Researchers identify new pathway for preventing cardiac fibrosis

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Researchers at the University of Colorado School of Medicine have discovered a new mechanism for slowing scarring of heart tissue—a process known as cardiac fibrosis.

"Fibrosis of the heart occurs in response to a variety of stresses," says the study's corresponding author, Timothy McKinsey, Ph.D., professor of medicine in the Division of Cardiology. "It can be good. For example, if you have a heart attack and a significant amount of your cardiac muscle dies, you need to replace that muscle with something. In that case, the fibrotic scar keeps the heart from rupturing and prevents someone from dying. But we're more interested in pathological fibrosis, which is uncontrolled fibrosis that occurs in someone who has long-standing hypertension or other comorbidities. That can cause stiffening of the heart and lead to something called diastolic dysfunction."

A unique inhibitor

The CU study, published today in the American Heart Association's *Circulation Research* journal, shows that the compound SW033291 slows fibrosis by inhibiting the action of 15-hydroxyprostaglandin dehydrogenase (15-PGDH), an enzyme that degrades eicosanoids, which are lipid signaling molecules that help to prevent fibrosis.

"Chronic fibrosis is thought to be a major player in the pathogenesis of heart failure," McKinsey says. "Heart failure affects millions of people worldwide, and there aren't any good therapies to prevent or reverse cardiac fibrosis. That's why we initiated these studies."

Showing effectiveness in human samples

McKinsey and his research team started their study by performing phenotypic high throughput screening with a number of compounds, looking to block activation of fibroblasts, the cells responsible for driving fibrosis.

They hit upon nine small molecules that had the common ability to block

activation of heart, lung, and kidney fibroblasts. Of those nine, the compound SW033291 seemed the most promising.

In addition to laboratory tests and animal models, the CU researchers worked with Michael Bristow, MD, Ph.D., professor of cardiology, and Amrut Ambardekar, MD, associate professor of cardiology, and their teams to create a new biobank of failing human cardiac fibroblasts taken from patients receiving heart transplants, as well as nonfailing donor control cardiac fibroblasts. SW033291 exhibited a remarkable ability to reverse the activated state of failing human cardiac fibroblasts, McKinsey says, supporting the notion that 15-PGDH inhibition could be useful for ameliorating existing cardiac fibrosis in patients.

Next steps

As their research continues, McKinsey and his team plan to focus on the roles of 15-PGDH in different cell populations, including fibroblasts, immune cells, and cardiomyocytes. They also want to perform additional efficacy studies with SW033291, testing it in more severe models of cardiac fibrosis and diastolic dysfunction.

McKinsey says the group also plans to look more closely at the functions of different eicosanoids in inhibiting fibroblast activation, and how they activate signaling pathways to prevent fibroblasts from causing fibrosis.

"This research has led to the identification of a new pathway that regulates cardiac fibrosis," he says. "No one has studied 15-PGDH in the heart. This opens a whole new avenue of investigation and suggests ways to target fibrosis in the heart to treat a plethora of cardiac diseases, including heart failure."

More information: Marcello Rubino et al, Inhibition of Eicosanoid Degradation Mitigates Fibrosis of the Heart, *Circulation Research*

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