Estrogen Receptor-Mediated Regulation of Macrophage Phenotype and Sex Differences in Ozone Toxicity

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Ground level ozone generated from the reaction of vehicle emissions with UV sunlight is a ubiquitous toxicant that causes respiratory toxicity in healthy and susceptible individuals. Alveolar macrophages contribute to respiratory problems associated with ozone exposure by regulating the acute and later pro-resolution phase of the inflammatory response to inhaled ozone. These diverse actions are mediated by M1/ pro-inflammatory and M2/ anti-inflammatory macrophages, respectively. Epidemiological studies suggest females are more vulnerable to respiratory complications derived from exposure to ozone compared to males and enhanced estrogen signaling in lung macrophages in females is suspected to contribute to toxicity by promoting pro-inflammatory activation. Estrogen signals by binding to and activating estrogen receptor alpha (ESR1) found in most cells including lung macrophages. The purpose of this study is to investigate mechanisms contributing to sex-based differences in ozone using transgenic mice deficient in estrogen signaling. We hypothesize that ESR1 contributes to enhanced ozone toxicity in females by promoting activation of M1/ pro-inflammatory macrophages due to increased levels of estrogen signaling. We will test this hypothesis by exposing ESR1 knockout and wild-type mice to ozone by whole-body inhalation. Flow cytometry and qPCR will be used to analyze macrophage phenotypes in bronchoalveolar lavage, while markers of lung injury and inflammation will be assessed in histological sections by immunohistochemistry. We expect that the ESR1 knockout mice will exhibit a decrease in M1/pro-inflammatory macrophages and lung injury compared to the wild-type mice suggesting ESR1 promotes proinflammatory macrophage phenotype. We expect that this will be associated with a decrease in markers of lung injury and inflammation. The importance of conducting this research is to fully understand the role that ESR1 plays in sex differences in ozone toxicity, and possibly help lay the groundwork for developing treatments to counter ozone-induced lung toxicity. Supported by NIH Grants ES004738, ES030984,ES020721, and the ASPET SURF Program.