Chapter 11
Antigenicity, Immunogenicity, Allergenicity

Jianguo Zhang and Ailin Tao

Abstract The term "*immune*" pertains to the body keeping itself free from diseases, not to trigger any diseases. In this regard, it makes sense for us to divide *antigenicity* into *immunogenicity* and *allergenicity*. This distinction allows for the characterization of all types of modern antigens, i.e., to evaluate and modify a priori the allergenicity of an antigen before it is applied to humans. In this chapter, we also formulated the hypothesis that "Balanced Stimulation by Whole Antigens" is essential for immune development. This hypothesis revives the practicality of the "Hygiene Hypothesis" and can provide a fundamental solution to curb the increasing prevalence of allergic disease, namely, early exposure, at 0–1 year old or earlier, in utero, of representative allergens/protein antigens with immunogenicity retained or improved and allergenicity attenuated or eliminated.

Keywords Antigenicity · Immunogenicity · Allergenicity · Immune response · Balanced stimulation

11.1 Introduction

Allergic diseases are caused by an inappropriate initiation of Type 2 (T_H2) immune responses to innocuous environmental antigens that affect the upper airway mucosa (rhinitis), lung (asthma), the gut (food allergy), and the skin (dermatitis) (Julia et al. 2015). Over the last two to three decades, the prevalence of allergic

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Table 11.1 Composition of the immune system

Immune organs		Immunocytes	Immune molecules	
Central immune organ	Peripheral immune organ		Membrane surface molecules	Secretory molecule
Thymus	Spleen	Stem cell line	TCR	Immunoglobulin
		Lymphocyte	BCR	
Marrow	Lymph node	Mononuclear phagocyte	CD molecule	Complement
Bursa of Fabricius (birds)	Mucosa-associated lymphoid tissue	Other APC (dendritic cell, endothelial cell, etc.)	Adhesion molecule	Cytokines
	Skin-associated lymphoid tissue	Other immune cells (granulocyte, mast cell, platelet, erythrocyte, etc.)	MHC, etc.	

diseases has significantly increased and this has often been explained by a decline in infections during early life. It is thought that those who have had bacterial and viral infections during childhood are able to direct their maturing immune system (Table 11.1) toward a T_H1 type and counterbalance any pro-allergic responses of T_H2 cells (Yazdanbakhsh et al. 2002). The induction of a robust anti-inflammatory regulatory network by early life exposure to allergens offers a solution to the inverse association of allergen exposure with allergic disorders (Du Toit et al. 2008; Wu et al. 2014).

11.2 Differentiation of Antigenicity, Immunogenicity and Allergenicity

In textbooks, an antigen, also called an immunogen in some references, is a substance that binds to a specific antibody or is any molecule or molecular fragment that can be bound by a major histocompatibility complex (MHC) and presented to a T cell receptor (TCR). Two features, antigenicity and immunogenicity, are generally used to describe each antigen. Immunogenicity is the ability to induce a humoral and/or cell-mediated immune response. Antigenicity is the ability to specifically combine with the final products of the immune response (i.e., secreted antibodies and/or surface receptors on T cells) (Owen et al. 2013). Although all molecules that are immunogenic are also antigenic, the reverse is not true.

If we carefully contemplate these two characteristics that are used to define an antigen, we discover that immunogenicity and antigenicity are tightly related and are always duplicated. Antibodies are produced as the result of immune induction, not from thin air. And antigens cannot trigger an immune response unless they bind with their corresponding antibodies or receptors. The above two concepts

simply and repeatedly describe a single generality of all antigens, yet this alone does not allow us to completely characterize various antigens and cannot help us to understand antigens in various guises. However, different antigens produce different immune responses as they encounter their antibodies or receptors. Using this feature, antigens can be more accurately defined by the difference in the type of immune responses they induce.

