European Respiratory Society
Annual Congress 2013

Abstract Number: 1650

Publication Number: P622

Abstract Group: 3.2. Airway Cell Biology and Immunopathology

Keyword 1: COPD - mechanism **Keyword 2:** Epithelial cell **Keyword 3:** Molecular pathology

Title: A role for WNT-5B in airway remodeling in COPD by activation of TGF-β/Smad3 signaling?

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Body: Aberrant epithelial repair responses to cigarette smoke contribute to airway remodeling in COPD, a chronic inflammatory respiratory disease. The WNT pathway is re-activated upon inflammation, tissue injury and repair in multiple organs, including the lung, but its role in COPD is unknown. We aimed to investigate whether dysregulated expression of WNT genes may contribute to airway remodeling in COPD. We studied expression of various WNT ligands, WNT receptors and WNT target/remodeling genes (e.g. fibronectin, periostin, MMP-2 and MMP-9) in the presence and absence of cigarette smoke extract (CSE) in primary bronchial epithelial cells (PBECs) from COPD patients and (non-)smoking controls and/or human bronchial epithelial BEAS-2B cells (qPCR, immunodetection). Additionally, we studied mRNA expression of WNT genes in lung homogenates from Balb/c mice upon 5 days of smoking. CSE induced a significant increase in the mRNA expression of WNT-5A and WNT-5B, but not of the other detected WNT ligands (WNT-4,-7B,-10B) or FZD receptors (FZD-2,-8) in PBECs from COPD patients, but not in control PBECs. CSE also increased WNT-5B mRNA and protein expression in BEAS-2B cells, which did not express WNT-5A. Further, lungs of smoke-exposed mice displayed 2-fold higher WNT-5B mRNA expression than air-exposed mice. Recombinant human WNT-5B induced Smad3 activation and TGF-β/Smad3 signaling-dependent upregulation of fibronectin, periostin, MMP-2 and MMP-9 expression in BEAS-2B cells. Together, our results indicate that exaggerated WNT-5B expression in cigarette smoke-exposed bronchial epithelium may lead to TGF-β/Smad3-dependent expression of multiple remodeling genes and thus contribute to airway remodeling in COPD.