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Title: Interdependence of endothelin-1 and transforming growth factor-β_1 on Wnt3a expression in idiopathic pulmonary fibrosis

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Body: Introduction: The Wnt signaling pathways may be involved in the development of idiopathic pulmonary fibrosis (IPF). Wnt has been demonstrated to down-regulate the expression of CCAAT enhancer-binding protein α (C/EBPα), and the pro-fibrotic cytokines transforming growth factor-β (TGF-β) and endothelin-1 (ET-1) are controlled by Wnt3a signaling. Aim: To study the effect of TGF-β and ET-1 on ECM production and Wnt expression in primary human IPF fibroblasts. Methods: Fibroblasts were isolated from IPF lungs (n=4) and from non-fibrotic controls (n=4). After stimulation with TGF- β_1 and/or ET-1, ECM was measured by ELISA. Total protein was harvested and immuno blot analysis was performed. Results: TGF-β (0.5 – 10 ng/ml) dose dependently increased total ECM deposition by 180%. ET-1 alone (0.5 – 10 ng/ml) had no effect on ECM. When combined, ET-1 super-induced the TGF-β-effect in a synergistic manner. Expression of Wnt3a was up-regulated by TGF-β in IPF fibroblasts whereas no effect was seen after ET-1 treatment. When ET-1 was added together with TGF-β, Wnt3a expression was further enhanced in comparison to TGF-β alone. Expression of Wnt3a was weak in control fibroblasts, and no induction by ET-1/TGF-β was observed. Expression of total C/EBPα in IPF fibroblasts was lower than in controls. Conclusions: In IPF fibroblasts, ET-1 exerted its pro-fibrotic effect only in the presence of TGF-β, and a similar interconnection was observed for the up-regulation of Wnt3a expression. This suggests a disease-specific and interdependent pro-fibrotic effect of ET-1 and TGF-β, which might be mediated via the up-regulation of Wnt3a and the down-regulation of the C/EBPα.