Advances in environmental and occupational disorders in 2014

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In 2014, the *Journal* published a number of studies that have advanced our understanding of the effects of various environmental factors and immune responses in patients with allergic diseases. In this review we emphasize reports that have appeared in the *Journal* over the past year that deal with environmental and occupational respiratory disorders and novel approaches to their treatment. The review will focus on the effects of environmental factors and immune responses in allergic airway diseases, identification of new allergens, and risk factors in stinging insect allergy, development of asthma in different age groups, effects of viral infections, and benefits of new therapies. (J Allergy Clin Immunol 2015;136:866-71.)

Key words: *Air pollution, allergens, anaphylaxis, viral infections, immune responses, asthma*

Abbreviations used
COPD: Chronic obstructive pulmonary disease
CRSsNP: Chronic rhinosinusitis without nasal polyps
CRSwNP: Chronic rhinosinusitis with nasal polyps
HRV: Human rhinovirus
PAF: Platelet-activating factor
PAF-AH: Platelet-activating factor acetylhydrolase
SOCS3: Suppressor of cytokine signaling protein 3
STAT3: Signal transducer and activator of transcription 3
TLR: Toll-like receptor

The *Journal of Allergy and Clinical Immunology* published a number of articles focused on environmental factors that affect allergic diseases. Other reports advanced our knowledge of therapeutic approaches to these conditions. Areas involved in the advances included (1) studies on the effects of environmental exposure on immune responses and disease pathophysiology, (2) identification and characterization of new allergens, (3) description of risk factors in systemic allergic reactions, (4) investigations of the role of viral infections in airway disease, and (5) reports on new therapies. In this review we highlight the advances in environmental and occupational disorders reported in the *Journal* in 2014.

EFFECTS OF ENVIRONMENTAL EXPOSURE ON IMMUNE RESPONSES AND AIRWAY DISEASES

In a comprehensive review Miller and Peden[1] discussed the effects of air pollution on immune responses in patients with allergic respiratory diseases. Exposure to ambient fine particulate matter (particulate matter of 2.5 μm) and ozone account for a large number of asthma exacerbations, emergency department visits, and hospitalizations for asthma. Further exposure to these and other pollutants, such as polycyclic aromatic hydrocarbons and nitrogen dioxide, can result in decreased lung function. Children appear to be especially vulnerable to reduced lung growth and predisposed to chronic airway inflammation caused by these exposures. Atopy, stress, and obesity can enhance the adverse effects of air pollution. The authors describe a number of alterations in innate and adaptive immune responses that result from air pollutant exposure, including Toll-like receptor (TLR) signaling, damage-associated molecular pattern production, and proinflammatory epithelial responses. Furthermore, pollutants can upregulate T_H2, IL-17, and dendritic cells and impair regulatory T-cell function. In addition, gene-environment interactions can alter oxidative stress genes and cause epigenetic changes that result in increased inflammatory responses. Potentially, antioxidants might have therapeutic benefits in reducing pollutant-induced airway disease. Legislative initiatives to reduce air pollution have reduced asthma morbidity, but further research into the mechanisms and treatment of air pollution–induced airway disease are needed.

In another thorough review Bublin et al[2] described the role of lipids in the allergic sensitization process. Many allergens from pollens, house dust mites, pets, cockroaches, and food contain binding sites for lipid ligands that can enhance T_H2 responses. The authors provide a comprehensive discussion of the allergens, lipid mediators, mechanisms of action, and immune responses involved in allergic sensitization and disease. TLR4- and TLR2-dependent and CD1d-restricted mechanisms are especially relevant. Moreover, lipids can protect food allergens from proteolysis and enhance their uptake by intestinal epithelial cells. Because allergens are associated with lipids in a variety of contexts, this review is especially significant.

The role of environmental factors (allergens) in nonatopic asthma is not entirely clear. Increased total serum IgE levels are associated with an increased risk for asthma, regardless of atopic status. To evaluate the role of local specific IgE production in

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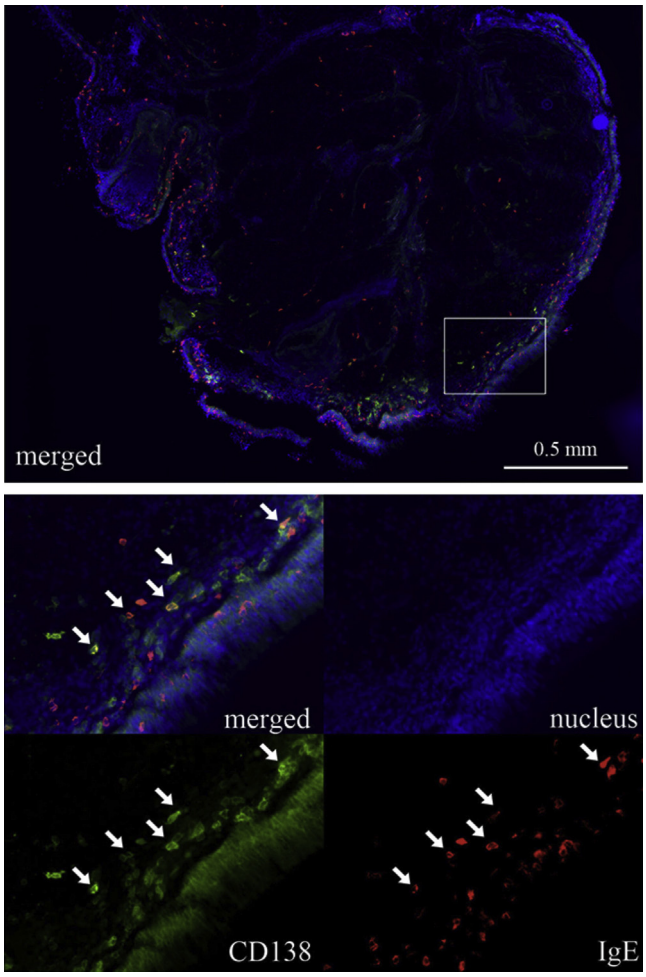

