Arthritis drugs may relieve long COVID lung symptoms

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University of Virginia School of Medicine researchers have identified a potential treatment for the respiratory symptoms of long COVID after discovering an unknown cause of the condition inside the lungs.

The UVA researchers, led by Jie Sun, Ph.D., found that COVID-19 infection can cause sweeping changes in immune cells inside the lung tissues, promoting scarring and driving ongoing inflammation even after the initial infection has passed. This ongoing inflammation, they believe, drives the lasting respiratory symptoms, such as cough and difficulty breathing, associated with long COVID.

The new research from Sun and his colleagues indicates that doctors may be able to halt this chronic inflammation using a class of drugs, including baricitinib, that are already used to treat rheumatoid arthritis. The anti-inflammatory drugs previously received emergency authorization from the federal Food and Drug Administration to treat the uncontrolled inflammation seen in severe COVID-19 infections.

The findings are published in the journal *Science Translational Medicine*.

"Our study identified a root cause of the respiratory complication of long COVID by performing comparative analysis of both clinical samples and a relevant animal model," said Sun, of UVA's Carter Center for Immunology Research and UVA's Division of Infectious Diseases and International Health.

"We hope that the identification of the 'driving' mechanisms will help to rationally design clinical studies repurposing those FDA-approved drugs for respiratory long COVID soon."

Millions struggle with long COVID

Long COVID is estimated to affect more than 60 million people around the world. For these patients, a COVID-19 infection turns into a seemingly endless ordeal, with symptoms lasting weeks, months or even years. Symptoms of long COVID can range from uncomfortable to debilitating; for example, respiratory symptoms can include shortness of

breath, chest pain and even chronic lung scarring known as interstitial lung disease.

Prior research into long COVID has sought answers in patients' blood, but Sun and his team wanted to see what changes were taking place in the lung tissues themselves. So the UVA researchers looked at cell samples collected from the lower airways of both lab mice and human patients.

In both cases, they found that immune cells known as macrophages and T cells had gone haywire and were having faulty, harmful interactions. These cells normally help the body fight off the disease, but, in this case, they never stopped fighting, even after the initial COVID infection had passed.

The macrophages, the researchers found, had flooded into the lungs in abnormal numbers and were promoting tissue scarring. The T cells, meanwhile, were pumping out a substance called interferon that spurs continued inflammation.

Sun and his team believe that doctors may be able to break this cycle of inflammation using drugs that are already approved to treat the harmful inflammation seen in rheumatoid arthritis, a chronic autoimmune disease that affects joints. Additional research will be needed, but Sun hopes that UVA's new discoveries will lead to much-needed new treatments for patients struggling with respiratory symptoms from long COVID.

"We hope our clinical colleagues around the globe could perform clinical trials soon to test the efficacy of baricitinib or other similar drugs targeting the same inflammatory pathway in long COVID," Sun said. "Our new study has established a foundation for identification of new therapeutic interventions for long COVID by combining rigorous clinical testing and basic scientific research."

The research team consisted of Chaofan Li, Wei Qian, Xiaoqin Wei, Harish Narasimhan, Yue Wu, Mohd Arish, In Su Cheon, Jinyi Tang, Gislane de Almeida Santos, Ying Li, Kamyar Sharifi, Ryan Kern, Robert Vassallo and Sun.

More information: Chaofan Li et al, Comparative single-cell analysis reveals IFN-γ as a driver of respiratory sequelae after acute COVID-19, *Science Translational Medicine* (2024). DOI: 10.1126/scitranslmed.adn0136

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