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| **AT2R agonist Compound 21 inhibits *ex vivo* IPF fibrogenesis in human precision cut lung slices**  |
| Young ON1, Papagianis PC1, Richards EA1, Chen Y2, Bardin PG2,3, Jaffar J4, Westall GP4, Widdop RE1, Bourke JE1 |
| 1Pharmacology, Monash University, Melbourne, Australia2Monash Lung and Sleep, Monash Medical Centre, Clayton, Australia3Centre for Innate Immunity and Infectious Diseases, Hudson Institute of Medical Research, Clayton, Australia4Allergy, Immunology and Respiratory Medicine, Alfred Hospital, Prahran, Australia |
| **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)  |