PPARgamma Regulates the Inflammatory Response to Ozone-Induced Lung Injury in Mice

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Ozone is an urban air pollutant that is highly reactive causing 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; these cells 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 PPARγ, a transcription factor important in anti-inflammatory signaling in macrophages, phagocytosis of apoptotic neutrophils (efferocytosis), and the resolution of inflammation. We hypothesized that administration of a pharmacological agonist of PPARγ would reduce ozone-induced lung injury by altering macrophage phenotype. Female C57BL/6J mice were exposed to air or ozone (0.8 ppm, 3 hr) and treated with vehicle control or rosiglitazone, a PPARγ agonist, daily via intraperitoneal injection beginning 24 hr prior to ozone exposure; mice were euthanized 24, 48, and 72 hr post ozone. Bronchoalveolar lavage fluid (BAL) was collected and analyzed for total protein and phospholipid content. 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 phospholipid content, consistent with lung injury. In rosiglitazone-treated animals, there was a trend towards reduced BAL protein levels at 48 hr and significant reduction in phospholipid content at 72 hr, suggesting accelerated injury resolution. Flow cytometric analysis showed increases in both pro- and anti-inflammatory macrophages in the 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, at 72 hr. mRNA expression of Caveolin 1, a downstream target of PPARγ involved in lipid catabolism, was reduced in response to ozone but maintained in rosiglitazone-treated animals. Collectively, these results suggest that PPARγ may modulate ozone-induced lung injury by regulating inflammatory signaling and lipid metabolism in alveolar macrophages. *Supported by NIH Grants ES004738, ES005022, ES029254, ES007148, ES030984.*