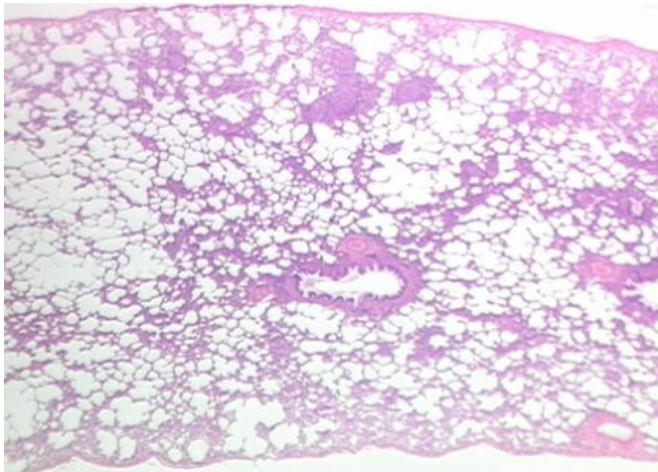


Study finds cause of pulmonary fibrosis in failure of stem cells that repair lungs

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Lung tissue. Credit: Rutgers University

Cedars-Sinai investigators have pinpointed a major cause of pulmonary fibrosis, a mysterious and deadly disease that scars the lungs and obstructs breathing. The disease, which has no known cure, appears to result from the failure of special lung stem cells that help airways recover from injury, the investigators reported in the journal *Nature Medicine*.

The study is a major step toward understanding and one day treating [pulmonary fibrosis](#), which affects about 100,000 people in the U.S. The disease often is called [idiopathic pulmonary fibrosis](#) because, in most cases, the cause cannot be found. While the prognosis is unpredictable, patients typically survive only three to five years after diagnosis, according to the U.S. National Library of Medicine.

"Pulmonary fibrosis slowly robs patients of breath and finally life," said Paul W. Noble, MD, professor and chair of the Department of Medicine and director of the Women's Guild Lung Institute at Cedars-Sinai. "In our study, we identified novel

potential pathways to finding treatments for this relentless disease." Noble was the study's principal investigator.

The investigators focused on alveoli, the small air sacs at the ends of lung airways. In the alveoli, oxygen and carbon dioxide are exchanged with blood during respiration. Epithelial cells that line the alveoli also make a substance that helps keep the airspaces open. In pulmonary fibrosis, these epithelial cells become abnormal, and fibrous tissue builds up in the lungs, causing severe scarring. Researchers don't know why this scarring process happens.

The Cedars-Sinai research team found an answer in special [stem cells](#) known as AEC2s that are found in adult lungs and are critical to repairing and regenerating [epithelial cells](#). When viral infections, pollution or other injuries damage [lung tissue](#), AEC2 cells come to the rescue.

In people with pulmonary fibrosis, something goes wrong with AEC2 cells, the study found. Compared with lung tissue of disease-free individuals, lung tissue from patients with pulmonary fibrosis had far fewer AEC2 cells, and those that remained were less able to renew themselves. Surfaces of these cells had lower concentrations of hyaluronan, a chemical substance that promotes tissue repair and renewal. Further, in laboratory mice, the team found that by deleting this substance, they could produce the type of scarring found in pulmonary fibrosis after lung injury.

"These findings are the first published evidence that idiopathic pulmonary fibrosis is primarily a disease of AEC2 stem cell failure," said Carol Liang, MD, assistant professor of Medicine at Cedars-Sinai and the study's first author. "In further studies, we will explore how the loss of hyaluronan promotes fibrosis and how it might be restored to cell surfaces. These endeavors could lead to new therapeutic approaches."

One promising approach may be to develop drugs that stimulate the reproduction of AEC2 cells in the lungs of patients who lack enough of these cells, Noble said. "The exciting aspect is that we have learned how to isolate these stem cells from diseased lungs. We can use these [cells](#) to create tiny 'lungs in a dish' as tools for drug development," he explained.

In an accompanying commentary in *Nature Medicine*, Paul F. Mercer, PhD, and Rachel C. Chambers, PhD, from the University College London in England noted another novel finding from this study. They said it identifies a new link between innate immune receptors, which help mobilize the immune system to fight bacterial invaders, and hyaluronan. This link, which promotes normal AEC2 renewal, is lost in pulmonary fibrosis, the study showed.

More information: Jiurong Liang et al. Hyaluronan and TLR4 promote surfactant-protein-C-positive alveolar progenitor cell renewal and prevent severe pulmonary fibrosis in mice, *Nature Medicine* (2016). [DOI: 10.1038/nm.4192](https://doi.org/10.1038/nm.4192)

Provided by Cedars-Sinai Medical Center

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