Advances in adult asthma diagnosis and treatment in 2013

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In 2013, several themes emerged: (1) a dedicated search for new therapies using new mechanisms; (2) the importance of the plasticity of the immune system (eg, that molecules that mediate inflammation in one setting can promote its resolution and return to homeostasis in other circumstances); (3) the complex role of viruses in asthma exacerbations; (4) the similarities and differences among asthma, asthma in smokers, and chronic obstructive pulmonary disease; and (5) the importance of understanding asthma phenotypes and their stability over time. Once new therapeutics pass the initial clinical trials, patient-oriented and real-world research will be needed. (J Allergy Clin Immunol 2014;133:49-56.)

Key words: *Asthma, adults, inhaled corticosteroids, asthma management*

For several years, it has been my task to review the advances in clinical asthma in adults[1] alongside Dr Szefler's corresponding and excellent reviews of advances in pediatric asthma.[2] This assignment allows me to identify themes that have evolved over the past year based on the collective thoughts of the investigators and to get a glimpse of where their research is headed. In 2013, several themes emerged: (1) a dedicated search for new therapies using new mechanisms; (2) the importance of the plasticity of the immune system (eg, that molecules that mediate inflammation in one setting can promote its resolution and return to homeostasis in other circumstances); (3) the complex role of viruses in asthma exacerbations; (4) the similarities and differences among asthma, asthma in smokers, and chronic obstructive pulmonary disease (COPD)[3]; and (5) the importance of understanding asthma phenotypes and their stability over time. These themes organize this review.

Abbreviations used

ACQ:	Asthma Control Questionnaire
$C_{alv}NO$:	Alveolar fraction of exhaled nitric oxide
COPD:	Chronic obstructive pulmonary disease
CRTH2:	Chemoattractant receptor homologous molecule expressed on T_H2 cells
EBC:	Exhaled breath condensate
F_{ENO}:	Fraction of exhaled nitric oxide
ICS:	Inhaled corticosteroid
LABA:	Long-acting β-agonist
OA:	Occupational asthma
PGD_2:	Prostaglandin D_2
PROM:	Patient-reported outcome measure
SLIT:	Sublingual immunotherapy
TLR:	Toll-like receptor
WEA:	Work-exacerbated asthma
WRA:	Work-related asthma

MECHANISMS OF DISEASE

In recent years, there have been few commercially available new drugs with novel mechanisms for treating asthma. Thus studies of mechanisms are important for their potential therapeutic implications. For example, protectin D1 is an anti-inflammatory lipid mediator that promotes resolution of inflammation by stimulating clearance of apoptotic cells and debris. Previously, it was found to attenuate eosinophilic inflammation in a mouse model. Studying eosinophils from peripheral blood of asthmatic and healthy subjects, Miyata et al[4] observed that protectin D1 is produced by human eosinophils and its production is impaired in patients with severe asthma. This finding has implications for protectin D1 both as a biomarker and a potential therapeutic agent.

T-cell influences on asthma are understood to be complex, involving several T-cell subsets and their many cytokines, all with genetic variation, and are influenced by the microenvironment, which determines phenotypic plasticity and the resulting heterogeneity of response to therapeutics (Fig 1).[5] One such is IL-22, which was previously shown to have proinflammatory and anti-inflammatory properties in mice but has not been extensively studied in human lung disease for its therapeutic potential. Pennino et al[6] found that IL-22 might have a tissue-restricted anti-inflammatory role: it antagonized the effect of IFN-γ on human bronchial epithelial cells from healthy and asthmatic subjects. Interestingly, Nanzer et al,[7] examining PBMC cultures from patients with severe asthma, found increased levels of T_H17 cytokines, including IL-22 and IL-17A, which were inhibited by $1,25(OH)_2D3$. They proposed a possible steroid-enhancing role of vitamin D in asthmatic patients, particularly in this phenotype.

The *IL33* gene was first described in the setting of cedar pollinosis. IL-33 promotes IL-4, IL-5, and IL-13 production and eosinophilic airway inflammation. Grotenboer et al[8] review the mechanisms by which variants of genes for IL-33 and its receptor can increase asthma susceptibility. Gabriele et al[9] have developed a murine model of allergic asthma to cypress pollen that links it to the T_H2-polarizing activity of dendritic cells involving IL-33 and its receptor. This model could be adapted for testing the dendritic cell– and IL-33–modulating effects of potential treatments for allergic asthma.

