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Increased FGF1-FGFRc expression in idiopathic pulmonary fibrosis

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Abstract

© 2015 MacKenzie et al. Background: Recent clinical studies show that tyrosine kinase inhibitors slow the rate of lung function decline and decrease the number of acute exacerbations in patients with Idiopathic Pulmonary Fibrosis (IPF). However, in the murine bleomycin model of fibrosis, not all tyrosine kinase signaling is detrimental. Exogenous ligands Fibroblast Growth Factor (FGF) 7 and 10 improve murine lung repair and increase survival after injury via tyrosine kinase FGF receptor 2b-signaling. Therefore, the level and location of FGF/FGFR expression as well as the exogenous effect of the most highly expressed FGFR2b ligand, FGF1, was analyzed on human lung fibroblasts. Methods: FGF ligand and receptor expression was evaluated in donor and IPF whole lung homogenates using western blotting and qPCR. Immunohistochemistry for FGF1 and FGFR1/2/3/4 were performed on human lung tissue. Lastly, the effects of FGF1, a potent, multi-FGFR ligand, were studied on primary cultures of IPF and non-IPF donor fibroblasts. Western blots for pro-fibrotic markers, proliferation, FACS for apoptosis, transwell assays and MetaMorph analyses on cell cultures were performed. Results: Whole lung homogenate analyses revealed decreased FGFR b-isoform expression, and an increase in FGFR c-isoform expression. Of the FGFR2b-ligands, FGF1 was the most significantly increased in IPF patients; downstream targets of FGF-signaling, p-ERK1/2 and p-AKT were also increased. Immunohistochemistry revealed FGF1 co-localization within basal cell sheets, myofibroblast foci, and Surfactant protein-C positive alveolar epithelial type-II cells as well as co-localization with FGFR1, FGFR2, FGFR3, FGFR4 and myofibroblasts expressing the migratory marker Fascin. Both alone and in the presence of heparin, FGF1 led to increased MAPK-signaling in primary lung fibroblasts. While smooth muscle actin was unchanged, heparin + FGF1 decreased collagen production in IPF fibroblasts. In addition, FGF1 + heparin increased apoptosis and cell migration. The FGFR inhibitor (PD173074) attenuated these effects. Conclusions: Strong expression of FGF1/FGFRs in pathogenic regions of IPF suggest that aberrant FGF1-FGFR signaling is increased in IPF patients and may contribute to the pathogenesis of lung fibrosis by supporting fibroblast migration and increased MAPK-signaling.

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