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Notch signaling prevents mucous metaplasia in mouse conducting airways during postnatal development

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ABSTRACT

Goblet cell metaplasia and mucus overproduction contribute to the pathogenesis of chronic lung diseases, including asthma and chronic obstructive pulmonary disease (COPD). Notch signaling regulates cell fate decisions and is critical in controlling goblet cell differentiation in the gut epithelium. Little is known, however, about how endogenous Notch signaling influences the goblet cell differentiation program that takes place in the postnatal lung. Using a combination of genetic and in vitro approaches here we provide evidence of a novel role for Notch in restricting goblet cell differentiation in the airway epithelium during the postnatal period. Conditional inactivation of the essential Notch pathway component *Pofut1* (Protein O-fucosyltransferase1) in *Tgfb3-Cre*-expressing mice resulted in an aberrant postnatal airway phenotype characterized by marked goblet cell metaplasia, decreased Clara cell number and increase in ciliated cells. The presence of the same phenotype in mice in which the Notch transcriptional effector *Rbpjk* was deleted indicated the involvement of the canonical Notch pathway. Lineage study in vivo suggested that goblet cells originated from a subpopulation of Clara cells largely present in proximal airways in which Notch was disrupted. The phenotype was confirmed by a panel of goblet cell markers, showed no changes in cell proliferation or altered expression of proinflammatory cytokines and was associated with significant downregulation of the bHLH transcriptional repressor-*Hes5*. Luciferase reporter analysis suggested that Notch directly repressed *MUC5AC* transcription in lung epithelial cells. The data suggested that during postnatal life Notch is required to prevent Clara cells from differentiating into goblet cells.

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