyclically interacts with cytoskeletal actin filaments to convert chemical energy—through its hydrolysis of ATP—into force and motion that powers the heart's pumping action. Muscle cells of the heart shorten by the sliding of actin filaments past myosin filaments in the sarcomere, the cell's smallest contractile unit. Each myosin filament is composed of ~300 myosin molecular motors that generate power through their interaction with actin (see the figure). Mutation in the human β -cardiac myosin gene (*MYH7*) results in the amino acid substitution of arginine at position 403 with glutamine (R403Q) in the molecular motor. With 50% of R403Q patients dying by age 35 (3), understanding the molecular basis of the mutation's primary insult to the myosin motor's power-generating capacity has been a matter of vigorous debate.

Initially, it was proposed that a loss in myosin power output was the causative factor of HCM, and that remodeling of the heart was a failed compensatory response (4, 5). To address this question, a mouse model of HCM was generated in which the animal develops a hypertrophied heart and dies suddenly when physically challenged—outcomes resulting from a single R403Q allele, as occurs in humans (6). Mice homozygous for R403Q die within 7 days of birth, emphasizing the devastating impact of this mutation (6). Analysis of pure mutant α -cardiac myosin (which is 92% identical in its wild-type primary sequence to human β -cardiac myosin) isolated from the hearts of these mutant mice revealed that the motor protein had twice the force- and motion-generating capacity compared to normal myosin (in a simplified in vitro model of cardiac contraction), and also had equally enhanced ATPase activity (7). These characteristics raise the potential for excessive ATP utilization and, consequently, boost energy demand, which could signal hypertrophic remodeling (8). These gains of function for the mutant form of myosin should not have been

surprising, given that clinical measures of cardiac performance describe the HCM heart as hyperdynamic (9). Many of the mutations discovered in myosin's motor domain have a tendency toward enhanced mechanical and/or ATPase capacities (10)—specifically, the R403Q, R453C, and R719W mutations studied by Green et al., in which arginine (R) at position 403, 453, and 719 is substituted with glutamine (Q), cysteine (C), and tryptophan (W), respectively.

In some patients with HCM, surgical thinning of the septal wall between the right and left ventricle can reduce the thickened wall's encroachment on the left ventricle's outflow tract (11); for severe cases, cardiac transplantation may be the only option. With 1 in 500 individuals having HCM, a far less invasive intervention is desirable. Green et al. tested the hypothesis that if HCM mutations lead to enhanced myosin power production, then early intervention using small-molecule inhibitors of myosin power generation should prevent hypertrophy. MyoKardia, a company founded by four authors of the Green et al. study, developed such a small-molecule inhibitor (MYK-461). Green et al. observed that the small molecule reduced both myosin's power generation, as measured in isolated rodent cardiac muscle fibers, and ATPase rate. The authors tested two protocols for administering MYK-461 (via drinking water) to HCM (i.e., R403Q, R453C, and R719W) mice: at age 8 to 15 weeks before detectable cardiac hypertrophy, myocyte disarray, and fibrosis; and at age 30 to 35 weeks, once cardiac remodeling has occurred. Amazingly, early, chronic drug administration effectively prevented the development of hypertrophy, muscle cell disarray, and fibrosis, and diminished both hypertrophic and profibrotic gene expression. However, these dramatic and positive effects were seen only with early drug administration, but not observed in the older HCM mice once the pathologic cardiac remodeling occurred. Whether the benefits of early intervention last if MYK-461 treatment is halted, or instead unleash the hypertrophic program has yet to be determined.

Mutations to virtually every contractile protein of the heart can lead to HCM (10); most notably, cardiac myosin-binding protein-C (cMyBP-C), which serves as a “brake” to limit myosin power production through its interactions with both myosin and actin (12). Mutations in cMyBP-C are a leading cause of HCM and compromise cMyBP-C braking action (13), resulting in increased myosin power production. Enhanced cardiac contractility is a recurrent theme (10), suggesting that the myocardium is finely tuned to myosin's normal steady-state stress levels (force/unit area of muscle). By analogy, placing the engine of an Indy race car (i.e., mutant myosin) in a stock car chassis (i.e., the heart's connective tissue matrix) could lead to internal stress and structural damage; for the heart, this amounts to inducing cardiac fibrosis and muscle cell disarray that are characteristic of HCM patients. If enhanced sarcomeric power production is the driving signal for cardiac hypertrophy, then simply throttling back the myosin engine with a small-molecule inhibitor may be a generalized approach to deal with the vast array of contractile protein mutations (e.g. actin, troponin, tropomyosin, cMyBP-C).

Interestingly, mutations in some of the same cardiac contractile proteins lead to dilated cardiomyopathy (DCM), where thin ventricular walls are almost incapable of pumping blood. In stark contrast to HCM mutations, myosin mutant forms S532P and F764L (in which serine at position 532 and phenylalanine at position 764 are replaced by proline and

leucine, respectively) that cause DCM have diminished power production and ATPase activity (14). Could early intervention with small-molecule activators of cardiac myosin power production effectively treat genetic DCM? The myosin activator omecamtiv mecarbil is now in phase 2 clinical trials for treating human heart failure (15).

Early identification of HCM and DCM mutations could rely on family genetic history or a more ethically challenging agenda of genetically screening segments of the population. Perhaps genetic cardiomyopathies will be best served by a taking a daily pill to suppress the genetic programs that may lead to sudden death. Maybe gene therapy based on the use of clustered regular interspaced short palindromic repeats (CRISPR) technology will be commonplace in the future. Only time will tell, but Green *et al.* suggest that basic science can push clinical treatments from managing symptoms to correcting a defect.

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Myosin and muscle contraction

Myosin generates power that moves actin filaments in the sarcomere, in turn contracting muscle cells. Mutations in myosin that increase this capacity cause hypertrophic cardiomyopathy (HCM).

Young HCM patient

Genetic predisposition but no pathology yet

Older HCM patient

Genetic predisposition and pathology seen

Figure. Targeting myosin

Mutations in myosin that increase power generation lead to hypertrophic cardiomyopathy (HCM). In a mouse model of HCM, early intervention with a small-molecule inhibitor of myosin reverses the disease (hypothetical patient scenario is shown). Such intervention could simplify treatment and become a generalized approach to control many contractile protein mutations that lead to HCM, or the use of myosin activators for dilated cardiomyopathy (DCM). DCM is characterized by less power production by myosin, heart muscle atrophy, and heart failure.