Deletion of Acyl-Coenzyme A Acyltransferase in Myeloid Cells Enhances Oxidative Stress And Dyslipidemia in the Lung Following Ozone Inhalation

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Exposure to ozone, an air pollutant known to cause oxidative stress, has been shown to alter lipid handling in the lung. Acyl-coenzyme A acyltransferase 1 (ACAT1) is responsible for esterification and sequestration of cholesterol and is a major isoenzyme present in alveolar macrophages. ACAT1 has been implicated in the formation of foam cells due to dysregulated lipid metabolism in macrophages. The role of ACAT1 in ozone (O3) toxicity is unknown. We hypothesized that loss of ACAT1 will reduce macrophage activation and injury. To test this, myeloid specific ACAT1 knockout mice (ACAT1-M/-M) and C57BL/6 wild type (WT) mice were exposed to filtered air or O3 (0.8 ppm) for 3 hours. Mice were euthanized 24 hours later and bronchoalveolar lavage (BAL) fluid and lung samples collected. Following exposure of ACAT -M/-M mice to O3, BAL protein levels significantly increased when compared to air exposed ACAT -M/-M mice. By comparison, there was a greater increase in protein in BAL of O3 exposed WT mice suggesting more robust epithelial leakage. BAL fluid from O3 exposed ACAT -M/-M mice also contained significantly higher levels of phospholipids relative to O3 exposed WT mice indicative of dyslipidemia. Loss of ACAT1 in myeloid cells was also correlated with a significantly increased expression of heme oxygenase-1 (HO-1) in lung macrophages indicating exaggerated oxidative stress. These data suggest activation of the Nrf2 pathway resulting in the up-regulation of HO-1 and potentially other anti-oxidants; further studies are in process to explore this possibility. Supported by NIH Grants R01ES004738 and P30ES005022.