According to the classical definition of immunology, the major function of the immune system, as in the integrated anatomic system and other systems, is to avoid disease in the human body. The immune system has its own mechanisms for maintaining a general physiological balance in life by co-operating with other systems of the body. Here, we attempt to redefine and differentiate antigenicity into immunogenicity and allergenicity. We refer to antigenicity as the ability of an antigen to induce an immunological response when it is encountered by the human body. Antigenicity involves two types of immune characteristics, immunogenicity, and allergenicity. Immunogenicity refers to the ability of an antigen to trigger normal and protective immune responses after being encountered by the human body. We describe the immunogenicity of an antigen using the following three aspects: (1) the ability to defend the immune system (**immunological defense**), which is the ability to repel an exogenous antigen and to fight against infection; (2) the ability to keep the immune system stable (**immunological homeostasis**), which is the ability of the body to recognize and eliminate damaged tissue, inflammation and/or senescent cells, and (3) the ability to kill and to remove abnormally mutated cells so as to monitor and inhibit the growth of malignancies in the body (**immunological surveillance**). Thus, immunogenicity reflects the strength of these three functions.

Allergenicity refers to the ability of an antigen to induce an abnormal immune response, which is an overreaction and different from a normal immune response in that it does not result in a protective/prophylaxis effect but instead causes physiological function disorder or tissue damage.

To further simplify, each antigen carries immunogenic and allergenic properties:

$$\text{Antigenicity} = \text{Immunogenicity} + \text{Allergenicity}$$

11.3 How to Measure *Allergenicity*?

Allergenicity, like immunogenicity, also exhibits antigen specificity. Due to different antigen/antibody specificities, each antigen has different levels of allergenicity and immunogenicity and each individual has a different immune system, thus, antigens can be allergens in individuals of different ages and different immune statuses. In general, the most potent allergens are proteins, with polysaccharides ranking second.

Allergy usually is characterized by T_H2 (T helper 2) responses, which are described by increases in the levels of interleukin (IL)-4 and other T_H2-type

cytokines (IL-5, IL-9, IL-13, and IL-21, etc.), activation and expansion of CD4+ T_H2 cells, induction of plasma cells secreting IgE, and activation of eosinophils, mast cells, and basophils, all of which can produce several types of T_H2-type cytokines (Anthony et al. 2007). Hence, the levels and duration of the T_H2 response define allergenicity.

Researchers can also ascertain a protein's identity by scrutinizing its history of medical use or by searching the literature to see whether any adverse reactions have been reported or by doing experiments to investigate the allergenicity and immunogenicity of the candidate protein(s) to be encountered by the human body. Literature reviewing also provides bioinformatics data that can be used to evaluate immunogenicity and allergenicity.

11.4 Important Factors for Early Exposure and Hygiene Hypothesis

Allergies are a major cause of chronic disease in all countries of the world with the incidence of reported cases significantly increasing over the past two to three decades. This increase has often been explained by some experts as the Hygiene Hypothesis (Cramer et al. 2012; Liu and Murphy 2003; Maizels et al. 2014; Sherriff and Golding 2002), that is, a decline in infections during early life could predispose children to be susceptible to allergy and that exposure to microbial products such as endotoxin can reduce the risk for allergic sensitization during early childhood. However, on the contrary, allergic sensitization among adults and in the elderly increased with increasing endotoxin levels (Min and Min 2015). The same observation has been made for the development of food allergy. Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy (Du Toit et al. 2008, 2015). Higher maternal intake of peanut, milk, and wheat during early pregnancy was associated with a decreased incidence of mid-childhood allergy and asthma (Bunyavanich et al. 2014). The role of diet, therefore, has been highlighted as a key factor that influences immune homeostasis and the development of allergic diseases (Julia et al. 2015). There is no benefit to delaying the introduction of any potentially allergenic food, such as milk, eggs, peanuts, or fish food beyond 6 months of age to prevent food allergy (Chin et al. 2014). Regarding the development of inhalant allergy, a similar conclusion has been drawn but with an exception for mites. It was demonstrated that early exposure to high levels ($\geq$10 μg/g dust) of dust mite allergen was associated with an increased risk of asthma and late-onset wheeze at age 7 years compared with exposure to low levels (< 0.05 μg/g dust) of dust mite allergen (Celedon et al. 2007). Also, pet exposure during the first year of life and an increasing number of siblings were both associated with a lower prevalence of allergic rhinitis and asthma in school children (Hesselmar et al. 2008).

