Researchers reverse emphysema in mice by injecting blood vessel wall cells

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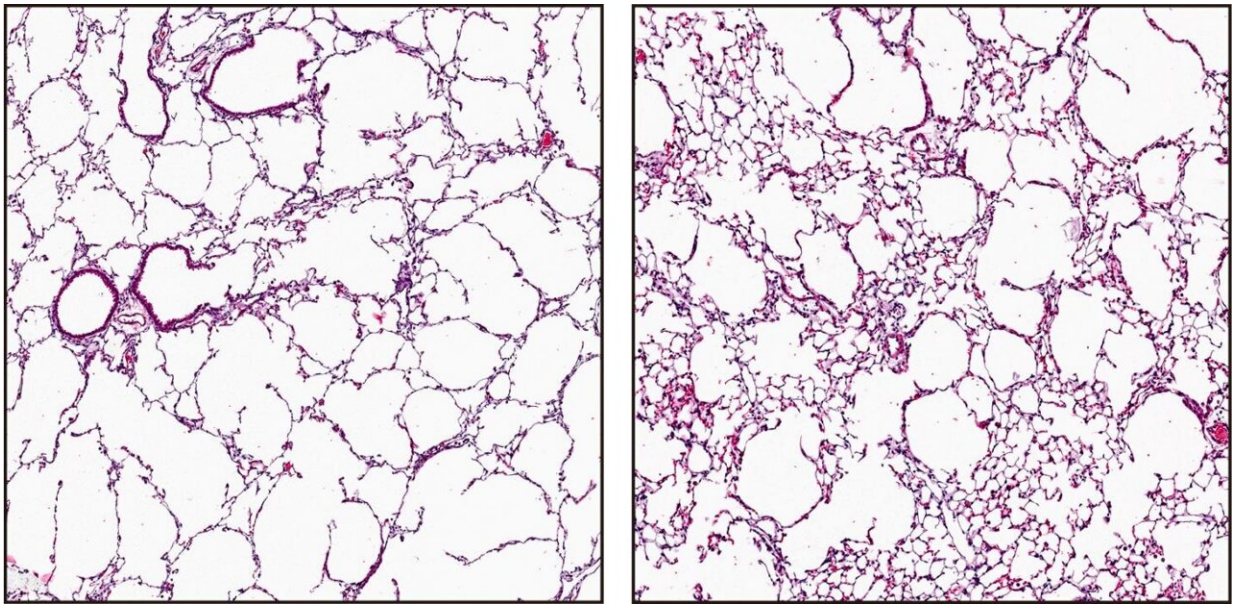

Injection of healthy lung endothelial cells (right) reverses the destruction of lung tissue seen in mice with emphysema (left). Credit: 2021 Hisata et al.

Researchers at Weill Cornell Medicine and NewYork-Presbyterian in New York have discovered that injecting mice with pulmonary endothelial cells—the cells that line the walls of blood vessels in the lung—can reverse the symptoms of emphysema. The study, which will be published July 21 in the *Journal of Experimental Medicine* (*JEM*), may lead to new treatments for chronic obstructive pulmonary disease (COPD), an inflammatory lung disease associated with smoking that is

thought to be the third leading cause of death worldwide.

Emphysema is one of the characteristic features of COPD in which the tiny air sacs, or alveoli, within the lungs are gradually destroyed, leading to breathing difficulties and, eventually, respiratory failure. The loss of alveoli is accompanied by a remodeling of the lung's blood vessels that could indicate changes in the endothelial cells that form the blood vessel walls. Under normal circumstances, endothelial cells secrete molecules that help surrounding tissues maintain and repair themselves, but dysfunctional endothelial cells can drive various diseases, including tissue fibrosis and cancer.

"However, it is not clear whether endothelial dysfunction drives COPD pathophysiology or is simply the consequence of damaged alveolar surface area," says Dr. Augustine M.K. Choi, the Stephen and Suzanne Weiss Dean of Weill Cornell Medicine and a co-senior author of the new *JEM* study.

Choi and colleagues found that various markers of healthy endothelial cells were reduced in the lungs of COPD patients, as well as in laboratory mice with an induced form of emphysema. Indeed, in the lung endothelial cells of mice with emphysema, numerous genes were associated with endothelial dysfunction, including genes that promote inflammation, cell death, and vascular remodeling.

"We took these features to denote a potentially dysfunctional state that could drive the development of emphysema," says co-senior author Dr. Shahin Rafii, Chief of the Division of Regenerative Medicine, Director of the Ansary Stem Cell Institute, and the Arthur B. Belfer Professor in Genetic Medicine at Weill Cornell Medicine. "This could indicate that re-establishing a healthy vasculature—by either intravenous delivery of normal lung endothelial cells or reversing aberrant endothelial cell signaling—could encourage repair and regeneration of damaged lung

tissue."

Remarkably, injecting mice with healthy lung endothelial cells reduced the alveolar destruction associated with emphysema and restored lung function. Other cell types—even endothelial cells from other tissues—failed to have any beneficial effect.

Choi and colleagues then investigated the role of leucine-rich alpha-2-glycoprotein-1 (LRG1), a cell signaling protein linked to diabetic nephropathy and various forms of cancer that the researchers found to be elevated in the lung endothelial cells of patients with COPD. Removing LRG1 from endothelial cells protected mice from the tissue destruction associated with emphysema, the researchers discovered.

"Taken together, our data strongly suggest the critical role of endothelial cell function in mediating the pathogenesis of COPD/emphysema," says co-first author Dr. Alexandra Racanelli, an Instructor in Medicine at Weill Cornell Medicine. "Targeting endothelial cell biology by administering healthy lung endothelial cells and/or inhibiting the LRG1 pathway may therefore represent strategies of immense potential for the treatment of patients with advanced COPD or emphysema."

More information: Shu Hisata et al, Reversal of emphysema by restoration of pulmonary endothelial cells, *J Exp Med* (2021). DOI: 10.1084/jem.20200938