

Chapter 3

The Pathogenesis of Allergy: A Brief Introduction

Zhi-Qiang Liu and Ping-Chang Yang

Abstract Allergic diseases are mainly IgE-mediated diseases that include allergic rhinitis, allergic asthma, allergic dermatitis, and food allergy, etc. The precise causative factors of allergic diseases are not clear. It has been proposed that some people are genetically prone to develop allergic diseases. When these people encounter foreign antigens, dendritic cells capture and process the antigens, transfer the antigen information to T helper (T_H) cells, and a skewed immune response is induced that results in a T_H2 polarization status in the body. These antigen-specific T_H2 cells present the antigen information to B cells and drive these cells to become plasma cells that produce antigen-specific IgE. This antigen-specific IgE sensitizes mast cells by binding to the high-affinity IgE receptors on their surface. When the sensitized mast cells are re-exposed to the specific antigens, they are activated to release allergic mediators such as histamine, tryptase, leukotrienes, and serotonin, etc. that initiate allergic attacks.

Keywords Pathogenesis · Immunoglobulin E · Cytokines · Predisposition

3.1 Introduction

Allergy, formally called type I hypersensitivity, is described as an immediate reaction of the immune system to certain antigens that is largely mediated by IgE antibodies (Uzzaman and Cho 2012). Broadly, allergy is a mistargeted immune response that occurs after the body has been primed with certain exposed antigen(s) that then triggers an abnormal immune response seen mainly as physiological dysfunction or tissue damage. Allergens are usually external, innocuous

Z.-Q. Liu · P.-C. Yang (✉)

Allergy and Immunology Branch, College of Medicine, Shenzhen University,
Nanhai Avenue 3688, Shenzhen, Guangdong 518060, People's Republic of China
e-mail: pcy2356@163.com

substances that include: (1) airborne particles such as dust and pollen, which are the causes of asthma symptoms; (2) foods, insect stings, and some medications such as penicillin that may result in allergies; and (3) substances such as latex coming in contact with the skin that can cause contact dermatitis or eczema. The allergic reactions can sometimes be severe and result in life-threatening reactions called anaphylaxis. Some people have a predisposed and exaggerated tendency to become sensitized to a variety of common environmental allergens, which is termed atopy. Two things, host and environment, are generally responsible for this predisposition. The internal host factors are mainly heredity, sex, race and age. Exposure to infectious diseases in early childhood, environmental pollution, allergen levels, and dietary changes are some of the external environmental factors. In recent decades, the prevalence of allergy has increased greatly, while the pathogenic processes that initiate a skewed T_H2 cell polarization and antigen-specific IgE antibody production still need further study.

3.2 Mechanisms of Allergy

The immunological mechanisms involved in allergic reactions can be generally categorized into three types: IgE mediated, mixed (IgE/Non-IgE), and non-IgE mediated (cellular, delayed type hypersensitivity) (Ho et al. 2014). Because it is one of the most common allergies, food allergy has been the most extensively studied. Both immunological and nonimmunological mechanisms can cause adverse food reactions, with the most common immunological responses being IgE mediated. Non-IgE-mediated hypersensitivity to foods can also occur, such as enterocolitis, benign eosinophilic colitis, allergic eosinophilic gastroenteritis, and celiac disease. The same foods that cause food allergies can also be responsible for non-IgE-mediated hypersensitivity (Fodey 2009). Different from food allergies, food intolerance is defined as an adverse food reaction that includes metabolic, toxic, psychological, and pharmacological reactions, but without the involvement of immunological mechanisms (Ja et al. 2010).

