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PHOSPHOLIPASE D INHIBITION MITIGATES PULMONARY FIBROSIS BY ATTENUATING BRONCHIAL EPITHELIAL CELL MITOCHONDRIAL DNA DAMAGE AND APOPTOSIS

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Idiopathic pulmonary fibrosis (IPF) is a pernicious lung disease characterized by alveolar epithelial apoptosis, dysregulated repair of epithelial injury, scar formation and respiratory failure. Currently there are only two FDA approved drugs for IPF; which do not cure the disease, but just slow the progression of disease, there is a need to identify new therapeutic targets for the disease. Phospholipase D (PLD), an important lipid mediator involved in several pathophysiologies, catalyzes the hydrolysis of phosphatidylcholine, generating phosphatidic acid (PA) and choline. PLD mediated PA generation is involved in regulation of various cellular processes including cell survival, cell migration, cell proliferation, differentiation, cytoskeletal changes, membrane trafficking, and autophagy. In this study, we have identified phospholipase D (PLD) generated phosphatidic acid (PA) signalling in the development of pulmonary fibrosis (PF). Phospholipase D (PLD), an important lipid mediator involved in several pathophysiologies, catalyses the hydrolysis of phosphatidylcholine, generating phosphatidic acid (PA) and choline. Of the PLD isoenzymes, the protein expression of PLD2, but not PLD1, was up-regulated in lung tissues from IPF patients and bleomycin challenged mice. Both PLD2 ($Pld2^{-/-}$) and PLD1 ($Pld1^{-/-}$) deficient mice were protected against bleomycin induced lung inflammation and fibrosis, thereby establishing the role of PLD in fibrogenesis. To further understand how PLD mediates epithelial injury during PF, challenging of bronchial airway epithelial cells (Beas2B) with bleomycin stimulated PLD activity and PLD2 expression in the cells. Further, inhibition of PLD2 with VU0364739 attenuated bleomycin-induced mitochondrial (mt) superoxide production and mtDNA damage that leads to apoptosis in Beas2B cells. These results support a critical role for PLD2 signalling in promoting pulmonary fibrosis in humans and mice. We reason that PLD2 may be a novel therapeutic target in mitigating IPF.

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