Viral infection and specialized lung cells linked to chronic obstructive pulmonary disease

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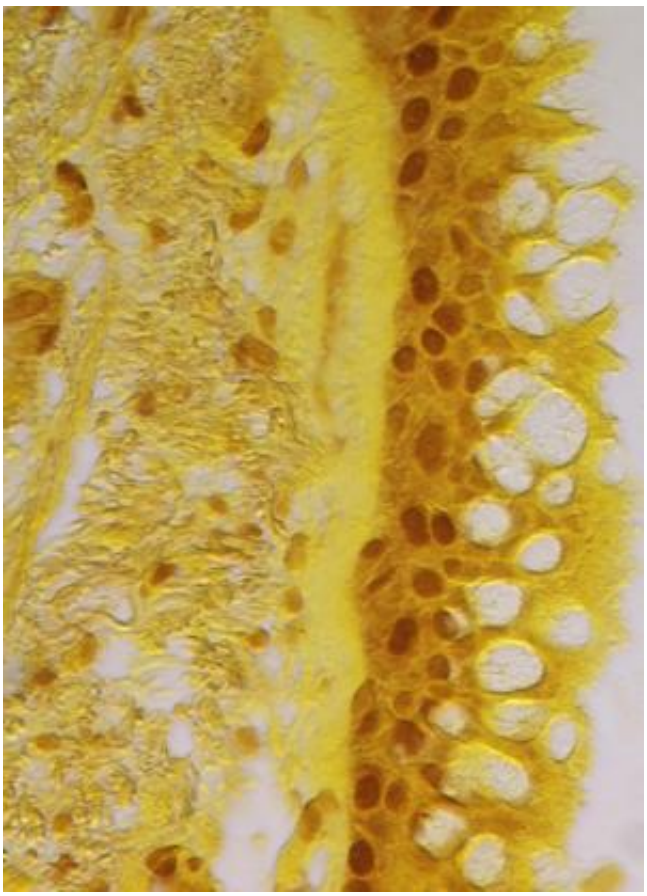

This photomicrograph depicts airway epithelial cells from lung tissue of a COPD patient. The cell nuclei have been stained to reveal IL-33, a type of signaling molecule found at high levels in COPD patients. New research shows that viral infection can induce these cells to proliferate. Release of IL-33 from these cells promotes inflammatory mucus production. These findings provide insight into the mechanisms linking acute infection to chronic inflammatory lung disease.

Credit: Holtzman lab

Investigators at Washington University School of Medicine in St. Louis have described another link in the chain of events that connect acute viral infections to the development of chronic obstructive pulmonary disease (COPD). Their discovery points to a new therapeutic target for COPD, an extremely common disease of the lower airways that is seen in chronic bronchitis and emphysema.

COPD affects about 12 million people in the United States, where it is the third leading cause of death. Worldwide, it is the fifth leading cause of death. It is characterized by inflammation of the lower airways and destruction of lung tissue that limit airflow and pulmonary function. No effective treatments exist to specifically address a major cause of disease advancement and death from COPD – excess inflammatory mucus that blocks airways and prevents normal breathing.

It is well established that smoke exposure is a major risk factor for COPD, but in this new research, investigators show that the cells that line the airways also can respond to viruses in a way that leads to long-term lung inflammation and mucus production that are typical of COPD.

The research, featured on the cover of the September issue of the *Journal of Clinical Investigation*, reconciles the discrepancy between the transient nature of most viral infections and the relatively permanent nature of chronic inflammatory diseases such as COPD.

Michael J. Holtzman, MD, the Selma and Herman Seldin Professor of Medicine at Washington University, has devoted much of his career to understanding the connections between environmental agents and development of chronic lung disease. Five years ago, he and his

colleagues reported that a signaling molecule called interleukin-13 (IL-13) was the key driver of excess production of chronic airway mucus after viral infection. Since then, they have pursued the basis for IL-13 production and its usefulness as a marker and a target for more precise therapeutic intervention in COPD and related diseases such as asthma.

The team traced the source of IL-13 to the immune cells of the innate immune system that had not previously been described as part of COPD. But until now, they didn't know how this type of immune response could be perpetuated to cause such a long-term disease like COPD.

"The innate immune response is conventionally viewed as built for short- rather than long-term activation," said Holtzman. "So the type of pathway that we identified was thought to be activated for only short periods of time. However, we found that it could be persistently activated after viral infection and became even more active with time."

The new research identifies another signaling molecule that plays a key role in this phenomenon.

"We reasoned that events upstream from IL-13 production might be involved in keeping the immune response active," said the study's lead author, Derek Byers, PhD, MD, assistant professor of medicine. "When we checked for candidates, we focused our efforts on the types of molecules that are associated with controlling the immune response and especially the production of IL-13."

One of these candidates, a signaling molecule called IL-33, was strongly linked to production of IL-13 in a mouse model of chronic obstructive lung disease that developed after viral infection. In fact, delivery of IL-33 directly to the airway in these animals was also enough to cause production of IL-13 and accumulation of mucus in the lungs.

Working further in this experimental model, co-lead author Jennifer Alexander-Brett, MD, PhD, a postdoctoral fellow, traced the source of the upstream signaling molecule IL-33 to a specialized set of cells within the epithelial layer that lines the airways of the lung. These IL-33-producing epithelial cells were found to possess the characteristics of progenitor cells—meaning that these cells, like stem cells, had the ability to self-renew and to execute a program that gave rise to a complete airway.

"To translate our findings from the mouse model to humans, we used whole lungs removed from patients undergoing lung transplantation for very severe COPD," said Alexander-Brett. Analysis of these human tissue samples also pointed to epithelial cells with progenitor properties as the source of IL-33.

"From this work, we now know that a respiratory viral infection leads to an increase in lung epithelial progenitor cells that are programmed for increased production of IL-33," said Holtzman. "We also provided the initial evidence that an additional stress or danger, such as smoking or pollution or even another infection, could cause these cells to release IL-33, which then stimulates immune cells to produce IL-13 and in turn the airway mucus typical of COPD and related respiratory diseases. It's also possible that smoke exposure predisposes individuals to the development of these cells and, in turn, the susceptibility to exacerbation and progression of this type of disease."

He noted that it is reasonable to think that monitoring the IL-33 to IL-13 pathway will allow physicians to identify which patients would benefit from strategies to interrupt this cascade and prevent an otherwise progressive and devastating respiratory disease.

"This work suggests that previous viral infections of the lung may worsen COPD by stimulating a particular type of lung cell that

overactivates the immune system," noted James P. Kiley, PhD, director of the Division of Lung Diseases at the National Heart, Lung, and Blood Institute, of the National Institutes of Health (NIH). "Additional research on these cells and their products may lead to new ways to diagnose and treat COPD."

More information: Long-term IL-33-producing epithelial progenitor cells in chronic obstructive lung disease, *J Clin Invest.* doi:10.1172/JCI65570

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