Advances in environmental and occupational disorders in 2016

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In this review we highlight recent studies that advance the knowledge and understanding of the effects of various environmental factors and associated immune responses in patients with allergic diseases. This review will focus on new literature regarding allergic and immune responses to a variety of environmental factors, including aeroallergens, stinging insects, fungi, pollutants, viral respiratory tract infections, climate change, and microbial exposures. (J Allergy Clin Immunol 2017;140:1683-92.)

Key words: *Aeroallergens, fungi, air pollutants, viral respiratory tract infections, climate change, occupational asthma*

Abbreviations used
ABPA: Allergic bronchopulmonary aspergillosis
APIC: Asthma Phenotypes in the Inner City
BALF: Bronchoalveolar lavage fluid
BAT: Basophil activation test
CF: Cystic fibrosis
DEP: Diesel exhaust particle
ECAT: Elemental carbon attributable to traffic
HDM: House dust mite
HP: Hypersensitivity pneumonitis
HRV: Human rhinovirus
ILC2: Type 2 innate lymphoid cell
PM: Particulate matter
RSV: Respiratory syncytial virus
SLIT: Sublingual immunotherapy
TET1: Ten-eleven translocation 1 gene
TLR: Toll-like receptor

Environmental factors play a major role in the development of allergic sensitization and the persistence of symptomatic allergic diseases. Extensive knowledge has been gained from important birth cohorts[1] and other recent studies. In this selective review we highlight articles published primarily in 2016 that advance our knowledge of the effect of environmental factors on allergic diseases. We focus on allergens, viral infections, and air pollution, which alone or in combination affect allergic diseases, particularly asthma. Major contributions (Table I)[2-14] addressed include the following: (1) the importance of climate change and its potential to increase the risk of allergic respiratory diseases in the future; (2) the fact that sensitization to Fel d 1 and Can f 1, especially polysensitization, in childhood (age ≤4 years) is significantly associated with allergic symptoms to these pets in adolescence (age 16 years); (3) the ability of viral infections to induce fibroblast proliferation; (4) the multiplicity of effects of air pollution on lung function, epigenetics, airway inflammation, and preterm birth in pregnant women with asthma; and (5) the role of school-specific allergenic exposures in asthma morbidity. Emphasis is also directed at severe asthma in residents of inner cities, where allergen exposure and sensitization are significant players in defining asthma phenotypes and are associated with difficult to control asthma. In addition to allergens, environmental tobacco smoke exposure also contributes to the pathogenesis of severe asthma in these populations. Understanding the contribution of environmental factors in the inception and progression of allergic diseases, as discussed in this review, will hopefully lead to improved treatments for these conditions.

IgE RESPONSES TO ENVIRONMENTAL FACTORS

IgE plays a central role in the pathogenesis of allergic diseases. A host of environmental factors influence IgE production. Among these factors, allergens are classically recognized, but viral infections, air pollution, and tobacco smoke can also contribute.[15] Another factor leading to increased plasma IgE levels is high alcohol consumption (ingestion of ≥28 drinks containing 12 g of ETOH/week).[16] However, there was no correlation between these findings and the presence of allergic diseases. Additional studies will be needed to determine the clinical significance of these findings.

Aging can affect allergen-specific and total IgE levels in adults. A large study of adults in the European Community Respiratory Health Survey examined the effects of aging on specific IgE levels

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TABLE I. Key advances

Advances	References
Proximity of IgE epitopes on an allergen affects its allergenic activity.	Gieras et al[2]
Early-life sensitization to Fel d 1 and Can f 1 or polysensitization to cat and dog allergens can predict development of allergic symptoms in adolescence.	Asarnoj et al[3]
Sensitivity and specificity of Hymenoptera allergen components depend on the diagnostic assay.	Schrautzer et al[4]
Chitinases might represent a novel biomarker for CF-associated fungal disease.	Hector et al[5]
Early-life HRV-triggered wheezing episodes continue to be important in the development of asthma because they can result in airway remodeling and have been associated with persistence of asthma into adolescence.	Rubner et al[6] Shelfoon et al[7]
Air pollution exposure early in life in conjunction with allergen exposure might promote a stronger inflammatory response compared with allergen exposure alone.	Brandt et al[8] Brandt et al[9]
Climate change has increased the burden of asthma and allergies in a variety of ways.	Annesi-Maesano[10]
Exposure to traditional farming environments can be protective against development of asthma by activating innate immune responses.	Stein et al[11]
Exposure to mouse allergen in inner-city schools was associated with increased asthma symptom days in students with asthma, irrespective of sensitization status.	Sheehan et al[12]
Results of randomized home allergen reduction intervention trials can be affected by motivations in the control groups.	DiMango et al[13] Matsui et al[14]

to common aeroallergens and on total IgE levels over a 20-year period.[17] Aging was associated with lower levels of sensitization to house dust mite (HDM) and cat allergen and a significant decrease in total IgE levels. The kinetics of IgE sensitization decreased differently for different allergens (ie, grass pollen was less likely to decrease). A better understanding of the mechanisms involved might clarify the cause and treatment of allergic diseases.

