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Allergen sensitization is the first step in the development of allergic diseases. It is estimated that nearly 50% of the U.S. population has evidence of allergic sensitization as documented by a positive skin test to environmental allergens such as house dust mite or other allergens. Fortunately, most of these individuals do not have allergic symptoms despite sensitization. However, nearly 10% of the population has a clinically significant allergic sensitization and clinical manifestations such as hay fever/allergic rhinitis, asthma, or a food allergy.

Allergic sensitization begins early in life and occurs primarily in high risk infants, who have a parent with underlying allergic disease. Initial sensitization is usually to foods such as egg or milk. This sensitization may lead to clinical symptoms, but by 3–5 years of age, tolerance to foods has often developed. Beginning at 1–2 years of age, the 'allergy-prone' child begins to develop sensitization to aeroallergens including antigens like house dust mites. Allergen sensitization results in immunoglobulin E (IgE) antibody production to specific allergens and their attachment to populations of IgE-receptor bearing cells such as mast cells or basophils. Following sensitization, re-exposure to antigen results in a recognition by specific IgE antibodies and a rapid activation of sensitized mast cells and basophils with release of mediators, which then account for or contribute to clinical reactions.

Our understanding of the immune processes involved in allergic sensitization and eventual contribution of these events to disease states has expanded considerably in the past decades. This expansion has followed on key epidemiological observations, which have carefully defined the influence of environmental factors that participate in sensitization. In addition, technology now exists to detect and recognize the multiple components of the immune system that are integrated in this reaction and involved not only in sensitization but also in the eventual expression of allergic disease and inflammation.

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These aspects of allergic sensitization are 'framed' in Fig. 1, which indicates that the eventual expression of allergic diseases is a complex product of a 'gene-by-environment' interaction. Identifying the various genetic and environmental factors and how they influence, over time, the development of allergic diseases has been an important step forward to better understand, appreciate, and treat these diseases.

In this volume, we focus on a number of aspects of this gene-by-environment interaction, including the genetics of allergic diseases and asthma, immune responses and their regulation, and key environmental components that contribute to the eventual development and expression of allergic diseases: allergens, respiratory viruses, and pollutants.

Ober and Yao (1) begin this issue with a comprehensive review of 'The genetics of asthma and allergic disease: a 21st century perspective.' As these authors clearly detail, the study of genetics in disease states and the search for genes, or gene-products that determine or regulate the development of disease has undergone amazing advances in the past 15 years. In their article, they describe the various approaches to the study of genetics in asthma and allergic disease as well as the strengths and shortcomings associated with these individual approaches. What follows is a clear and lucid description of the genetic pathways that have been discovered, which have resulted in a list of now well-validated asthma and allergy susceptible genes and have served to expand our understanding of key pathways that are dysregulated, thus leading to disease expression. Discovering these pathways and their contribu-

tions has and will continue to identify targets to not only define mechanisms of diseases but also to provide insight for new therapeutics that are more specific, hopefully more effective, and may lead to prevention or a cure.

A major characteristic feature of asthma is allergic inflammation that contributes to altered pulmonary physiology, including airflow obstruction and airway hyperresponsiveness. As described and illustrated by Barnes (2), this process represents a complex interplay between inflammatory cells, including mast cells, basophils, lymphocytes, dendritic cells, eosinophils, and, under some circumstances, neutrophils as well as a multitude of mediators. The orchestration of these events, as we now know them, is well described by Dr. Barnes as well as their consequences on the airway and how they lead to clinical manifestations. As he points out, this process is likely dysregulated in asthma and, as a consequence, ongoing airway injury is allowed to occur. Understanding the extent, the primary cellular repertoire, and target organ response should continue to provide direction to more effective treatment.

