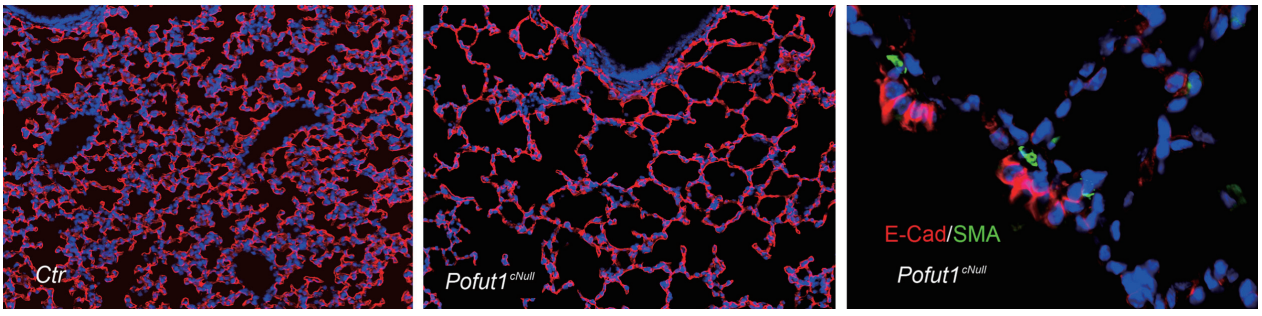
The epithelial-mesenchymal interaction in distal lung development



A research team led by Professor Po-Nien Tsao at the National Taiwan University (NTU) Hospital discovered that Notch signaling is crucial for the differentiation, repair and regeneration of the airway epithelium and could serve as a potential target for the treatment of pulmonary diseases.

How epithelial Notch signaling contributes to alveologenesis is unclear. By using a genetic mouse model, Tsao's team found that *Pofut1F/-:ShhCre/+* mutants (*Pofut1*^{cnull}) exhibited failure to thrive starting at postnatal day 3 with a mortality rate of approximately 80% within 2 weeks after birth. They also observed poor alveolarization in the lungs of the mutant mice. During embryonic development prior to alveolarization, the distal lungs of *Pofut1*^{cnull} mouse appeared similar to those of the control mice. However, at postnatal day 3, the Notch mutant lungs failed to initiate alveolarization, which presented as fewer secondary crests and enlarged air spaces. At postnatal day 21, when alveolarization is mostly complete, the Notch mutant lungs exhibited an emphysema-like phenotype. Furthermore, Tsao's team found that Notch2 but not Notch1 mutant lungs also presented the emphysema-like phenotype. A pulmonary function test confirmed that the Notch2 mutant lungs had dramatically increased static compliance and decreased tissue elasticity. This phenotype mimics that of human chronic obstructive pulmonary disease (COPD) in adults and bronchopulmonary dysplasia (BPD) in preterm infants. The phenotype was caused, at least in part, by poor alveolar myofibroblast differentiation, which resulted from decreased epithelial PDGF-A expression in the Notch mutant lungs. In addition to the alveolar phenotype, Tsao's team also observed a significant decrease in the number of epithelial cells in the distal airway of Notch mutants. Interestingly, this also influenced the development of the surrounding airway smooth muscle, which likely resulted from decreased Wnt7b secretion from the epithelium.

In conclusion, deletion of Notch from the epithelium disrupted alveolar myofibroblast development, which resulted in poor alveologenesis. Moreover, epithelial Notch signaling integrates postnatal morphogenesis of the distal lungs via epithelial-mesenchymal interactions. These data suggest the potential benefit of targeting the Notch pathway in pulmonary disorders that affect the airway or alveolar epithelium.

Reference

Po-Nien Tsao, Chisa Matsuoka, Shu-Chen Wei, Atsuyasu Sato, Susumu Sato, Koichi Hasegawa, Hung-kuan Chen, Thai-Yen Ling, Munemasa Mori, Wellington V. Cardoso, and Mitsuru Morimoto. (2016) Epithelial Notch signaling regulates lung alveolar morphogenesis and airway epithelial integrity. *Proceedings of the National Academy of Sciences of the United States of America (PNAS)*, 113(29), 8242-8247. DOI: 10.1073/pnas.1511236113.

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