Some experts have argued that appropriately targeted allergic hypersensitivity evolved to elicit anticipatory responses and to promote avoidance of suboptimal

environmental substances (Palm et al. 2012). However, if allergen avoidance really benefited the immune system, there would not be a need for the immune system to establish immune memory. On the other hand, different allergens belong to different groups (see Chap. 5 in this book). Single-allergen avoidance means avoiding an entire group of allergens, making complete avoidance impossible. Moreover, complete avoidance can cause malnutrition, mental retardation and lost enjoyment of life (Wang 2010). Even worse, avoiding the consumption of certain substances may trigger defects in the immune system. In fact, our meta-analysis concluded that allergen avoidance may not always be successful in preventing allergic symptoms (Wu et al. 2014), especially for newborns.

A study of the prevalence of allergy in adults demonstrated that infection with pulmonary TB contributes significantly to atopy, particularly allergic rhinitis symptoms (Lin et al. 2013). A pilot experiment showed the cross-reactivity between antigens from roundworm *Ascaris lumbricoides* (AL) and house dust mite (HDM) allergens (Acevedo et al. 2009). Another experiment with larger samples further demonstrated that AL-antigens can inhibit up to 92 % of HDM-specific IgE-reactivity among allergic subjects, while only up to 54 % of AL-specific IgE-reactivity among ascariasis subjects was inhibited by HDM allergens (Valmonte et al. 2012), suggesting that AL antigens have broader and higher allergenicity than HDM allergens and noting that the latter would sensitize up to 70 % of the allergic population (He et al. 2014). A further study from Hagel I et al. indicates that it only took a mild infection with *A. lumbricoides* (0–5000 eggs/g feces) to significantly elevate the levels of IL-13, IL-6, IL-10 as well as the levels of IFN-γ and no mention of IgE or IgG in this group, while in the moderately infected group (> 5001–50,000 eggs/g feces), IL-13 and IL-10 are very significantly increased but no increase of IgE, IgG, IFN-γ, or IL-6 was observed in comparison with those in the urban nonparasitized control group. This result indicated that the protective response against allergy development by *A. lumbricoides* relies on IL-10 but is independent of the production of IFN-γ, IgE, or IgG. These observations are complicated by concurrent infections with *Giardia duodenalis* and *A. lumbricoides*. A study evaluated the effect of *A. lumbricoides* on *G. duodenalis* infection and T_H1/T_H2 type immune mechanisms toward this parasite in 251 rural parasitized and 70 urban nonparasitized school children (Hagel et al. 2011). In the group of children mildly infected with *A. lumbricoides*, the levels of IgG, IgE, IL-13, IL-6, IL-10, IFN-γ, and IL-6 are all very significantly increased, while in the group of children moderately infected with *A. lumbricoides*, only IL-13 and IL-10 are highly elevated and IFN-γ is significantly increased but with no significant effects on the levels of IgG, IgE, or IL-6. These results suggest that *A. lumbricoides* can modulate the immune responses by affecting both T_H1 and T_H2 type immunity (Hagel et al. 2011). Therefore, the conditions regarding the severity of the *A. lumbricoides* infection and whether or not co-infection with other species of parasites has occurred are very important in reaching the real conclusion. This information would have been helpful in a study (Palmer et al. 2002) that demonstrated in a cross-sectional sample of 2164 children that *A. lumbricoides* infection is associated with increased risk of childhood asthma and atopy in rural China

but it did not contain detailed data on the above-mentioned two parameters. This could explain why previous studies of birth cohorts with participants in (sub)-urban environments that examined similar associations have yielded inconsistent results. In conclusion, the protective immune response induced by parasites in humans is dependent on the particular parasite (Ek et al. 2012) and, therefore, discussion of the protective effects without the antibody and cytokine measurements (IgG, IgE, IL-13, IL-6, IL-10, IFN-γ and IL-6) or investigation into the presence of co-infection is limited and insufficient. It is tempting to conclude that *A. lumbricoides* has high immunogenicity and low allergenicity and that this type of circumstance could significantly contribute to the maturation of our immune systems.

