

Researchers discover key to heart failure, new therapies on horizon

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Some 5.8 million Americans suffer from heart failure, a currently incurable disease. But scientists at Temple University School of Medicine's (TUSM) Center for Translational Medicine have discovered a key biochemical step underlying the condition that could aid the development of new drugs to treat and possibly prevent it.

"Drugs we currently use for heart failure are not very effective," explained lead investigator Walter J. Koch, PhD, Professor and Chairman of the Department of Pharmacology at TUSM, and Director of the Center for Translational Medicine at TUSM. But, he added, "The more we learn about the disease mechanism, the more [drug targets](#) we'll find."

That is what Koch and colleagues at Thomas Jefferson University and the University of California, Davis, achieved in their latest study, which appears in the March 5 issue of the online journal [PLOS ONE](#). The report is the first to show that an enzyme called GRK5 ([G-protein coupled receptor](#) kinase 5) can gain access to a heart cell's nucleus – its command center, where control of its genes is maintained – by way of a transport mechanism involving calcium and a protein known as calmodulin. Once calcium and calmodulin deliver GRK5 to the nucleus, the enzyme usurps control over specific genes, ultimately causing hypertrophy, in which [heart cells](#) grow larger in size. Hypertrophy is a biological hallmark of heart failure.

GRK5 had previously been identified as a key player in maladaptive

[cardiac hypertrophy](#), which is the end stage of heart failure, when the [heart muscle](#) becomes enlarged and unable to pump enough blood to keep [vital organs](#) functioning. While GRK5's ability to get inside the nucleus was known, Koch and colleagues worked to fill in the missing links in its transport mechanism. Those links, they hope, will not only allow them to better understand GRK5's role in causing heart cells to increase in size but also find ways to block that process to more effectively treat [heart failure](#).

The GRK5 enzyme is a unique member of the GRK family, owing to its presence in the nucleus. Its journey begins at the cell membrane, where signals received by a molecule at the cell surface known as a Gq-coupled receptor prompt "escorts" – one of which is calmodulin, as the researchers discovered – to attach to GRK5 and guide it to the nucleus.

The team found that GRK5's transport requires calmodulin after examining different places on the enzyme where various escort molecules attach. They then introduced mutations that altered the attachment sites. Only when calmodulin-binding residues on GRK5 were mutated was the enzyme prevented from reaching the nucleus. Those mutations led to dramatic decreases in nuclear GRK5 levels and corresponding declines in the activity of genes known to drive cardiac hypertrophy. Calmodulin's ability to bind to GRK5 is in turn dependent on calcium. The same results were obtained both in vitro, using human heart muscle cells cultivated under laboratory conditions, and in vivo, in mice.

The team's research also marks a breakthrough in scientists' understanding of the role of neurohormones in hypertrophy. Released by specialized neurons into the bloodstream, neurohormones have long been cited as a cause of heart cell enlargement.

"One of the novel findings to fall out of this paper is that not all

hypertrophic signals from neurohormones are the same," Koch explained. "That's something to keep in mind as we move forward."

The next step, according to Koch, is to test the ability of different agents to keep GRK5 out of the nucleus. "We are now discussing a trial on inhibition of another cardiac GRK, GRK2," he said. He cautioned, however, that trials in patients with GRK5 inhibition are years away. First, agents capable of blocking GRK5 transport must be identified and tested in animals.

The work is an important advance for Temple's Center for Translational Medicine. GRK5 enters the pipeline of novel drug targets under investigation by the Center's scientists and clinicians, who share the common goal of coordinating clinical practice and basic research to speed the delivery of new therapies to patients.

"It's another entry into larger, pre-clinical animal studies," Koch said. "Something new to start down the path of translational medicine."

Provided by Temple University

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