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Environmental effects on immune responses in patients with atopy and asthma

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Despite attempts and some successes to improve air quality over the decades, current US national trends suggest that exposure to outdoor and indoor air pollution remains a significant risk factor for both the development of asthma and the triggering of asthma symptoms. Emerging science also suggests that environmental exposures during the prenatal period and early childhood years increase the risk of asthma. Multiple mechanisms mediate this risk because a wide range of deleterious air pollutants contribute to the pathogenesis of asthma across a variety of complex asthma phenotypes. In this review we will consider the role of altered innate and adaptive immune responses, gene-environment interactions, epigenetic regulation, and possibly gene-environment-epigene interactions. Gaining a greater understanding of the mechanisms that underlie the effect of exposure to air pollution on asthma, allergies, and other airway diseases can identify targets for therapy. Such interventions will include pollutant source reduction among those most exposed and most vulnerable and novel pharmaceutical strategies to reduce asthma morbidity. (J Allergy Clin Immunol 2014;134:1001-8.)

Key words: *Air pollution, mechanisms, innate immunity, adaptive immunity, epigenetic regulation*

Abbreviations used

AHR:	Airway hyperreactivity
β2AR:	β_2-Adrenergic receptor
BC:	Black carbon
CCCEH:	Columbia Center for Children's Environmental Health
DAMP:	Damage-associated molecular pattern
DC:	Dendritic cell
DEP:	Diesel exhaust particle
FOXP3:	Forkhead box P3
GST:	Glutathione-S-transferase
MyD88:	Myeloid differentiation primary response gene 88
NO_2:	Nitrogen dioxide
NOx:	Oxidized nitrogen species
O_3:	Ozone
PAH:	Polycyclic aromatic hydrocarbon
PAMP:	Pathogen-associated molecular pattern
PM:	Particulate matter
$PM_{2.5}$:	Particulate matter of 2.5 μm in diameter
PM_{10}:	Particulate matter of 10 μm in diameter
SNP:	Single nucleotide polymorphism
TLR:	Toll-like receptor
Treg:	Regulatory T

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Despite the strengthening of the Clean Air Act in 1990 and improvements in air quality, current US national trends suggest that exposure to outdoor and indoor air pollution remains a significant risk factor for both the development of asthma and the triggering of asthma symptoms.[1-3] Based on data from the Children's Health Study in Southern California, where exposure to traffic-related air pollution is relatively high, almost 40% of asthma exacerbations were attributable to exposure to air pollution.[4] Within the New England, New Jersey, and New York area, which was studied in one public health effect analysis, 72% of the population lives in densely populated cities with increased ambient fine particulate matter (particulate matter of 2.5 μm in diameter [$PM_{2.5}$]) concentrations.[5] The consequences of these exposures can be great. As an example, using modeled and measured ambient measurements of $PM_{2.5}$ and ozone (O_3), 2,500,000 asthma exacerbations in children and 110,000 pediatric emergency department visits for asthma were attributed to 2005 ambient $PM_{2.5}$ concentrations nationwide; 27,000 hospital admissions for respiratory causes and 19,000 pediatric emergency department visits for asthma were attributed to ambient O_3.[6]

As the effects of air pollution become increasingly important, a unifying biological theme is that many pollutants modify innate and acquired immune responses and that susceptibility can vary by age, other modifying factors, and additional exposures. This review will provide updates on the effect of pollutant exposure on innate and adaptive immune responses, genetic and epigenetic modifiers of response to pollutants, and potential interventions to mitigate these effects.

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Terms in boldface and italics are defined in the glossary on page 1002.

EFFECT OF TIME WINDOWS OF SUSCEPTIBILITY

Murine and human birth cohort studies suggest that the prenatal period is a time when the effects of ambient air pollution are heightened.[7,8] Studies from the Columbia Center for Children's Environmental Health (CCCEH) showed that prenatal exposure to ***polycyclic aromatic hydrocarbons*** (PAHs) in association with exposure to secondhand smoke[9,10] or higher cockroach allergen levels[11] was associated with asthma-related symptoms in children and cockroach allergic sensitization in urban children, respectively. African American children in the San Joaquin Valley of California born to mothers who smoked during pregnancy in association with prenatal exposure to nitrogen dioxide (NO_2), particulate matter of 2.5 μm in diameter (PM_{10}), and carbon monoxide exhibited decreases in lung function.[12]

The very young also are particularly susceptible. In the Genes-Environments and Admixture in Latino Americans II study and the Study of African Americans, Asthma, Genes and Environments II, a 5-ppb increase in average NO_2 levels during the first year of life was associated with an odds ratio of 1.17 for asthma among 8- to 21-year-olds. Odds ratio for higher NO_2 exposure during the first 3 years was 1.26.[13] The preschool years (age 2-5 years) demonstrated the greatest association between O_3 levels and nighttime primary care visits for asthma exacerbations in a Japanese cohort.[14] In daily time series analyses of more than 6000 intensive care unit admissions for asthma in New York City hospitals, children aged 6 to 18 years had a higher risk for each 12 $\mu g/m^3$ increase in $PM_{2.5}$ and for each 22-ppb increase in O_3 compared with risks seen in adults.[3] When combined, these results suggest that there is greater vulnerability of the growing lungs and the developing immune system, thus predisposing to more airway inflammation later in life.[15] As discussed later, epigenetic regulation might underlie the mechanisms occurring during the prenatal period in particular.

