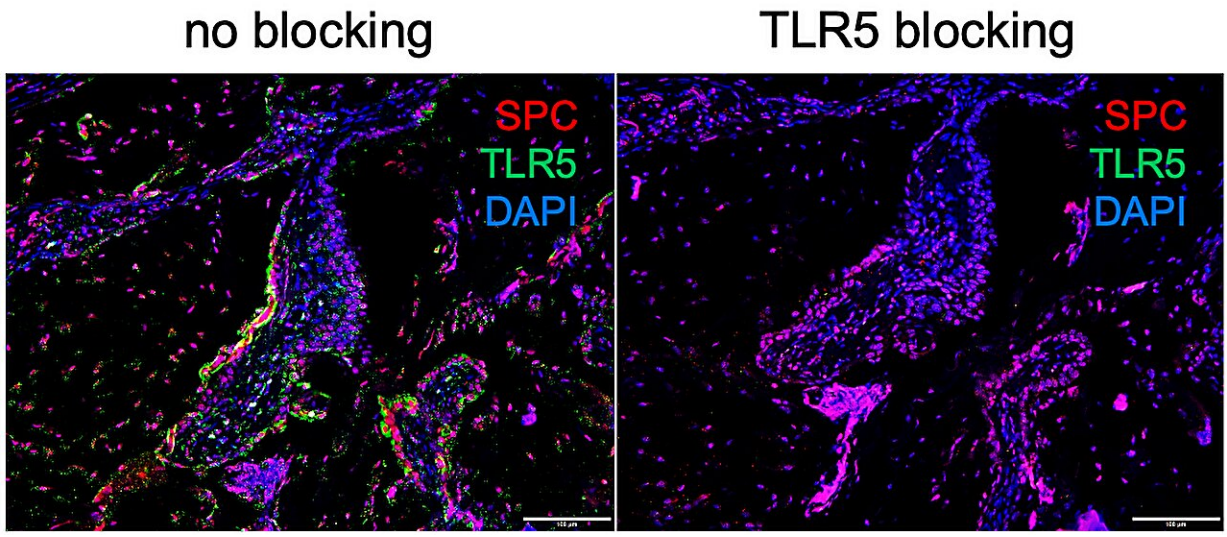
Hidden immune-microbiome link may explain lung disease's mysterious origin

June 5 2026, by Sanjukta Mondal



Immunohistochemical staining of TLR5 in human IPF lung sections. Credit: Yosuke Sakamachi

Over the last few years, people have become quite aware of the gut microbiome and its impact on our overall health. Microbiome, however, isn't exclusive to the gut, as a host of bacteria also reside inside our lungs, and an imbalance in them can increase the chances of developing lung diseases.

A recent study shed light on how genetics and the lung microbiome

jointly influence the scarring process underlying idiopathic pulmonary fibrosis (IPF), a chronic, progressive disease in which scar tissue accumulates in the lungs, making it increasingly difficult to breathe.

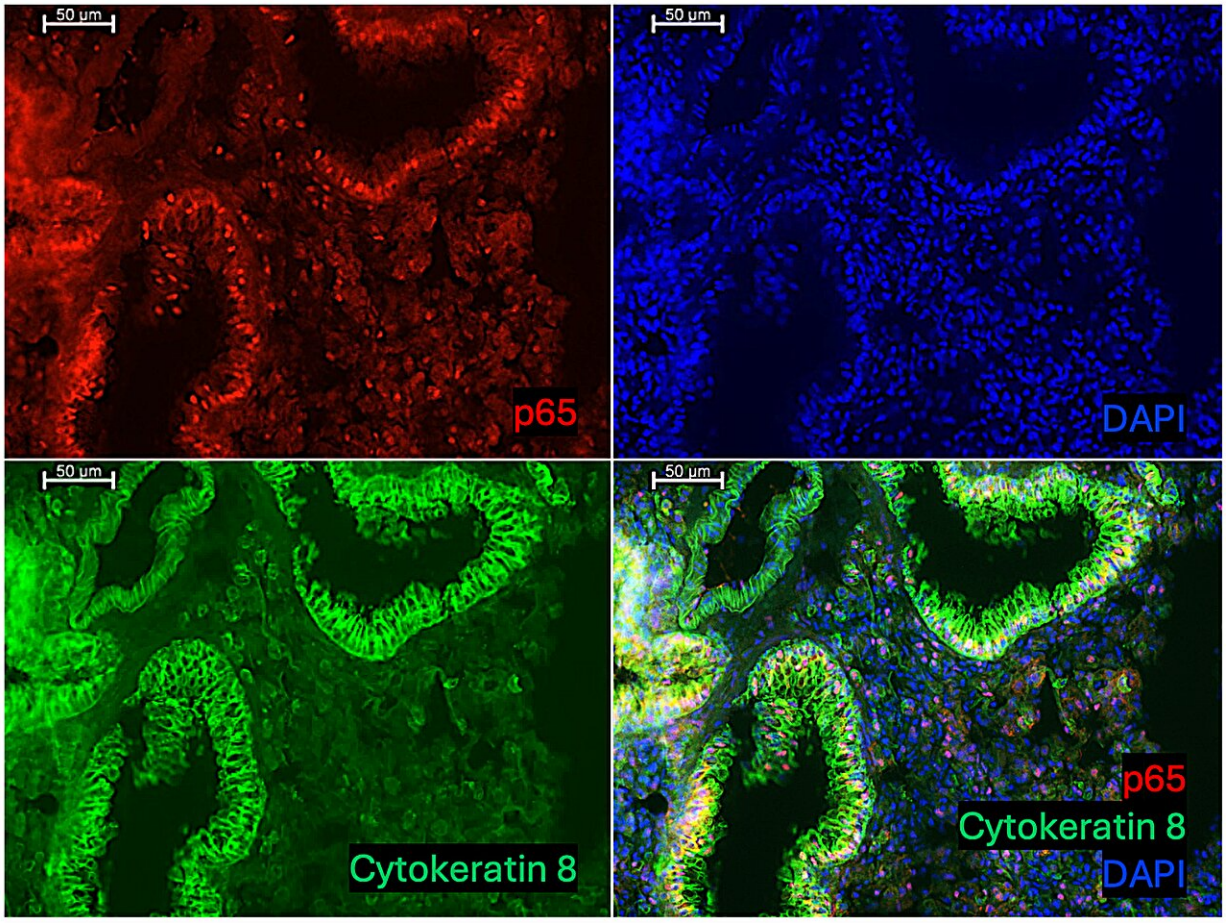
The progression of the disease might be linked to the presence of a faulty version of the Toll-like receptor 5 (TLR5) protein, which is part of the body's first line of defense against infection.

