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Scientists offers way to disrupt fibrosis

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A team of scientists that includes Saint Louis University researchers has identified a new way to intervene in the molecular and cellular cascade that causes fibrosis – a condition where the body's natural process of forming scars for wound healing goes into overdrive and causes diseases. The findings, published Nov. 10 in the advance online issue of *Nature Medicine*, demonstrate a potential novel therapeutic approach to treat fibrotic diseases such as idiopathic pulmonary fibrosis and liver fibrosis.

The research targets a pathway that turns off the trigger for the major molecular mediator of fibrosis, a protein called Transforming Growth Factor (TGF) beta. This protein is normally present in the body in an inactive state and must be turned on to cause fibrosis. Once activated, TGF beta protein stimulates cells called myofibroblasts to produce excess collagen, which is a principle component of scars.

The researchers showed that removing a gene in the myofibroblasts that makes a specific subset of proteins called alpha v integrins blocks the ability of these cells to trigger activation of TGF beta. Furthermore, they were able to replicate the effect of the gene deletion by treatment with a small molecule compound, thus opening the door to a potential new therapy for patients.

"This is the first foray into targeting not just a single integrin, but rather several integrins that appear to be working in concert to promote fibrosis," said David Griggs, Ph.D., Director of Biology at Saint Louis University's Center for World Health and Medicine and an author of the paper.

"We have developed small molecular compounds that selectively inhibit these integrins, which suppress TGF beta protein, and these have been effective in animal models of lung and liver fibrosis."

The small molecule was not only able to prevent fibrosis; it made fibrosis less severe even when the treatment was started after fibrosis had begun, Griggs added.

"It's really a platform technology that could be applied to a number of fibrotic conditions," Griggs said.

In tandem with the drug discovery research, scientists working on another part of the study found they could protect mice from pulmonary fibrosis, liver fibrosis and renal fibrosis by deleting a gene that makes the same specific integrins in myofibroblasts that were targeted by the drug.

"We want to hit the integrins that are linked to fibrosis, but leave integrins that are not involved in fibrosis alone," said Peter Ruminski, Executive Director of Saint Louis University's Center for World Health and Medicine and an author of the paper. "We're trying to bring TGF beta levels back to normal."

Fibrosis, which can occur in any of the body's organs, can contribute to deadly diseases by preventing organs from functioning properly because the fibrotic tissue hardens and swells. For instance, there is no FDA-approved treatment for pulmonary fibrosis, which has a high mortality rate and affects up to 150,000 Americans. Because there are no available drug treatments for pulmonary fibrosis in the US, the only effective therapy is an organ transplant. However transplants are expensive and demand for organs exceeds the supply, creating the need for more effective therapies.

The next steps, Ruminski said, are to determine exactly how much of the compound is needed to allow normal healing to occur instead of fibrosis. Scientists also need to study the best way to deliver the drug. Different fibrotic conditions could warrant different delivery methods, Ruminski speculated. For instance, an inhaled delivery method could be better to treat pulmonary fibrosis or a topical cream could be preferable for skin scarring, he said.

More information: Targeting of alphav integrin identifies a core molecular pathway that regulates fibrosis in several organs, DOI: 10.1038/nm.3282

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