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CIP2A-Mediated Activation of Akt and SMAD3 Pathways Drives Pulmonary Fibrosis: Restoring PP2A Activity as a Therapeutic Strategy

Objectives:
This study examined whether a PP2A activator (PA) reduces fibrosis progression and preserves lung function in a bleomycin (BLM) mouse model. We also investigated how CIP2A regulates fibrotic responses in lung fibroblasts.
Materials and Methods:
A diarylmethyl-pyran-sulfonamide PA was tested in primary human lung fibroblasts exposed to TGFβ or BLM. C57BL/6J mice received daily PA for 2 weeks, starting 8 days after intratracheal BLM instillation. CIP2A was overexpressed in fibroblasts using lentiviral technology. Pathway inhibitors targeting Akt (MK-2206), ERK (SCH772984), and SMAD3 (SIS3) were used to assess CIP2A-driven fibrotic signaling.
Results and Discussion:
PA-treated fibroblasts and mice showed enhanced PP2A activity and reduced α-smooth muscle actin (α-SMC actin) and fibronectin expression. PA administration also mitigated BLM-induced lung physiological and histological changes associated with fibrosis. CIP2A overexpression (CIP2A OE) significantly upregulated COL1A1 and CTHRC1 at both mRNA and protein levels. Akt and ERK inhibition markedly reduced CIP2A-driven COL1A1 and CTHRC1 expression, whereas SMAD3 inhibition had a lesser effect. PCR, Western blot, and densitometry confirmed CIP2A OE increased COL1A1 and CTHRC1 protein levels, which were significantly reduced by Akt and SMAD3 inhibition, respectively. CIP2A suppression correlated with p21 upregulation in lung fibroblasts, but PA treatment did not suppress BLM-induced p21 indicating the regulation of p21 by CIP2A is independent of PP2A.
Conclusions:
PA administration appears to restore PP2A activity and preserve lung function in experimental models of IPF. CIP2A negatively regulates PP2A activity while promoting COL1A1 and CTHRC1 expression via Akt and SMAD3 signaling. Targeting CIP2A-mediated pathways may offer novel therapeutic strategies for IPF.