Research team traces pathway to cardioprotection in post-ischemic heart failure

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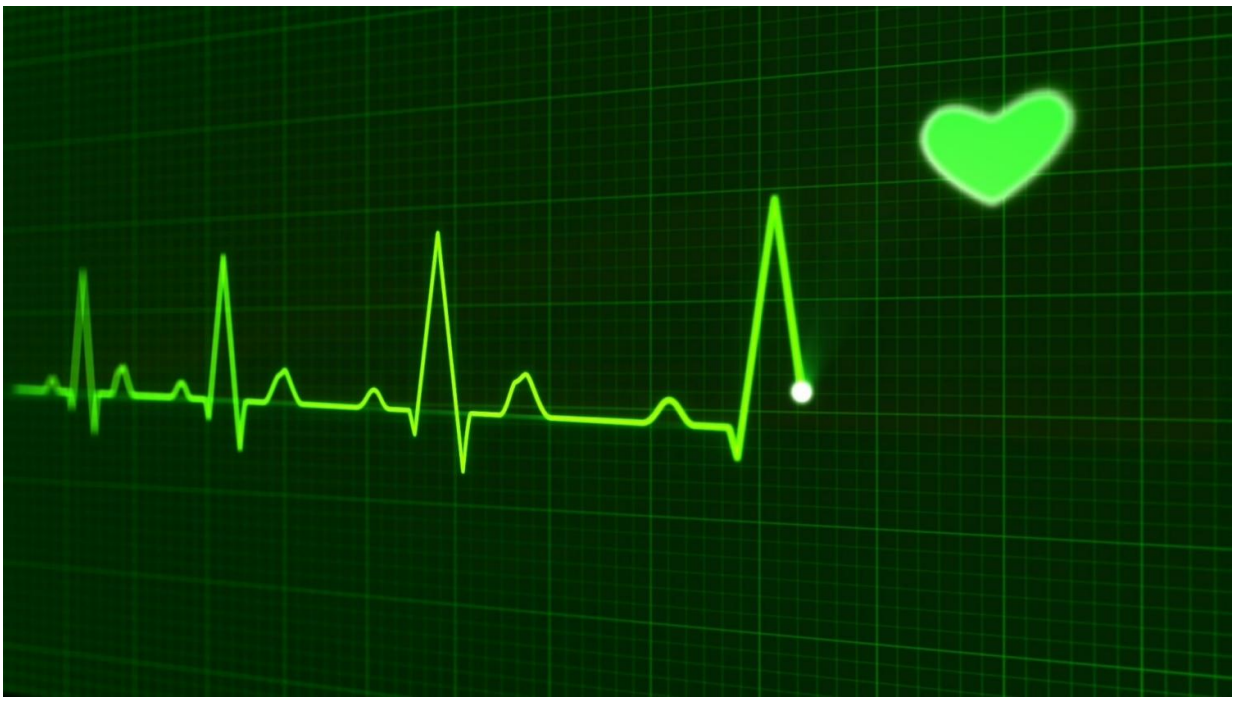

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During an ischemic attack, the heart is temporarily robbed of its blood supply. The aftermath is devastating: reduced heart contractility, heart cell death, and heart failure. Contributing to these detrimental changes is a signaling molecule, G protein-coupled receptor kinase 2 (GRK2),

which following ischemia accumulates in mitochondria, the energy-producing powerhouses of cells. Now, a Temple-led research team shows for the first time that blocking GRK2 localization to mitochondria protects heart cells from ischemic injury and death, casting new light on GRK2 as a potential therapeutic target in post-injury heart failure.

"We knew from our previous work that GRK2 accumulates in mitochondria following ischemia, but the detrimental impacts of mitochondrial pooling of GRK2 were unclear," explained Walter J. Koch, Ph.D., W.W. Smith Endowed Chair in Cardiovascular Medicine, Professor and Chair of the Department of Pharmacology, and Director of the Center for Translational Medicine at the Lewis Katz School of Medicine at Temple University (LKSOM) and senior investigator on the new report. "We now show that the mitochondrial pool of GRK2 is not only damaging but also is associated with GRK2 phosphorylation and dysfunctional cardiac metabolism, leading to declines in heart cell function and increased heart cell death." The findings were published online December 11 in the journal *Science Signaling*.

Dr. Koch's team landed on their latest discovery after developing a knock-in mouse model, in which mice were made to express a form of GRK2 carrying a mutation at the Serine670 residue. The Serine670 alteration prevented GRK2 phosphorylation and ultimately its ability to localize to mitochondria. As a result, following ischemia-reperfusion injury, in which blood flow through the coronary artery was stopped briefly and then restarted, mimicking an ischemic attack in human patients, mutant mice showed no GRK2 accumulation in mitochondria. By contrast, wild-type mice had significant mitochondrial pooling of GRK2.

Investigation of heart tissue revealed that the knock-in mice sustained far less heart cell damage compared to wild-type animals. The size of ischemic injury was smaller in knock-in mice, and heart cell viability

was increased. Mutant mice also had improved mitochondrial respiration and glucose oxidation rates.

"The lower levels of tissue injury observed in our mutated GRK2 mice were associated with better glucose metabolism, which is critical to attenuating oxidative stress and maintaining heart contractility and function," Dr. Koch said. The findings are consistent with his team's previous discovery that mitochondrial levels of GRK2 increase in response to oxidative stress and that mitochondrial GRK2 pooling is harmful to heart cells.

"Our findings [also] reinforce the link between cardiac injury and metabolism," explained first author Priscila Sato, Ph.D., Assistant Professor in the Department of Pharmacology and Physiology at Drexel University College of Medicine and formerly a researcher in Dr. Koch's laboratory at LKSOM. "We uncovered a novel role of GRK2 that helps us [better] understand the metabolic response to cardiac injury."

Dr. Koch and colleagues plan next to investigate the effects of blocking GRK2 phosphorylation in models of chronic heart failure. They also plan to search for proteins that might interact with GRK2 within the mitochondria to determine whether the detrimental effects of GRK2 are due to kinase activity or to a scaffolding effect that involves multiple proteins.

GRK2 levels are also known to be elevated in mice on high fat diets, suggesting that the molecule interacts with dietary factors. "In future studies we may be able to delineate how Western diet influences cardiac disease as it pertains to GRK2 signaling," Sato added.

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More information: "Restricting mitochondrial GRK2 post-ischemia confers cardioprotection by reducing myocyte death and maintaining glucose oxidation," *Science Signaling* (2018). stke.sciencemag.org/lookup/doi … 26/scisignal.aau0144

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