Since this gene is responsible for maintaining the balance of the bacterial colony in the lungs, a defect can lead to dysbiosis, allowing harmful bacteria to take over and trigger or worsen lung scarring. They found that reintroducing a healthy microbiome helped restore the protective effects of TLR5.

The findings were published in *Science Translational Medicine*.

Broken gene

Idiopathic pulmonary fibrosis, or IPF, is a devastating chronic lung disease which attacks the delicate tissue wrapped around the tiny air sacs, or alveoli, deep in your lungs, which are crucial for the exchange of oxygen with blood. The disease causes these tissues to gradually thicken and stiffen, and as the damage builds, it leaves behind permanent scarring in the lungs, which not only makes breathing difficult but also prevents the brain and other organs from getting the oxygen they need. While a lot is known about what happens as a result of the disease, its cause remains a mystery.



Immunohistochemical staining of mouse lung sections with anti-p65 and anti-cytokeratin 8 antibodies, two hours after TLR5 agonist treatment. Credit: Yosuke Sakamachi

Scientists already knew that lung dysbiosis is linked to IPF progression and mortality, and that in mice it appears before fibrosis develops, while gene variants like MUC5B—which help clear mucus and defend the lungs—were linked to risk factors. The role of innate immune receptors such as TLR5 in IPF, which act as the body's first line of defense against pathogens, was not well understood.

To investigate the role of TLR5 in pulmonary fibrosis, the researchers

first examined DNA from thousands of individuals with and without IPF to determine whether mutations in the TLR5 gene were associated with IPF in both groups or only in those with IPF. They then genetically knocked out TLR5 in mice to see if its absence increased susceptibility to lung injury.

Finally, by sequencing bacterial DNA from the lungs of both humans and mice, they explored how the loss of TLR5 reshaped the lung microbiome and whether these changes were linked to disease development.

People with a specific variation in the TLR5 gene called single-nucleotide polymorphism (SNP) known as rs5744168, were more likely to develop IPF. In mouse studies, the absence of the TLR5 receptor was associated with greater lung scarring, increased weight loss, and lower survival after lung injury.

Both humans and mice exhibited an altered lung microbiome, with reduced bacterial diversity and a substantial increase in proteobacteria when TLR5 was deficient. When researchers introduced antibiotics into the picture, the mice did not develop severe lung scarring. Also, rejuvenating the bacterial diversity and balance in mice via fecal microbiota transplantation had some positive effects.

The researchers note that the findings reveal how TLR5 protects against pulmonary fibrosis through its influence on the lung microbiome, pointing to new therapeutic possibilities for patients with IPF.

To support clinical application, future studies could focus on identifying the specific bacteria involved and the mechanisms by which TLR5 shapes the lung microbiome.

More information: Yosuke Sakamachi et al, Toll-like receptor 5

protects against murine lung fibrosis through reduced dysbiosis, and TLR5 deficiency is associated with human IPF, *Science Translational Medicine* (2026). DOI: 10.1126/scitranslmed.adw1028