Pet exposure during the first year of life and an increased number of siblings were both associated with a lower prevalence of allergic rhinitis and asthma in school children (Hesselmar et al. 2008). Moreover, there is no benefit to delaying the introduction of any potentially allergenic food, such as milk, eggs, peanuts, or fish food beyond 6 months of age to prevent food allergy (Chin et al. 2014). In any case, it should be emphasized that early exposures to prevent the development of allergy should be with allergens, probiotics and non-infectious microbes (Douwes et al. 2006) but without exposure to bio-contaminants (such as biomass smoke), as these can obviously reduce lung function in young adults compared to exposure to smoke from liquefied petroleum gas (Kurmi et al. 2013).

Furthermore, the phenomenon of allergic sensitization is overrepresented among first-born or only children and less frequent in children from large families and those attending day care, suggesting that the frequent exchange of infections may protect children from allergic sensitization (Yazdanbakhsh et al. 2002). A study of gut commensals demonstrates that different rates of microbial colonization and infections with different bacterial types (*Clostridia* vs. *Lactobacilli*) would predispose children to allergy or no allergy (Sepp et al. 1997). This is similar to the situation seen with parasitic infections in children. **The protective effect of infections strictly depends on the specific species and the microbial/parasitic burden**. Thus, it is tempting to think that for immune system development and homeostasis, there are microbial and parasitic friends and foes that are very distinct and explicit. Therefore, **to better characterize the antigen, it is crucial to know how harmful (allergenic) and how beneficial (immunogenic) the antigen is to the immune system**.

Regarding mechanisms, early exposure to soil, house dust, and decaying plants increases gut microbial diversity and decreases serum immunoglobulin E levels, thus enhancing innate immunity (Zhou et al. 2015). Exposure to a non-hygienic environment did not induce significant airway neutrophilia, yet it altered the number of immunologically active cells in the lung and reduced subsequent allergic inflammation (George et al. 2006). Further studies suggested that early exposure to unhygienic conditions and infections is associated with different expression of Toll-like receptors (Majak et al. 2009) and early exposure to a farm environment seems to influence methylation patterns in distinct genes (Michel et al. 2013), therefore, epigenetic mechanisms may contribute to the development of asthma and other allergies.

11.5 Balanced Stimulation by Whole Antigens for Immune System Development

Based on what has been stated for early exposure factors in the previous sections, allergen number reduction results (see Chap. 5 in this book), and the Hygiene Hypothesis, we hypothesized that **Balanced Stimulation by Whole Antigens is necessary for healthy immune system development**. This hypothesis contains three essential parts: (1) Administration of all types of allergens in very early life contributes to the healthy maturation of the immune system and protects children from allergy development; those infants who miss exposure to one or some types of allergens during the key period of immune system expansion may develop atopy to these substances when they grow up. After a diagnosis of allergy, the affected cases would be treated by immunotherapy with these allergens. (2) Regarding mechanisms, the maternal immune status is a key factor in whether the fetus is primed for a T_H1 or T_H2 response. A balanced level of T_H1 cytokines (IFN-γ, IL-10) provided by maternal T cells drives the direction of the homeostatic development of the initial T_H0 cells of the fetus that are then further educated for tolerance during infancy and improved by a balanced stimulation with all types of allergens, even if the developing immune status is T_H2-biased. Conversely, an unbalanced stimulation that lacks of one or more types of allergens in the first year of life would negatively influence the evolving balance and/or enhance any existing T_H2-biased immune status, thus allowing the development of allergic disease. Furthermore, maternal milk, a tight link between mothers and their children, contains free dietary and environmental allergens, IgM/IgG/IgA, tolerogenic factors (such as interleukin 10, transforming growth factor-β (TGF-β), lactoferrin, antioxidants, etc.), gut growth factors (such as cortisol, thyroxine, epidermal growth factor, TGF-β, etc.) and microbiota-influencing factors (such as prebiotics, oligosaccharides, casein, etc.). These factors can be transferred to the infant during breastfeeding. During childhood and adolescence (Fig. 11.1), tolerance develops to dietary and inhalant allergens and reinforces the immune system memory to these antigens (Julia et al. 2015). (3) There is a necessity for lasting memory T cells to be restimulated in order to sustain their immortality and immunotolerance capability. It is the exposure of antigens in a certain space-time continuum that stimulate and reinforce the development of the immune system. During the naïve stage, early exposure to superantigens with attenuated allergenicity could potentially strengthen and confer immune system tolerance to their allergenicity-untouched natural counterparts—this is similar to the process of allergen-specific immunotherapy. A good example comes from the progression of smallpox vaccination (Fig. 11.2). Smallpox vaccines were originally made with whole smallpox virus that then evolved over generations to being made with the cowpox virus, which was actually a type of allergenicity attenuation that resulted in a vaccine that could therefore be safely administered to humans for protection against the smallpox virus (Fig. 11.2). It is tempting to speculate that other infectious diseases (SARS, AIDS, Ebola, etc.) could be eradicated by vaccination with their allergenicity-attenuated counterparts.

