



2014 Year in Review

Year in review: basic science



The past year has been a great one for basic science in the *Annals*! We have worked hard to bring you basic science that is relevant to your practice. In 2014 we saw publications of important novel work on the basic science of asthma, allergic rhinitis, food allergy, and drug allergy.

In terms of asthma, there were several publications identifying or clarifying biomarkers for stratifying asthma phenotypes. One study looked at phorbol myristate acetate-stimulated blood cytokine levels to determine whether they would discriminate asthma phenotypes in 18- to 21-year-olds.¹ The investigators found that those with a history of allergic asthma had a T-helper cell type 2 polarized response, whereas those with a nonallergic asthma history demonstrated T-helper cell type 1 polarization. Although not necessarily surprising, these results do reinforce the fact that asthma is not a single disease. Another study examined whether a novel cell type, the low-density granulocyte (LDG), was associated with specific severities of asthma.² The LDGs were found in the peripheral blood of subjects with asthma, with the level of LDGs being highest in those subjects with severe persistent disease. Whether there is a mechanistic association between LDGs and asthma was not studied, but this report does add another cell type to our phenotyping armamentarium. Also adding to our list of biomarkers was a study examining plasma connective tissue growth factor levels in healthy subjects and those with stable asthma.³ In this study, connective tissue growth factor levels negatively correlated with worsening lung function and asthma control test scores, suggesting that connective tissue growth factor could be a useful biomarker for the degree of airway obstruction in patients with stable asthma. In addition, peripheral blood levels of high-sensitivity C-reactive protein were found to predict airway remodeling in steroid-naïve (but not steroid-treated) subjects with asthma.⁴ All these articles provide novel biomarkers to be studied further in phenotyping asthma.

One phenotypic difference in patients with asthma is their responsiveness to steroids. In 1 study, the researchers examined whether steroid sensitivity made a difference in expression of the leukotriene B4 receptor (BLT1) on peripheral blood T cells.⁵ They found that BLT1-expressing cells were more frequent in patients with asthma and were found more often on CD8 T cells than on CD4 T cells. In steroid-resistant subjects, ex vivo expansion of BLT1-expressing CD8 T cells was unaffected by steroid treatment, whereas cells from those who were steroid sensitive decreased when steroid was added to the culture. Moreover, there were differences in cytokine production from the various cell types, suggesting that BLT1 and leukotriene B4 (its ligand) could play

important roles in the cellular inflammation seen in asthma and especially in those with steroid-resistant disease.

As discussed at the 2014 annual meeting of the American College of Allergy, Asthma, and Immunology, there is debate about whether asthma and chronic obstructive pulmonary disease (COPD) represent different diseases or simply different points on the spectrum of obstructive lung disease. Catalase is an enzyme that is associated with asthma and COPD, and one study hypothesized that if the pathophysiology of the two diseases were related, then they should have similar polymorphisms associated with them.⁶ In fact, the investigators did find at least one genotype associated with smoking and adult-onset asthma and with a non-emphysematous type of COPD. These data provide some initial evidence for the *catalase* gene being a common player in some forms of asthma and COPD. Two other studies examined genes and the risk of asthma. In one, a pathway analysis was performed to find proteins that might interact with the gene *ADAM33*.⁷ The investigators identified several novel proteins that could be important in disease development and provide novel pathways for future study. Using a panel of single-nucleotide polymorphisms already associated with asthma risk, the other study examined whether specific “gene-to-gene interactions” could better predict the risk of asthma.⁸ These researchers found that having more risk genotypes was better associated with development of asthma, and that IgE levels also correlated with the number of risk genotypes. These data suggest that the risk of asthma development could be magnified by the number of at-risk single-nucleotide polymorphisms an individual carries.