There are a number of well-recognized environmental factors, e.g. allergens, respiratory viruses, and pollutants that activate and interact with genes to contribute to allergic responses. Platts-Mills and Woodfolk (3) provide a comprehensive and thoughtful discussion of environmental allergens and their ability to initiate IgE sensitization. Exposure to allergens is widespread and, for most people, does not result in allergic sensitization or clinical symptoms. In addition to genetic risk factors, other aspects of this exposure contribute to the host's response. For example, dose and size of the inhaled particles is one factor that determines allergenicity. However, likely very important in determining the eventual outcome of an 'allergen' and host interaction is the mixture of various materials found in association with inhaled antigens. For example, some of the materials associated with the allergen can act as an adjuvant to enhance the effectiveness of a specific substance to stimulate IgE production. Therefore, in viewing the contribution of allergen to sensitization, it is important to realize that exposure to environmental material does not consist of 'isolated' antigenic material. Appreciating these complexities provides a better understanding of what may regulate the development of allergic sensitization and how, and where, to most effectively intervene.

Respiratory viruses, along with allergens and allergic sensitization, are major risk factors for the expression of asthma. In their chapter, 'Rhinoviruses, Allergy Inflammation, and Asthma,' Gavalá et al. (4) bring us up to date on the role of respiratory viruses, particularly rhinovirus, in the develop-

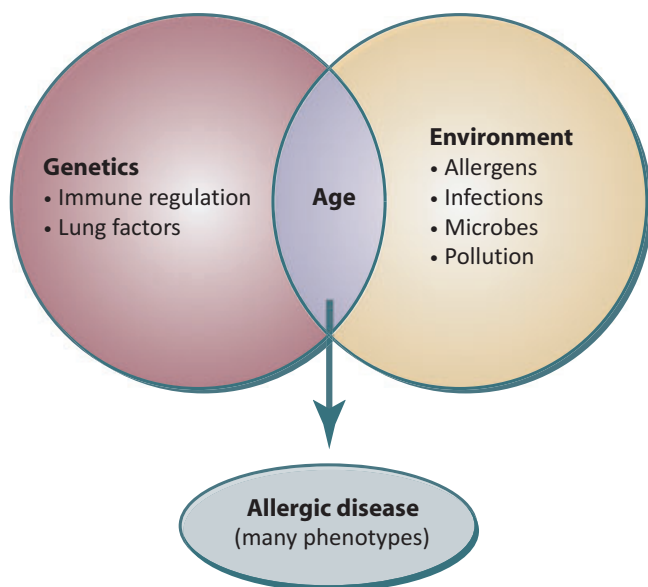


Fig. 1. The development of allergic diseases and asthma represents an interaction between genetic and environmental processes, which may also be influenced by age or development.

ment of asthma and their interaction with allergic inflammation. Key new information includes the recognition of a new strain of rhinovirus, type C, which has been identified by molecular techniques, as these viruses have not been cultured. This new class of rhinovirus appears more likely to provoke asthma. Rhinoviruses also interact with a variety of airway cells to initiate an inflammatory response. The intracellular pathways involved in this cellular activation may explain patterns of inflammation that develop and how, even though these viruses, which are not cytotoxic to airway tissue, can activate an asthmatic response. Important to understanding the consequence of virus provoked asthma will be the unraveling of how allergic inflammation and respiratory infections interact to lead to either the expression of asthma or asthma exacerbations.

Another well recognized but less clearly defined environmental factor in the pathogenesis of allergic diseases and asthma is pollutants. Peden (5) has been a leader in describing the role, contribution, and mechanisms by which these factors interact with underlying allergic inflammation to enhance this process. Using ozone and endotoxins as representatives of environmental contaminants, this review explores and thus explains how these factors are capable of inducing neutrophilic inflammation and eliciting specific changes in airway macrophages to enhance the response to inhaled allergens in sensitized hosts. The pathways by which these interactions occur have just begun to be defined but promise to form new targets for more effective treatment and prevention.