FIG 1. Immunofluorescence image of a bronchial biopsy specimen from a nonatopic asthmatic patient stained for plasma cells (CD138; *green*), IgE *(red)*, and nucleus *(blue)*. *Top,* View of the whole biopsy specimen showing area of magnification. *Bottom,* Magnified view with a merged image and individual stains. *Arrows* indicate cells with dual staining (plasma cells expressing IgE). From Pillai et al.[3]

patients with nonatopic asthma, Pillai et al[3] performed bronchial mucosal biopsies on patients with nonatopic asthma, patients with atopic asthma, and nonasthmatic control subjects (n = 10 in each group) and examined the tissue for total and specific IgE to 100 known allergens. Biopsy specimens from both asthmatic groups showed increased total IgE levels compared with those in nonasthmatic control subjects. Specific IgE to the allergens tested was not detectable in biopsy specimens from nonatopic asthmatic patients. Although the data suggest that local IgE production occurs in nonatopic asthmatic patients, it is directed against targets other than allergens. Further studies will be needed to determine the exact role of this finding (Fig 1).[3]

Chronic rhinosinusitis with nasal polyps (CRSwNP) is believed to reflect a T_H2 response, whereas chronic rhinosinusitis without nasal polyps (CRSsNP) is characterized by neutrophilic inflammation. However, the immune response in patients with either condition are complex. Previous studies suggest that increased expression of suppressor of cytokine signaling protein 3 (SOCS3) is associated with T_H2-mediated diseases, and increased SOCS3 protein levels were found in ethmoid tissue in both patients with CRSwNP and those with CRSsNP.

To further evaluate the role of phosphorylated signal transducer and activator of transcription 3 (STAT3) and SOCS3 in nasal polyp tissue, Hulse et al[4] studied these proteins in uncinate tissue from control subjects (n = 5), patients with CRSsNP (n = 18), and patients with CRSwNP (n = 24) and polyp tissue (n = 31). Levels of phosphorylated STAT3 were diminished in uncinated tissue and polyps from the patients with chronic rhinosinusitis compared with those in control subjects. Total STAT3 levels were similar in all groups. Surprisingly, SOCS3 levels were decreased in uncinate and polyp tissue from patients with CRSwNP. The fact that these findings differed from those of previous work suggests that tissue sampling (ethmoid vs uncinated tissue) and patient demographics (eg, ethnicity) might affect the results. Thus further investigations will be needed to better understand the role of potential environmental factors in the pathogenesis of CRS.

ALLERGENS

Identification of allergens and their characterization is important in the development of new diagnostic and therapeutic approaches to allergic diseases. Pollen-induced allergic rhinitis and asthma are common clinical problems. Grass pollen allergens are a major source of sensitization in many parts of the world. Group 5 grass pollen allergens, including Phl p 5 from timothy grass, are recognized as the most frequent and potent sensitizers. Focke-Tejkl et al[5] examined the immune-dominant IgE and T-cell recognition sites on the Phl p 5 protein molecule. Using synthesized peptides of 31- to 38-amino-acid sequences, they found that Phl p 5 IgE epitopes are conformational and located on both the N- and C-terminal domains of Phl p 5. One peptide, P4, stimulated strong T-cell responses but was not part of the strongest IgE-reactive region. The dissociation of the major IgE- and T-cell–reactive domains in Phl p 5 could lead to novel therapeutic approaches.

Identification and characterization of new allergens can lead to new diagnostic tests. Mas et al[6] conducted a complete immunoproteomic study of ash pollen extracts using 1-dimensional electrophoresis and molecular cloning. They identified 6 new allergens and showed a high degree of sequence identity with olive pollen allergens. Similarly, in studies of the allergens of *Plantago lanceolata* (English plantain) by Gadermaier et al,[7] reactivity to English plantain pollen was largely due to IgE cross-reactivity to profilin that was probably induced by grass pollen sensitization. However, they identified the nonglycosylated rPla l 1 as a potential marker for true plantain sensitization. Lastly, Goldblum et al[8] investigated the IgE-binding epitopes on the major mountain cedar pollen allergen Jun a 1. The molecule displayed at least 4 distinct IgE epitopes that are brought together by means of protein folding (conformational). These studies can lead to novel therapeutic approaches and serve as a model for studying the structural basis of allergenicity of protein allergens.

Allergen microarray–based assays are increasingly used to diagnose IgE-mediated allergic diseases. Cabauatan et al[9] pointed out the limitations of such an approach in selected populations. They found that subjects residing in tropical climates exhibited a very high frequency of IgE sensitization to grass pollen–derived carbohydrate epitopes and little or no IgE reactivity to grass