Study IDs 'master' protein in pulmonary fibrosis

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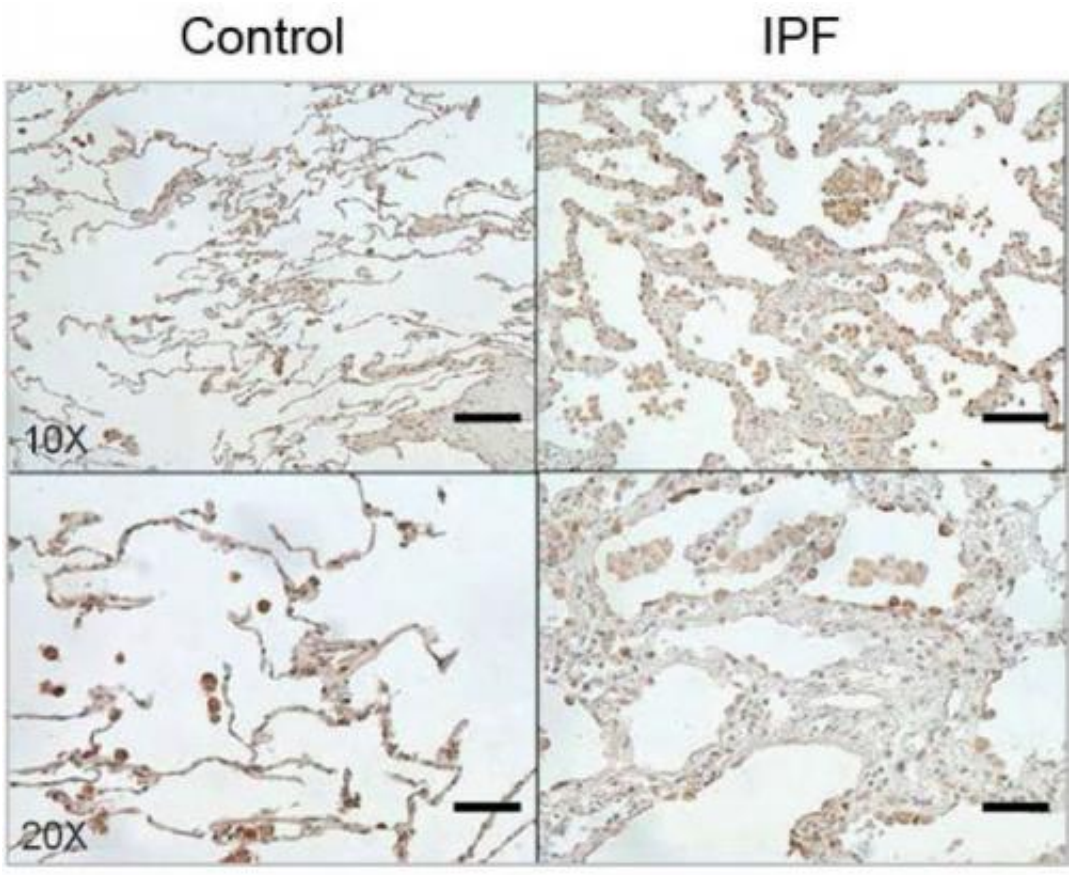

The protein CHI3L1 works to protect injured cells and to repair damage. In lung tissue, damage repair means a buildup of scar tissue, which compromises the lung. Levels of CHI3L1 are higher in patients with idiopathic pulmonary fibrosis (right) than in healthy controls. Credit: Brown University/Yale University

This spring has brought rare but tangible moments of progress against the devastating lung disease idiopathic pulmonary fibrosis (IPF), which afflicts millions of people worldwide. Two drugs recently showed promise in clinical trials, and now a study in *Science Translational Medicine* offers both an unprecedentedly deep explanation of how the disease progresses and introduces another potential therapeutic avenue.

The new study features a central figure: an evolutionarily ancient protein called "chitinase 3-like-1" (CHI3L1). The authors implicate it as the "master regulator" of what appears to be a tragically errant repair response to the mysterious lung injuries that give rise to the disease. In describing how CHI3L1 works in IPF, the research also points to a strategy for treatment.

The report demonstrates that CHI3L1 is produced to help in response to the injury. It feeds back to protect injured cells from dying and simultaneously stimulates tissue repair to patch the damage that has occurred. But the study also shows how this dual role contributes to the ultimate problem. If IPF resulted from a single injury, like a paper cut, CHI3L1 would decrease the injury and cause local scarring while it restored tissue integrity. In that case, the amount of scarring would not be excessive and tissue function would not be significantly altered. But in IPF lungs, cells undergo ongoing injury, so CHI3L1 is chronically elevated and scar tissue accumulates. As CHI3L1 rescues cell after cell, the scarring builds up, eventually compromising the lung's ability to breathe. In IPF, 70 percent of patients die within five years.

