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Title: WNT5A antagonizes canonical WNT/β-catenin signaling in lung epithelial cells

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Body: Rationale: The WNT signaling pathways are important in lung repair and tissue remodeling. Canonical WNT signaling is defined by activation β-catenin signaling, whereas non-canonical WNT signaling does not. β-Catenin signaling is reduced in alveolar epithelial cells in emphysema, a pathological feature of COPD. The mechanisms involved in WNT/β-catenin down regulation are unknown. We investigated the cross-talk between canonical and non-canonical WNT signaling in lung epithelial cells. Methods: Human and murine lung epithelial cells were treated with the WNT ligands WNT3A and WNT5A. β-Catenin signaling was activated by GSK3 inhibition. WNT signaling was monitored by β-catenin sensitive luciferase assay (TOP/FOP-flash) and immunoblotting. Results: Stimulation of lung epithelial cells with WNT3A led to LRP6 phosphorylation, β-catenin stabilization and activation of TOP/FOP-flash reporter, confirming canonical WNT signaling. WNT5A did not activate β-catenin signaling, but induced DVL phosphorylation indicating non-canonical WNT signaling. Co-stimulation with WNT3A and various doses of WNT5A resulted in a dose-dependent decrease in TOP/FOP-flash reporter activation, due to attenuated LRP6 phosphorylation and decreased β-catenin stabilization. GSK3 inhibition activated TOP-flash luciferase activity, which was antagonized WNT5A. Basal signaling by WNT5A was mediated by PKC, but not JNK or TAK1. Importantly, WNT5A was up regulated in the lungs of mice after cigarette smoke exposure. Conclusion: Canonical WNT signaling activated by either WNT3A or by GSK3 inhibition is attenuated by the non-canonical WNT ligand WNT5A in lung epithelial cells. HB is supported by an ERS long-term fellowship (LTRF 79-2012).