ALVEOLAR REGENERATION IN IDIOPATHIC PULMONARY FIBROSIS IS NOT IMPAIRED BY ABERRANTLY ACTIVATED NOTCH1 SIGNALLING

Dartsch, RC[1,3], Wasnick, R[1], Seeger, W[1-4], Ruppert, C[3,4], Günther, A[1-4]
[1]Department of Internal Medicine, Justus Liebig University Giessen, 35392 Giessen,
[2]Excellence Cluster Cardio-Pulmonary System, 35392 Giessen,
[3]German Center for Lung Research (DZL), 35392 Giessen,
[4]European IPF Registry / Biobank, 35392 Giessen

Idiopathic pulmonary fibrosis (IPF) is the most abundant idiopathic interstitial pneumonia with a fatal median survival worse than many solid cancers. Chronic repetitive type II alveolar epithelial cell (AECII) injury as the major initiating disease mechanism facilitates a defective alveolar regeneration and AECII cell death. Until today there is no treatment available improving this disturbed epithelial regeneration process. Notch signalling, a highly conserved developmental pathway is persistently activated after major lung injury and promotes an aberrant alveolar regeneration and alveolar cyst formation reminiscent of microscopic honeycombing in IPF.We previously identified Notch signalling in AECII in the Bleomycin model of lung fibrosis and hypothesized that aberrantly activated Notch1 signaling facilitates hyperproliferation in IPF AECII subpopulations. Histological analysis of explanted IPF lungs revealed no signature of an overwhelming Notch1 activation in hyperplastic human IPF AECII. Instead, IPF AECII only rarely showed signs of Notch activity, as indicated by the Notch target gene Hes1. We investigated the proliferative potential of alveolar epithelial derived cells in a human alveolospheres assay. Rather than being hyperproliferative, IPF AECIIs subpopulations showed a significantly reduced proliferative capacity compared to AECIIs isolated from healthy organ donors. Interestingly, a specific Notch1 receptor blockade showed no impact on the proliferating human IPF AECII, whereas global Notch inhibition by -Secretase inhibition did. Instead, activation of Wnt signalling by GSK3 inhibition promoted AECII growth, as evidenced by significantly larger sphere sizes of Wnt-activated AECII. To further clarify the Notch activation status in IPF AECII protein analysis of sorted IPF AECII showed no upregulated Hes1 as well as Notch1 level compared to donor organ AECII. Finally, induction of Endoplasmatic Reticulum Stress as a major hallmark of chronic IPF AECII injury and apoptosis in a human Notch positive lung adenocarcinoma cell line revealed a dampened Notch activity represented by a Notch target gene downregulation.