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# Study adds to efforts to find more effective anti-inflammatory drugs

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Researchers have discovered a previously unknown function for a protein that could add to the expanding arsenal of potential new drugs for battling inflammation and tissue fibrosis in a number of disease processes.

Scientists from Cincinnati Children's Hospital Medical Center report Sept. 27 in *Developmental Cell* that, a protein called TRPC6 mediates a molecular pathway critical to the body's repair processes following various forms of injury caused by disease.

After injury – such as that caused by a heart attack – the TRPC6-controlled pathway prompts cells called fibroblasts to change into myofibroblasts, according to the study.

Myofibroblasts secrete a substance called extracellular matrix, an important building block needed for wound healing and tissue remodeling, which includes inflammation and scarring.

"Our study suggests that a TRPC inhibitor could be a good anti-fibrotic or anti-inflammatory agent in heart failure, muscular dystrophy, pulmonary disorders and other diseases where tissue fibrosis becomes a problem," said Jeffery Molkentin, PhD, principal investigator and a scientist at the Cincinnati Children's Heart Institute and Howard Hughes Medical Institute. "As well, activation of the TRPC pathway with an agonist compound could be used in select situations to enhance wound healing."

Although the body needs a certain amount of inflammation and scarring to heal and return to normal function, in chronic diseases the process can get stuck in the "on" mode. This can lead to fibrosis (the buildup of excess connective tissues) and cause serious medical complications. Effectively and safely controlling complex inflammation processes in these situations remains an unmet clinical need, and is also the impetus behind a concerted effort in biomedical research to find new therapeutic options.

Researchers on the current study were encouraged by how effectively the TRPC6 pathway (TRPC6-calcineurin-NFAT) appeared to influence the transformation of fibroblasts into myofibroblasts, the secretion of extracellular matrix, wound healing and fibrosis. The authors wrote that identification of this cell repair signaling mechanism "offers an additional avenue for developing targeted intervention points in fibrotic diseases."

Calcineurin is a calcium-dependent enzyme involved in the immune system, the regulation of T-cells and also important in the function of heart cells. NFAT (nuclear factor of activated T-cells) is a family of proteins important to the immune system and the development of different tissues in the body.

Including first author Jennifer Davis, PhD. – a member of Molkentin's laboratory – the researchers started their study by running a genomic screen of molecules that regulate the transformation of fibroblast cells into myofibroblasts. The screen and subsequent laboratory tests identified TRPC6 as a promising candidate. Prior to the current study, TRPC6 had not been associated with fibrosis, although it has been linked to other cellular functions in kidneys, skin cells and hippocampal neurons of the brain.

The scientists used a virus expressing TRPC6 to infect cell cultures of

mouse embryonic fibroblasts, rat cardiac fibroblasts and human dermal fibroblasts. TRPC6-infected fibroblasts fully activated the transformation to myofibroblasts, while fibroblasts lacking TRPC6 were resistant to transformation. In TRPC-6 gene deleted mice, the animals showed impaired dermal and cardiac wound healing after injury.

Molkentin said there are TRPC inhibitors in the early stage drug development pipeline, although their initial design has not targeted heart disease, inflammation or fibrosis. He added the current study may provide an impetus for widening the development focus to include these medical needs.

Provided by Cincinnati Children's Hospital Medical Center