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Effects of air pollutants on innate immunity: The role of Toll-like receptors and nucleotide-binding oligomerization domain–like receptors

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Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

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List of Design Committee Members: Rebecca N. Bauer, BA, David Diaz-Sanchez, PhD, and Ilona Jaspers, PhD

Activity Objectives

1. To demonstrate understanding of the involvement of Toll-like receptors (TLRs) in the inflammatory response to air pollutants.
2. To discuss the key hypotheses or models regarding activation of inflammasomes by air pollutants.

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Interactions between exposure to ambient air pollutants and respiratory pathogens have been shown to modify respiratory immune responses. Emerging data suggest key roles for Toll-like receptor (TLR) and nucleotide-binding oligomerization domain–like receptor (NLR) signaling in pathogen-induced immune responses. Similarly, immune responses elicited by exposure to air pollutants are mediated by specific TLR- and NLR-dependent mechanisms. This review article will summarize current knowledge about how air pollutants modify TLR- and NLR-dependent signaling and host defense responses in the lung. (J Allergy Clin Immunol 2012;129:14-24.)

Key words: *Toll-like receptor, NOD-like receptor, pattern recognition receptor, inflammasome, cigarette smoke, particulate matter, ozone, diesel exhaust, nanoparticles, air pollutant, innate immunity, host defense, pathogen-associated molecular pattern, danger-associated molecular pattern, lung, airway*

Since the 1970 ***Clean Air Act***, many cities have experienced dramatic improvements in air quality. Levels of large ***particulate matter*** (PM_{10}) have decreased by 83% in this period, even though there has been an increase of 178% in the number of vehicle miles traveled.[1] Despite these advances, the American Lung Association estimates that more than half of persons in the United States live in counties that have unhealthy levels of pollution.[2] The last 40 years has also seen important advancements in our understanding of the risks posed by high levels of both indoor and outdoor air pollutants on respiratory health. Accordingly, numerous reviews have described the potential of gaseous pollutants, such as ***ozone***, and particulate pollutants, such as diesel, cigarette smoke (CS), and biomass, to impair lung function and exacerbate and promote asthma.[3,4] In addition to direct physiologic changes, many have highlighted the ability of these agents to modulate the adaptive

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Terms in boldface and italics are defined in the glossary on page 15.

immune response and thereby increase IgE levels and promote a T_H2 milieu that can promote allergic airway disease.[5] Recently, there has been a growing appreciation that pollutants might also significantly affect respiratory innate immune responses.

Therefore here we will review the potential cellular mechanisms by which exposure to air pollutants modulates respiratory immunity and host defense. The public health significance is clear: respiratory tract infections are among the most common source of illness in the United States and Europe. Their effects are felt most acutely in susceptible populations, such as children, the elderly, and asthmatic patients. Focusing on the role of Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain (NOD)–like receptors (NLRs), this review will summarize current evidence on how air pollutants might alter innate immunity.

POLLUTANTS AND HEALTH RISKS FROM RESPIRATORY TRACT INFECTIONS

The strongest evidence of a link between pollutants and respiratory tract infections comes from studies in the developing world of those exposed to the high levels of particles generated from the combustion of biomass fuels (eg, wood and dung) for cooking or heating. Chronic bronchitis, acute respiratory tract infections, recurrent pneumonia, and tuberculosis have all been shown to be significantly more prevalent in mothers who cook or their children.[6] Fewer studies have been completed in the developed world, where better ventilation results in much lower exposure levels. These studies tend to show an increased risk of acute respiratory tract infections from woodstoves.[7] Similarly, exposure to CS has long been thought to reduce host defense because smokers have much higher rates of respiratory tract infections.[8] Numerous studies have now shown that secondhand smoke can also significantly increase the risk from lower respiratory tract infections in children and infants.[9,10]

The United States Environmental Protection Agency is mandated to set National Ambient Air Quality Standards for 6 criteria pollutants, including ozone and PM. These have tended to receive the most attention of the studies on air pollution and respiratory health effects. Evidence of increased susceptibility to infections

GLOSSARY

CATHEPSIN: Cathepsins are proteases that are found in lysosomes. Newly discovered functions for cathepsins include activation of the innate immune system. For example, cathepsin K activates the innate immune system by altering TLR9 signaling and inhibiting the production of IL-6, IL-23, and T_H17 cells. Phagocytosis of large particles has been shown to cause lysosomal destabilization, leading to the release of cathepsin B from the lysosome and the activation of the NLRP3 inflammasome.

