New study finds blocking histones using antibodies alleviates lung fibrosis

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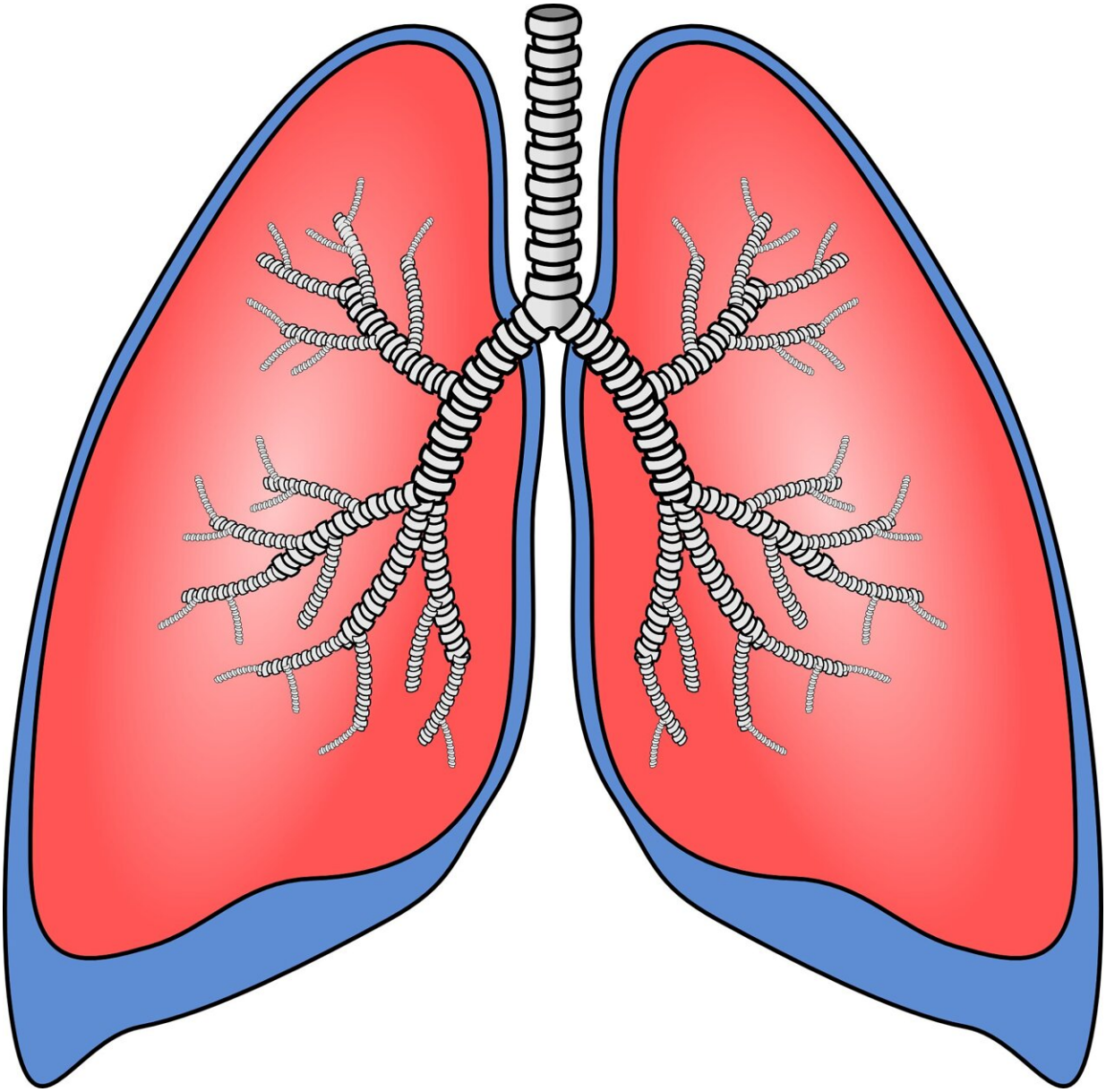

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Lung fibrosis is a debilitating disease affecting nearly 250,000 people in the U.S. alone with 50,000 new cases reported each year. There is currently no cure and limited available treatment options, underscoring the pressing need to better understand why people get this disease.

In a new study, Boston University Chobanian & Avedisian School of Medicine researchers have identified that abnormal interactions between different cell types, particularly platelets and lung immune cells, promote lung fibrosis.

According to the researchers, this study highlights how different cell types work together in lung fibrosis. Platelets are cells that normally form blood clots, but in lung fibrosis they become involved in immune cell functions that end up attacking healthy cells and damaging the lung. While the immune system is supposed to protect us from viruses and bacteria, in patients with lung fibrosis it harms their own body.

BU researchers found that chromosomal structural support proteins termed histones, released by immune cells called neutrophils, initiate this aberrant interaction by activating the production of the immune mediator, transforming growth factor β 1 (TGFβ1), from platelets. TGFβ1 in turn blocks the release of another mediator, interleukin-27 (IL-27), from specialized immune cells called macrophages. This inhibition prevents IL-27 from suppressing fibrosis.

"Although histones have previously been implicated in fibrosis, how they mediate the development of the disease is not completely understood. Our findings provide novel mechanistic insights into how the altered interactions between different cell types contributes to histone-mediated

fibrosis development," explain Arjun Sharma, one of the first authors, and Markus Bosmann, MD, the corresponding author and associate professor of medicine and pathology & laboratory medicine.

An initial investigation using samples from patients with idiopathic pulmonary fibrosis revealed higher histone release in those patients compared to healthy individuals. Subsequently, using an experimental model of lung fibrosis initiated by bleomycin-induced lung injury, neutrophils were established as a major source of histones.

Further experiments including screening lung airway fluid to assess levels of immune mediators after blocking histones, tissue staining and genetic deletion, all identified TGFβ1 and IL-27 as key downstream molecular mediators of histones during fibrosis. "This study helps bridge a crucial knowledge gap by elucidating the role of three key proteins—histones, TGFβ1, and IL-27 in fibrosis development, opening up avenues for new therapies," says Bosmann.

These findings appear online in the journal *Proceedings of the National Academy of Sciences*.

More information: Riehl, Dennis R. et al, Externalized histones fuel pulmonary fibrosis via a platelet-macrophage circuit of TGFβ1 and IL-27, *Proceedings of the National Academy of Sciences* (2023). DOI: 10.1073/pnas.2215421120. doi.org/10.1073/pnas.2215421120

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