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Wnt 11 inhibits the effects of transforming growth factor- β 1 (TGF- β 1) on lung epithelial phenotype

Background

Transforming Growth Factor- β 1 (TGF β 1) induces epithelial-to-mesenchymal transition (EMT) in alveolar type 2 (ATII) cells in vitro. This process is implicated in the pathogenesis of Idiopathic Pulmonary Fibrosis (IPF). SMADs are transcription factors activated by TGF β 1 signalling. When the TGF β 1 signalling pathway is activated, SMAD translocates from the cytoplasm to the nucleus. Wnt11 is a conserved glycoprotein secreted by macrophages and some ATII cells in the adult lung. Wnts bind to Frizzled (Fz) receptors. Previous work has shown that Wnt11 appears to inhibit both spontaneous and TGF β 1-driven EMT in ATII cell cultures.

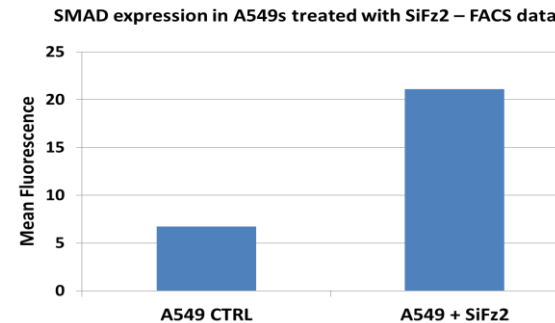
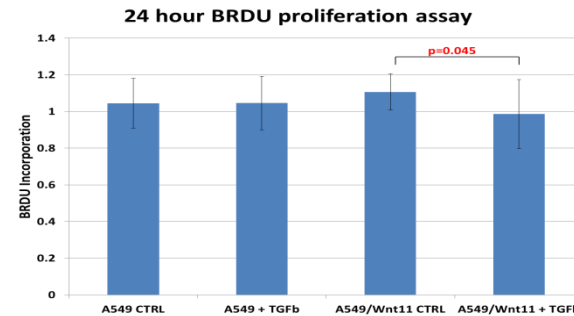
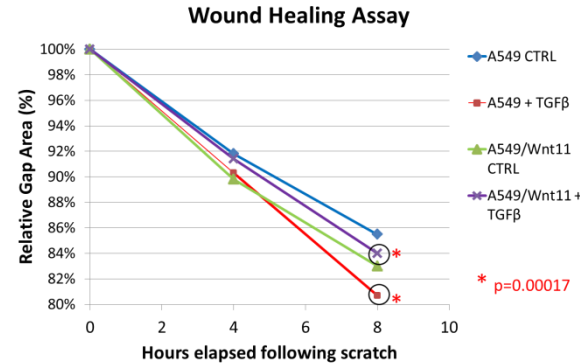
Aims: To investigate the role of Wnt11 – Frizzled receptor signalling on EMT in human ATII cells

Results

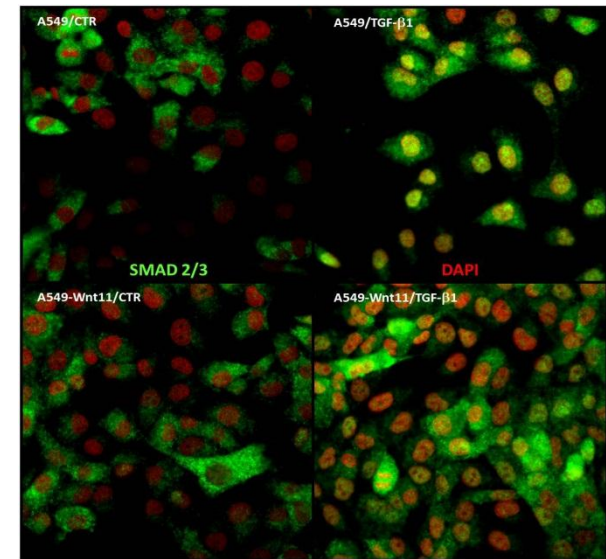
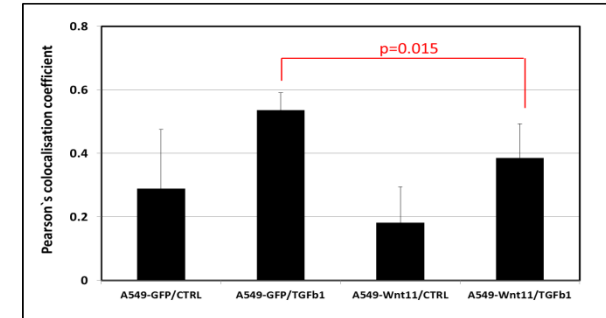
Wnt11 inhibits expression of mesenchymal markers & promotes expression of epithelial markers in cells treated with TGF β 1 (data not shown). Wnt11 inhibits TGF β 1-mediated migration of A549s and promotes A549 proliferation. Silencing Fz2 leads to increased expression of SMAD. Wnt11 inhibits SMAD nuclear translocation.

Methods

A549 cancer cell lines were used as a model for type II alveolar cells. We used 2 types of transgenic A549 cells, created by infecting cells with lentivirus vectors A549 cells which stably express Wnt11 and GFP A549 cells which stable express GFP alone (used as control). A549s were treated with 10ng/ml TGF β 1 for 24 hours. siRNAs targeted against mRNA coding for frizzled receptors were used to create a temporary “knockdown” effect. Epithelial and mesenchymal marker expression was assessed using RT-qPCR and FACS. BrdU proliferation assays & wound healing assays. Confocal microscopy was used to observe intracellular SMAD distribution.



SMAD2/3 nuclear localisation in A549 cells



Conclusions

The Wnt11-Fz2 and TGF β -SMAD signalling pathways appear to be antagonistic, with the Wnt11 pathway opposing TGF β -mediated EMT. Future therapies directed at promoting the Wnt11 may potentially be used in IPF.