Discovery has implications for heart disease

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A study, led by University of Iowa researchers, reveals a new dimension for a key heart enzyme and sheds light on an important biological pathway involved in cell death in heart disease. The study, published in the May 2 issue of *Cell*, has implications for understanding, and potentially for diagnosing and treating, heart failure and arrhythmias.

The UI researchers and colleagues from Vanderbilt University in Nashville, Tenn., focused on calmodulin kinase II, or CaM kinase II, a well-studied enzyme critical to many fundamental processes including heartbeat and thought.

Scientists know that CaM kinase's activity is sustained by adding a phosphate group -- a process known as phosphorylation. The new study proves that oxidation -- adding oxygen -- also can sustain the enzyme's activity, and like phosphorylation, the mechanism can be reversed to inactivate the kinase.

"Our results suggest that oxidation of CaM kinase is a dynamic and reversible process that may direct cell signaling in health and disease," said Mark Anderson, M.D., Ph.D., UI professor of internal medicine and molecular physiology and biophysics and senior study author. "Because CaM kinase activity is involved in arrhythmias, hypertrophy and heart cell death, this work also provides new insights into a disease pathway in heart that may lead to development of new drugs to treat heart disease."

In patients with heart failure, the level of angiotensin II -- a signaling molecule that promotes oxidation and cell death -- is elevated. Using a

specially created antibody, the researchers found that angiotensin II also increases the amount of oxidized CaM kinase.

In addition, by replacing the cell's normal CaM kinase with a CaM kinase unable to be oxidized, the scientists were able to block angiotensin-induced cell death. Scientists hope this discovery might lead to therapies that prevent cell death by blocking CaM kinase oxidation.

Currently, "angiotensin-blockers" are a mainstay for treating patients with sick hearts, but they work indirectly by targeting receptors on the cell surface. Anderson, who also is the Potter-Lambert Chair in Cardiology and director of the UI Division of Cardiovascular Medicine, suggested that by understanding the signaling mechanisms that occur inside the cell, it might be possible to inhibit the angiotensin pathway more directly. This approach may also preserve some of the good effects mediated by the cell surface receptor.

Using a wide range of scientific techniques and experimental methods, the team, led by Anderson and Jeffrey Erickson, Ph.D., a UI postdoctoral fellow, pinned down the details of the internal signaling mechanism.

Specifically, they showed that oxidation of two neighboring methionines -- sulfur-containing amino acids -- can sustain CaM kinase activity. Loss of these two methionines prevents activation by oxidation. They also found that they could return CaM kinase to its inactive state and inhibit heart cell death and dysfunction by using an enzyme called methionine sulfoxide reductase A (msrA), which reverses the methionine oxidation. Studies in worms, fruit flies and mice have shown that msrA increases lifespan, but, until now, the enzyme's targets in heart were unknown.

The UI team compared mice without the msrA enzyme to normal mice when the animals underwent disease stresses, including excess

angiotensin or induced heart attacks. The mice without msrA were more likely to die than normal mice under these circumstances, and the levels of oxidized CaM kinase were much higher in mice that lacked the enzyme.

Anderson speculated that the findings could implicate msrA as a susceptibility gene for patients – potentially, variations in the gene might help explain why some people do so badly after a heart attack where others do well.

The study demonstrates a direct link between CaM kinase activation and oxidative stress, two processes that are implicated in a wide variety of physiological and disease states. These findings will likely have broad implications and applications in basic research, diagnostics and new therapeutic approaches and represent an example of translation science of the type supported and encouraged by the new Institute for Clinical and Translational Science at the UI.

"This study also is a great example of collaborative science," added Anderson. "We had to apply expertise from several different labs to tackle this problem. So, the ease with which we can collaborate across disciplines at the UI and between institutions was enormously beneficial."

Source: University of Iowa

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