Study shows that blocking an inflammation pathway prevents cardiac fibrosis

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(Medical Xpress)—New research from UC Davis published in the *Proceedings of the National Academy of Sciences* shows that blocking an enzyme that promotes inflammation can prevent the tissue damage following a heart attack that often leads to heart failure.

Led by Nipavan Chiamvimonvat, cardiologist and professor of internal medicine, a team of researchers tested a compound that inhibits the enzyme soluble epoxide hydrolase—or sEH—one of the key players in the robust immune-system response that heals tissue following an injury. The enzyme, however, can become counterproductive after a cardiac event.

Chiamvimonvat explained that sEH increases proinflammatory lipid mediators, leading to long-term, heightened inflammatory conditions. It also causes cells, which typically link together and provide the foundation for heart tissue, to overwork. The outcome is scar tissue, or fibrosis, that results in an abnormal relaxation of the heart after each beat, taxing remaining heart muscle as it performs double duty and eventually leading to a decline in the heart's pumping action.

"We often see patients following a heart attack in clinic who initially respond well to current treatments, which address the initial causes of the cardiac event and try to preserve heart function," said Chiamvimonvat, whose research focuses on the biological mechanisms of heart disease. "Over time, though, heart function in some patients continues to worsen and can lead to heart failure. It would be ideal to

have new approaches that target the cellular overproduction that leads to heart muscle stiffening and cardiac fibrosis."

Heart failure progressively limits oxygen throughout the body, reducing mobility, respiration and quality of life. According to the Centers for Disease Control and Prevention, the condition affects 5.7 million people in the U.S. and costs the nation $34.4 billion in health-care services, medications and lost productivity. About half of people who have heart failure die within five years of diagnosis.

Previous research by Chiamvimonvat showed that an sEH inhibitor synthesized in the laboratory of entomology Professor Bruce Hammock can reduce the enlargement of heart muscle cells and associated arrhythmia. For the current study, she conducted a series of experiments to determine if it could also be a potential treatment for fibrosis.

Chiamvimonvat and her team tested the compound on a mouse model for heart attack. Because cardiac fibrosis can also be caused by other long-term cardiac diseases, the compound was also used on a mouse model for the chronic pressure overload commonly seen with hypertension. For both models, one group of mice was given the compound with their drinking water, while another group was not. The animals' heart functions were assessed using echocardiography.

The results showed that the mice receiving treatment had significant decreases in adverse cardiac muscle remodeling following a heart attack or due to chronic pressure overload. Their overall cardiac function also improved. Additional tests performed in Hammock's lab showed significantly reduced inflammatory factors in their systems.

"Our study shines new light on this inflammation pathway and identifies a potential therapeutic target that could greatly expand options for one of the biggest and most difficult-to-treat problems in cardiology," said

Javier Lopez, cardiologist, assistant professor of internal medicine and study co-author who developed methods used in the study to quantify fibrotic cells.

The team hopes to test the compound next on a larger animal model as a precursor to human clinical trials.

"This project is part of a long-term, exciting collaboration between two labs dedicated to combining their strengths to benefit human health," said Hammock. "The translational value of our research is significant."

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Provided by UC Davis