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Title: PI3K p110γ is overexpressed in IPF lung tissue and fibroblast cells. In vitro effects of its inhibition

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Body: Molecular pathogenesis of Idiopathic Pulmonary Fibrosis (IPF) remains unclear. We recently demonstrated a key role for the PI3K pathway in both proliferation and differentiation into myofibroblasts of lung fibroblasts treated with TGF-β. In this research we assessed the expression of Class I PI3K p110 isoforms in IPF lung tissue and tissue derived fibroblast cell lines. Moreover, we investigated the in vitro effects of the selective inhibition of p110 isoforms on IPF fibroblast proliferation and fibrogenic activity. To evaluate expression levels of PI3K p110 isoforms, IHC as well as Western blot and Flow Cytometry analysis were performed on normal and IPF lung tissue/fibroblasts. The in vitro effects of selective pharmacological inhibition as well as specific gene silencing by siRNAs were studied in fibroblast cell lines established from both normal and IPF tissues. No significant differences between normal and IPF tissue/cells were observed for the expression of PI3K p110 α, β and δ isoforms whereas p110γ resulted overexpressed in both IPF lung homogenates and ex-vivo fibroblast cell lines. The IHC results show a strong immunoreactivity for p110γ in myofibroblasts of IPF lungs. Moreover, in pathologic bronchiolar structures of IPF lungs, basal cells exhibited a pronounced nuclear expression of p110γ which was hardly detectable in normal lung tissues. Furthermore, as a consequence of both p110γ pharmacological inhibition and gene silencing, a significant inhibition of proliferation rate and α-SMA expression were observed in IPF fibroblasts whereas no effects were found on normal cells. Our data indicates that PI3K p110 γ isoform can be a novel pharmacological target.