Early life ozone exposure results in dysregulated innate immune function and altered microRNA expression in airway epithelium.

Abstract

Exposure to ozone has been associated with increased incidence of respiratory morbidity in humans; however the mechanism(s) behind the enhancement of susceptibility are unclear. We have previously reported that exposure to episodic ozone during postnatal development results in an attenuated peripheral blood cytokine response to lipopolysaccharide (LPS) that persists with maturity. As the lung is closely interfaced with the external environment, we hypothesized that the conducting airway epithelium of neonates may also be a target of immunomodulation by ozone. To test this hypothesis, we evaluated primary airway epithelial cell cultures derived from juvenile rhesus macaque monkeys with a prior history of episodic postnatal ozone exposure. Innate immune function was measured by expression of the proinflammatory cytokines IL-6 and IL-8 in primary cultures established following in vivo LPS challenge or, in response to in vitro LPS treatment. Postnatal ozone exposure resulted in significantly attenuated IL-6 mRNA and protein expression in primary cultures from juvenile animals; IL-8 mRNA was also significantly reduced. The effect of antecedent ozone exposure was modulated by in vivo LPS challenge, as primary cultures exhibited enhanced cytokine expression upon secondary in vitro LPS treatment. Assessment of potential IL-6-targeting microRNAs miR-149, miR-202, and miR-410 showed differential expression in primary cultures based upon animal exposure history. Functional assays revealed that miR-149 is capable of binding to the IL-6 3' UTR and decreasing IL-6 protein synthesis in airway epithelial cell lines. Cumulatively, our findings...
suggest that episodic ozone during early life contributes to the molecular programming of airway epithelium, such that memory from prior exposures is retained in the form of a dysregulated IL-6 and IL-8 response to LPS; differentially expressed microRNAs such as miR-149 may play a role in the persistent modulation of the epithelial innate immune response towards microbes in the mature lung.

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