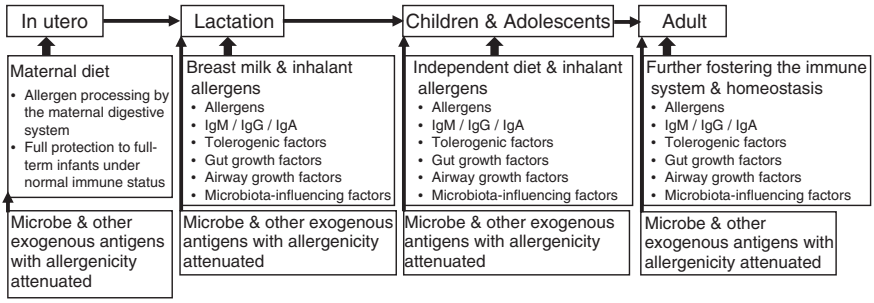

Fig. 11.1 Possible mechanisms of mother-to-offspring transfer of protection against allergy. Adapted from the reference (Julia et al. 2015). Maternal milk, a tight link between mothers and their children, contains free dietary and environmental allergens, IgM/IgG/IgA, tolerogenic factors (such as interleukin 10, transforming growth factor-β (TGF-β), lactoferrin, antioxidants, etc.), gut growth factors (such as cortisol, thyroxine, epidermal growth factor, TGF-β, etc.) and microbiota-influencing factors (such as prebiotics, oligosaccharides, casein, etc.). These factors can be transferred to the infant during breastfeeding. During childhood and adolescence, tolerance develops to dietary and inhalant allergens and reinforces the immune system memory to these antigens, otherwise the body could become allergic to these allergens/antigens along with the gradual induction of immune tolerance. Allergic disease would march onward if the adult immune system is not able to be tolerant to the allergens. In any case, the adult immune system also needs to be fostered by sustained antigen stimulation to avoid any damage to immune homeostasis. Nevertheless, the allergic status can be modified/reduced and the immune system enhanced/reinforced by immunotherapy with microbial and other exogenous antigens that can attenuate allergenicity

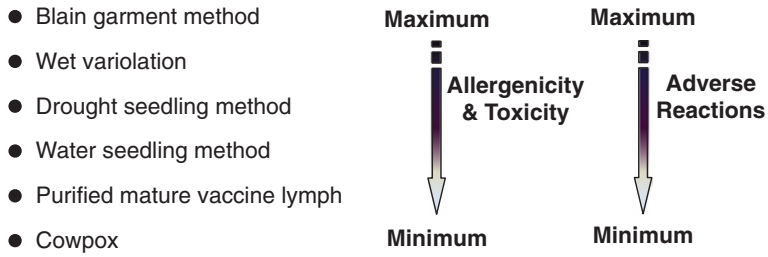

Fig. 11.2 Smallpox vaccines evolved from an original primitive type to fostered and purified vaccine lymph. The real essence lies in attenuation of the allergenicity

