

Land of hope and dreams

Selection of life science literature

by Marco Confalonieri



Pulmonary regenerative medicine is still at its beginning, but already we know that an adult healthy lung has some capacity to regenerate itself like the liver. The complexity of the lung, but also the slow rate of pulmonary cells' replication has made it difficult to date the identification of adult lung stem cells. Chronic diseases affecting the small airways of the lung can now be thought as a failure of reparative mechanisms involving an injury-repair cycle that leads to the breakdown of normal airway structure and function. A new insight on how lungs can repair injuries has been given by a recent study from the Penn Institute for Regenerative Medicine in the Perelman School of Medicine at the University of Pennsylvania in Philadelphia. Thanks to this study, Prof. Morrissey et al. looked at how epigenetics controls lung repair and regeneration. Epigenetics involves chemical modifications to DNA and its supporting proteins that affect gene expression without changing the nucleotide sequence. Previous studies found that smokers with COPD (chronic obstructive pulmonary disease) had the most significant decrease in one of the enzymes controlling these modifications, called HDAC2 (histone deacetylase 2). To carry out gene expression, a cell must control the coiling and uncoiling of DNA around histones. This is accomplished with the assistance of histone acetylases (HAT), which acetylate the lysine residues in core histones leading to a less compact and more transcriptionally active chromatin, and, on the converse, the actions of histone deacetylases (HDAC), which remove the acetyl groups from the lysine residues leading to the formation of a condensed and transcriptionally silenced chromatin. Reversible modification of the terminal tails of core histones constitutes the major epigenetic mechanism for remodeling higher-order chromatin structure and controlling gene expression. HDAC inhibitors (HDI) block this action and can result in hyperacetylation of histones, thereby affecting gene expression. Using genetic and pharmacological approaches, Morrissey et al. showed that development of progenitor cells in the lung is specifically regulated by the combined function of two highly related HDACs, HDAC1 and /2. HDAC1/2 deficiency leads to a loss of expression of the key transcription factor, a protein called Sox2, which in turn leads to a block in airway epithelial cell development. This is affected in part by deactivating a repressor of expression (derepressing) of two other proteins, Bmp4 and the tumor suppressor Rb1 — targets of HDAC1/2. In the adult

lung, loss of HDAC1/2 leads primarily to increased expression of inhibitors of cell proliferation including the proteins Rb1, p16, and p21. This results in decreased epithelial proliferation in lung injury and inhibition of regeneration.

Together, these data support a critical role for HDAC-mediated mechanisms in regulating both development and regeneration of lung tissue. For now, drugs for COPD treat only the symptoms. HDAC therapies may be useful for a real biopathologic intervention for COPD, as well other airways diseases. Since HDAC inhibitors and activators are currently in clinical trials for other diseases, including cancer, such compounds could be tested in the future for efficacy in COPD, acute lung injury, and other lung diseases that involve pulmonary defective repair and regeneration.

Development and regeneration of Sox2+ endoderm progenitors are regulated by a HDAC1/2-Bmp4/Rb1 regulatory pathway

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Abstract

The mechanisms that govern the maintenance and differentiation of tissue-specific progenitors in development and tissue regeneration are poorly understood. We show that development of Sox2+ progenitors in the lung endoderm is regulated by histone deacetylases 1 and 2 (Hdac1/2). Hdac1/2 deficiency leads to a loss of Sox2 expression and a block in proximal airway development. This is mediated in part by derepression of Bmp4 and the tumor suppressor Rb1, which are direct transcriptional targets of Hdac1/2. In contrast to development, postnatal loss of Hdac1/2 in airway epithelium does not affect the expression of Sox2 or Bmp4. However, postnatal loss of Hdac1/2 leads to increased expression of the cell-cycle regulators Rb1, p21/Cdkn1a, and p16/Ink4a, resulting in a loss of cell-cycle progression and defective regeneration of Sox2+ lung epithelium. Thus, Hdac1/2 have both common and unique targets that differentially regulate tissue-specific progenitor activity during development and regeneration.