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Researchers reveal missing link in a heart disease pathway

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University of Michigan scientists and their colleagues have helped characterize a previously unknown link in the chain of biochemical reactions implicated in some forms of heart disease. The finding provides a new target for future drug therapies.

A team led by U-M structural biologist John Tesmer obtained a high resolution image of three proteins caught in the act of transferring chemical signals inside a cell. Two of the proteins in the complex had previously been linked to heart disease, and Tesmer's team was able to resolve "the missing link" between them, he said.

"We've trapped all three proteins together, and we've learned how they interact. Essentially, it's a previously unrecognized pathway that one could target to treat cardiovascular disease," said Tesmer, a research associate professor at the Life Sciences Institute and an associate professor at the Medical School.

The work is reported in Friday's edition of the journal *Science*.

Two proteins in the trio had previously been linked to heart disease: G-alpha-q and RhoA.

Scientists have known for some time that patients suffering from high blood pressure and other maladies release hormones, such as angiotensin, that can trigger an abnormal growth of cardiac cells that sometimes leads to heart disease.

They also knew that these hormones, after binding to receptors on the surface of cells, activate G-alpha-q. Further along in the signaling pathway, RhoA, a protein that regulates cell growth and gene expression, also had been tied to heart disease.

The missing pieces of the puzzle were the intermediaries that relay cellular signals from G-alpha-q to RhoA. Tesmer and his colleagues have now determined the atomic structure of one of those go-betweens, an enzyme called p63RhoGEF. Scientists use such structures to study how molecules interact---and how one might block their function therapeutically.

Tesmer's lab captured a group portrait of all three proteins---G-alpha-q, p63RhoGEF and RhoA---in X-ray crystallographic images. Concurrently, animal studies conducted by German colleagues confirmed the interactions between these substances, as well as their importance to smooth-muscle function.

Source: University of Michigan