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**Authors**
Kathiriya, Jaymin J
Peng, Tien

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# An inflammatory switch for stem cell plasticity

**Jaymin J. Kathiriya**[1,2], **Tien Peng**[1,2,*]

[1]Department of Medicine, University of California San Francisco, San Francisco, CA 94143

[2]Cardiovascular Institute and Division of Pulmonary, Critical Care, Allergy and Sleep Medicine, University of California San Francisco, San Francisco, CA 94143

## Abstract

Tissue resident stem cells are capable of remarkable plasticity in areas of tissue damage, where inflammatory cells accumulate as part of the reparative response. A study in the lung now provides critical insight on how inflammatory signals alter cell-to-cell Notch signaling within the airway niche to drive stem cell plasticity.

Epithelial barrier organs have evolved to optimize localized regeneration by specialized stem cells in response to injury. The lung, constituting the largest barrier surface in the body, can be roughly divided into proximal (airway) and distal (alveoli) segments with segmental-specific stem cells along the arborized gas exchange network[1]. These stem cells reside in highly specialized niches that are capable of recruiting inflammatory cells to areas of damage to the epithelial surface. To produce a coordinated regenerative response, stem cells must possess a mechanism to sense and respond to inflammatory signals that accompany tissue breakdown. In this issue, Choi, Jang *et al.* uncovers a previously unappreciated airway stem cell niche interaction that integrates inflammatory signals to alter Notch activation[2].

Although the conducting airway of the lung constitutes only a small fraction of the total lung barrier surface, it contains a highly diverse repertoire of stem cells with remarkable plasticity and mobility for migration to distant sites of injury[1]. The airway stem cell reservoir includes $p63^{pos}/Krt5^{neg}$ distal basal progenitors, subpopulations of secretory cells including bronchioalvaeolar stem cells (BASCs), and other club/secretory-like cells such as variant club cells and $H2\text{-}K1^{high}$ cells that can give rise to other airway cells, but also mobilize to the alveolar compartment in varying capacity post severe alveolar injury[1]. The evolution of diverse airway stem cell populations specialized for the injury type and severity dictates that the cell-cell interactions and signaling events responsible for their activation should also be unique and specific to the stem cell-type. Paracrine signaling with mesenchymal niche cells through FGF10[3] and hedgehog/BMP[4] has been shown to modify secretory cell differentiation into basal cells in response to fibrotic alveolar repair. Furthermore, intercellular signaling requiring contact, such as Notch signaling, can further finetune the differentiation of airway stem cells. During development, ectopic activation of

*Address correspondence to: Tien Peng, MD, University of California, San Francisco, 513 Parnassus Ave., HSE Building, Room 13512, San Francisco, CA 94143, tien.peng@ucsf.edu.

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Notch attenuates alveolar differentiation, while promoting airway secretory fate[5]. During homeostasis in the adult airway, the balance of Notch activation controls the differentiation of secretory vs. ciliated lineages from basal stem cells[6]. Likewise, hyperactive Notch signaling induced by hypoxia in distal airway progenitors can inhibit alveolar fate and promote airway fate, as observed in the examples of $p63^{pos}/Krt5^{neg}$ distal basal progenitors that give rise to metaplastic honeycomb-like cysts after H1N1 influenza injury[7,8].

Even though intercellular signaling between stem cells and their neighboring epithelial or mesenchymal cells can clearly dictates stem cell fate, emerging work suggests that inflammatory cells that traffic into the stem cell niche also modify the regenerative outcome. For example, IL-1/TNF-α signaling through NF-kB contributes to alveolar epithelial Type 2 cell (AEC2) proliferation after viral injury[9]. Another recent study identified subsets of immune cells, such as CCR2+ monocytes and M2-like macrophages, that are activated by type 2 innate lymphoid cells and promote AEC2-regeneration after partial pneumonectomy[10]. Consistent with the notion that a transient inflammatory response is required for injury repair in alveolar injury, IL-1β secreted by interstitial macrophages promotes activation of AEC2s and their differentiation into AEC1s via transient states[11].

