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Study reveals new mechanism of lung tissue regeneration

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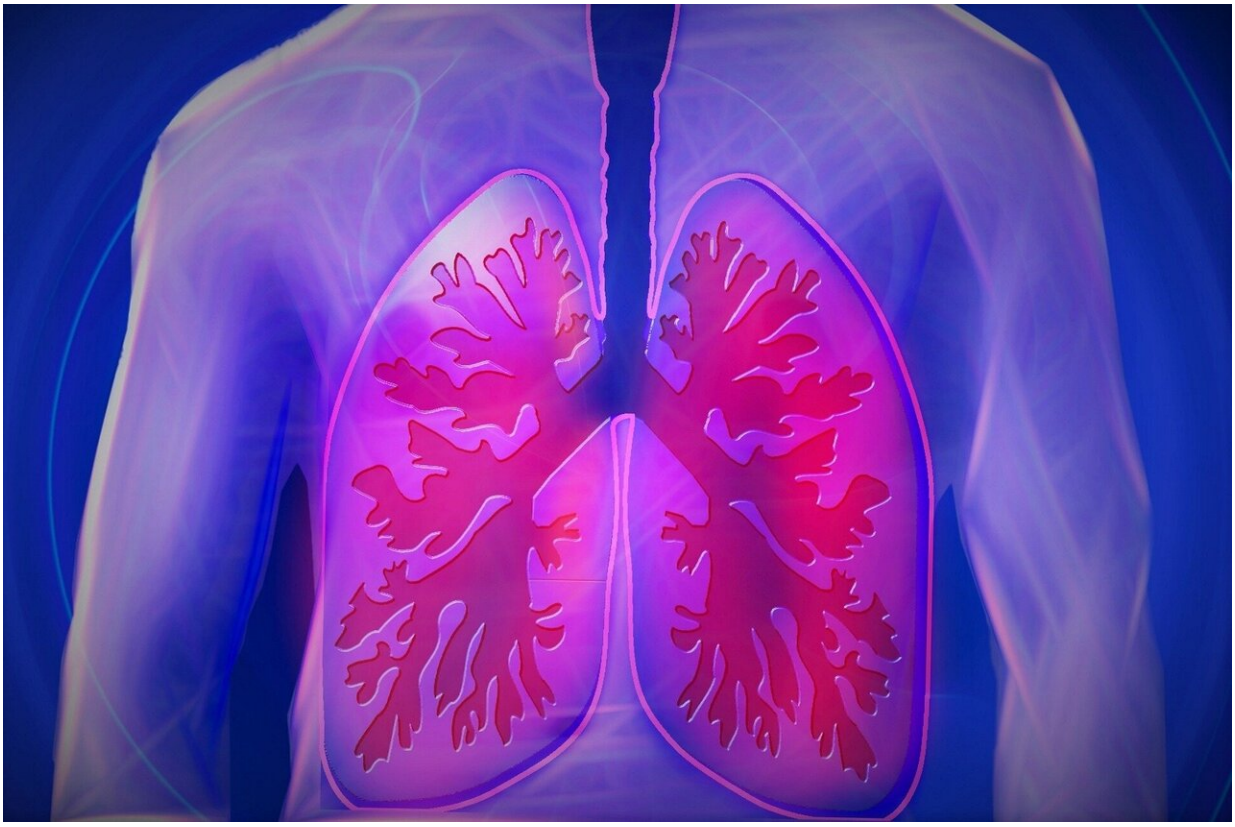

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New research performed in mice models at Penn Medicine shows, mechanistically, how the infant lung regenerates cells after injury differently than the adult lung, with alveolar type 1 (AT1) cells

reprograming into alveolar type 2 (AT2) cells (two very different lung alveolar epithelial cells), promoting cell regeneration, rather than AT2 cells differentiating into AT1 cells, which is the most widely accepted mechanism in the adult lung. These study findings, published today in *Cell Stem Cell*, show that the long-held assumption that AT1 and AT2 cells behave the same way in children and in adults is untrue.

The lung alveolus is where gas is exchanged between the environment and blood. While scientists have known about two very different lung alveolar epithelial cells since the 1940s, there had not been much insight into them on a molecular level before now. Furthermore, these findings reveal the molecular pathway that allows for this transformation. The Penn researchers also showed that by turning off this pathway, they could reprogram adult AT1 cells into AT2 cells. This unveils a previously unappreciated level of age-dependent cell plasticity, which could explain, in part, why pediatric lungs are not as heavily impacted by COVID-19 as adult lungs, and is a major step forward in understanding lung regeneration as a form of lung therapy.

"COVID-19 has led to millions of people contracting a terrible and damaging respiratory infection, which causes severe lung injury. Some of these patients are likely to have long-term chronic lung issues, with some severe enough to need a lung transplant. We are hopeful that our research on how these alveolar cells respond to acute injury will provide new targets that could be leveraged for the development of future therapies to treat acute lung injury, and that one day we will know how to manipulate these cell pathways so that lung tissue can regenerate and heal itself, without the need for organ transplant," said the study's senior author, Edward Morrisey, Ph.D., the Robinette Foundation Professor of Cardiovascular Medicine and the Director of the Penn-CHOP Lung Biology Institute (LBI) in the Perelman School of Medicine at the University of Pennsylvania.

The researchers analyzed changes in gene expression and the epigenome in mouse AT1 and AT2 cells across the lifespan. They compared these changes to those observed after acute lung injury and found that the current paradigm of how adult lungs repair themselves did not hold true for immature or mature mouse lungs.

"Scientists have long assumed that the one-way process of cell differentiation that has been well documented in the adult lung would also hold true in the infant lung, but those assumptions were overturned. We discovered that in pediatric lungs the direction of differentiation is in reverse after injury, whereas in the adult it's much more of a two-way street. In all of these contexts, it is controlled by a pathway called Hippo signaling," said the study's first author, Ian J. Penkala, a University of Pennsylvania VMD/Ph.D. student who works in the Morrisey Lab.

In the adult lung, regeneration of the lung cells is driven by the AT2 cell population expanding and differentiating into AT1 cells. The researchers also showed that after some acute lung injuries, adult AT1 cells can robustly reprogram into AT2 cells. However, in infant mice, AT2 cells do not efficiently regenerate AT1 cells after acute lung injury. Rather, AT1 cells reprogram into AT2 cells after injury, and it is these reprogrammed AT2 cells that can ultimately proliferate after injury.

Mouse lungs are somewhat similar to human lungs in that they both have AT1 and AT2 cells, increasing the likelihood that the conclusions in this study also hold true for human lungs. Research is expanding the mechanisms that can develop future therapies for acute lung injury. Normally lungs have the ability to repair and regenerate as they are constantly exposed to pollution and microbes from the external environment. The next phase in this research would be to determine whether harnessing the Hippo pathway can help promote the lung's natural ability to regenerate after injury.

"What this discovery provides is insight into a cell pathway that we can manipulate, possibly in the future with pharmaceutical therapies. This helps us build a map of how lung cells respond, and could have major implications down the line on how we care for patients with chronic lung disease," Morrisey said.

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