"The CHI3L1 is doing exactly what it is supposed to do—it is designed to shut off cell death and decrease injury," said Dr. Jack A. Elias, a co-senior author of the study and dean of medicine and biological sciences at Brown University. He is joined on the paper by a host of his former colleagues and students at Yale University where the research occurred. "But at the same time it is decreasing cell death it is driving the fibrosis.

You've got this ongoing injury so you've got these ongoing attempts to shut off injury which stimulate scarring."

In patients and the lab

The research team, including co-senior author Erica Herzog of Yale and co-lead authors Yang Zhou (who is transitioning to Brown from Yale), Huanxing Sun of Yale, and Hong Peng of Central South University in China used various means to uncover CHI3L1's central role in IPF.

They compared tissues and serum from normal patients, outpatients with IPF, and patients with an acute exacerbation (AE) of IPF. In AE, widespread lung injury is superimposed on the pulmonary fibrosis, which frequently occurs before patients die. In lung biopsies and serum, they found that CHI3L1 levels are elevated in both tissue compartments in the outpatients with IPF and that the levels of CHI3L1 correlated with their disease progression. In the patients with AE, elevated levels of CHI3L1 were not noted, showing that the levels of CHI3L1 decrease right before the patients die.

"This demonstrates that the CHI3L1 plays a key role in controlling lung injury in this setting," Elias said.

After documenting that elevated levels of CHI3L1 correlate with ongoing fibrosis and scarring and that a lack of the protein associates with widespread cell death, the team engaged in several manipulations of CHI3L1 in mice to see how levels and the clinical outcomes might be related. (In mice, CHI3L1 is also called BRP-39.)

Scientists can induce an IPF-like response in mice using a drug called bleomycin. In mice given bleomycin, the researchers found that the levels of CHI3L1 declined at first and then surged. At the times when the protein levels were low, cell damage occurred, and when the protein

surged, the excessive scarring set in.

In previous research the team had engineered several lines of genetically modified mice. Some were transgenic and can produce CHI3l1 on chemically delivered command. Other mice were engineered to never produce BRP-39—the mouse version of CHI3L1—at all.

Using these mice, the researchers found that if they triggered CHI3L1 production early after administering bleomycin, the mice fared well, experiencing less injury, less damage and less scarring than controls. If they waited several days after bleomycin to trigger CHI3L1, the mice fared very poorly and scarring and mortality went up.

Mice who couldn't produce CHI3L1/BRP-39, had acute lung cell damage, somewhat like AE patients who have a relative deficiency of CHI3L1. However, without CHI3L1 they did not generate much scarring.

All of these findings were supplemented with several other experiments that were designed to learn how CHI3L1 interacts with other cells involved in the tissue repair response in both human and mouse lungs. The experiments, including studies conducted in a bioengineered 3-D model of lung tissue seeded with relevant cells, showed that CHI3L1 regulates a pathway that recruits cells such as macrophages and fibroblasts that produce the scarring, or fibrosis.

In all, the results show that CHI3L1 plays a fundamental role in the course, if not the origin, of IPF. An ongoing buildup of it results in excessive scarring. Too little and cells die much more frequently.

"To my knowledge this is the first comprehensive paper that's been able to explain the many facets and presentations of IPF," Elias said. "It explains and links the injury and the repair responses that are critical in

the disease. It also provides an explanation for the slowly progressing patients and the patients that experience acute exacerbations."

Toward treatment

Elias said he hopes the insights will lead to new therapies for IPF. The idea would be to preserve the cell-protecting function of CHI3L1, while tempering its ability to stimulate tissue scarring and repair.

There may indeed be a way to do that, Elias said. Some data suggest that the mechanisms for each CHI3L1 function – cell protection and tissue repair – involve different pathways and or receptors. In people, therefore, separate drugs could hypothetically enhance the injury prevention pathway and temper the repair pathway. Indeed, drugs that block a key repair pathway receptor exist and are undergoing testing in other diseases, Elias said.

"This research lays the foundation for potential therapies that would be designed to diminish injury and ameliorate fibroproliferative repair," Elias said.

More information: "Chitinase 3-like 1 Suppresses Injury and Promotes Fibroproliferative Responses in Mammalian Lung Fibrosis," by Y. Zhou et al. *Science Translational Medicine*, stm.sciencemag.org/lookup/doi/ … scitranslmed.3007096

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