11.6 What Is the Future? Can We Ever Win?

Increasing allergic reactions have been described as the "Allergy March," which is the progression of atopic manifestations persisting over years and is characterized by a typical sequence of clinical symptoms from colic during infancy (tummy

pains, including bad stomach aches, vomiting and diarrhea, itchiness on the baby's face, lips and buttocks, etc.), to eczema when the child is under two-three years old (itchy skin as well as reactions to certain foods and allergens in the air), to rhinitis and then asthma. Nevertheless, we can safely heal this kind of disease by etiological immunotherapy with allergenicity-attenuated vaccines.

We have seen through vaccination that we can strengthen our immune system (Table 11.1) enough to protect us against all types of infectious diseases. It is conceivable that we can also protect from allergy development by early exposure to allergenicity-attenuated vaccines that have been genetically engineered from the environmental antigens. Thus, it is possible that **Immune Giants** could be created that would train our immune systems to be ready to handle all types of environmental antigens, no matter whether they are allergens or infectious microbes (Fig. 11.1). Regardless, the control of exposure to environmental antigens and undesirable commensal microorganisms will always be an important and challenging part of human health.

References

Acevedo N, Sanchez J, Erler A, Mercado D, Briza P, Kennedy M, Fernandez A, Gutierrez M, Chua K, Cheong N, et al. IgE cross-reactivity between Ascaris and domestic mite allergens: the role of tropomyosin and the nematode polyprotein ABA-1. Allergy. 2009;64(11):1635–43.

Anthony RM, Rutitzky LI, Urban JF Jr, Stadecker MJ, Gause WC. Protective immune mechanisms in helminth infection. Nat Rev Immunol. 2007;7(12):975–87.

Bunyavanich S, Rifas-Shiman SL, Platts-Mills TA, Workman L, Sordillo JE, Camargo CA Jr, Gillman MW, Gold DR, Litonjua AA. Peanut, milk, and wheat intake during pregnancy is associated with reduced allergy and asthma in children. J Allergy Clin Immunol. 2014;133(5):1373–82.

Celedon JC, Milton DK, Ramsey CD, Litonjua AA, Ryan L, Platts-Mills TA, Gold DR. Exposure to dust mite allergen and endotoxin in early life and asthma and atopy in childhood. J Allergy Clin Immunol. 2007;120(1):144–9.

Chin B, Chan ES, Goldman RD. Early exposure to food and food allergy in children. Can Fam Physician. 2014;60(4):338–9.

Cramer C, Link E, Koletzko S, Lehmann I, Heinrich J, Wichmann HE, Bauer CP, Berg AV, Berdel D, Herbarth O, et al. The hygiene hypothesis does not apply to atopic eczema in childhood. Chem Immunol Allergy. 2012;96:15–23.

Douwes J, van Strien R, Doekes G, Smit J, Kerkhof M, Gerritsen J, Postma D, de Jongste J, Travier N, Brunekreef B. Does early indoor microbial exposure reduce the risk of asthma? The prevention and incidence of asthma and mite allergy birth cohort study. J Allergy Clin Immunol. 2006;117(5):1067–73.

Du Toit G, Katz Y, Sasieni P, Mesher D, Maleki S, Fisher H, Fox A, Turcanu V, Amir T, Zadik-Mnuhin G, et al. Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. J Allergy Clin Immunol. 2008;122(5):984–91.

Du Toit G, Roberts G, Sayre PH, Bahnson HT, Radulovic S, Santos AF, Brough HA, Phippard D, Basting M, Feeney M, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. N Engl J Med. 2015;372(9):803–13.

Ek C, Whary M, Ihrig M, Bravo L, Correa P, Fox J. Serologic evidence that ascaris and toxoplasma infections impact inflammatory responses to Helicobacter pylori in Colombians. Helicobacter. 2012;17(2):107–15.

George CL, White ML, Kulhankova K, Mahajan A, Thorne PS, Snyder JM, Kline JN. Early exposure to a nonhygienic environment alters pulmonary immunity and allergic responses. Am J Physiol Lung Cell Mol Physiol. 2006;291(3):L512–22.

