

Chapter 6

From Allergen Extracts to Allergen Genes and Allergen Molecules

Jiu-Yao Wang

Abstract An allergen is a type of protein capable of instructing the immune system to start producing IgE antibodies. The main purpose for determining the structure of major allergens is to analyze the exposed surface areas and to map the conformational epitopes. These can be determined by experimental methods including crystallographic and NMR-based approaches or predicted by computational methods. Members of the same protein family may share IgE and T cell epitopes, which can cause allergic reactions by cross-reactivity. In the clinical practice, IgE epitopes shared between inhalant and food allergens can induce an immediate IgE-mediated reaction confined to the oral cavity, known as the oral allergy syndrome. Although several structural and functional properties have been identified that contribute to allergenicity, there is not a single common denominator. Allergic sensitization, a multifactorial process, is influenced by a protein's biological and molecular features and by its interaction pathway/s with the immune system. The innate immune system plays a fundamental role in shaping the response to potentially allergenic proteins. In this review, allergenic components of house dust mite that lead to activation of the innate immune system will be discussed as well as how allergen extracts and genes lead to allergen-induced airway inflammation. Understanding the role of mite allergen-induced innate immunity will facilitate the development of therapeutic strategies that exploit innate immunity receptors and associated signaling pathways for the treatment of allergic asthma.

Keywords Allergen • Allergenicity • Cross-reactivity • House dust mite • Innate immune system

J.-Y. Wang (✉)

Department of Pediatrics, Allergy and Clinical Immunology Research (ACIR) Center,
College of Medicine, National Cheng Kung University,
No.1, University Road, 70428 Tainan, Taiwan
e-mail: a122@mail.ncku.edu.tw

6.1 Introduction

An allergen is a type of antigen that produces an abnormally vigorous immune response in which the immune system fights off a perceived threat that would otherwise be seen as harmless to the body. In technical terms, an allergen is an antigen capable of stimulating a type I hypersensitivity reaction in atopic individuals through Immunoglobulin E (IgE) responses (Wasserman 2012). Most humans mount significant IgE responses only as a defense against parasitic infections. However, some individuals may respond to many common environmental antigens. This hereditary predisposition is called atopy. In atopic individuals, non-parasitic antigens stimulate inappropriate IgE production, leading to type I hypersensitivity. Sensitivities vary widely from one person (or other animal) to another and a very broad range of substances can be allergens in sensitive individuals. Recently, the determination of allergenicity, i.e., causing allergic sensitization to an allergen, through investigation of genes and allergen structure, has started to reveal the biological function of allergens, which may provide a tool in treating allergen-induced inflammation in allergic diseases.

6.2 Types of Allergens

Allergens can be found in a variety of sources, such as dust mite excretion, pollen, pet dander, or even royal jelly (Rosmilah et al. 2008). Food allergies are not as common as food sensitivities, but some foods such as peanuts (a legume), nuts, seafood, and shellfish are the causes of serious allergies in many people. Officially, the United States Food and Drug Administration recognizes eight foods as being a common cause of allergic reactions in a large segment of the sensitive population. These include peanuts, tree nuts, eggs, milk, shellfish, fish, wheat and their derivatives, soy and their derivatives, as well as sulfites (chemical based, often found in flavors and colors in foods) at concentrations of 10 ppm and over (<http://www.fda.gov> for complete details). It should be noted that in other countries, in view of the differences in the genetic profiles of their citizens and different levels of exposure to specific foods due to different dietary habits, the “official” allergen list changes from country to country. Canada recognizes all eight of the allergens recognized by the US, and, in addition, recognizes sesame seeds and mustard. The European Union additionally recognizes celery. Another type of allergen is urushiol, a resin produced by poison ivy and poison oak, which causes the skin rash condition known as urushiol-induced contact dermatitis by changing the configuration of skin cells so that they are no longer recognized by the immune system as part of the body (Llanchezian et al. 2012). Various trees and wood products such as paper, cardboard, MDF, etc. can also cause mild to severe allergy symptoms such as asthma and skin rash (Cook and Freeman 1997). An allergic reaction can be caused by any form of direct contact with the allergen—ingestion of food or drink,

inhalation of pollen, perfume or pet dander or direct contact with an allergy-causing plant that one is sensitive to. Other common causes of serious allergies are wasp, fire ant and bee stings, penicillin, and latex. A life-threatening form of allergic reaction is called anaphylaxis. One form of treatment for anaphylaxis is the administration of sterile epinephrine that suppresses the body's overreaction to the allergen and allows time for the patient to be transported to a medical facility.