The aforementioned reports focus on the direct interactions between stem cells and inflammatory cells. Going a step further, the current report by Choi, Jang *et al.* shows that inflammatory signals can also modify the signaling architecture of the niche. This niche effect occurs through an elegant mechanism where an inflammatory signal alters Notch ligand expression in the ciliated cells that are in direct contact with airway stem cells. Using several sophisticated use of several mouse models, the authors beautifully established that IL-1β targets Il1r1+ ciliated cells and downregulates Notch ligands, Jag1/2, providing direct evidence of immune-ciliated cell interaction and subsequent modulation of an intercellular signaling pathway. In addition, they demonstrated that downregulation of Notch ligands in ciliated cells results in downregulation of Notch activation in adjacent secretory cells, promoting alveolar fate conversion in the setting of alveolar injury. Conversely, constitutive activation of Notch signaling in secretory cells effectively inhibited alveolar regeneration. Downregulation of Notch signaling ultimately led to the upregulation of a Fra2/Fosl2 transcription program in the airway stem cells, representing an important step in the conversion of a secretory airway identity to alveolar fate.

A key insight from this study is that a highly coordinated division of labor exists within the stem cell niche, where niche cells are tasked with sensing changes to the inflammatory milieu. As the regenerative requirement changes during tissue damage, the immune cell composition at the injury site is also dynamically remodeled. In this current model proposed by Choi, Jang *et al.*, the niche cells (ciliated cells) serve as sentinels that can sense changes to the inflammatory environment and relay the information to neighboring secretory cells (Figure 1). The stem cells then focus on cellular programs that are geared towards proliferation, differentiation into alveolar stem cells, and mobilization into the alveolar compartment (Figure 1). This model highlights how the 3D architecture of the stem cell niche can support a signal-relay circuit to finetune the stem cell response to tissue inflammation.

Taken together, Choi, Jang *et al.* provide important insights into airway stem cell plasticity. However, some outstanding questions remain regarding the role of Notch signaling in the differentiation of airway stem cells into alveolar stem cells. It has been demonstrated that Notch activation is required for the maintenance of secretory fate, the loss of which results in differentiation into ciliated cells in the absence of alveolar injury[12,13]. Why does Notch inactivation produce these divergent outcomes, depending on the injury context and locale? It is clear that the loss of Notch is necessary but not sufficient in driving alveolar stem cell differentiation from airway stem cells. Prior studies have shown that Wnt and BMP signaling can promote alveolar differentiation from secretory cells[4,8], and Choi, Jang *et al.* postulate that a two-step process is required for this fate switch, where loss of Notch is followed by activation of another pro-alveolar differentiation pathway. The signaling cascade in the airway serves only as an initiating step in what is clearly a multi-step process where an airway stem cell needs to be mobilized and differentiate into an alveolar stem cell at a distant site. It is not clear whether Notch signaling plays a role in the trafficking of these stem cells into a distant compartment where stem cell repletion is required.

Finally, what is the relevance of these findings in the human lung? The human airway stem cell repertoire and lineage potential are not as well defined as their murine counterparts. Choi, Jang *et al.* demonstrate that Notch inhibition can promote the differentiation of KDR+ human airway secretory cells into alveolar epithelium *in vitro*, which presents a potential therapeutic angle. Human lung fibrotic diseases, such as idiopathic pulmonary fibrosis, are characterized by the loss of alveolar stem cells[14], and the question of whether human secretory cells can serve as a stem cell reservoir for alveolar repair is clinically relevant. Even though genetic lineage tracing is not possible in the human lung, single cell RNA sequencing studies of the fibrotic human lung might provide clues as to the lineage relationships between different epithelial cell types within the damaged alveoli. Further bioinformatic analysis of cellular trajectories in these studies could support or refute the existence of an airway-alveolar stem cell differentiation pathway in human disease, prompting more investigation into therapeutic interventions to modify stem cell plasticity in lung fibrosis.

