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Title: Roflumilast-N-oxide exerts anti-remodelling potencies in COPD patients in vitro

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Body: COPD is characterised by progressive airway remodelling and peribronchiolar fibrosis. The origin of pathologic remodelling in COPD is unknown and may result from local hypoxia and increased growth factor expression, including transforming growth factor-beta (TGF-β). TGF-β increases the synthesis of collagen1A1, connective tissue growth factor (CTGF), alpha smooth muscle actin (SMA). This study explores whether the phosphodiesterase-4 (PDE4) inhibitor roflumilast N-oxide (RNO), the active metabolite of roflumilast in use for severe COPD modifies TGF-β induced ECM composition. Methods: Lung fibroblasts from patients with COPD (GOLD II-III) (n=3) were isolated and cultured using standard protocols. Cells were preincubated with RNO (1µM), Budesonide (BUD, 100nM), or vehicle (0.1% DMSO) and stimulated with TGF-β (1 or 2ng/ml) for 24 hours. CTGF, Collagen (Col) 1A1, and SMA mRNA expression were measured by quantitative RT-PCR (18S mRNA served as reference gene) and results were depicted as relative expression. Results: In COPD lung fibroblasts, TGF-β induced CTGF (1.2 fold/ SD±0.19/ p=0.0069), Col1A1 (1.51/±0.41/p=0.003) and SMA (1.6/±0.15/p=0.0028) significantly, key modulators of extracellular matrix composition in vitro. The addition of RNO significantly reversed this induction after 24 hours for all parameters (CTGF:-21%, Col1A1:-23%, α-SMA:-30%), whereas BUD did not exert such an inhibitory effect for SMA and CTGF. Conclusion: Roflumilast N-oxide diminished TGF-β-induced gene transcription of different markers of remodelling (Col1A1, SMA, CTGF) in isolated human primary fibroblasts of COPD patients. These findings may support the notion of roflumilast N-oxide mitigating a fibrotic response in COPD.