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| **AT2R agonist Compound 21 inhibits *ex vivo* IPF fibrogenesis in human precision cut lung slices** |
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| **Introduction/Aim:** Idiopathic pulmonary fibrosis (IPF) is an incurable lung disease with current treatments unable to reverse established fibrosis. The angiotensin type 2 receptor (AT2R) agonist Compound 21 (C21) abrogates pulmonary fibrosis in a bleomycin mouse model (Rathinasabapathy et al. Front Physiol, 9[180] 2018) and is currently being trialled in IPF patients. The aim of the current study was to determine the potential antifibrotic effects of C21 in human precision cut lung slices (hPCLS).  **Methods:** Matched hPCLS prepared from agarose-inflated resection specimens or unused donor lungs were left untreated or stimulated with fibrotic cocktail (FC = TGFβ1, TNFα, LPA, PDGF) ± C21 (10µM) or pirfenidone (500µM) for 120h. *In situ* fibrosis was assessed by Masson's trichrome staining. hPCLS-conditioned media was collected at 48h and 120h to measure secreted procollagen 1α1 and fibronectin by ELISA, and MMP-2 and -9 activity via gelatin zymography.  **Results:** Therewas no difference in collagen deposition in FC-treated hPCLS compared to matched vehicle-treated hPCLS (% collagen area: vehicle 4.0 ± 1.0%; FC 5.0 ± 0.8, n=18 patient samples). However, FC induced an 8-fold increase in secreted procollagen 1α1 (ng/mL: vehicle 23.0 ± 11.1; FC 179.2 ± 48.03, n=13, p<0.01, paired t-test) and a 3-fold increase in fibronectin (ng/mL: vehicle 1412.0 ± 338.3 ; FC 4041.0 ± 446.3, n=8, p<0.001, paired t-test). C21, but not pirfenidone, significantly reduced secretion of procollagen 1α1 and fibronectin by 79.5 and 54.3% respectively (p<0.05, one-way ANOVA, n=13 and 8). FC significantly increased total MMP-2- and -9 activity at 120h, with a significant reduction in MMP-9, and a trend to decreased MMP-2, evoked by C21 only.  **Conclusion:** Fibrogenesis can be modelled *ex vivo* as increased procollagen 1α1 and fibronectin secretion fromhuman PCLS using a cocktail of IPF-relevant mediators. C21, at a 50-fold lower concentration than pirfenidone, significantly reduced fibrogenic markers in hPCLS. A mismatch between deposited collagen and secreted collagen may be explained by the significant FC-induced increase in MMP-2 and -9 activity in this model.  **Grant Support:** RTP scholarship and David Wilson PhD scholarship (LFA) |