

Directing the innate immune response to prevent and control allergic diseases

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The innate immune response has emerged as a critical driving force in the development and progression of allergic diseases. Invading pathogens and environmental allergens engage the host innate immune response as the first line of defense. This response is important in determining the initial microbial load, which shapes the subsequent adaptive immune response that ensues. Indeed, the hygiene hypothesis, which has been proposed as a potential cause of the allergy and asthma epidemic, is based on reduced microbial stimulation of Toll-like receptors in early life, resulting in decreased T_H1 and regulatory T-cell responses and thus allowing for enhanced T_H2 response to allergens.^{1,2} As a further refinement of this theory, gene variants (eg, involving CD14 or Toll-like receptor 4) that lead to reduced innate immune responsiveness have been reported to alter the prevalence of asthma and allergy.³ These interactions between gene, environment, and immune responses contribute to the complexities in predicting clinical outcomes for any given individual's course of allergic illness.

An effective innate immune response requires the host to recognize foreign pathogens and rapidly mount an appropriate response. During the past year, the *Journal of Allergy and Clinical Immunology* has published many outstanding reviews and original articles that address various aspects of the innate immune response and their role in allergic diseases. Important elements of the innate immune response include physical barrier, chemical barrier, warning systems for response to danger signals, inducible chemical responses, and cellular responses.

During the past few months, a series of articles on the skin innate immune responses were published in the *Journal*.⁴⁻⁶ These include compelling data on how breaches in barrier function can result in allergic skin disease. In this regard the identification of loss-of-function mutations in the skin structural protein filaggrin as a widely replicated major risk factor for eczema sheds new light on disease mechanisms in atopic dermatitis and allergic diseases in general.⁷ It has now been repeatedly demonstrated that filaggrin gene mutations are associated with persistent and more severe eczema, early onset of skin disease, and an increased

risk of asthma in patients with a previous history of eczema (ie, the so-called atopic march).^{8,9} Importantly, filaggrin protein is not found in the lung, and filaggrin mutations are associated with an increased prevalence of asthma only with pre-existing eczema.^{10,11} The filaggrin gene is not an "asthma gene," but it is likely that other allergic diseases, such as asthma, are driven by barrier defects unique to the respective target organ. In the case of asthma, there is considerable evidence that impaired barrier function is caused by primary disruption of epithelial tight junctions, allowing inhaled substances to pass more easily into the airway wall to interact with immune and inflammatory cells.¹²

The skin barrier story, however, is much more complex than simply filaggrin gene mutations. A variety of other chemicals involved in barrier function are also defective. These include lipid abnormalities, lack of protease inhibitors, and reduced expression of antimicrobial peptides required to control skin permeability, pathogen load, and inflammation.^{4,6} Aside from genetic abnormalities, it has been demonstrated that allergen sensitization and T_H2 responses can downregulate innate immune responses in both atopic dermatitis and asthma.^{13,14}

This month's theme of the *Journal* extends our interest in innate immunity to a careful review of the microbial sensing detection systems that are required to rapidly amplify other innate immune components. Dr Andrew Liu¹⁵ provides an overview of these innate microbial sensors and their relevance to allergic disease, relating to the potential recognition of allergens by these receptors, their inhibition by allergic immune responses and inflammation, and their upregulation by microbial exposures in early life that might help to protect against the development of allergic immune responses and disease. These studies exemplify the epidemiologic evidence in human subjects that supports a role for Toll-like receptor ligand exposures in altering allergy risk. Determinants of healthful outcomes include early timing, moderate dosing, and genetic influences on the innate response to the exposures. This is complementary to the innate immune paradigm that inadequate activation might not stimulate the full development of effector and homeostatic innate immune responses, resulting in inadequate regulatory cell development, adaptive T_H2 responses, and allergic disease.

In a second review Dr Angela Haczku¹⁶ examines evidence that the lung collectins play an important role in modulating innate immune cell function and maintenance of the immunologic homeostasis in the lung. The collectins are a small family of soluble pattern-recognition receptors containing collagenous regions and C-type lectin domains. In studies on pulmonary surfactant proteins (ie, surfactant proteins A and D), gene-inactivated mice have demonstrated increased susceptibility to infectious agents, enhanced acute inflammatory response to pathogen exposure, and vulnerability to chronic inflammation. These observations are supported by a recent article by Brandt et al¹⁷ that demonstrates a role for surfactant protein D in altering allergic lung inflammatory responses and another report by Hortobágyi et al,¹⁸ who showed that

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surfactant protein D is important in preventing constitutive activation of macrophages and dendritic cells in the airways.¹⁸

The ability of innate immune responses to direct adaptive immune responses is providing new strategies in the treatment of allergic diseases. There have now been numerous studies using probiotics for the prevention and treatment of allergic diseases, unfortunately with very variable results, which might depend on disease duration, dosing, and the nature of the probiotic used.^{19,20} Use of Toll-like receptor adjuvants for allergen-based immunotherapy, including peanut allergy²¹ and respiratory allergy, have been promising but still require definitive clinical trials.^{22,23} There has also been considerable interest in the hypothesis that vitamin D deficiency is fueling the asthma and allergy epidemic.²⁴ Indeed, recent studies using vitamin D for the treatment of atopic dermatitis have showed promising results in the augmentation of innate immune responses and clinical improvement of atopic skin disease.^{25,26} Although these observations are intriguing, they need to be backed up by well-controlled larger clinical trials before they become part of clinical practice.

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