Studies of amino acid sequences (peptide epitopes) on allergens indicate that those that acquire enhanced ability to cross-link IgE by means of oligomerization, aggregation, or expression of repetitive epitopes can gain allergenic potency. It has been proposed that repetitive epitopes represent allergen-associated molecular patterns by Pali-Scholl and Jensen-Jarolim.[18] In support of this concept, Gieras et al[2] found that the proximity of IgE-binding sites on an artificial allergen construct enhanced the magnitude of effector cell activation, basophil activation test (BAT) assays, and *in vivo* inflammation and systemic anaphylaxis in a mouse model. Further investigations into this mechanism, which might regulate allergic inflammation, will be of interest.

Component-resolved diagnostic testing for IgE sensitization to individual allergens has increased steadily in the past several years. An excellent review of the subject has appeared recently.[19] These tests were used to show that sensitization to specific pet allergens correlates with allergic diseases, such as Can f 1 with persistent rhinitis, Can f 2 with asthma, and Fel d 2 with an asthma diagnosis.[20] Further evidence from the Barn/Children Allergy/Asthma Milieu Stockholm Epidemiologic/Mechanisms for the Development of Allergy (BAMSE/MeDALL) study[3] indicates that early childhood sensitization to Can f 1, Fel d 1, or polysensitization was significantly better than IgE assays using cat or dog extracts in predicting longitudinal development of allergic symptoms. These studies support the benefits of a molecular diagnosis of IgE sensitization and mechanisms of allergic disease.

HDMs are a significant factor in the allergic march from sensitization to asthma. A recent report suggests that inclusion of the HDM allergen Der p 23 in IgE serologic testing is of value when conventional diagnostics fail.[21] The introduction of HDM sublingual immunotherapy (SLIT) tablets can lead to improved treatment of allergic rhinitis in adults and children.[22] In a randomized, double-blind, placebo-controlled phase III trial, standardized HDM SLIT reduced allergic rhinitis symptoms and medication scores and improved quality of life compared with placebo in adults with moderate-to-severe allergic rhinitis. Furthermore, Roux et al[23] demonstrated that an environmental exposure chamber was beneficial in establishing the dose-dependent safety and efficacy of HDM tablet SLIT. Such studies can lead to improved diagnostic and therapeutic approaches to HDM sensitivity.

Stinging insect reactions can be potentially fatal, and thus accurate diagnosis is critical. Skin tests, BATs, and *in vitro* IgE assays have been investigated extensively to identify patients at risk for serious reactions to stings. Component-resolved diagnostics are being used increasingly to identify high-risk patients, especially those with underlying mast cell disorders.[24] Frick et al[25] demonstrated that sensitization to Api m 10 was a risk factor for treatment failures with honeybee venom because some preparations lack this allergen. The presence of cross-reactive carbohydrate antibodies in the sera complicates diagnosis. Schrautzer et al[4] reported that the sensitivity and specificity of Hymenoptera allergen component-resolved testing depends on the assay used. One assay (Immulite; Siemens, Tarrytown, NY) was superior for detecting IgE to the honeybee allergy Api m 1, whereas another (CAP; Thermo Fisher Scientific, Waltham, Mass) was superior for the vespid allergen Ves v 5. Confirmation of these results will be helpful for diagnosis in individual patients and for epidemiologic studies.

Allergic reactions to medications are not uncommon. Investigations of alpha-gal have led to new insights into the mechanisms of drug reactions. Two reports in the *Journal*[26,27] describe severe immediate-type allergic reactions to pegnivacogin, a PEGylation RNA aptamer investigation agent being evaluated for the treatment of acute coronary artery syndromes. Preformed IgG antibodies to polyethylene glycol were detected in the sera of subjects who experienced reactions. The events were associated with evidence of complement activation (decreased CH50, increased C3a, and increased Factor B levels in sera) and increased tryptase levels (Fig 1).[27] The results suggest an IgG-mediated anaphylactic reaction because of antigen-IgG antibody complexes interacting with Fcγ receptors as the mechanism. With a growing interest in genetic factors in patients with drug hypersensitivity reactions,[28] it will be of interest to determine whether genetics play a role in these reactions as well.