

Session/Poster#

Presenter

B07

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Protein Phosphatase 2A Reactivation Prevents Bleomycin-Induced Fibrosis in Mice

The activity of protein phosphatase 2A (PP2A), a serine-threonine phosphatase, is reduced in the lung fibroblasts of idiopathic pulmonary fibrosis (IPF) patients. Our group recently demonstrated that chemical activation of PP2A reduces loss of lung function in a cigarette smoke model of chronic obstructive pulmonary disease (COPD). Here we present data on a new PP2A activator, a diarylmethyl-pyran-sulfonamide compound (ATUX-1215). ATUX-1215 has improved metabolic stability and bioavailability versus earlier types used in our COPD models. The objective was to determine whether reactivation of PP2A could counter TGF β ²-signaling and preserve pulmonary function.

Primary human lung fibroblasts were exposed to ATUX-1215 in combination with TGF β ². C57BL/6J mice were administered 5mg/kg ATUX-1215 daily following intratracheal delivery of bleomycin. 3-weeks later, forced oscillation and expiratory measurements were recorded in each animal using the Scireq Flexivent System.

PP2A activity was enhanced with ATUX-1215 in vitro and in vivo. Cells treated with ATUX-1215 had reduced phosphorylation of ERK and JNK; kinases that are sensitive to PP2A activity. Pre-treatment of fibroblasts with ATUX-1215 reduced TGF β ²-induced expression of ACTA2, FN1, COL1A1, and COL3A1. In vivo, ATUX-1215 prevented bleomycin-induced PV loop changes, compliance, tissue elastance, and forced vital capacity. Early ATUX-1215 treatment prevented establishment of collagen deposition with reduced trichrome positive lung tissues observed in these mice. ATUX-1215 also prevented bleomycin-induction of Acta2, Ccn2, Col1a1, and Fn1. Finally, treatment with ATUX-1215 reduced phosphorylation of ERK, p38, JNK, and Akt in bleomycin treated animals.

Our study indicates that the decrease in PP2A activity, which occurs in fibroblasts from the lungs of IPF subjects, could be restored with ATUX-1215 administration. Restoration of lung PP2A activity represents a feasible therapeutic approach to counter fibrotic diseases.