

TOXICOLOGICAL HIGHLIGHT

Ozone-Induced Mucous Cell Metaplasia

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The article highlighted in this issue is "Endotoxin Enhancement of Ozone-Induced Mucous Cell Metaplasia Is Neutrophil-Dependent in Rat Nasal Epithelium," by James G. Wagner, Steven J. Van Dyken, Jon A. Hotchkiss, and Jack R. Harkema (pp. 338–347).

Ozone, a ubiquitous air pollutant in ambient air, is derived from photochemical reactions involving hydrocarbon vapors and nitrogen oxides. Epidemiological, clinical and experimental studies indicate that inhalation exposure to ozone causes a variety of usually reversible lung changes in the upper airways characterized by reduced pulmonary function, airway hypersecretion, epithelial cell damage and pulmonary inflammation (reviewed by Koren *et al.*, 1989; Lippmann, 1989). Since pulmonary symptoms occur at ozone levels frequently encountered in urban areas of the United States, considerable efforts have been undertaken to identify safe levels in human populations as well as specific mechanisms of action. Regarding mechanisms of action, the current consensus is that the initial adverse effects of ozone may be attributed to its direct oxidant damage of cellular lipids and proteins in pulmonary epithelial cells, particularly in the centriacinar region, followed by an inflammatory response. The exact role of the ensuing inflammatory response, which probably originates at the site of the epithelial damage and not the alveolar macrophage as once thought, is still unclear. Most likely the inflammatory response contributes predominantly to repair process following acute exposure and exacerbates damage following chronic or high-dose exposure. Deciphering the specific contributions of the direct chemical-cell event from the ensuing inflammatory response in the toxicological process is a daunting task, as exemplified by recent observations involving the complex pathology of Alzheimer's disease (reviewed by Akiyama *et al.*, 2000). In this case highly insoluble amyloid β peptide deposits and neurofibrillary tangles provide stimuli for a complex inflammatory process involving mediators such as complement, cytokines, and acute phase reactants; over time this signifi-

cantly exacerbates the very pathogenic process that gave rise to it.

Ongoing studies conducted in the laboratory of J. R. Harkema (see References section of the article by Wagner and colleagues in this issue of *Toxicological Sciences*, pp. 338–347), describing ozone-induced mucous cell metaplasia (MCM), serve to illustrate the complexity of the inflammatory response. Using various cellular and molecular techniques, they determined that the sequence of events leading to ozone-induced MCM includes cell damage, neutrophilic inflammation, epithelial necrosis and exfoliation, followed by epithelial cell proliferation and hyperplasia and finally the appearance of mucous cells. Furthermore, this response is promoted by airway endotoxin. In the study presented by Wagner and colleagues in this issue, the authors utilize endotoxin to promote ozone-induced MCM and have confirmed that neutrophilic inflammation is required to enhance MCM. This study also presents data confirming that the expression of mucin-specific genes occurs at a very early time-point following endotoxin exposure, and in the absence of neutrophils. This is an important observation as it suggests that two distinct signaling events are required for MCM; one signal induces gene expression, and the other is responsible for protein synthesis or release. What is the therapeutic implication if two responses, acting at different times, are required to act in concert to produce a product, particularly if one response results from a chemical-cell interaction (i.e., ozone-epithelium) and the other represents an inflammatory mediator?

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