Researchers discover 'modus operandi' of heart muscle protein

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Researchers at the University of Pennsylvania School of Medicine have discovered that a protein called leiomodin (Lmod) promotes the assembly of an important heart muscle protein called actin. What's more, Lmod directs the assembly of actin to form the pumping unit of the heart. The findings appear in this week's issue of *Science*.

"Very little was known about Lmod when we began this study," says lead author Roberto Dominguez, PhD, Associate Professor of Physiology.

"It appeared that this protein was present in muscle cells but this had not been demonstrated directly and nobody knew what it did," explains Dominguez. "We compared the amino acid sequence of Lmod with the sequence of another protein called tropomodulin [Tmod] that was already known to bind actin filaments in muscle cells. We found that one part of Lmod was very similar to Tmod, but Lmod was a bigger protein than Tmod and contained unique features that made us suspect that it could assemble the actin filaments of the heart muscle. This is exactly what we found."

The results answer a question that scientists studying the heart have long asked: What controls the assembly of the pumping unit of the heart?

Actin is the most abundant protein in most animal cells and forms long polymers, or filaments, that make up the cell skeleton. In the cells that make up muscles and the heart, interactions of actin filaments with motor proteins produce the contractions that pump blood through the

body.

Actin spontaneously forms polymers in test tubes, but living cells use nucleator proteins to control the time and place where actin filaments forms. “For a long time, physiologists have wondered what serves as the nucleator protein in cardiac muscle cells,” says co-author Professor Thomas Pollard, PhD, of Yale University. “It was very satisfying after all these years to discover that Lmod can serve as the nucleator protein to initiate the forming of actin polymers in heart muscle cells.”

Lmod also directs actin filaments to the sarcomere, the part of the heart that controls contractions or pumping. When Lmod was knocked down in cardiac muscle cells by an RNA silencing technique, the sarcomeres became completely disorganized and could not direct muscles to contract.

Proper localization of Lmod in heart cells is critical, because even moderately elevated levels promote the formation of abnormal actin bundles in the nuclei of cardiac muscle cells where actin does not belong. A similar disorganization of actin bundles is characteristic of a disease of skeletal muscle weakness called intranuclear rod myopathy. Although this disease is caused by a mutation in a skeletal muscle-specific actin gene, the similarity in appearance suggests that mutations in Lmod could cause the same type of disease in cardiac muscle cells.

The Penn team is currently studying how the heart regulates the level of Lmod and how Lmod might be relevant to cardiac muscle disease. In addition, the team is attempting to crystallize Lmod in order to study its structure directly.

Source: University of Pennsylvania