CLEAN AIR ACT: The US Clean Air Act was first signed in 1970 and was followed by a number of amendments in 1977 and 1990. The purpose of the Clean Air Act was to protect the public from exposure to high levels of air pollutants. In 1990, the US Environmental Protection Agency estimated that it prevented more than 200,000 premature deaths and almost 700,000 cases of chronic bronchitis in its first 20 years. Since 1970, total emissions of the 6 principal air pollutants have decreased by greater than 41%.

HYALURONIC ACID (HA): HA is a major component of the extracellular matrix protein that is found in connective, epithelial, and neural tissues. HA is an endogenous DAMP that is recognized by the innate immune system through TLR2 and TLR4, thereby inducing interleukin production (eg, IL-8).

IL-6: IL-6 acts as both a proinflammatory and anti-inflammatory agent but is most commonly associated with acute-phase reactions and fever. IL-6 is released by numerous cell types, including macrophages, dendritic cells, T cells, and epithelial cells. IL-6 can be released in response to various microbial stimuli through activation of pattern recognition receptors (eg, Toll-like receptors).

IL-33: IL-33 is an IL-1 family member that is produced by epithelial cells, smooth muscle cells, and fibroblasts. IL-33 induces the production of type 2 cytokines, such as IL-5 and IL-13, from T_H2 cells, mast cells, eosinophils, and basophils. IL-33 is transcribed in a proform, which must be cleaved to the active form by caspase-1 for secretion.

IFN-γ–INDUCED PROTEIN 10 (IP-10): IP-10 (also known as CXCL-10) is secreted by several cell types, such as endothelial cells, epithelial cells, fibroblasts, and monocytes, in response to microbial, IFN-γ, or TNF-α stimulation. IP-10 is involved in chemoattraction of T and natural killer cells and binds to CXCR3.

INTERFERONS: Interferons are a class of cytokines produced in response to pathogenic infections and tumors. The interferon family consists of type I (IFN-α and IFN-β), type II (IFN-γ), and type III (IFN-λ) interferons. Interferons are produced by activation of Toll-like receptor and retinoic acid–inducible gene I–like receptor signaling. Interferons play a key role in innate immunity through such functions as antiviral defense, activation of immune cells (eg, natural killer cells and macrophages), and upregulation of antigen presentation to T cells.

MATRIX METALLOPEPTIDASES (MMPs): MMPs, or matrix metalloproteinases, break down extracellular matrix and promote tissue remodeling. MMPs are involved in several physiologic and pathologic processes, including tissue repair, angiogenesis, morphogenesis, cirrhosis, and metastasis. The activity of MMPs is balanced by tissue inhibitors of metalloproteinases (TIMPs). Misbalance between MMPs and TIMPs is thought to contribute to asthma pathogenesis.

MYELOID DIFFERENTIATION PRIMARY RESPONSE GENE 88 (MYD88): MyD88 is an adaptor protein for all Toll-like receptors except Toll-like receptor 3, as well as IL-1 receptors. MyD88 serves as a link between the extracellular receptors and intracellular signaling pathways leading to activation of the transcription factor NF-kB and expression of many genes important for innate immunity. Autosomal recessive MyD88 deficiency causes increased susceptibility to *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*, as well as other gram-negative infections.

NANONOPARTICLES: Nanoparticles are between 1 and 100 nm in size and have been used for consumer, manufacturing, and medical purposes (eg, drug delivery). Inhalation of nanoparticles has uncertain pulmonary toxicity but has been increasingly shown to have potential adverse effects on the respiratory tract and vasculature.

OZONE: Ozone is a naturally occurring gas, which can be formed at low levels in the atmosphere through the interaction between hydrocarbons and nitrogen oxides (eg, as produced by fuel exhaust) and sunlight. Because of its strong oxidizing capabilities, ozone is a primary irritant and can affect the eyes and respiratory system. Ozone can induce the production of reactive oxygen species, leading to oxidative stress and tissue and cellular damage.

PARTICULATE MATTER (PM): PM consists of solid and liquid compounds from organic, inorganic, and biological sources. A major source of PM is diesel exhaust. PM is broken into the following 3 classes by size: coarse ($PM_{2.5\text{-}10}$), fine ($PM_{0.1\text{-}2.5}$), and ultrafine ($PM_{<0.1}$). Fine and ultrafine particles are capable of depositing into the lung, with ultrafine particles reaching the small airways. The components of PM are toxic to cells and can induce DNA damage. Chronic exposure has been associated with airway diseases, such as asthma, and cardiovascular disease.

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