Researchers identify specific genes and cell pathways as key players in rare female lung disease

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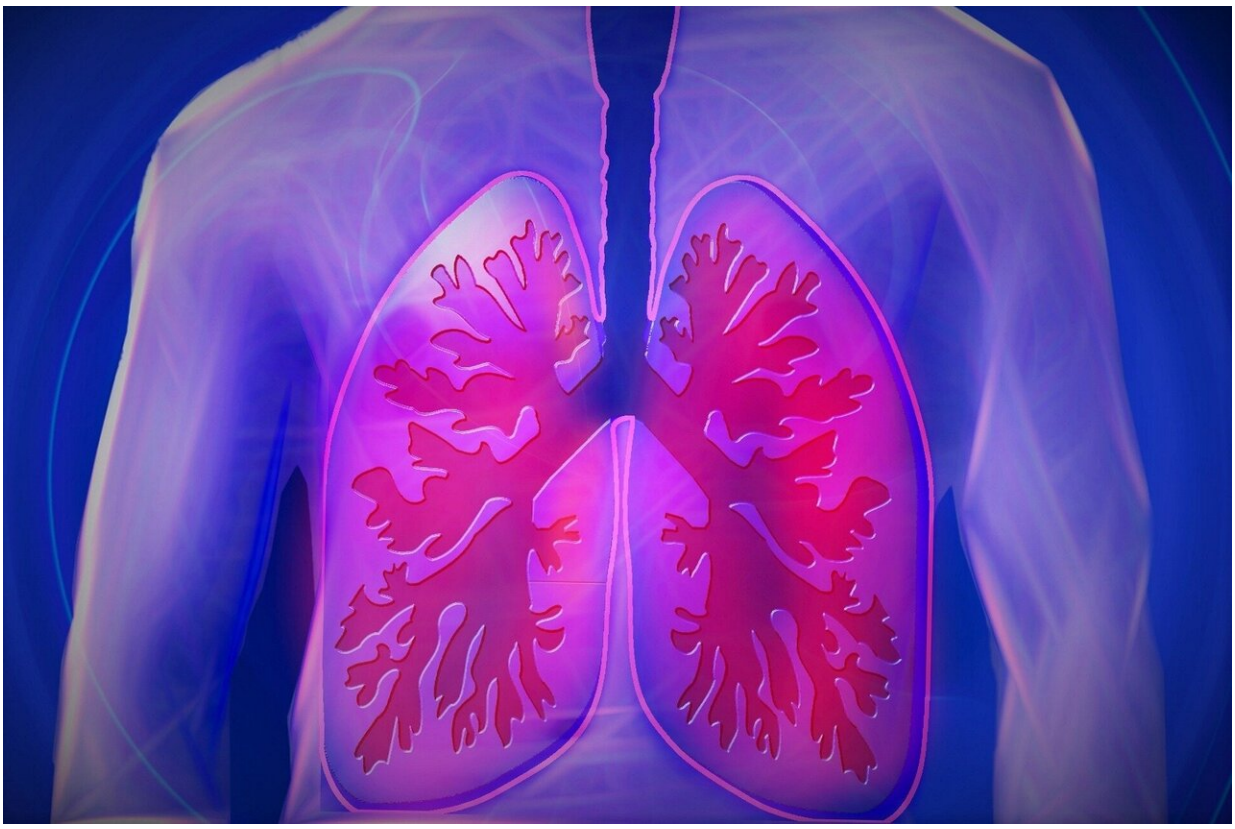

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Deleting the TSC2 gene in specific lung cells of mice led to the activation of the mTORC1 signaling pathway and pulmonary disease

characteristics consistent with human LAM disease, particularly in female breeder mice. These mice without TSC2 also exhibited a dysfunctional WNT cellular signaling pathway, which is also tied to lung development and is activated in multiple common pulmonary diseases, according to researchers in the Perelman School of Medicine at the University of Pennsylvania. This new research suggests targeting mTORC1 and WNT pathways may be a way to treat LAM. The findings are published in the latest issue of *Nature Communications*.

LAM, a rare pulmonary disease that predominantly affects women of child-bearing age and is exacerbated by pregnancies, is a cancer-like disease that leads to cysts developing in the lungs, respiratory failure, and increasingly severe and potentially fatal complications. Sirolimus (rapamycin) is the first, and only, treatment approved by the FDA for the treatment of LAM. However, this drug is not effective or well tolerated by some LAM patients, and declining lung function has been shown to continue after treatment. Therefore, there is an urgent unmet clinical need for new LAM therapies.

After single cell RNA sequencing of a human LAM lung and comparing that to an age and sex match of a control lung, Penn researchers, led by senior author Vera P. Krymskaya, Ph.D., MBA, a professor of Medicine at Penn, who has studied LAM disease for the last two decades, and first author Kseniya Obraztsova, Ph.D., a postdoctoral researcher in Pulmonary, Allergy, and Critical Care, found a unique cellular appearance of LAM cells. They found presence of cells in LAM lungs that had no equivalent in the control lungs—a hub of lung cells with activated mTORC1 affecting alveolar epithelial and mesenchymal lung cells. The researchers deleted the TSC2 gene in mouse lung cells called mesenchymal precursor cells, and this led to age- and sex-linked structural and functional lung decline, exacerbated by pregnancies. These lung cells also exhibited increased activation of the WNT signaling pathway.

Next, the Penn researchers genetically inhibited the WNT pathway in the Tsc2-null mouse lung, and found that this reversed age-related, mTORC1 pathway-activated pulmonary structure decline. However, activating the WNT pathway in a normal mouse lung did not induce LAM lung characteristics, indicating that while targeting the WNT pathway alone may not be effective in LAM disease, a combination therapy inhibiting this pathway and knocking out or impairing other mechanisms could be a potentially successful treatment.

"The cellular cause of LAM is likely a complex relationship between subsets of lung cells affected by TSC2-deficient LAM cells," said Krymskaya. "Nevertheless, our research has shown that targeting drugs against proteins in the WNT pathway may provide new ways to treat LAM patients."

Prior to this study, the WNT pathway was already shown to be tied to much more common lung diseases like Chronic Obstructive Pulmonary disease (COPD), Idiopathic Pulmonary Fibrosis (IPF), asthma, and pulmonary arterial hypertension (PAH). There are very few diseases like LAM that appear in a distinct age and sex specific population of people, so finding cellular changes that followed the age and sex characteristics of the patients was critical to this research.

"We fortuitously found that dysregulation of the WNT pathway in LAM and TSC2-null mouse lung may be important in the development of LAM," Krymskaya said. "Our discovery also underscores the value of studying rare diseases like LAM and how this research can offer broader insight into more common lung diseases."

Future studies will investigate how the WNT and mTOR pathways interact and how treatments that target the WNT pathway, in combination with Sirolimus, may help prevent, stabilize or reverse LAM disease.

More information: Kseniya Obraztsova et al. mTORC1 activation in lung mesenchyme drives sex- and age-dependent pulmonary structure and function decline, *Nature Communications* (2020). DOI: 10.1038/s41467-020-18979-4