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# Breakthrough could lead to new treatment for heart attack

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The stop and start of blood flow to the heart during and after a heart attack causes severe damage to heart cells, reducing their capacity to function and potentially causing their death. But a recent study led by researchers at Temple University School of Medicine suggests that it is possible to limit the extent of that damage using a drug. In experiments in mice that recapitulated a human clinical scenario, they discovered that inhibition of a heart protein called TNNI3K reduced damage from heart attack and protected the heart from further injury.

The findings have significant potential for translation into heart attack patients in a clinical setting. "Many times, what is done in a lab setting can't be done in patients," explained Ronald Vagnozzi, PhD, lead author on the new study, which appeared October 16 in *Science Translational Medicine*. "But we were interested in a real-world scenario."

Working with senior investigators Thomas L. Force, MD, Professor and Clinical Director at Temple University School of Medicine's (TUSM) Center for Translational Medicine, and Muniswamy Madesh, PhD, Assistant Professor in Temple's Department of Biochemistry, Cardiovascular Research Center, and Center for Translational Medicine, Vagnozzi created a real-world clinical scenario in mice by mimicking blockage of an artery to induce heart attack and then administering a TNNI3K inhibitor. When cardiac function was subsequently improved in treated mice versus untreated controls, Vagnozzi and colleagues realized that a TNNI3K inhibitor could have important clinical benefits for human patients.

"TNNI3K is found only in the heart, which makes it interesting biologically and therapeutically," Vagnozzi said. "Although its function was not well understood, TNNI3K lent itself to being a potential therapeutic target for heart attack."

The researchers found that TNNI3K expression is elevated in patients who are suffering from heart failure, which can develop in the years following heart attack. To explore the significance of that elevation, they engineered mice to overexpress TNNI3K. They also created a second set of engineered mice, in which the protein was deleted. They then measured the animals' response to heart attack.

When overexpressed, Vagnozzi and colleagues found that TNNI3K promoted the injury of heart tissue from ischemia (blockage of blood flow) and reperfusion (restoration of blood flow) during and after a heart attack. TNNI3K overexpression in heart cells encouraged the production of superoxide, a reactive molecule from mitochondria, and activated p38 mitogen-activated protein kinase (MAPK), an enzyme that responds to stress signals in cells. The combined result of those activities was impaired mitochondrial function and heart cell death, which worsened ischemia/reperfusion injury. The opposite occurred in mice in which TNNI3K had been deleted—superoxide production and p38 activation were reduced, and injury to the heart was limited. Reductions in heart dysfunction and fibrosis (hardening of heart tissue) were also observed.

The team next collaborated with the pharmaceutical company GlaxoSmithKline (GSK) to identify compounds that were capable of blocking TNNI3K activity. Treatment of wild-type (nonengineered) mice with the compounds following heart attack produced effects that were similar to those observed in mice with TNNI3K deletion.

The new findings open the way to a large-animal study and the development of a TNNI3K inhibitor that can be used in humans.

According to Force, the team is planning to move ahead with a large-animal study, which will determine whether the drugs are effective in animals other than mice and allow for the development of pharmacological and safety profiles of the compounds. "Because TNNI3K is only expressed in the heart, drugs targeting it should be reasonably safe," Force noted.

A major aim of Temple's Center for Translational Medicine is facilitating the delivery of new medicines to patients in the clinic, which could happen for TNNI3K inhibitors, if they are proven safe and effective in the next round of animal studies. According to Vagnozzi, who is now at Cincinnati Children's Hospital Medical Center, the continued collaboratory effort between Temple and GSK will be a key component in moving the drugs into the clinic.

Vagnozzi and colleagues' paper was selected for F1000Prime, in which articles in biology and medical research are chosen and their importance rated by leading scientists and clinicians.

Other researchers contributing to the work include Gregory J. Gatto Jr., Lara S. Kallander, Victoria L. T. Ballard, Brian G. Lawhorn, Patrick Stoy, Joanne Philp, and John J. Lepore with the Heart Failure Discovery Performance Unit, Metabolic Pathways and Cardiovascular Therapeutic Area Unit, GlaxoSmithKline; Nicholas E. Hoffman, Karthik Mallilankaraman, and Erhe Gao at Temple's Center for Translational Medicine; Alan P. Graves with Platform Technology and Sciences, GlaxoSmithKline; and Yoshiro Naito from the Cardiovascular Division, Department of Internal Medicine, Hyogo College of Medicine in Japan.

Provided by Temple University

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