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Initiation and maintenance of allergic inflammation: Team work at the interface of innate and adaptive immunity

Editorial overview

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Allergic diseases comprise a series of distinct clinical syndromes like atopic dermatitis, allergic asthma, allergic rhinitis, food allergy, and systemic anaphylaxis that have a common genetic and pathophysiological basis. Central to these diseases is the presence of an immunoglobulin (Ig)-E response to common allergens like pollen, animal dander, insect-derived toxins, house dust mite (HDM), or fungi. Once formed, allergen-specific IgE can then arm crucial effector cells of the innate immune system like mast cells and basophils so that these degranulate and release mediators of acute allergic inflammation upon allergen-crosslinking with repeated allergen encounters. The crucial importance of this IgE/mast cell/basophil axis in certain aspects is illustrated by the therapeutic use of blocking antibodies to IgE that inhibit the binding to the high affinity IgE receptor and have been successfully used for the treatment of severe allergic asthma.

The production of allergen-specific IgE responses by B lymphocytes is controlled by Th2-type T helper cells that produce IL-4 and IL-13 and promote IgE class switching. Despite the fact that we still do not know exactly where and by which B lymphocyte type (memory B cell or plasma cell in periphery versus bone marrow) IgE responses to allergens are maintained, a great deal of research effort has been put in understanding the instructive signals that determine Th2 polarization to common allergens. This is important not only for understanding IgE synthesis but also for better understanding chronic allergic inflammation that is often accompanied by accumulation of eosinophils, functional alterations of structural components in the skin, nose and lung, and by structural tissue remodeling (e.g. epidermal thickening of the skin in AD, basement membrane thickening in asthma). Through their production of IL-5, the Th2-type lymphocytes support the development of tissue eosinophilia, while secretion of IL-4 and IL-13 leads to mucus hypersecretion and goblet cell metaplasia in the lung and gut.

Many allergens are relatively harmless proteins or lipid antigens, which we should easily tolerate and for which mounting an immune response is not a matter of life or death, and for which therefore there should not have been evolutionary pressure (contrary to antimicrobial immunity). The process of allergic sensitization (by strict definition the production of IgE responses) has been mainly studied from the perspective of understanding how aberrant cellular Th2 responses to allergens are initiated and controlled, and has often been addressed from the angle of failure of tolerance

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mechanisms, or comparisons with immunity to helminths where Th2 immunity does seem protective. Not surprisingly, most investigators have focused on the immune system as the primary culprit of allergic disease. Great progress has also been made as to how allergens can activate the structural cells of the skin, lung and gut.

As pointed out in the articles of Willart and Hammad on allergic sensitization in the lung, as well as those of Novak and Leung on atopic dermatitis, it is clear now that structural cells that line the outside world like keratinocytes, gut epithelial cells and airway epithelial cells also play a crucial role in determining the outcome of the adaptive immune response to allergens, not only by providing barrier function and impeding allergen entry, but also by secreting the crucial cytokines that instruct antigen presenting dendritic cells (DCs) to mount a particular type of T helper response. Many of the genome wide association studies in allergic disease have come up with genetic polymorphisms in genes that control various aspects of epithelial biology like integrity, permeability, and expression of pattern recognition receptors. As pointed out in several of the articles that follow, structural cells within allergic inflammation produce a common set of 'innate immune system' cytokines like thymic stromal lymphopoietin (TSLP), GM-CSF, IL-25, IL-33 and other IL-1 family members (like IL-36 in the skin) that have tissue-specific intrinsic effects, but share the propensity of promoting Th2 immunity.

Drs. Natalija Novak and Donald Leung focus on new advances in atopic dermatitis (AD), the most common skin disease of childhood. Recent studies indicate that AD results from barrier defects combined with abnormal immune responses involving the innate and the adaptive immune system to exogenous and endogenous factors. The central role of skin barrier in driving systemic allergic responses is supported by the observation that patients with filaggrin null mutations develop high systemic allergen sensitization and are predisposed to the development of food allergy and asthma. Beyond its critical role in contributing to the mechanical function of the skin, filaggrin degradation products have been to have moisturizing properties and inhibit the growth of *Staphylococcus aureus*. Loss of filaggrin could thereby result in the dry skin and *S. aureus* colonization observed in AD. It is noteworthy that even patients with filaggrin gene mutations outgrow their AD suggesting that the environment and immune response play an important role in the phenotypic expression of AD. Other examples of barrier defects are mutations in hornerin and claudin-1, important structural component of the epidermal layer, that are associated not only with atopic dermatitis, but also with peanut allergy and development of asthma in AD patients.

As pointed out in several reviews of this issue, allergens are often proteolytic and can thus activate protease-activated

receptors or the complement system and in this way activate structural cells to release the innate pro-Th2 cytokines. Often, allergens are also contaminated by classical activators of innate immunity like endotoxins or C-type lectins that can trigger pattern recognition receptors not only on immune cells but also on structural cells of the skin, gut, and lung. In this regard, epithelial expression of TLR4 on lung structural cells or keratinocyte expression of the Nod-like receptors NLRP3 was found to be essential for the development of Th2 immunity to HDM in lung and skin, respectively. Strikingly, NLRP3 was not necessary for Th2 immunity to HDM in the lung, whereas it clearly was in the skin [1]. Others have shown that dectin-2 is also involved in mediating allergenicity of HDM [2]. How exactly organ-specific factors determine the predominance of a particular PRR recognition system in determining allergenicity, and how genetic predisposition impinges upon this require further detailed study, but is probably crucial to understand why some individuals develop mainly AD, whereas others are more asthmatic, despite shared genetic risk factors. Strikingly, the mechanisms that promote allergic tissue-specific disease also put the individual at risk for bacterial colonization, or promote viral replication in otherwise resistant tissues. The crucial question to address here will be if these effects are cause or effect of the allergic phenotype. As pointed out in several reviews in this issue, microbial stimulation is increasingly considered an important risk factor for the inception and perpetuation of allergic disease by promoting cytokine production and influencing tissue healing and remodeling (Natalia Novak and Donald Leung).

