Clues to heart disease in unexpected places, researchers discover

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A major factor in the advance of heart disease is the death of heart tissue, a process that a team of scientists at Temple University School of Medicine's (TUSM) Center for Translational Medicine think could be prevented with new medicines. Now, the researchers are one step closer to achieving that goal, thanks to their discovery of a key molecule in an unexpected place in heart cells – mitochondria, tiny energy factories that house the controls capable of setting off cells' self-destruct sequence.

The study is the first to identify the molecule, an enzyme known as GRK2 (G protein-coupled receptor kinase 2), in mitochondria. It was led by Walter J. Koch, Ph.D., Professor and Chairman of the Department of Pharmacology at TUSM, and Director of the Center for Translational Medicine at TUSM.

"We have known that GRK2 is involved in the pathological development of certain heart diseases, such as chronic heart failure, and that its increased activity can lead to the death of heart cells. But its mechanism for the latter was unclear," Koch said. In addition, while the enzyme was known to be present in elevated levels in the hearts of patients with heart failure, the reasons for its rise were not fully understood.

Normally, GRK2 hangs out near the plasma membrane of heart cells, where it turns off certain signals transferred from the blood to the tissue. But the researchers at Temple found that it moves to mitochondria in response to two classic features of heart disease, ischemic insult and ensuing oxidative stress. These two processes, in which a momentary

lapse in the delivery of oxygen-rich blood to diseased tissues causes a sudden increase in damaging reactive molecules, converge to stimulate the self-destruct program of heart cells. They ultimately cause whole sections of heart tissue to die, leaving behind scars that can severely compromise the ability of the heart to function properly.

Koch's team found that in ischemic heart cells the movement of GRK2 from the cell membrane to mitochondria is chaperoned by a substance called heat-shock protein 90 (Hsp90), which is produced in cells in response to stress. By blocking Hsp90's ability to bind to GRK2, the researchers were able to prevent the enzyme's delivery to mitochondria.

They reached the same result after mutating a residue called Ser670 in the tail end of GRK2's amino acid structure. When the Ser670 residue is activated by a chemical signal, Hsp90 is nudged into action, attaching to GRK2 and carrying it to mitochondria. Mutation of Ser670 also resulted in a wholesale reduction in pro-death signaling in affected heart cells. The effects were observed in human heart muscle cells grown in the laboratory and in mice that had experienced induced heart attacks. The results are detailed in the April 12 issue of the journal *Circulation Research*.

Koch explained that the translation of the new findings to the clinic, where they would benefit patients, lies in developing new therapeutic approaches that are capable of limiting both the activity of GRK2 and its ability to associate with mitochondria.

"We have a great opportunity here to develop new medicines against heart failure and improve upon this significant disease syndrome," he said. He added that this will take some time but that molecular and pharmacological strategies against GRK2 are in the works. "We are developing a gene therapy tool known as the ßARKct, which is a peptide inhibitor of GRK2, and are quite excited about a clinical trial."

Koch and his team have shown in pre-clinical studies that delivery of the ßARKct to failing hearts can inhibit GRK2 and thereby protect the heart from death. In the new study, ßARKct was found to block the enzyme's transit to mitochondria after ischemia, an important step now believed to contribute to the peptide's beneficial effects in heart failure.

There is much yet to learn about GRK2, however, according to Koch. "We still need to find out exactly what GRK2 is doing in the mitochondria," he said. "We need to figure out what it interacts with and specifically regulates."

What the team uncovers could solidify GRK2 as a key target for therapeutic strategies against heart disease.

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