The role of the inflammasome in cigarette smoke-induced inflammation

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Chronic Obstructive Pulmonary Disease (COPD) is a treatment resistant, cigarette smoke (CS)-driven inflammatory airways disease with increasing global prevalence. Understanding the mechanism by which CS leads to the inflammation would be a major step forward in the development of effective medication. Recently it has been shown that the production of cytokines (IL-1β and IL-18) linked to a protein complex called the NALP3 inflammasome are increased in animal models of COPD and patients with the disease. Furthermore, an activator of the inflammasome, ATP (through activation of the P2X7 receptor), has also been found to be increased in diseased samples. We hypothesise that CS leads to the release of mediators (e.g. ATP) which agonise the P2X7 receptors which then activates the inflammasome and caspase-1 causing the subsequent release of inflammatory cytokines. These cytokines then play a central role in the inflammation and subsequent pathogenesis of COPD.

We have shown in a pre-clinical murine model that CS-induced neutrophilia is temporally associated with markers of inflammasome activation, (increased caspase 1 activity and release of IL-1β/IL-18) in the lungs. To confirm a role for the P2X7/Inflammasome pathway in the murine model, we utilized mice genetically modified so that the P2X7 channels were non-functional and a selective P2X7 receptor antagonist. Compared to wild type (WT) mice the P2X7 -/- mice had less caspase-1 activation and IL-1β production in the lung after CS exposure. This was associated with a significant decrease in airway neutrophilia (WT 37.5 ± 8.7 x 10³ vs P2X7 -/- 2.9 ± 1.1 x 10³ cells/ml; p<0.05). We confirmed this data with a selective P2X7 receptor antagonist. A 438079 (30-1000 mg kg⁻¹, p.o.) caused a dose-related inhibition of CS-induced airway neutrophilia (Vehicle: 55.9 ± 10.2 x 10³; Compound 1000 mg kg⁻¹: 13.8 ± 3.2 x 10³ cells/ml; p<0.05).

Furthermore, we demonstrated that the role of this pathway was not restricted to early stages of disease development by showing increased caspase-1 activation in lungs from a chronic model (up to 28 days of CS exposure) and from patients with COPD compared to smokers without COPD and healthy tissue obtained from lung transplantation programme. This translational data suggests the P2X7/Inflammasome pathway plays an ongoing role in disease pathogenesis.

In conclusion, these results advocate the critical role of the P2X7/Inflammasome axis in CS-induced inflammation, highlighting it as a possible therapeutic target for the treatment of COPD.