Study finds new enzyme with structure that could explain how heart can beat optimally

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The heart is the only muscle that contracts and relaxes continuously over a lifetime to pump oxygen-rich blood to the body's organs. Researchers at UT Southwestern Medical Center now have identified a previously unrecognized enzyme that could optimize contraction and lead to new strategies to treat heart failure.

The heart's contractions depend on a motor enzyme called myosin pulling on the muscle's fiber-like actin filaments. Those contractions are improved when myosin has a phosphate molecule attached to it (phosphorylation), said Dr. Audrey Chang, Assistant Professor of Physiology and first author of the study, published in today's *Proceedings of the National Academy of Sciences*.

A constant amount of phosphorylation is essential for normal heart function. The optimum phosphorylation level is maintained by balancing the activities of myosin kinase enzymes that add the phosphate and an opposing enzyme that removes the phosphate. If the amount of phosphorylation is too low, the result is heart failure - which affects about 5.7 million adults in the United States. In addition, animal models with increased myosin phosphorylation have shown enhanced cardiac performance that resists stresses that cause heart failure, explained senior author Dr. James Stull, Professor of Physiology.

The international study led by UT Southwestern identifies a new myosin kinase, called MLCK4, and provides the first three-dimensional structure for any member of the MLCK family, Dr. Stull said.

The researchers found that compared to myosin kinases in other kinds of muscles (skeletal and smooth), the heart-specific MLCK4 lacks a conserved regulatory segment that inhibits kinase activity, a structural finding consistent with biochemical studies that indicated this kinase is always turned on.

In addition, they found that another myosin kinase found only in heart muscle (MLCK3) contains a modified regulatory segment that allows the protein's activity to be enhanced by the calcium modulator protein, calmodulin. Thus, both of the MLCK enzymes that are unique to cardiac muscle provide phosphate to myosin in normal beating hearts to optimize performance and prevent heart failure induced by stresses, Dr. Stull explained.

"The heart-specific expression of these kinases, and the linkage between low myosin phosphorylation and heart failure, makes targeting of these cardiac myosin kinases to improve cardiac function compelling," he said.

Additional studies are underway, Dr. Stull said, to understand the signaling pathways that fine tune kinase activities with the goal of targeting these two kinases therapeutically to improve myosin phosphorylation in those affected by heart failure.

More information: Cardiac myosin light chain is phosphorylated by Ca2+/calmodulin-dependent and -independent kinase activities, *PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1600633113

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