3.3 IgE-Dependent Mechanism of Allergy

The pathophysiology of IgE-dependent type I hypersensitivity generally consists of two phases: the acute response and the late-phase response. In the early stage, antigen is processed and presented by antigen-presenting cells, mostly by dendritic cells, in the form of a MHC II-antigen peptide complex. The antigenic peptide is then recognized by naïve $CD4^+$ T cells on a specific T cell receptor (TCR), resulting in their proliferation and differentiation into T_H2 lymphocytes. This response also includes the release of cytokines and costimulatory factors from stimulated dendritic cells. The expression of costimulatory molecules is essential for the

activation of naïve T cells (Ruiter and Shreffler 2012). T_H2 cells produce interleukin (IL)-4, IL-5, IL-13, which are important in responses against extracellular, multicellular pathogens such as parasites. With the help of T_H2 cells, antigen-specific B lymphocytes differentiate into plasma cells that undergo immunoglobulin class switching to IgE production. Secreted IgE circulates in the blood and binds to the surface of mast cells and basophils on IgE-specific receptors (FcεRI), resulting in the sensitization of these cells to specific allergens. Later, when re-exposed to the same allergens, cross-linking of the allergen bound IgE and FcεRI activates the sensitized cells to undergo degranulation, during which they release histamine and other inflammatory chemical mediators that cause allergic symptoms. With the subsidence of the acute response, the late-phase response may occur, which begins with the migration of other leukocytes such as neutrophils, eosinophils, and macrophages to the initial site of allergen exposure (Grimbaldeston et al. 2006).

3.4 IgE-Independent Mechanism of Allergy

For non-IgE-mediated allergy, the mechanism may involve immune complexes formed by food antigens and antibodies to them, such as IgG, IgM, and IgA, as well as cell-mediated immunity. Non-IgE-mediated allergy to foods causes a wide range of diseases from atopic dermatitis to celiac disease (Pasha and Saeed 2013). Studies suggest that non-IgE-mediated gastrointestinal food allergy may be a nonimmediate type allergic reaction in which antigen-presenting cells, T cells, epithelial cells, and eosinophils are involved, but the precise mechanism of non-IgE-mediated allergy remains elusive (Nomura et al. 2012). Non-IgE-mediated and irritant-induced occupational rhinitis is caused by work exposure to drugs, wood dust, chemicals, etc., and is different than allergic occupational rhinitis, which is an IgE-mediated hypersensitivity reaction. Non-IgE-mediated occupational rhinitis may be due to contact with low molecular weight chemicals. The allergic mechanism of this disorder has not yet been characterized and needs to be studied further (Siracusa et al. 2013).

3.5 Understanding IgG Involvement in Allergy

Allergic diseases are usually defined as a group of allergic reactions driven by IgE-dependent mechanisms and affect approximately 22 % of the world population. In some allergy-like reactions, the serum IgE levels are normal, suggesting that the IgE-mediated mechanism might not be the only mechanism causing allergic disorders. IgG may also play a role in the pathogenesis of allergy (He 2013). The role of IgG and FcγR signaling in humans with allergic disease is still controversial, but allergen-specific IgG could contribute to the pathogenesis of allergy. IgG may interact with the Fc-gamma receptor (FcγR) on antigen-presenting cells and

cause the induction of allergic inflammation. Studies showed that IgE-deficient mice were able to develop airway hyperactivity, and specific IgG may have played a role. High-affinity human IgG receptors FcγRIIA and FcγRI may be involved in an IgG-mediated allergic response and anaphylaxis (Hofmaier et al. 2014). It has been reported that FcγRI contributes to IgG2a-induced type I hypersensitivity and passive systemic anaphylaxis, while FcγRIIB negatively regulates hypersensitivity reactions in mice (Bruhns 2012). In addition, some studies found increases in allergen-specific IgG antibodies in humans after specific immunotherapy. One of the IgG subclasses, IgG4, may be able to block IgE antigens from binding to mast cells and, thus, inhibit the allergic response (Williams 2012). The role of antigen-specific IgG in the pathogenesis of allergic diseases remains obscure and varies according to the level of exposure to specific antigens.

