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Allergy and hypersensitivity

Editorial overview

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Allergic and hypersensitivity disorders consist of a diverse group of diseases whose incidence has dramatically increased over the last several decades. The pathogenesis of these disorders is intimately tied to the immune system, and the dynamic interplay between the innate and adaptive immune systems contributes to the pathologic response that occurs secondary to exposure to allergens, infections and metals. In this issue of *Current Opinion in Immunology*, the assembled reviews are focused on recent advances in our understanding of: firstly, innate immune pathways, including innate lymphoid cells and dendritic cells, that drive Th2- and Th17-polarized immune responses; secondly, the effects of infections on asthma severity and the generation of novel allergic diseases; thirdly, metal-induced hypersensitivity; and fourthly, therapeutic interventions in food allergy. Although it is not possible to highlight all areas of allergy and hypersensitivity in this issue, we have chosen to focus the reviews on significant advances that have recently occurred and could potentially lead to therapeutic intervention. We hope that the readers find these topics of interest.

In addition to CD3⁺ lymphocytes, innate lymphoid cells are recently described innate immune cells that play a critical role in mucosal immunity. [Drs. Kim, Wojno and Artis](#) review a subset of innate lymphoid cells, group 2 innate lymphoid cells (ILC2), and their role in allergic inflammation. These cells respond to epithelial cell-derived cytokines such as IL-25, IL-33 and thymic stromal lymphopoietin (TSLP) at mucosal and skin surfaces and secrete the type 2 cytokines IL-4, IL-5, IL-9 and IL-13. Despite their protective role in helminth infections, these cells are pathogenic in that they induce allergic inflammation at barrier surfaces and are associated with the development of airway hyperreactivity, allergic rhinitis, and food allergy in animal studies. In addition, mouse studies implicate ILC2 in influenza pathogenesis. The exact role of ILC2 in human disease is still yet to be defined. The potential development of therapeutics targeting the effector mechanisms of ILC2 in allergic inflammation is currently an intense area of investigation.

The initiation of the adaptive immune response depends on the ability of dendritic cells to scan the environment and sense potentially harmful pathogens and substances. Dendritic cells are professional antigen-presenting cells that phagocytose foreign antigen, migrate to draining lymph nodes and present processed antigen to naive T cells, resulting in T cell activation and clonal proliferation. While dendritic cells evolved to initiate protective adaptive immune responses, they also play a critical role in the initiation of harmful immune responses directed against normally harmless allergens, thus initiating the allergic cascade. [Drs. van Helden and Lambrecht](#) review the role of dendritic cells in the development of allergic disease. It is clear

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that dendritic cells are sufficient and necessary to induce allergic responses against several inhaled harmless allergens. Dendritic cells in the lung are a heterogeneous population of antigen-presenting cells that exert specific functions, and the current concepts for differentiating dendritic cell subset phenotypes and functions in the lung are highlighted in this review. Recent evidence also suggests that epithelial cells play a major role in activating dendritic cells to various inhaled allergens while macrophages strive to maintain the airways in a tolerogenic state through the prevention of dendritic cell activation.

Despite the importance of allergen-specific CD4⁺ Th2 cells in the initiation of allergic reactions, patients with moderate to severe asthma have increased airway neutrophils and increased Th17 cytokines, IL-17A, IL-17F, and IL-22, in the bronchoalveolar lavage fluid. [Drs. Newcomb and Peebles](#) review the importance of this T helper cell subset in the immunopathogenesis of asthma. Th17 cells play an important role in infections, recruiting neutrophils to the site of inflammation. However, they play a pathogenic role in the setting of autoimmunity. In severe asthma, Th17 cytokines recruit neutrophils to the airway by increasing secretion of epithelial-derived neutrophilic chemokines. Th17 cytokines also induce mucous cell metaplasia and airway smooth muscle narrowing. The role of Th17 cytokines in regulating Th2 cytokine expression and allergic airway inflammation remains unclear. However, it is clear that IL-4 and IL-13 negatively regulate IL-17A secretion from human and mouse Th17 cells *in vitro* and from mouse Th17 cells *in vivo*, suggesting that biologic agents that selectively antagonize these Th2 cytokines might have the unintended effect of increasing IL-17A production. It will be important to examine the effect of IL-4 and IL-13 antagonism on IL-17A expression in human *in vivo* studies. More importantly, ongoing clinical trials with therapeutics targeting IL-17A and IL-17 receptor signaling will shed light on the importance of Th17 cells in asthma.

