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Title: A functional role for WNT-5A in driving airway myocyte proliferation

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Body: Increased airway smooth muscle (ASM) mass is a common pathological feature associated with chronic airway diseases, notably asthma. The mechanisms, however, remain poorly understood. The WNT (Wingless/integrase-1) signaling pathway has been implicated in various proliferative diseases, including lung cancer. In addition, the phosphorylation of GSK-3β, a key regulator of the WNT pathway, correlates with ASM hypertrophy. The WNT pathway may therefore be of particular significance in understanding ASM remodeling. Using immortalized human bronchial smooth muscle cell lines, we investigated the role of the WNT pathway in ASM remodeling. Our approach was twofold: first, to establish which WNT ligands are expressed in ASM and determine their ability to induce a mitogenic response and second, to characterize the potential mechanisms of action. An initial screen for all known WNT ligands showed WNT-5A, WNT-5B and WNT-16 to be strongly expressed in serum-deprived ASM cells, while displaying an additional increase after stimulation with platelet derived growth factor (PDGF) or fetal bovine serum (FBS). The increase in gene expression appeared to be concentration-dependent. Interestingly, recombinant WNT-5A exhibited a strong mitogenic effect on ASM cells, using [3H]thymidine incorporation and Alamar blue conversion assays, whereas WNT-5B and WNT-16 had no effect. Moreover, WNT-5A knockdown attenuated PDGF induced proliferation. A subsequent microarray study confirmed the modulatory role of WNT-5A, highlighting a wide subset of genes involved in cell-cycle progression and proliferation. Together, these findings underline a previously unidentified role for WNT-5A in the regulation of airway smooth muscle proliferation in vitro.