3.6 Innate and Adaptive Immunity in Allergy

Innate immunity is a primitive system for host defense that occurs at the time of the initial encounter with antigen and does not require prior exposure. The development of an adaptive immune response requires gene rearrangement, which evolved specifically for antigen recognition. Innate immune responses are characterized by rapid and transient reactions, while adaptive immunity develops slowly but is more powerful and rapid upon re-exposure to the same antigens due to immunological memory (Vighi et al. 2008). The T_H2 promoting milieu is essential; however, the causes and the origin of this milieu are unclear (Wambre 2012). In fact, innate immunity and adaptive immunity are two undifferentiable parts of the immune system; both of them play an important role in the T_H2 response promoting milieu (Finn and Bigby 2009). Airway epithelium or skin barrier tissue can be stimulated by allergens or viral infection to secrete IL-25, IL-33 and TSLP and these cytokines act on dendritic cells to bias the response towards T_H2 differentiation (Saenz 2008; Schleimer et al. 2007).

The gastrointestinal system is a major site of the body that is in contact with external stimuli and commensal flora. It is a prominent part of the immune system, with gut-associated lymphoid tissue (GALT) orchestrating the generation of immune tolerance, eliminating luminal antigens, and also damaging the intestinal mucosa through innate and adaptive immune responses. Food allergy is a specific immune response that repeatedly occurs on exposure to a given food (Burks et al. 2012). Why this occurs is still obscure (Sicherer 2011). Immune adjuvants play an important role in the generation of a skewed T_H2 response and have the capacity to speed and amplify the immune response to an antigen through pattern recognition receptors (PRRs), resulting in proinflammatory cytokine release, innate immune cell activation, and initiation of an adaptive immune response. The structural and functional properties of food proteins play an important role in their allergenicity. However, in order to elicit immune responses, food allergens must survive or bypass digestion, as only intact allergens can be recognized by

specific IgE. Protein glycosylation may contribute to protein stability and some proteins in both food and inhalant allergens bind lipids that protect the antigens from digestion and enhance absorption. Environmental exposure to peanut through an impaired skin barrier increases allergy risk and maternal early intake of peanut reduces the infant's risk of peanut allergy. The offspring of peanut-sensitized mice are prone to developing peanut allergy. A diverse and healthy infant diet has a protective effect in inhibiting the development of atopic disease (Sicherer and Leung 2015).

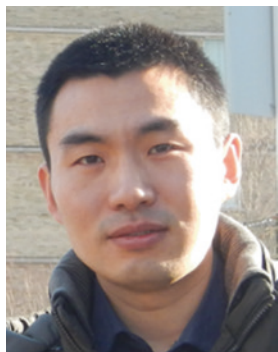
In summary, allergy is an immediate immune reaction of the body to allergens and is mostly mediated by IgE antibodies. It may occur in certain individuals with genetic susceptibility under certain environmental influences. The incidence of allergic diseases has increased rapidly in recent decades; thus, it is important that the pathogenesis of allergy continue to be further elucidated.

