Title: Notch signaling via hairy/enhancer of Split-5 (Hes5) & paired-box containing gene 6 (Pax6) controls progenitor cell reservoir for repair of airway injury

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Body: Background: The airways of the mammalian lung are lined with specialized epithelial cell types that are the target of airborne toxicants and injury. Notch signaling plays an important role in the ontogeny of these cells, but its contributions to recruitment, expansion or differentiation of resident progenitor/stem cells in repair of injured airways remains unknown. Aims & Objective: To elucidate the role of Notch signaling in repair of injured airway epithelium. Methods: We used targeted inactivation of, Notch1, via the epithelial-specific Gata5-cre line in the embryonic lung epithelium. Results: Notch1(-/-) mice are viable with intact pulmonary epithelial cell fate determination/differentiation. However, Notch1 was found to be required for normal repair of the injured airway epithelium. Absence of Notch1 reduced the ability of cells distinguished by expression of PGP9.5, a marker of pulmonary neuroendocrine cells, which serve as a reservoir for regeneration of Clara cells. Hairy/Enhancer of Split-5 (Hes5) and a paired-box containing gene 6 (Pax6) were found to be downstream targets of Notch1. Both Hes5 and Pax6 expression were significantly increased in association with Clara cell regeneration in wild type lungs. Ablation of Notch1 reduced Hes5 and Pax6 and inhibited airway epithelial repair. Thus, although dispensable in developmental ontogeny of airway epithelial cells, normal activity of Notch1 is required for repair of the airway epithelium. The signaling pathway by which Notch1 regulates the repair process also includes stimulation of Hes5 and Pax6 gene expression. Supported by NIH, NHLBI & The Hastings Foundation.