Hagel I, Cabrera M, Puccio F, Santaella C, Buvat E, Infante B, Zabala M, Cordero R, Di Prisco M. Co-infection with *Ascaris lumbricoides* modulates protective immune responses against *Giardia duodenalis* in school Venezuelan rural children. Acta Trop. 2011;117(3):189–95.

He Y, Liu X, Huang Y, Zou Z, Chen H, Lai H, Zhang L, Wu Q, Zhang J, Wang S, et al. Reduction of the number of major representative allergens: from clinical testing to 3-dimensional structures. Mediat Inflamm. 2014;2014:291618.

Hesselmar B, Aberg N, Aberg B, Eriksson B, Björkstén B. Does early exposure to cat or dog protect against later allergy development? Clin Exp Allergy. 2008;29(5):611–7.

Julia V, Macia L, Dombrowicz D. The impact of diet on asthma and allergic diseases. Nat Rev Immunol. 2015;15(5):308–22.

Kurmi OP, Devereux GS, Semple WC, Steiner S, Simkhada MF, Lam P, Hubert KB, Ayres JG. Reduced lung function due to biomass smoke exposure in young adults in rural Nepal. Eur Respir J. 2013;41(1):25–30.

Lin CT, Gopala K, Manuel AM. The impact of pulmonary tuberculosis treatment on the prevalence of allergic rhinitis. Ear Nose Throat J. 2013;92(8):358–99.

Liu AH, Murphy JR. Hygiene hypothesis: fact or fiction? J Allergy Clin Immunol. 2003;111(3):471–8.

Maizels RM, McSorley HJ, Smyth DJ. Helminths in the hygiene hypothesis: sooner or later? Clin Exp Immunol. 2014;177(1):38–46.

Majak P, Brzozowska A, Bobrowska-Korzeniowska M, Stelmach I. Early exposure to unhygienic conditions and infections is associated with expression of different Toll-like receptors. J Investig Allergol Clin Immunol. 2009;19(4):260–5.

Michel S, Busato F, Genuneit J, Pekkanen J, Dalphin JC, Riedler J, Mazaleyrat N, Weber J, Karvonen AM, Hirvonen MR, et al. Farm exposure and time trends in early childhood may influence DNA methylation in genes related to asthma and allergy. Allergy. 2013;68(3):355–64.

Min KB, Min JY. Exposure to household endotoxin and total and allergen-specific IgE in the US population. Environ Pollut. 2015;199:148–54.

Owen JA, Punt J, Stranford SA, Jones PP (2013). Kuby immunology, 7th edn (Susan Winslow).

Palm N, Rosenstein R, Medzhitov R. Allergic host defences. Nature. 2012;484(7395):465–72.

Palmer LJ, Celedon JC, Weiss ST, Wang B, Fang Z, Xu X. *Ascaris lumbricoides* infection is associated with increased risk of childhood asthma and atopy in rural China. Am J Respir Crit Care Med. 2002;165(11):1489–93.

Sepp E, Julge K, Vasar M, Naaber P, Bjorksten B, Mikelsaar M. Intestinal microflora of Estonian and Swedish infants. Acta Paediatr. 1997;86(9):956–61.

Sherriff A, Golding J. Hygiene levels in a contemporary population cohort are associated with wheezing and atopic eczema in preschool infants. Arch Dis Child. 2002;87(1):26–9.

Valmonte G, Cauyan G, Ramos J. IgE cross-reactivity between house dust mite allergens and *Ascaris lumbricoides* antigens. Asia Pac Allergy. 2012;2(1):35–44.

Wang J. Management of the patient with multiple food allergies. Current Allergy Asthma Rep. 2010;10(4):271–7.

Wu H, Guo Y, Wang J, Zhang J, Wang S, Zhang X, Tao A. The importance of allergen avoidance in high risk infants and sensitized patients: a meta-analysis study. Allergy Asthma Immunol Res. 2014;6(6):525–34.