EFFECT OF MODIFYING FACTORS

Susceptibility to the hazards of exposure to air pollution and its molecular and clinical consequences can be modified by the presence of atopy, stress, and obesity. Modification by atopy was well described in the Northeast Chinese Children's Health Study of more than 30,000 Chinese children aged 3 to 12 years selected in 2009, which examined associations by using multipollutant (PM_{10}, sulfur dioxide, NO_2, O_3, and carbon monoxide) models.[16] In contrast, in the New York City CCCEH birth cohort, repeated exposure to the PAH pyrene was associated with asthma among nonatopic children.[17] Shankardess et al[18] from the Children's Health Study published a seminal article showing that the risk of asthma attributable to exposure to traffic-related air pollution measured by using a line source dispersion model was significantly higher for subjects with high parental stress (measured by using the Perceived Stress Scale) than for subjects with low parental stress. More recently, the same group showed that children from high-stress households, again measured by using the Perceived Stress Scale, exhibited decreases in lung function in association with higher home and school oxidized nitrogen species levels.[19]

Being overweight also has been shown to increase susceptibility to the respiratory effects of exposure to air pollution. Lu et al[20] reported that overweight or obese children had more asthma symptoms but not worse lung function or airway inflammation after higher exposure to fine particulate matter and NO_2 than normal-weight participants across a range of asthma symptoms. In the CCCEH cohort, among the obese children, a significant positive association was observed between select semivolatile PAH concentrations and asthma that was not observed among the nonobese children.[21]

When combined, these studies suggest that factors such as chronic low-grade systemic inflammation associated with obesity and stress might predispose to asthma, although other

GLOSSARY

CD14: CD14 is the LPS receptor and mediates TLR4 signaling. CD14 is expressed on monocytes, macrophages, and neutrophils.

CD44: CD44 is expressed on multiple cell types, including white and red blood cells. Its ligands include hyaluronate, osteopontin, and fibronectin.

DANGER-ASSOCIATED MOLECULAR PATTERN (DAMP) AND PATHOGEN-ASSOCIATED MOLECULAR PATTERN (PAMP): DAMPs and PAMPs are recognized by pattern recognition receptors, such as TLRs. PAMPs are exogenous or endogenous molecules, but DAMPs are almost all endogenous molecules. TLR4 binds LPS from gram-negative bacteria, heat shock protein 6, and respiratory syncytial virus protein F. TLR7 and TLR8 bind single-stranded RNA and are important for antiviral defense.

HYALURONIC ACID: A component of the extracellular matrix that is capable of effecting cell migration and proliferation. Hyaluronic acid can bind to CD44, and its degradation products can activate TLRs.

IL-18: IL-18 has effects similar to those of IL-12 and induces IFN-γ production. Production of an IL-18 binding protein by some viruses, such as molluscum contagiosum, allows evasion of the immune system.

IL-33: IL-33 is an IL-1 family member that is produced by epithelial cells, smooth muscle cells, and fibroblasts and increases IL-5 and IL-13 production.

INFLAMMASOME: The inflammasome is a multimeric protein complex activated by the innate immune system through DAMPs and PAMPs to ultimately cleave pro–IL-1β to IL-1β and pro–IL-18 to IL-18. Specific components of the inflammasome can vary based on the initiating signal, but nucleotide-binding oligomerization domain-like receptor (NLRs) are critical components.

LINE1: The only complete retrotransposon in the human genome, *LINE1* is 6 kB in length, contains 2 open reading frames, and exists at about 516,000 copies. Retrotransposons are "genomic parasites," represent 17% of the human genome, and can induce spontaneous genetic diseases when they become mobile.

MYELOID DIFFERENTIATION PRIMARY RESPONSE GENE 88 (MYD88): MyD88 is an essential component of TLR signals. All TLRs except TLR3 use MyD88 as an adaptor molecule that precedes the activation of IL-1 receptor–associated kinase and TNF receptor–associated factor 6, ultimately leading to nuclear factor κB or activator protein 1–mediated gene transcription. MyD88-deficient mice have decreased autoimmunity.

N-ACETYL-CYSTEINE (NAC): NAC acts as an antioxidant to counter the effects of diesel exhaust particles. It can decrease bronchial hyperreactivity and alter micro-RNA expression induced through diesel exhaust exposure.

POLYCYCLIC AROMATIC HYDROCARBON: A group of more than 100 substances that are formed during burning of coal, tobacco, oil, gas, and garbage and also during grilling of meats.

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