[Drs. Moore, Stokes and Hartert](#) review the importance of viral genotypes in the pathogenesis and severity of two common viruses: respiratory syncytial virus (RSV) and human rhinovirus (HRV). RSV is the leading cause of lower respiratory tract infection and viral death in infants while HRV is the most common cause of upper respiratory tract infection in humans. Importantly, both have been implicated in the pathogenesis of asthma. Within RSV and HRV, viral genetic differences play a key role in disease severity and/or prevalence in patient populations, and viral genetic differences affect pathogenesis. For example, RSV strain-specific mucus induction has been mapped to the viral fusion (F) protein, and distinct RSV F proteins induce more or less neutrophils, which regulate IL-13. Collectively, viral strain-specific phenotypes can be used to dissect the underlying pathogenetic mechanisms of these viruses and their effects on airway hyperreactivity.

[Drs. Platt-Mills and Commins](#) explore the emergence of new allergic diseases, such as cetuximab-induced hypersensitivity, and the immunopathogenetic mechanisms underlying their development. Investigations established that reactions to this monoclonal antibody occurred in patients who had preexisting IgE antibodies directed against the oligosaccharide, galactose- α -1,3-galactose, on the Fab portion of the molecule. Further investigations revealed that this response occurred predominantly in the Southeastern United States. Epidemiologic studies linked bites from the lone star tick, *Amblyomma americanum*, and its larvae to the presence of high titer IgE antibodies against galactose- α -1,3-galactose. Thus, IgE directed against galactose- α -1,3-galactose provides a model of a parasite-induced IgE response that is not related to asthma and established that foreign antigens can enter through the skin and induce IgE antibodies.

Pathological immune responses to metal ions such as beryllium (Be), nickel (Ni), and others are among the most common causes of T cell-mediated hypersensitivities in humans, yet the nature of cation presentation to the T cell receptor (TCR) is unknown. [Drs. Dai, Falta, Bowerman, McKee and Fontenot](#) provide a review of the structural basis of chronic beryllium disease. Their HLA-DP2 structure identifies a beryllium-binding site within the footprint of the TCR. In addition, recent work suggests that beryllium converts HLA-DP2-binding self-peptides into neoantigens that are subsequently recognized as non-self, further blurring the distinction between hypersensitivity and autoimmunity.

Food allergies continue to increase in prevalence in westernized countries. Despite strict dietary avoidance, which is the only approved management for food allergy, accidental exposures regularly occur and lead to significant patient anxiety and diminished quality of life. In the final review of this issue, [Drs. Moran, Vickery and Burks](#) provide an overview of recent oral and sublingual immunotherapy trials in the treatment of food allergy. It is clear that oral immunotherapy (OIT) and sublingual immunotherapy (SLIT) can desensitize patients with food allergy. However, despite the enthusiasm for implementation of OIT and SLIT for the treatment of food allergy, definitive evidence of safety and efficacy are lacking, and methods for improving safety and long-term efficacy are needed.

In summary, there has been tremendous advancement in our understanding of allergic and immunologic based disorders in the early years of this decade; however, further “outside the box” thinking is desperately needed to develop innovative concepts that will more precisely define pathogenesis of allergic diseases. Only through paradigm changing innovation will major strides in treatment be made to help the increasing number of people who suffer from allergic diseases.