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Researchers discover disease-causing stem cells in lungs of cystic fibrosis patients

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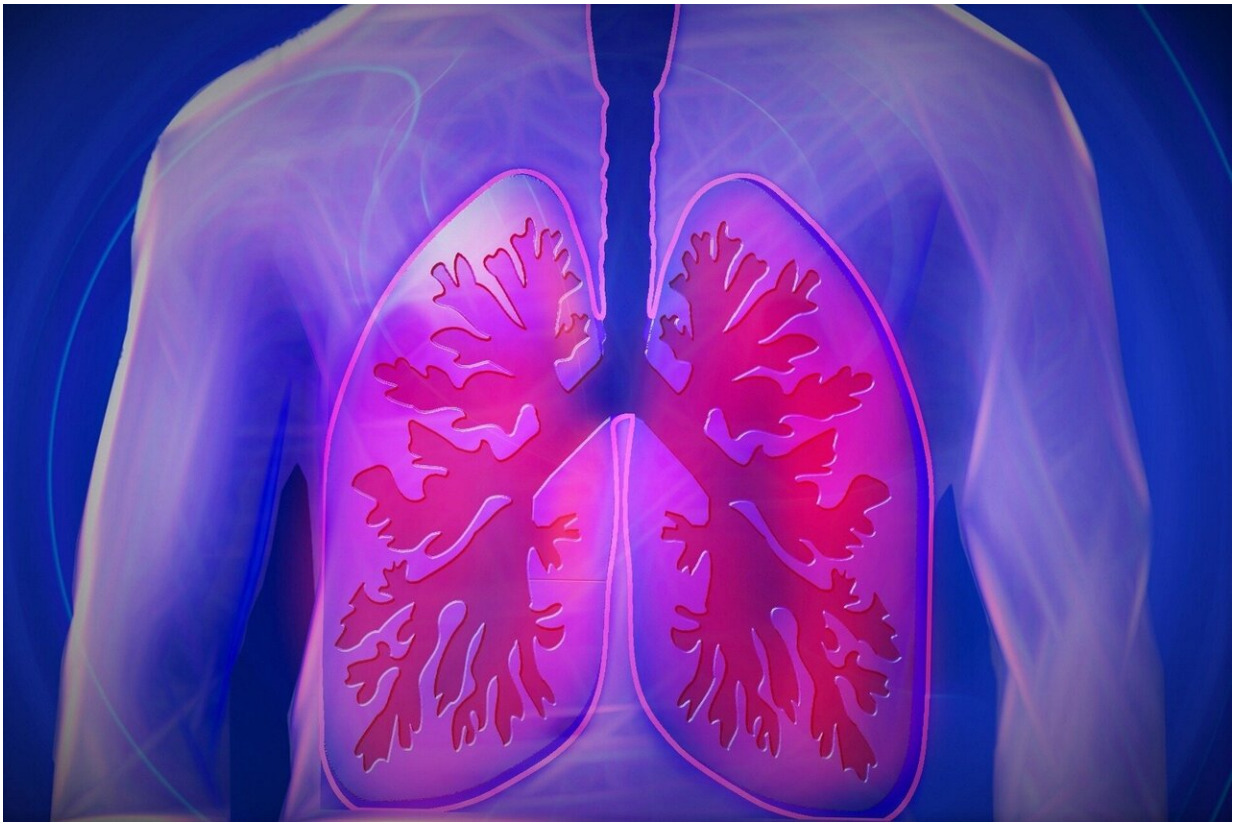

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Two nationally recognized experts in cloning and stem cell science from the University of Houston, Wa Xian and Frank McKeon, are reporting that five lung stem cell variants dominate the lungs of patients with

advanced cystic fibrosis (CF), and that these variants drive key aspects of CF pathology including inflammation, fibrosis and mucin secretion.

Cystic fibrosis is an inherited and progressive disease that causes long-lasting lung infections and limits the ability to breathe. It is caused by a defect in a gene called the cystic fibrosis transmembrane conductance regulator (CFTR) and affects nearly 40,000 people in the United States. Defects in the CFTR gene lead to the production of abnormally sticky and thick mucus that clogs organs, particularly lungs, causing chronic lung disease marked by infections and inflammation.

Recently introduced drugs known as CFTR modulators act to rescue the function to the mutant CFTR gene and yield remarkable improvements in lung function of CF patients. However, in patients with established lung disease, lung inflammation remains despite treatment with CFTR modulators. This persistence is concerning as inflammation is thought to be a key factor in the progression of CF lung disease.

This gap in CFTR modulator efficacy renders the work of the Xian-McKeon laboratory particularly relevant.

"Using single cell cloning technology that detailed stem cell heterogeneity in lungs from patients with COPD and idiopathic pulmonary fibrosis (IPF), we identified five stem cell variants common to lungs of patients with advanced CF, including three that show hyperinflammatory gene expression profiles and drive neutrophilic inflammation upon xenografting to immunodeficient mice," said Xian, research professor in biology and biochemistry.

"We found that CFTR-modulating drugs did not suppress the proinflammatory activity or gene expression of the three CF variants that drive inflammation," reports McKeon, professor of biology and biochemistry and director of the Stem Cell Center, in the American

Journal of Respiratory and Critical Care Medicine.

"These findings raise the possibility that these inflammatory stem cell variants are the source of the persistent inflammation in patients treated with CFTR modulators."

If true, their findings suggest that the inflammatory stem cell variants are key targets for drug discovery to augment the major therapeutic advances brought by CFTR modulators. Identifying such lead drugs is a major effort in the Xian-McKeon laboratory, in collaboration with the Center for Drug Discovery, the UH Sequencing Center and colleagues in the Department of Chemistry and the Center for Biotechnology at Texas A&M in the Texas Medical Center.

More information: Shan Wang et al, Inflammatory Activity of Epithelial Stem Cell Variants from Cystic Fibrosis Lung Is Not Resolved by CFTR Modulators, *American Journal of Respiratory and Critical Care Medicine* (2023). DOI: 10.1164/rccm.202305-0818OC

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