Despite the fact that Th2 cells are clearly involved in controlling many aspects of the allergic response, clearly not all aspects of allergic disease are exclusively controlled by these cells. A number of recent studies, highlighted in the review by Joshua Milner, demonstrate that Th17 cells also could play a predominant role in IgE synthesis and allergic disease. Classically, Th17 cell have been linked to autoimmunity, but it is similarly clear that these cells also control immunity to some extracellular bacteria and fungi. A major breakthrough has been the realization that some Th2 cells have features shared with Th17 cells and produce both IL-4 and IL-17. In studies in mouse and man, these double producing cells were crucial in causing the bronchial hyperreactivity seen in asthma. Likewise, these double producers have been demonstrated in acute lesional skin of AD patients. Strikingly, this propensity of IL-17 production was gradually lost in chronic lesions, potentially putting patients at increased risk for *S. aureus* infection. Whether there is a similar loss in chronic asthma is not known, but could be related to the increased susceptibility of chronic asthmatics to bronchial infection with viruses, a common cause for asthma exacerbation.

As pointed out in the review by David Voehringer, great progress has also been made in the precise elucidation of

the role of basophils and mast cells to innate and adaptive immunity in allergic disease. This progress is driven by the recent availability of genetically engineered mouse models that allow for specific ablation of mast cells or basophils, or allow the cell-specific deletion of genes of interest in mast cells or basophils exclusively (through Cre-mediated recombination of floxed alleles of genes of interest). These models were complicated to develop, but results of the first published studies have refuted the idea that basophils are important antigen presenting cells in the immune response to allergens, and merely seem to enforce Th2 immunity generated by other APCs. They have also provided unique and thought-provoking insights into disease pathophysiology of tick bites and acquired resistance to ticks [3]. The development of complex genetic modeling to address long standing issues in allergy is slowly gaining field, but clearly our field lags behind compared with the field of mucosal immunology of colitis or autoimmunity. As one example, we still do not have a TCR transgenic model to a relevant allergen like HDM, cat allergen or cockroach, which could greatly facilitate studying the mechanisms of allergic sensitization.

Research over the last 2 years has provided great advances in clinical and translational research of allergic diseases. Drs. Cecilia Berin and Scott Sicherer provide new insights into mechanisms and treatment of food allergy. Recent studies indicate that regulatory T cells play a key role in preventing food allergy. Emerging evidence suggests that allergic sensitization may occur if the naturally tolerogenic oral route is not the primary route of exposure. In this regard, sensitization via the skin may break tolerance to peanuts. Indeed, flaggrin gene mutations which enhance skin permeability to allergens have been found to be associated with peanut allergy. Other host factors, such as enhanced TSLP expression of the gastrointestinal epithelium, can also promote sensitization to foods. Given that orally ingested allergens are poised toward immune tolerance, a variety of new studies have examined whether oral delivery of graded amounts of food allergen via either oral immunotherapy or sublingual immunotherapy can be used for the treatment of food allergy. Although a subset of individuals do not achieve desensitization and others may encounter adverse reactions, there may be a significant proportion of patients who benefit from these approaches. Furthermore, combining these therapies with anti-IgE approaches may reduce adverse events and therefore improve the threshold of reactivity to any food allergens. Studies involving traditional Chinese herbal medicine has also provided encouraging results and boosted the overall optimism that substantial progress will be made in the near future toward the treatment of food allergy.

Drs. Stanley Szefer and Azzeddine Dakhama review the benefits and limitations of current approaches to asthma management, new insights related to mechanisms of asthma and allergic airways inflammation and new studies that could impact new directions in asthma management. It is noteworthy that despite the many advances in our understanding of asthma and the development of national guidelines for asthma care, current asthma management is still primarily symptom based. Recent reports suggest that asthma management could be improved through steps to better understand the natural history of asthma, individualization of asthma care to reduce asthma exacerbations, and the management of inner city asthma. The primary risk factor for atopic asthma has been found to be sensitization to perennial aeroallergens. Prenatal factors, for example, life style involving the farm environment, however, alter the predisposition of an infant to develop asthma. Worsening airflow limitation is associated with lower vitamin D levels in asthmatics. Anti-IgE therapy has been reported to attenuate seasonal peaks in asthma exacerbations. New tools to monitor disease activity, including biomarkers and epigenetic markers, hold promise for identifying gaps in disease management and the treatment of asthma.

In the final review of this issue, Drs. Jeffrey Stokes and Thomas Casale examine the use of allergens, environmental control, allergen immunotherapy, and immunomodulators for the management of asthma and allergic rhinitis. While the basic premise of subcutaneous injections of increasing concentrations of relevant aeroallergens to induce clinical tolerance has remained true during the past century, new advances are being made in terms of new approaches and novel formulations of allergen extracts. Most of the major allergens are now molecularly characterized. This, combined with new insights into the immunologic mechanisms by which immunotherapy induces tolerance to specific allergens, will lead to better diagnostic and therapeutic tools. Identification of the molecular basis of allergic diseases will also lead to the development of new immunomodulators targeting critical causes of allergic diseases and reducing adverse events from current forms of immunotherapy.

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