

PPAR γ and the Inflammatory Response to Ozone-Induced Lung Injury in Mice

Callum Malcolm, Cody Smith, Debra Laskin

University of Aberdeen and Rutgers, The State University of New Jersey

Ozone, an urban air pollutant, is a highly reactive toxic gas that causes tissue damage and inflammation in the lung. Long term exposure is linked to various health complications and increased mortality due to respiratory diseases. The inflammatory response to ozone is regulated by distinct populations of macrophages, which consist of M1/pro-inflammatory and M2/anti-inflammatory subsets which are involved in the acute response to injury and long term resolution of tissue damage, respectively. Previous studies from our laboratory demonstrated that exposure of mice to ozone caused significant downregulation of Pparg, a transcription factor important in anti-inflammatory signaling in macrophages, phagocytosis of apoptotic neutrophils (efferocytosis), and the resolution of inflammation. We hypothesized that pharmacological agonists of PPAR γ activity would reduce ozone-induced lung injury and change macrophage phenotype. Female C57BL/6J mice were exposed to air or ozone (0.8 ppm, 3 hr) and treated with an intraperitoneal injection of vehicle control or rosiglitazone, a PPAR γ agonist, daily beginning 24 hr prior to ozone exposure; mice were euthanized 24 hr, 48 hr, and 72 hr post ozone exposure. Bronchoalveolar lavage fluid (BAL) was collected and analyzed for total protein and IgM content, cell counts, and cell differentials. BAL was enriched for alveolar macrophages by gentle lung massage and isolated cells analyzed by flow cytometry and qPCR. Ozone caused increases in total protein and IgM content consistent with lung injury. In rosiglitazone-treated animals, there was a trend towards reduced BAL protein levels at 48 hr suggesting accelerated injury resolution. Flow cytometry analysis showed increases in both pro- and anti-inflammatory macrophages in lungs of ozone-exposed animals throughout the time-course; a trend towards reduced numbers of these cells was observed in rosiglitazone-treated animals at 72 hr. These results were consistent with reduced mRNA expression of pro- and anti-inflammatory markers Ptgs2 and Arg1, respectively. Conversely, mRNA expression of Cd36, a downstream target of PPAR γ , was not significantly altered in rosiglitazone-exposed animals, relative to control. Collectively, these results suggest that PPAR γ may regulate cellular signaling mechanisms in macrophages, however, a more targeted strategy may be necessary to probe a role for PPAR γ in regulating their phenotype.

