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EUROPEAN RESPIRATORY SOCIETY
INTERNATIONAL CONGRESS 2023
MILAN Italy, 9-13 September

The senolytic effect of Dasatinib and Quercetin on cellular senescence in COPD in vitro and in vivo models

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Background: COPD is a disease of accelerated ageing, with elevated number of senescent cells within the lung. Senescent cells may prevent lung repair and drive chronic lung inflammation. Dasatinib and Quercetin (D+Q) is a senolytics combination which removes senescent cells but has not been studied in COPD.

Aim: Examine the effects of D+Q on COPD airway epithelium and in a cigarette smoke mouse model.

Methods: Senescence markers p16 and/or p21 were detected in air-liquid interface (ALI) airway epithelium from non-smokers (NS) and COPD and the lungs from cigarette smoke exposed mice by western blot. Cytokine profile was analysed by O-Link proteomics.

Results: COPD ALIs displayed significantly higher levels of p16 (n=5), whereas p21 was unchanged compared to NS. COPD ALIs treated with D (200nM) +Q (50 µM) for 24h showed a significant reduction in p16, and reduced release of CXCL8 (p<0.05). O-Link proteomics showed significant reductions in MMP-2, IL-33, CCL3 and IL-15RA by D+Q. Cigarette smoke exposed mice had significantly increased p16 and p21 compared to air exposed mice and this was significantly decreased by D (5 mg/kg) + Q (50 mg/kg) treatment for 3 days post exposure (n=6 per group) (p<0.01). Significantly elevated numbers of macrophages and neutrophils in bronchoalveolar lavage fluid induced by cigarette smoke were reduced in D+Q treated mice, along with the chemokine KC (p<0.01).

Conclusion: Our data suggest that senolytic D+Q can reduce senescent cells within COPD epithelium and in cigarette exposure mouse model. More work is needed to understand the consequences of removing senescent cells from the lung but suggest these as a possible therapeutic target.