6.3 Allergen Nomenclature

Hundreds of allergen-containing reagents are routinely employed for skin testing and IgE antibody assays. Allergen products have been previously classified by the manufacturer into different allergen groups, designated by a coding system. Different manufacturers may assign a different code for the same allergen or they may use the same code for an allergen product derived from different species of the same genus or from different allergen sources all together. This lack of consistency has caused a lot of confusion and difficulties with the comparison of data. The official nomenclature for allergenic proteins is based on the Linnaean binominal nomenclature, identifying genus and species of all organisms, and was first published in 1986 (Marsh et al. 1986) and revised in 1994 (King et al. 1994a, b, 1995). The committee was founded in 1984 to establish a system for the nomenclature of allergens and is composed of leading experts in allergen characterization, structure, function, molecular biology, and bioinformatics. Allergens for which names have been updated include respiratory allergens from birch and ragweed pollen, midge larvae, and horse dander as well as food allergens from peanut, cow's milk, tomato, and cereal grains. The International Union of Immunological Societies (IUIS) Allergen Nomenclature Sub-Committee encourages researchers to use these updated allergen names in future publications. The allergen nomenclature is overseen by the IUIS Allergen Nomenclature Sub-Committee under the auspices of the World Health Organization (WHO) and the (IUIS). This committee maintains the database of approved allergen names (www.allergen.org), which has developed from a plain text list to a fully functional, searchable database. In order to maintain a consistent allergen nomenclature that complies with the guidelines established by the subcommittee, researchers are required to submit newly described allergens to the Allergen Nomenclature Sub-Committee before submitting their manuscript to a journal for consideration for publication. Submissions are kept confidential by the subcommittee, and no specific information other than the name of the new allergen will be disclosed on the Web site before publication. The submission form is available at www.allergen.org (Radauer et al. 2014).

6.4 The Structure and Function of Allergens

Elucidating the three-dimensional structure of clinically relevant allergens is of central importance for the following reasons: (1) It allows the visualization and analysis of surface-exposed residues and, in combination with experimental or computational methods, the actual or putative B cell epitopes can be elucidated. (2) Structure can yield information about bound ligands (proteins and/or small molecules), which may modulate the protein's allergenicity. (3) The allergen structure forms the basis for the rational design of hypoallergenic derivatives, which may be generated through various methods (point mutations, truncations, mosaic proteins, fusion with carrier proteins, etc.) (Dall'Antonia et al. 2014).

Most allergens are relatively small, stable, and well-structured proteins. Therefore, they are perfectly suited for structural studies by both X-ray crystallography and NMR spectroscopy. Patients with type I allergy make IgE antibodies against some, but not all, environmental or dietary proteins they are exposed to. In fact, most allergens belong to a rather limited number of protein families. An absolute prerequisite for a molecule to be designated an allergen is that it binds to specific IgE antibodies. The minimum requirement for a molecule to be designated as an allergen is that it binds IgE antibodies and it can itself act as primary sensitizer, i.e., be able to instruct the immune system to start producing these IgE antibodies. Clear examples of allergens that are not able to do so are those in fruits, nuts, and vegetables that are cross-reactive with the major birch pollen Bet v1. Their allergenicity is dependent on their structural (and functional) similarity to the "parent" molecule Bet v 1, the primary sensitizer (Thomas 2013).

The more intriguing question is, however, what determines whether a protein is capable of being a primary sensitizer. Sensitization is a complex interplay of the susceptibility of the exposed individual (inherited risk of becoming allergic), the timing of exposure (the immune system is more susceptible to sensitization but also to the induction of tolerance earlier in life), the dose (high exposure early in life may skew toward tolerance), the context of exposure (environmental exposures such as pollution, microbes, parasites, diet, and lifestyle can exacerbate the development of atopy), and endogenous properties of the protein.

Glycosylation per se has often been mentioned as marker for allergenicity, but convincing evidence for such a general claim cannot be found. Some properties of proteins, including specific types of glycosylation and binding of lipids, seem to determine their role as allergens via interaction with the innate immune system. Many known allergens are indeed lipid-binding proteins (e.g., Bet v 1 and homologues, house dust mite (HDM) group 2 allergens, lipocalins of pets, plant lipid transfer proteins) and some are glycoproteins (e.g., peanut Ara h 1 and grass pollen Phl p 1) (Vieths et al. 2002). Their lipid ligands and conjugated glycans have been shown to interact with pathogen-recognition receptors such as Toll-like receptors (TLRs) and C-type lectins on antigen-presenting cells, thereby skewing the immune systems toward T_H2-type responses and IgE production. In addition, protease activity, such as that of the cysteine protease Der p 1, has been shown to

drive T_H2 inflammation. It is important to note that all these innate T_H2 -skewing properties may also turn other proteins without these proallergenic properties into allergens during simultaneous exposure (Chapman et al. 2007).

In summary, several structural and functional properties have been identified that contribute to allergenicity, but there is not a single common denominator.

