Role of PPARγ in the Resolution of Ozone-Induced Lung Injury

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Ozone is a ubiquitous urban air pollutant that causes airway inflammation and hyperresponsiveness in both healthy and susceptible populations. Macrophages play a role in ozone-induced lung injury by regulating the acute initiation and later resolution phases of the inflammatory response. The distinct activities of macrophages are mediated by subpopulations broadly classified as M1/pro-inflammatory and M2/anti-inflammatory that sequentially accumulate in injured tissues. RNA-seq analysis of alveolar macrophages revealed that exposure of mice to ozone resulted in alterations in inflammatory and lipid metabolism pathways, and down-regulation of PPARγ, a nuclear transcription factor important in M2 macrophage activation, inflammation resolution, and tissue repair. We hypothesized that administration of a PPARγ agonist would reduce ozone-induced lung injury by regulating macrophage activity and tissue repair. Female C57BL/6J mice were treated with rosiglitazone or vehicle control by daily intraperitoneal injection beginning 24 hr prior to exposure to ozone (0.8 ppm, 3 hr) or air. 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 in BAL, consistent with lung injury. Rosiglitazone treatment resulted in decreases in BAL protein levels at 48 hr and phospholipid content at 72 hr when compared to ozone-only exposed mice, suggesting accelerated injury resolution. Flow cytometric analysis showed increases in both M1 and M2 macrophages in lungs of ozone-exposed animals throughout the time-course; reduced numbers of these cells were observed in rosiglitazone-treated animals at 72 hr. These results were consistent with reduced mRNA expression of pro- and anti-inflammatory genes Ptgs2 and Arg1, respectively, in macrophages at 72 hr. mRNA expression of Caveolin 1, a downstream target of PPARγ involved in lipid catabolism, was reduced in macrophages in response to ozone but sustained in rosiglitazone-treated animals. Collectively, these results suggest that PPARγ accelerates the resolution of ozone-induced lung injury by regulating inflammatory signaling and lipid metabolism in alveolar macrophages. *Supported by NIH Grants ES004738, ES005022, ES029254, ES007148, HL086621, and ES030984.*