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Title: PBI-compound, a novel first-in-class anti-fibrotic compound, inhibits CTGF and collagen production in murine and human fibroblasts, and reduces lung fibrosis in the bleomycin-induced lung fibrosis model

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Body: Background: Interstitial fibroblasts are the principal effector cells of organ fibrosis. Transforming growth factor (TGF)-β-stimulated fibroblasts secrete connective tissue growth factor (CTGF) that functions as a downstream mediator of TGF-β action on fibroblastic cell types, and are important in collagen production. Aims: To investigate the effect of PBI-Compound on CTGF and collagen production in TGF-β-stimulated murine (NIH/3T3), and human fibroblasts (normal human dermal fibroblasts, NHDF). Methods: The effect of PBI-Compound on CTGF and collagen mRNA expression was investigated on TGF-β stimulated NHDF and NIH/3T3 fibroblasts. Results: In both cell types, TGF-β induced a robust increase of CTGF (10 to 25 fold increase) and collagen I (2 fold increase). In TGF-β-stimulated NHDF, PBI-Compound reduced CTGF and collagen I by 80% and 30%, respectively. Modulation of mRNA expression was also translated at the protein level, as TGF-β-induced CTGF production was significantly inhibited by PBI-Compound in NHDF. In NIH/3T3 fibroblasts, TGF-β-induced CTGF mRNA overexpression was also significantly reduced by PBI-Compound. These results correlate with in vivo inhibition of CTGF and collagen I mRNA expression observed in bleomycin-induced pulmonary fibrosis. Oral administration of PBI-Compound significantly decreased the overexpression of CTGF (60%) and collagen I (40%) mRNA expression in the lung. Conclusions: PBI-Compound acts on fibroblasts as observed by an inhibition of CTGF and collagen I mRNA expression and this is translated by a significant reduction of lung fibrosis.