Polymorphisms in the β_2 -adrenergic receptor have been shown to affect the response to β -adrenergic agonists, but little is known on whether they have a similar effect with β -adrenergic antagonists. In a short communication, propranolol was shown to decrease airway function in patients with steroid-treated mild to moderate asthma and the Arg16 genotype, but not in those with the Gly16 genotype.⁹ This study does raise questions about the role of these genotypes with other diseases and therapies that we, as allergists, often do not think about.

In some patients with asthma, clearance of *Aspergillus fumigatus* from the airways is impaired. Using a mouse model, the impact of allergic sensitization on clearance of this fungus was studied.¹⁰ Interestingly, just sensitizing mice to dust mites was sufficient to impair clearance of *A. fumigatus*, and this was associated with decreased alveolar macrophage phagocytic activity and expression of Toll-like receptor-4 and dectin-1, which the researchers suggested might explain the persistence of the fungus in the airways.

An interesting publication in 2014 looked at why some college students report increased allergic symptoms when returning home to an environment with a cat that previously did not cause problems.¹¹ When examining college students over the school year, the investigators found that cat-specific IgE did not change in sensitized students, but levels of cat-specific IgG did decrease. This led to significant decreases in the IgG-to-IgE ratio, providing a plausible

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explanation for the increase in symptoms those students had after returning home.

Two publications explored therapeutics for allergic rhinitis. The first took advantage of the fact that anticholinergic drugs have some utility in allergic rhinitis.¹² In this study, treatment of mice with ipratropium bromide led to decreases in almost all markers of allergic disease (IgE, nasal eosinophils, and interleukin-4), whereas the transcription factor associated with regulatory T cells (*Foxp3*) was noted to increase. These mouse data support an idea that anticholinergic therapies have the potential to be anti-inflammatory and provide symptomatic relief. The second study used a DNA vaccine expressing Der p 1 and ubiquitin, in which intranasal inoculation of mice drove a T-helper cell type 1 response with high levels of dust mite-specific IgG.¹³ Although this prevented development of disease, it was not studied whether the vaccination strategy could shut off already existent allergic rhinitis.

In terms of mechanisms of disease, there were several impactful publications in the past year. Food allergy is a major health problem and Chinese herbal therapy has shown some promise, but the mechanism of action was not known. Using an in vitro system for IgE production, two compounds, berberine and limonin, were identified from the herbal therapy that suppressed IgE production and might be the active compounds that could be purified and used as treatment.¹⁴ Another study looked at mechanisms that could drive non-immediate drug hypersensitivity.¹⁵ Because these reactions are primarily in the skin, the investigators examined serum levels of chemokines known to be important for skin homing. They found that these drug reactions were associated with elevated thymus- and activation-regulated chemokine (CCL17; TARC), cutaneous T cell-attracting chemokine (CCL27; CTACK), and interleukin-10 levels in the blood, suggesting strong signals to attract T cells to the skin are present during these reactions. Another study examined the potential role of mast cells in oral inflammatory diseases in which trigeminal nerve stimulation was demonstrated to lead to degranulation of mast cells in the mouths of rats—and only on the side stimulated.¹⁶ Therefore, vascular permeability in the oral cavity could be due to the effect of nerve stimulation of mast cells, suggesting that inflammatory diseases of the oral cavity might be amenable to therapies that block mast cell degranulation. Although this study was performed in rodents, it does have potential relevance to humans, as long as we keep focused on the reason for animal models—something that was discussed in an insightful editorial in 2014.¹⁷

In addition to the research mentioned earlier, there were review articles that provided important and timely information from experts in the field. In 2014, these articles focused on the eosinophil, featuring the role of eosinophils in eosinophilic esophagitis, hypereosinophilic syndrome, and even health and disease.^{18–20} In addition, the developing importance of the microbiota to immune cell development was explained in a way that was relevant to practicing clinicians.²¹ From “mice to men,” these publications show the breadth of basic science in the *Annals* and span the field of allergy and immunology. We look forward to a productive 2015 with many more impactful breakthroughs in the science that underlies our clinical practices every day!

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