New study provides insight into lung scarring diseases without risky biopsy

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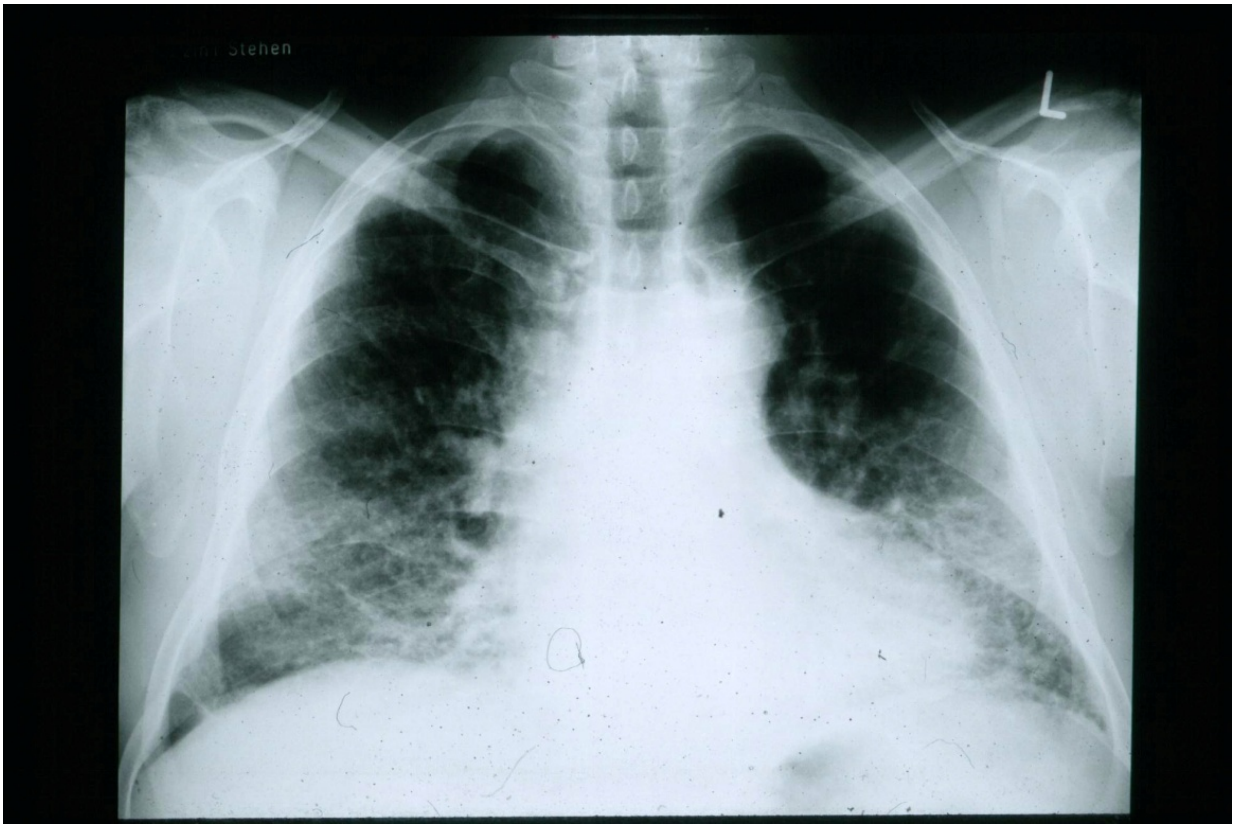

A chest radiograph of a patient with Idiopathic Pulmonary Fibrosis (IPF). Credit: Wikipedia/CC BY-SA 3.0

Idiopathic pulmonary fibrosis (IPF) is the most common and severe form of lung disease characterized by relentless scarring leading to death

within an average of four years from the time of diagnosis. The poorly understood pathogenesis of IPF, in part due to the lack of human disease models, has been a major hurdle in developing effective therapies.

Now, a team of regenerative medicine researchers at Boston University and the University of Pennsylvania have created a model (using pluripotent stem cells) to show how dysfunction of a highly specialized cell of the air sacs, the type 2 pneumocyte, initiates the fibrotic cascade that characterizes a number of adult and pediatric lung diseases, including IPF and childhood interstitial lung disease (chILD).

"Understanding how dysfunction of the highly specialized cells of the air sacs initiates the fibrotic cascade can result in development of novel targeted therapies for this devastating disease. Furthermore, this model has the potential to serve as a platform for testing new therapeutics," explains first author, Kontantinos Alysandratos, MD, Ph.D., assistant professor of medicine at Boston University School of Medicine (BUSM).

The researchers used two groups of patient-specific cells. The first group had an altered gene that made them dysfunctional. The second group consisted of normal cells which were engineered by gene editing to correct the altered gene. When both sets of cells were examined using a number of different methods, the cells with the altered gene displayed abnormal proliferation, aberrant recycling of unnecessary cellular components, altered metabolic profiles, and inflammatory activation. When both sets of cells were exposed to hydroxychloroquine, a medication commonly used in pediatric patients carrying this altered gene, aggravation of the observed disturbances occurred in the cells with the altered gene, while no changes were seen in the normal cells.

According to the researchers, studying lung diseases in children, particularly those diseases that affect the air sac cells that reside deep in

the lung, is very difficult since it is hard to access those cells for biological studies. "Generating stem cell-based in vitro models of lung disease, using easily accessible blood or skin cells from these children that are then reprogrammed into induced pluripotent stem cells, remains a very attractive approach for studying pediatric lung disease because it avoids risky biopsies of the deep lung, yet provides a simulation in the laboratory dish of the same processes that we think are occurring in the in vivo lung tissue itself," says corresponding author Darrell Kotton, MD, the David C. Seldin Professor of Medicine at BUSM and Director of the BU/Boston Medical Center's Center for Regenerative Medicine (CReM).

The researchers believe it should now be possible to take similar approaches to study many other types of interstitial lung diseases that arise from dysfunction in the air sacs and affect both children and adults. "In this way, these in vitro models should really expand drug development efforts to treat these diseases that until now have suffered from a lack of access to living cells from patients," Alysandratos says. The work was led by co-senior authors, Kotton and Michael F. Beers, MD, the Robert L. Mayock and David A. Cooper Professor in Pulmonary Medicine at the University of Pennsylvania Perelman School of Medicine.

These findings appear online in the journal *Cell Reports*.

More information: Patient-specific iPSCs carrying an SFTPC mutation reveal the intrinsic alveolar epithelial dysfunction at the inception of interstitial lung disease, *Cell Reports* (2021). DOI: 10.1016/j.celrep.2021.109636

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