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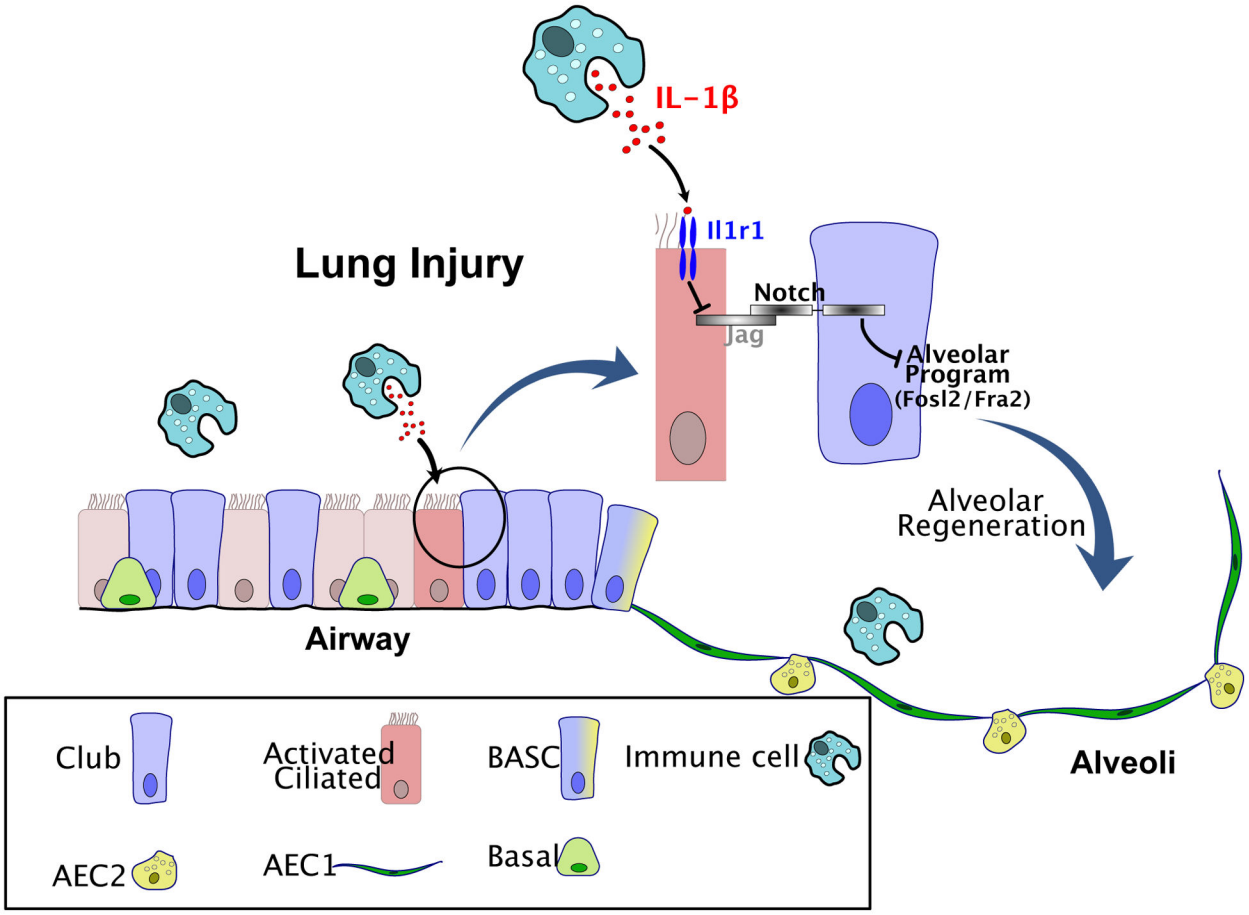


**Figure 1. Model of inflammation-sensing in the stem cell niche to promote airway secretory cell plasticity.**

Choi, Jang *et al.* describe a key interaction between immune cells and niche cells that modify airway stem cell fate. In this model, immune cells that traffick to site of damage secrete IL-1β that targets ciliated cells in the airway stem cell niche. IL-1β activation suppresses Notch ligands in ciliated cells, which in turn represses Notch activation in the airway stem cells to allow alveolar differentiation. Abbreviations: AEC1/2: Alveolar epithelial type 1/2 cells, BASC: Bronchoalveolar stem cells