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Title: Regulation and role of notch signaling in epithelial progenitor cell differentiation and proliferation in the normal and the fibrotic lung

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Body: Introduction: Differential regulation of the TGF-β, Wnt and Notch pathway was recently identified by transcriptome profiling of still normal appearing, microdissected alveolar septae from IPF lungs. The Notch signaling pathway is involved in cell fate decisions, differentiation and proliferation during development, but it may also play a key role in repair processes of the injured lung. Results: There were no significant changes in the expression of Notch receptors and ligands on mRNA level in lung homogenates of organ donors and IPF patients. On protein level, however, the receptor Notch1 (NICD1) and the Notch ligand Delta1 were found to be upregulated in lungs of IPF patients and bleomycin-challenged mice. Expression of the Notch1 receptor was immunohistochemically detected in AECII of IPF lungs. MLE12 cells showed an increased proliferation when transfected with NICD1 and reduced proliferation upon treatment with POFUT1 siRNA and DAPT. We also confirmed influence of Notch pathway on primary mouse alveolar epithelial type II cells (AECII) proliferation. Furthermore, after NICD1 overexpression decreased expression of SP-C and Aq5 was detected in MLE15 cells. The Notch signaling pathway had no impact on apoptosis of lung epithelial cells. Discussion: Our findings suggest that the Notch system is activated in IPF as well as in a murine fibrosis model. It can be concluded that NICD1 is implicated in alveolar epithelial cell proliferation and differentiation but not in apoptosis. This may indicate a key role of Notch signaling pathway in the repair process of the alveolar epithelium in response to the chronic injury of AECII in IPF.