Although an appreciation of allergic sensitization has largely focused on adaptive immunity and the generation of allergen-specific IgE molecules, another contribution of the immune system to this process, which is integrated into these reactions as well, is the innate immune system. Minnicozzi *et al.* (6) have provided a comprehensive overview of innate immunity and, in keeping with the theme of this volume, discuss the role of innate immunity to allergic diseases. As these NIH-based authors describe, the innate immune system consists of multiple cell types that form a first line response to environmental stimuli. These cells have encoded pattern recognition receptors that have the ability to recognize pathogen-associated molecular patterns (PAMPs) or danger-associated molecular patterns (DAMPs). As the authors clearly explain and carefully depict, allergens are frequently found in multiple forms and mixtures that may contain PAMPs and DAMPs. The innate immune system can then serve as a major bridge between environmental factors and acquired immunity. Defects in immature immunity may also be key factors in allowing allergic sensitization to develop.

Central to the development and clinical expression of allergic disease is the production of IgE antibody. Burton and Oettgen's chapter (7) expands upon the importance and contribution of IgE antibodies to immediate hypersensitivity reactions. Their review sets the stage for an expanded discussion of their own work by first reviewing the established functions of IgE in immediate hypersensitivity. The authors then go on to present the argument that IgE has an important role in protective immunity against parasites, and, intriguingly, also exerts a regulatory influence on the expression of its own receptors, FcεRI and CD23, as well as controlling mast cell homeostasis, and represents the multiple and complex interactions of the arms of the immune system.

As described in the overview of allergic inflammation by Barnes (2), the cellular processes of these responses are multiple, diverse, and interactive. To illustrate this point, this volume has focused on a number of these players. Schroeder (8) leads this discussion by examining the basophil, whose presence is numerically small but may have an influence that is profound. As Dr. Schroeder indicates, the basophil has been viewed as a cell redundant to the tissue mast cell when evaluated in terms of IgE activation and mediators generated. His chapter provides evidence that the basophil can produce relatively large quantities of key cytokines, interleukin-4 (IL-4) and IL-13, whose presence are central for the development of allergic diseases. As he also describes, the basophil, at least in the mouse, can function as an antigen-presenting cell to initiate Th2-directed responses. If similar findings are noted in humans, an expanded role for the basophil will likely emerge as well as a potential target for treatment.

The eosinophil is often a ubiquitous finding in allergic inflammation and is considered as one of the primary effector cells in this process. As clearly explained by Kita (9), the role in and contribution to allergic disease processes by the eosinophil is re-evaluation and an undergoing expanded role. Dr. Kita provides emerging evidence that the eosinophils are multifunctional leukocytes and are involved in tissue homeostasis, as well as modulation of adaptive and innate immunity to certain microbes. As evidence of these findings on eosinophil functions emerges, it will be important to determine what will be the balance between regulation and initiation of inflammation by these cells and under what conditions, e.g. disease states, may this cell be directed toward protection versus injury.

The airway smooth muscle is a critical contributor to pulmonary dysfunction in asthma as a result of excessive contraction and subsequent narrowing of the airways. As detailed by Koziol-White and Panettieri (10), airway smooth muscle

contributions to allergic airway events are more expansive and complex than previously considered. In addition to its key role in pulmonary physiology, the airway smooth muscle is an immune organ that can modulate immune responses through its generation and secretion of mediators as well as expression of cell surface molecules. As these authors explain, airway smooth muscle immune responses can serve to amplify, or dampen, the inflammatory reaction. The findings of these authors are a further example of how the various cell types involved in allergic inflammation are undergoing an expanded role.

Airway epithelial cells form the barrier between the lung and the environment. Although initially viewed as primarily a 'protective' barrier, epithelial cells are now known to be important in the development and regulation of allergic airway responses. Proud and Leigh (11) have been major investigators of epithelial cell function, and their chapter details how and what are the pathogenic results of epithelial cell interactions with environmental factors, especially rhinoviruses, and the interactions with innate immune responses in the eventual airway processes. In addition, the authors begin a discussion on how the epithelial cells may respond to asthma treatment and consequences of these interactions on regulation of allergic inflammation.

