Suberanilohydroxamic Acid (SAHA) Inhibits Collagen deposition in a Transforming Growth Factor β1-driven Precision Cut Lung Slice (PCLS) model of Pulmonary Fibrosis.

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Introduction and Objectives: Idiopathic Pulmonary Fibrosis (IPF) is a chronic, progressive interstitial lung disease that is refractory to current treatment options. Transforming growth factor (TGF)-β1 is a key pro-fibrotic cytokine that plays a crucial role in IPF pathogenesis. Our group previously demonstrated distinct epigenetic modifications involved in repression of the antifibrotic gene cyclooxygenase-2 (COX-2) in fibroblasts from IPF (F-IPF) lungs compared with fibroblasts from non-fibrotic lungs (F-NL). Epigenetic drugs capable of inhibiting DNA and histone modifications may, therefore, represent a putative novel therapy. The aim of this study was to investigate the ability of 4 epigenetic inhibitors to regulate TGF-β-driven fibrosis in ex vivo mouse lung.

Methods: A precision-cut lung slice (PCLS) model of fibrosis was established using the previously described [1] CC10-tTTS-rtTA-TGFB1 transgenic (tgTGF-β1) mouse. The model was first assessed by investigating PCLS overexpression of TGF-β1 in response to stimulation of the transgene by doxycycline treatment. Gene expression of COX-2 and fibrotic markers including collagen were assessed after 4 days of treatment. The anti-fibrotic potential of 4 epigenetic inhibitors; BIX01294 (BIX, inhibitor of G9a histone methyltransferase), 3-deazaneplanocin A (DZNep, inhibitor of EZH2 histone methyltransferase), SAHA (inhibitor of histone deacetylases, HDACs) and Decitabine (DAC, DNA demethylating agent) was investigated. Viability of PCLS was assessed by MTT and Prestoblue® viability assay.

Results: Treatment of PCLS from tgTGF-β1 mice with doxycycline induced a concentration-dependent increase in global TGF-β1 pro-fibrotic markers including collagen and pro-inflammatory COX-2, which was comparable to recombinant TGF-β1 treatment. Treatment with three of the epigenetic inhibitors BIX01294, DZNep and DAC did not reduce the pro-fibrotic response following doxycycline treatment. However SAHA demonstrated a significant suppressive effect on COX-2 and collagen expression, while not directly affecting TGF-β1 transgene expression.

Conclusions: The data suggests that SAHA has the potential to reduce fibrosis in a TGF-β1 driven model of pulmonary fibrosis. Further work is currently underway to assess the anti-fibrotic potential of this drug in tgTGF-β1 animals.

Reference