References

- Bruhns P. Properties of mouse and human IgG receptors and their contribution to disease models. *Blood*. 2012;119(24):5640–9.
- Burks AW, Tang M, Sicherer S, Muraro A, Pa Eigenmann, Ebisawa M, et al. ICON: food allergy. *J Allergy Clin Immunol*. 2012;129(4):906–20.
- Finn PW, Bigby TD. Innate immunity and asthma. *Proc Am Thorac Soc*. 2009;6(3):260–5.
- Fodey TL, Greer NM, Crooks SR. Antibody production: Low dose immunogen vs. low incorporation hapten using salmeterol as a model. *Anal Chim Acta*. 2009;637(1–2):328–32.
- Grimbaldeston MA, Metz M, Yu M, Tsai M, Galli SJ. Effector and potential immunoregulatory roles of mast cells in IgE-associated acquired immune responses. *Curr Opin Immunol*. 2006;18(6):751–60.
- He SH, Zhang HY, Zeng XN, Chen D, Yang PC. Mast cells and basophils are essential for allergies: mechanisms of allergic inflammation and a proposed procedure for diagnosis. *Acta Pharmacol Sin*. 2013;34(10):1270–83.
- Ho MH, Wong Wh, Chang C. Clinical spectrum of food allergies: a comprehensive review. *Clin Rev Allergy Immunol*. 2014;46(3):225–40.
- Hofmaier S, Comberiati P, Matricardi PM. Immunoglobulin G in IgE-mediated allergy and allergen-specific immunotherapy. *Eur Ann Allergy Clin Immunol*. 2014;46(1):6–11.
- Ja Boyce, Assa'ad A, Aw Burks, Sm Jones, Ha Sampson, Ra Wood, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol*. 2010;126(6 Suppl):007.
- Nomura I, Morita H, Ohya Y, Saito H, Matsumoto K. Non-IgE-mediated gastrointestinal food allergies: distinct differences in clinical phenotype between Western countries and Japan. *Curr Allergy Asthma Rep*. 2012;12(4):297–303.
- Pasha I, Saeed F, Sultan MT, Batool R, Aziz M, Ahmed W. Wheat allergy & intolerance; recent updates and perspectives. *Crit Rev Food Sci Nutr*. 2013;2:2.
- Ruiter B, Shreffler WG. Innate immunostimulatory properties of allergens and their relevance to food allergy. *Semin Immunopathol*. 2012;34(5):617–32.
- Saenz SA, Taylor BC, Artis D. Welcome to the neighborhood: epithelial cell-derived cytokines license innate and adaptive immune responses at mucosal sites. *Immunol Rev*. 2008;226:172–90.
- Schleimer RP, Kato A, Kern R, Kuperman D, Avila PC. Epithelium: at the interface of innate and adaptive immune responses. *J Allergy Clin Immunol*. 2007;120(6):1279–84.
- Sicherer SH. Epidemiology of food allergy. *J Allergy Clin Immunol*. 2011;127(3):594–602.

- Sicherer SH, Leung DY. Advances in allergic skin disease, anaphylaxis, and hypersensitivity reactions to foods, drugs, and insects in 2014. *J Allergy Clin Immunol*. 2015;135(2):357–67.
- Siracusa A, Folletti I, Moscato G. Non-IgE-mediated and irritant-induced work-related rhinitis. *Curr Opin Allergy Clin Immunol*. 2013;13(2):159–66.
- Uzzaman A, Cho SH. Chapter 28. Classification of hypersensitivity reactions. *Allergy Asthma Proc*. 2012;33(Suppl 1):S96–9.
- Vighi G, Marcucci F, Sensi L, Di Cara G, Frati F. Allergy and the gastrointestinal system. *Clin Exp Immunol*. 2008;1:3–6.
- Wambre E, James EA, Kwok WW. Characterization of CD4⁺T cell subsets in allergy. *Curr Opin Immunol*. 2012;24(6):700–6.
- Williams JW, Tjota MY, Sperling AI. The contribution of allergen-specific IgG to the development of th2-mediated airway inflammation. *J Allergy*. 2012;236075(10):21.

Authors' Biography



Dr. Zhi-Qiang Liu PhD is an Associate Professor and Senior Research Scientist at Longgang Central Hospital and ENT Institute of Shenzhen. He is working on the pathogenesis of food allergy, allergic rhinitis, and the immune mechanisms of inflammatory bowel diseases. Dr. Zhi-Qiang Liu has published more than 20 scientific papers in internationally well-recognized journals and has written one book chapter.



Professor Ping-Chang Yang PhD is the Director of the Allergy and Immunology Center at Shenzhen University School of Medicine in Shenzhen, China. Dr. Yang's research focuses on the pathogenesis of allergy, specifically immune regulation and immune tolerance. One of Dr. Yang's research findings is that intestinal epithelial cells play a critical role in initiating the development of antigen-specific immune tolerance and that T_H2 cytokines, such as IL-13, can compromise established immune tolerance. Using several immune-competent molecules, Dr. Yang has found that the compromised immune tolerance can be restored in an allergic environment. Dr. Yang's next goal is to elucidate the mechanism by which the IgE isotype switch is initiated in B cells.