Building on the theme of epithelial cell contribution to the immune response, Holgate (12) extends this discussion and presents evidence that asthma may be primarily an epithelial cell disorder which results from altered epithelial cell physical and functional barrier properties. Dr. Holgate presents the argument that, in an at risk person, impaired barrier function of epithelium makes the airways vulnerable to early life virus infections, which, in turn, may provide a key stimulus to prime immature dendritic cells toward directing T-helper 2 (Th2) responses. Furthermore, once this altered process has been established, there is an impaired epithelial cell repair to contribute to the development of persistent asthma. This scenario explains how persistent asthma may result in a vicious cycle that can become self-perpetuating.

Asthma does not represent a single, uniform disease but rather is characterized by multiple phenotypes. Bhakta and Woodruff (13) begin their chapter by explaining that asthma is heterogeneous in terms of clinical features, cellular sources of inflammation, and response to treatment. Their work has shown that important and telling differences exist in cytokine-driven inflammation and these distinctions may serve to underlie differences in the multiple phenotypes. From their work, the authors have begun to identify new biomarkers that may reflect this heterogeneity and also serve an impor-

tant function to identify patients who will be most responsive to various treatment interventions. If this premise is confirmed, treatment can become more specific, direct, and effective.

Atopic dermatitis is an early manifestation of allergic sensitization and altered skin barrier that also serves to illustrate a disease arising from these defects. Boguniewicz and Leung (14) provide a clear picture with new evidence that key features of atopic dermatitis are structural abnormalities in the epidermis and immune dysfunction, both of which may also be instrumental in the development of allergic sensitization and asthma. As they note, defects in the epidermal barrier predispose the skin to colonization or infection by microbial organisms, notably *Staphylococcus aureus*. Skin colonization can then become an important factor in the persistence of cutaneous lesions and resistance to conventional treatment. Like asthma, atopic dermatitis is a clinical example of how barrier defects in susceptible patients can lead to a clinical allergic syndrome.

Anaphylaxis is a clinical example of an acute, IgE-dependent allergic reaction. As discussed in Boden and Burks' review (15), the immune features of anaphylaxis, immune responses, and target organ reactions can be life-threatening in selected patients. An area of anaphylaxis where there has been tremendous progress in the past 15 years is food allergies. There is now a greater appreciation of the scope of these reactions, the antigenic composition of foods, and treatment. This review uses anaphylaxis as a clinical example and model to illustrate how information about this immune information can lead to more specific and effective treatment.

With an expanded knowledge of immune reactions, their contribution to disease patterns, and the technology to develop interventions, treatment of allergic diseases is evaluating new, mechanism-specific molecules. Nguyen and Casale (16) present data on strategies of immune modulation of allergic diseases which have gone to human studies. These trials are most often directed toward Th2 responses and have included blockade of Th2 cytokines, Th2 effector molecules, and cells involved in the Th2 responses. These clinical trials have not only been helpful to identify new and, in some cases, effective treatments but have also been helpful to unravel immune mechanisms in human diseases. Most of the immunomodulators under development have had their origin in mouse models where mechanisms of disease can be well-defined and less heterogeneous than in humans. The application of immune-modulators to human disease can act as knockout molecules to clarify the contribution of immune mechanisms to allergic diseases.

The application of knowledge on the immune system and technologies to apply this information has led to major advances in our understanding of allergic reactions and disease. The culmination of these advances will hopefully lead to a greater understanding and treatment of these very common diseases. The reviews included in this volume

represent examples of the advances in allergic disease and direction for future advances. Progress has been significant and continues. It is hoped that these discussions will lead to a better appreciation of the complexities of allergic inflammation and integration of immune mechanisms in these processes.

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