

**Eya1 controls cell polarity, spindle orientation, cell fate and Notch signaling in distal embryonic lung epithelium.**

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**Public Summary:**

**Scientific Abstract:**

Cell polarity, mitotic spindle orientation and asymmetric division play a crucial role in the self-renewal/differentiation of epithelial cells, yet little is known about these processes and the molecular programs that control them in embryonic lung distal epithelium. Herein, we provide the first evidence that embryonic lung distal epithelium is polarized with characteristic perpendicular cell divisions. Consistent with these findings, spindle orientation-regulatory proteins Insc, LGN (Gpsm2) and NuMA, and the cell fate determinant Numb are asymmetrically localized in embryonic lung distal epithelium. Interfering with the function of these proteins in vitro randomizes spindle orientation and changes cell fate. We further show that Eya1 protein regulates cell polarity, spindle orientation and the localization of Numb, which inhibits Notch signaling. Hence, Eya1 promotes both perpendicular division as well as Numb asymmetric segregation to one daughter in mitotic distal lung epithelium, probably by controlling aPKCzeta phosphorylation. Thus, epithelial cell polarity and mitotic spindle orientation are defective after interfering with Eya1 function in vivo or in vitro. In addition, in Eya1(-/-) lungs, perpendicular division is not maintained and Numb is segregated to both daughter cells in mitotic epithelial cells, leading to inactivation of Notch signaling. As Notch signaling promotes progenitor cell identity at the expense of differentiated cell phenotypes, we test whether genetic activation of Notch could rescue the Eya1(-/-) lung phenotype, which is characterized by loss of epithelial progenitors, increased epithelial differentiation but reduced branching. Indeed, genetic activation of Notch partially rescues Eya1(-/-) lung epithelial defects. These findings uncover novel functions for Eya1 as a crucial regulator of the complex behavior of distal embryonic lung epithelium.

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