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Chemical Activation of Protein Phosphatase 2A Counters TGFβ-Dependent Induction of Extracellular Matrix Proteins in Fibroblasts

Introduction: The activity of protein phosphatase 2A(PP2A), a serine-threonine phosphatase, is reported to be reduced in lung fibroblasts of IPF patients. Our group recently demonstrated that chemical activation of PP2A reduces loss of lung function in a cigarette smoke model of COPD. Here we present data on a small molecule activator of PP2A, ATUX-792, with enhanced bioavailability in an in vitro fibroblast model. The objective was to confirm that PP2A activity is lower in fibroblasts of IPF patients, and determine whether reactivation of PP2A in fibroblasts would counter TGFβ-dependent expression of several extracellular matrix proteins.

Methods: PP2A activity assays were undertaken with protein collected from fibroblasts that were isolated from healthy and IPF subjects. Fibroblasts were exposed to several concentrations of ATUX-792, a novel tricyclic-sulfonamide compound with improved metabolic stability and oral bioavailability, to determine non-toxic concentrations. Fibroblasts were exposed to ATUX-792 and PP2A activity and the expression of smooth muscle cell actin (ACTA2), collagen genes (COL1A1, COL1A2, and COL3A1), and fibronectin (FN1) were analyzed.

Results: PP2A activity is significantly reduced in the fibroblasts isolated from the IPF subjects. Treatment with 1 μM ATUX-792 restored PP2A activity levels in the fibroblasts isolated from the IPF subjects. Cells treated with ATUX-792 also had reduced phosphorylation of ERK and JNK; kinases that are sensitive to PP2A activity. Pre-treatment of fibroblasts with ATUX-792 reduced TGFβ-induced expression of ACTA2, FN1, COL1A1, and COL3A1.

Conclusions: Our study indicates that the decrease in PP2A activity, which occurs in fibroblasts from the lungs of IPF subjects, could be restored with ATUX-792 administration. Restoration of lung PP2A activity represents a feasible therapeutic approach to counter the excessive extracellular matrix protein production observed in IPF, and potentially other fibrotic diseases.