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Effects of Telaglenastat, a glutaminase inhibitor, on airway inflammation and cellular senescence in Cigarette-smoke exposed mice

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Background: COPD is characterized by pulmonary inflammation and accelerated lung aging, where elevated number of senescent cells are observed. Senescent cells may prevent lung repair and drive chronic lung inflammation. Telaglenastat, a non-competitive glutaminase inhibitor, is recently reported as a senolytic agent which removes senescent cells (Johmura et al., Science, 2021).

Aim: Examine the therapeutic effects of Talaglenastat on airway inflammation and cellular senescence in the lung of cigarette smoke (CS) exposed mice.

Methods: A/J mice were exposed to CS for 11 days and Telaglenastat (5mg/mL) was administered intra-nasally once daily for 3 days after the last CS exposure. Macrophages and neutrophils in BALF were quantified by FACS analysis. CXCL1 and IL-6 in BALF were also determined by ELISA. p21Waf1 expression, as a senescence marker, was determined in the lung homogenates by western blotting.

Results: The expression of glutaminase and p21 were increased in the lung tissue post CS exposure as well as the number of inflammatory cells and CXCL1/IL-6 in BALF compared with air exposed controls. Telaglenastat significantly inhibited accumulation of alveolar macrophages and neutrophils and elevated CXCL1/IL-6 in the BALF (n=5 per group) ($p<0.01$). It also significantly reduced p21 protein expression in lung homogenates ($p<0.01$).

Conclusion: Telaglenastat displayed significant anti-inflammatory and senolytic activities by a short course therapeutic treatment in CS exposed mice. This profile suggests that Telaglenastat offers the potential therapeutic treatment for patients with COPD.