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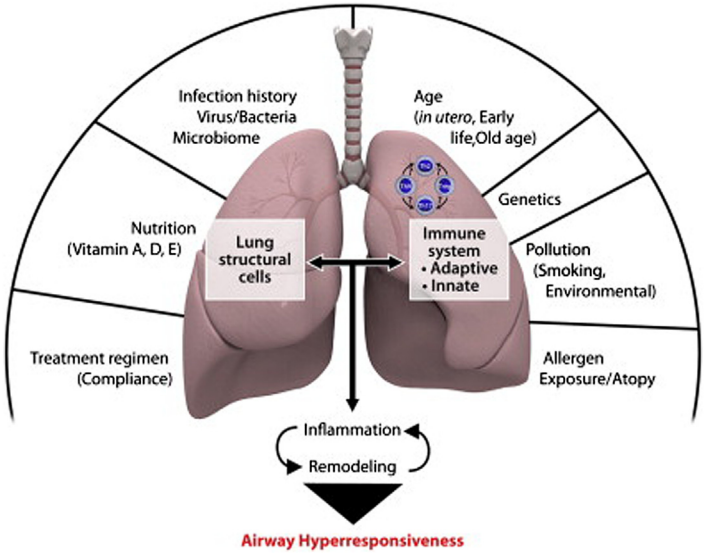

FIG 1. Interplay between environmental exposures, lung structural cells, and immune cells in determining asthma pathophysiology. The lungs are continuously exposed to numerous environmental exposures, which determine responses from both lung structural cells (primarily epithelial cells) and immune cells in a susceptible asthmatic patient. The microenvironment seems critical in determining T effector cell function and likely contributes to alterations in T-cell phenotype and determines development of T_H lineage plasticity. Reprinted with permission from Lloyd and Saglani.[5]

Viruses play a role in asthma inception and exacerbations and might contribute to atopic development.[10] In this year's *Journal*, Kaiko et al[11] identified a new defect in the mouse Toll-like receptor (TLR) 7 gene. Because TLR7 is a product of plasmacytoid dendritic cells, the host's immediate source of type I interferon in response to virus, defects in TLR7 can increase T_H2 responsiveness, suggesting another venue by which virus-related asthma exacerbation can be studied in human subjects and possibly treated. Campbell-Harding et al[12] found that IFN-β upregulates IL-13 receptor α2 and suppresses responsiveness to IL-13 in fibroblasts exposed to double-stranded RNA used as an *in vitro* mimic of a viral respiratory tract infection. Thus enhancing IL-13 receptor α2 activity could have therapeutic benefit in asthmatic patients. In another study closer to clinical relevance and also informed by response to viral infection, Beeh et al[13] conducted a randomized, controlled double-blind, phase II study of the TLR9 agonist QbG10 (bacteriophage Qβ-derived virus-like particle with CpG-motif G10 inside). QbG10 is a recombinant viral protein shell filled with DNA and a ligand for TLR9. It is postulated to stimulate T_H1 and suppress T_H2 responsiveness. QbG10 or placebo was administered to 63 patients whose symptoms were stable with inhaled corticosteroids (ICSs). Patients were maintained on ICSs for 4 weeks and then entered an 8-week period of ICS withdrawal. QbG10 was associated with improved asthma control. FEV_1 remained constant while worsening in the control group.

Finally, Barnes[14] reviewed mechanisms of corticosteroid resistance in asthmatic patients that might include alteration of glucocorticoid receptor activities, which are detailed by Oakley and Cidlowski[15] and likely have future therapeutic relevance.

GENETIC INFLUENCES OF CLINICAL RELEVANCE

Li et al[16] conducted meta-analyses of genome-wide association studies of lung function measured as FEV_1 percent predicted in 1544 patients from 4 white populations of European origin whose asthma severity ranged from mild to severe. They confirmed 7 of 28 previously identified lung function loci and also found that genes involved in airway structure and remodeling were associated with lung function in the general population and those with asthma. Interestingly, 4 of 32 identified loci associated with FEV_1 were T_H1 or IL-12 (stimulator of IFN-γ production) cytokine genes participating in antivirus/bacterial immune responses.

Microchimerism is the presence of small numbers of non-self cells in a subject. Maternal microchimerism, the presence of maternal cells in offspring, occurs in up to 55% of healthy children and has been associated with autoimmune disease. Thompson et al[17] found lower rates of asthma development among subjects with maternal microchimerism, suggesting the opposite effects of the accompanying immune dysregulation on autoimmunity and asthma.

Telomeres are terminal regions of chromosomes, and their shortening is associated with cell senescence and apoptosis. In a brief report Kyoh et al[18] noted that leukocytes of asthmatic patients, as in patients with COPD, demonstrate accelerated aging, as judged based on telomere length.

ENVIRONMENTAL EXPOSURES: INNER AND OUTER

Research on the association of microbes and asthma has until now focused on a limited number of organisms identified by means of culture or PCR techniques. Marri et al[19] used metagenomic methods to analyze the entire lower respiratory tract microbiome. Using induced sputum from 10 young asthmatic and 10 nonasthmatic adults, they found those with mild asthma had an altered microbial composition similar to that of patients with more severe asthma and different from that seen in nonasthmatic subjects. Organisms from the Proteobacteria phylum (which includes the gram-negative species *Escherichia coli*, *Proteus*,