Yazdanbakhsh M, Kremsner PG, van Ree R. Allergy, parasites, and the hygiene hypothesis. Science. 2002;296(5567):490–4.

Zhou D, Zhang H, Bai Z, Zhang A, Bai F, Luo X, Hou Y, Ding X, Sun B, Sun X, et al. Exposure to soil, house dust and decaying plants increases gut microbial diversity and decreases serum immunoglobulin E levels in BALB/c mice. Environ Microbiol. 2015;. doi:10.1111/1462-2920.12895.

Author's Biography

Jianguo Zhang is a Chief Physician and Director of the Otolaryngology Department of the Second Affiliated Hospital of Guangzhou Medical University. He is engaged in otolaryngology diagnosis and research and has directed several clinical trials on the diagnosis and immunotherapy of allergic rhinitis. Prof. Zhang has received funding for many research projects and published dozens of research articles. His research focuses on novel immunotherapeutic methods and allergenicity evaluation and modification for toxins and transgenic candidate genes. Prof. Zhang significantly contributed to the hypothesis "Balanced Stimulation by Whole Antigens." He is also interested in the integrated application of multiple surgical treatments and developed the Sleep Apnea Treatment Center. Prof. Zhang was given the Anti-SARS Advanced Individual of Guangdong and Guangzhou Award for his excellent contribution to SARS control in 2003 and received the Guangdong "Outstanding Teachers" Award for his exceptional teaching.

Ailin Tao is a Professor at Guangzhou Medical University, Director of Guangdong Provincial Key Laboratory of Allergy and Clinical Immunology, Principal Investigator of the State Key Laboratory of Respiratory Disease, Deputy Director of the State Key Clinical Specialty in Allergy of the Second Affiliated Hospital of Guangzhou Medical University, Member of the State Committee for Transgenic Safety Assessment, Standing Committee Member of Allergy Branch of Guangdong Medical Association, Member of Guangdong Provincial Committee for Transgenic Safety Assessment. Email: Aerobiologiatao@163.com. Professor Ailin TAO earned his doctorate degree from the State Key Laboratory of Crop Genetic Improvement of Huazhong Agricultural University in 2002, followed by a postdoctoral training at Postdoctoral Station of Basic Medicine in Shantou University Medical College, majoring in allergen proteins. His most recent research has been on allergy bioinformatics, allergy, and clinical immunology and disease models, such as allergic asthma, allergic rhinitis, infection and inflammation induced by allergy, inflammatory, and protracted diseases caused by antigens or superantigens. He has gained experience in the field of allergology including the mechanisms of immune tolerance, allergy triggering factors, and chronic inflammation pathways and allergenicity evaluation and modification for food and drugs. He proposed some new concepts including "Representative Major Allergens," "Allergenicity Attenuation" of immunotoxin and allergens, "broad-spectrum immunomodulator" as well as the theoretical hypothesis of "Balanced Stimulation by Whole Antigens." Prof. TAO's laboratory focuses on the diagnosis of allergic disease and the medical evaluation of food and drug allergenicity and its modification. Prof. TAO has now constructed a

system for the prediction, quantitative assessment and simultaneous modification of epitope allergenicity, which has been applied to more than 20 allergens, and he also developed a bioinformatics software program for allergen epitope prediction, SORTALLER (http://sortaller.gzhmu.edu.cn), which performed significantly better than the other existing software, reaching a perfect balance of high specificity (98.4 %) and sensitivity (98.6 %) for discriminating allergenic proteins from several independent datasets of protein sequences of diverse sources. Furthermore, this program has a Matthews correlation coefficient as high as 0.970, a fast running speed and can rapidly predict a set of amino acid sequences with a single click. The software has been frequently used by researchers from many institutions in China and over 30 countries worldwide, thus becoming the number one allergen epitope prediction software program. Prof TAO has set up an allergen database ALLERGENIA (http://ALLERGENIA.gzhmu.edu.cn) that has several advantages over other databases, such as a wide selection of nonredundant allergens, excellent astringency and accuracy, and user-friendly analytical functions.