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Sonic hedgehog gene maintains normal physiological state and repair process of adult lungs

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The whimsically named sonic hedgehog gene, best known for controlling embryonic development, also maintains the normal physiological state and repair process of an adult healthy lung, if damaged, according to new research from the Perelman School of Medicine at the University of Pennsylvania published online this week in *Nature* in advance of the print edition.

Tissues are not all created equal in their ability to regenerate. Skin and blood cells are continually turning over, making entirely new populations of cells every few days. At the other end of the spectrum, heart and brain cells regenerate slowly, if at all, after injury. Between these two extremes are tissues such as the lung and liver, which have little cellular turnover in normal adults, but can regenerate extensively after injury. Such tissues, overall, are thought to be quiescent.

This inactive state was previously thought to be the default mode of many tissues, including the lung, in the absence of a proliferative stimulus such as injury. However, it has remained unclear how quiescence is maintained in organs such as the lung that display a low level of cell turnover.

"We demonstrated that quiescence in the adult lung in an animal model is an actively maintained state and is regulated by hedgehog signaling," said senior author Ed Morrisey, PhD, the Robinette Foundation Professor of Medicine and a professor of Cell and Developmental Biology. Morrisey is also director of the Penn Center for Pulmonary Biology and scientific director of the Penn Institute for Regenerative Medicine.

"We were surprised," Morrisey recalled. "This was the exact opposite of what other researchers had suggested and pretty much the opposite of what happens during development. We scratched our heads for a long time."

First author Tien Peng, MD and other members of the Morrisey lab used multiple approaches to determine what hedgehog was doing in the adult lung. First, they deleted the gene sonic hedgehog in airway epithelial cells of the adult lung. The protein made from sonic hedgehog is secreted from airway epithelial cells and acts on the adjoining cells surrounding the airways called mesenchymal cells.

The team observed that after the loss of sonic hedgehog expression,mesenchymalcells began to spontaneously proliferate. This also occurred when they directly inactivated hedgehog signaling in mesenchymal cells themselves.

To determine what occurred after lung injury, the researchers performed multiple different injuries to lung tissue and found that in contrast to previous reports,hedgehogsignaling decreased. This decline correlated with the loss of the cells that normally express the sonic hedgehog gene, which were destroyed as a result of the injury.

With this new concept of what sonic hedgehog is doing in the adult lung, the researchers then asked what would happen if they turned on the hedgehog pathway after lung injury. Consistent with their other observations, the Morrisey team found that activation of the hedgehog pathway inhibited proliferation of the mesenchymal cells surrounding the lung airways.

Overall, they found that activation of hedgehog during an injury to epithelial cells weakens replication of mesenchymal cells, whereas inactivation of hedgehog signaling prevents the restoration of quiescence after an injury. Finally, they showed that hedgehog signaling in mesenchymal cells also regulates epithelial quiescence and loss of this regulation leads to abnormal epithelial regeneration after injury. Loss of hedgehog in the adult lung leads to too many epithelial cells lining the airways after injury whereas increased hedgehog signaling blocks regeneration of the airway epithelium. Such results suggest that increased hedgehog signaling causes a breakdown of the normal regenerative properties of the lung airways, leading to degenerative disease states.

"These results demonstrate that epithelial-mesenchymal interactions coordinated by hedgehog maintains the normal state of a healthy lung, and turning off hedgehog during injury can lead to abnormal cell repair and regeneration in the lung," Morrisey said. "We think that mistakes in the hedgehog feedback loop could contribute to many adult lung diseases characterized by a chronic injury and regeneration cycle."

Indeed, the hedgehog pathway has been implicated in previous genome-wide association studies of adult lung

disease. "We now have a better idea of what is going on in lung disease - in adults, hedgehog suppresses proliferation and maintains cell quiescence, as opposed to its opposite role in embryo development," Morrisey explained. "These surprising findings suggest that researchers have to be careful in predicting the function of developmental pathways in adult organs. We need to remember that they will not always function in the same manner."

Source:
Perelman School of Medicine at the University of Pennsylvania