Land of hope and dreams

Selection of life science and translational medicine literature

by Marco Confalonieri

How pathways controlling lung embryonic development maintain lung repair and regeneration when airways and alveoli are injured?

The knowledge on lung repair, remodeling and regeneration is increased in recent year giving a new look at lung pathobiology and pathophysiology. Also the research on lung development processes may help to better understand how the lung maintain or loose its integrity during adult life.
During repair, epithelial progenitors undergo marked changes in cell shape, migrate, proliferate, and re-differentiate to restore the respiratory epithelium with the appropriate cell type composition and structural organization. Several pathways that regulate lung morphogenesis are also involved in regeneration of the lung epithelium following injury, including Wnt, Shh, Fgf, Tgf-beta, Hippo/Yap and Notch signaling. Similarly to the liver, the lungs have little cellular turnover in normal adults, but can regenerate extensively after injury. Such tissues, overall, are thought to be almost quiescent in healthy subjects. This inactive state was previously thought to be the default mode of many tissues, including the lung, in absence of a proliferative stimulus such as injury. However, it has remained unclear how quiescence is maintained in organs like the lung that display a low level of cell turnover. The research group for pulmonary biology of the Perelman School of Medicine at U Penn, lead by Ed Morrisey, found that quiescence in the adult lung is an actively maintained state and is regulated by hedgehog signaling. The researchers observed in mice that after the loss of sonic hedgehog expression, mesenchymal cells began to spontaneously proliferate. This also occurred when they directly inactivated hadgehog signaling in mesenchymal cells themselves. Hedgehog signaling decreased even when multiple different injuries were performed to lung tissue. 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. This observation is in contrast to previous reports that seemed to predict the same function of developmental pathways in adult organs. However, the Morrisey's group showed convincingly that hedgehog suppresses proliferation and maintains cell quiescence in adult mice, as opposed to its opposite role in embryo development. In fact, 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, the Morrisey's Lab team 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.
Another important pathway in lung development and regeneration is the Hippo/Yap signaling, repeatedly reported as crucial for proliferation and differentiation of lung stem cells. A study by investigators of the University of Cincinnati found that the Hippo/Yap pathway activity is a critical regulator of cell proliferation, differentiation, and progenitor cell behavior in respiratory epithelial cells of both the developing and adult mature lung. The findings showed that dysregulation of core pathway kinases and activation of Yap in respiratory epithelial cells regulates transcriptional networks promoting cell proliferation, migration, and adhesion and inhibiting specific aspects of differentiation, supporting the concept that precise regulation of Hippo/Yap activity coordinates diverse cellular functions to control tissue morphogenesis and maintain homeostasis. Putting together the two studies, a question might arise: how to combine the findings by the Morrisey and those by this last research? Interplay of several signaling cascades, such as Notch, Wnt, Sonic hedgehog, and other pathways, are known to control cell proliferation during tissues differentiation. For example, it was suggested that sonic hedgehog signaling may act downstream of YAP in regulating neuronal differentiation. Nevertheless, further elucidation of Hippo/Yap pathway upstream regulators, signaling interactions, and transcriptional targets in lung development and adult life are needed to advance the understanding of lung progenitor cell behavior and improve targeted therapeutic strategies for lung diseases and cancer.

1) Hedgehog actively maintains adult lung quiescence and regulates repair and regeneration

Peng T, Frank DB, Kadzik RS, Morley MP, Rathi KS, Wang T, Zhoung S, Cheng L, Lu MM, Morrisey EE
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Postnatal tissue quiescence is thought to be a default state in the absence of a proliferative stimulus such as injury. Although previous studies have demonstrated that certain embryonic developmental programs are reactivated aberrantly in adult organs to drive repair and regeneration, it is not well understood how quiescence is maintained in organs such as the lung, which displays a remarkably low level of cellular turnover. Here we demonstrate that quiescence in the adult lung is an actively maintained state and is regulated by hedgehog signaling. Epithelial-specific deletion of sonic hedgehog (Shh) during postnatal homeostasis in the murine lung results in a proliferative expansion of the adjacent lung mesenchyme. Hedgehog signaling is initially downregulated during the acute phase of epithelial injury as the mesenchyme proliferates in response, but returns to baseline during injury resolution as quiescence is restored. Activation of hedgehog during acute epithelial injury attenuates the proliferative expansion of the lung mesenchyme, whereas inactivation of hedgehog signaling prevents the restoration of quiescence during injury resolution. Finally, we show that hedgehog also regulates epithelial quiescence and regeneration in response to injury via a mesenchymal feedback mechanism. These results demonstrate that epithelial-mesenchymal interactions coordinated by hedgehog actively maintain postnatal tissue homeostasis, and deregulation of hedgehog during injury leads to aberrant repair and regeneration in the lung.

2) Hippo/Yap signaling controls epithelial progenitor cell proliferation and differentiation in the embryonic and adult lung

Lang AW, Sridharan A, Xu Y, Stripp BR, Perl AK, Whitsett JA
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The Hippo/Yap pathway is a well-conserved signaling cascade that regulates cell proliferation and differentiation to control organ size and stem/progenitor cell behavior. Following airway injury, Yap was dynamically regulated in regenerating airway epithelial cells. To determine the role of Hippo signaling in the lung, the mammalian Hippo kinases ,Mst1 and Mst2, were deleted in epithelial cells of the embryonic and mature mouse lung. Mst1/2 deletion in the fetal lung enhanced proliferation and inhibited sacculation and epithelial cell differentiation. The transcriptional inhibition of cell proliferation and activation of differentiation during normal perinatal lung maturation were inversely regulated following embryonic Mst1/2 deletion. Ablation of Mst1/2 from bronchiolar epithelial cells in the adult lung caused airway hyperplasia and altered differentiation. Inhibitory Yap phosphorylation was decreased and Yap nuclear localization and transcriptional targets were increased after Mst1/2 deletion, consistent with canonical Hippo/Yap signaling. YAP potentiated cell proliferation and inhibited differentiation of human bronchial epithelial cells *in vitro*. Loss of Mst1/2 and expression of YAP regulated transcriptional targets controlling cell proliferation and differentiation, including Ajuba LIM protein. Ajuba was required for the effects of YAP on cell proliferation *in vitro*. Hippo/Yap signaling regulates Ajuba and controls proliferation and differentiation of lung epithelial progenitor cells.

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