6.5 Allergen Cross-Reactivity

Allergens belong to a relatively low number of different protein families according to their intrinsic features, e.g., similar amino acid sequences and/or three-dimensional folding (Radauer et al. 2008). Members of the same protein family may share IgE and T cell epitopes, which can cause allergic reactions by cross-reactivity. In this context, birch pollen-related food allergy has been well studied (Bohle et al. 2006). This special form of food allergy affects more than 70 % of birch pollen-allergic patients and is one of the most frequent food allergies in adults. Bet v 1, the single major birch pollen allergen belongs to the Pathogenesis-related Protein Family 10 and homologous molecules are present in various foods, e.g., Mal d 1 in apple, Pru av 1 in cherry, Gly m 4 in soy, and Ara h 8 in peanut. Although these proteins derive from plant species unrelated to birch trees, their primary and tertiary structures are highly homologous with Bet v 1. Bet v 1 contains mainly conformational IgE epitopes, as destruction of its three-dimensional structure leads to a dramatic reduction of its IgE-binding capacity (Dall'Antonia et al. 2011). Due to similar protein folding, Bet v 1 homologs contain surface patches forming epitopes that may be recognized by Bet v 1-specific IgE antibodies. Although not all IgE epitopes are shared, Bet v 1-related food allergens contain sufficient epitopes to achieve cross-linkage of IgE bound to the surface of mast cells and basophils. In most cases, this induces the oral allergy syndrome, an immediate IgE-mediated reaction confined to the oral cavity (Jahn-Schmid et al. 2005). Destruction of the three-dimensional protein structure, e.g., by gastrointestinal degradation or heat processing, reduces IgE cross-reactivity, which explains why cooked foods containing Bet v 1-related proteins usually are tolerated by birch pollen-allergic patients.

Cross-reactivity at the T cell level depends on amino acid sequence homologies. After uptake by antigen-presenting cells, allergens are degraded into short linear peptides, which are then loaded onto MHC class II molecules to be presented to T cells. Proteins with homologous amino acid sequences are processed in analog fashion resulting in similar peptides. These activate cross-reactive T cells to proliferate and produce cytokines. Clinically, T cell activation by Bet v 1-related food allergens may result in a worsening of atopic eczema in birch pollen-allergic patients.

The analysis of the immune mechanisms underlying birch pollen-related food allergy has markedly contributed to our understanding of how immunological cross-reactivity can induce allergy. Birch pollen-related food allergy is now

currently being investigated as a disease model to elucidate whether immunological cross-reactivity can cure allergy, e.g., by cross-reactive regulatory T cells and/or cross-reactive blocking IgG4 antibodies.

In summary, members of the same protein family may share IgE and T cell epitopes, which can cause allergic reactions by cross-reactivity. In the clinical practice, shared IgE epitopes between inhalant allergens and food allergens can induce an immediate IgE-mediated reaction confined to the oral cavity, known as the oral allergy syndrome. Therefore, cross-reactivity at the T cell level represents one of the mechanisms responsible for the worsening of atopic eczema in birch pollen-allergic patients. In the future, immunological cross-reactivity should be explored as a possible cure for allergy by inducing cross-reactive regulatory T cells and/or cross-reactive blocking IgG4 antibodies.

6.6 Mechanisms of Protein Antigens Becoming Allergens

Allergens interact with various parts of the innate immune system, which plays a fundamental role in shaping adaptive immune responses (Thomas 2013): C-type lectin receptors (CTRs) interact with carbohydrate moieties present on allergens; protease-activated receptor (PAR) 2 acts via the allergens' proteolytical activity; and inflammasome complexes are stimulated (Dai et al. 2011; Dombrowski et al. 2012; Varga et al. 2013). In addition, the presentation of lipids from the allergen source by CD1d to invariant natural killer T cells (iNKTs) (Brennan et al. 2013), which enhances sensitization or in some cases even drives it, has been demonstrated. The innate immune system comprises several cell types that express pattern recognition receptors (PRRs). PRRs recognize pathogen- or damage-associated molecular patterns (PAMPs, DAMPs), which are frequently present on allergens.

TLRs are a conserved family of PRRs. The allergens Der p 2 (house dust mite), Fel d 1 (cat), and Can f 6 (dog) bind lipopolysaccharide (LPS) and interact with TLR4, shifting the LPS-response curve to a T_H2 -inducing range. Bacterial contaminants present on pollen, as shown for ryegrass and *Parietaria*, are responsible for triggering TLR2, TLR4, and TLR9 signaling. CTRs contain carbohydrate recognition domains that bind glycosylated allergens and trigger pathways that determine T cell polarization. Ara h 1 (peanut), Der p 1 (HDM), and Can f 1 (dog) interact with the CTRs DC-SIGN. Ara h 1, Der p 1 and 2, Fel d 1, Can f 1, and Bla g 2 (cockroach) interact with the mannose receptor. PARs signal in response to extracellular proteases. Allergens of HDM (Der p 1, 3, 9) and mold (Penc 13) activate PAR-2 and induce IL-25 and thymic stromal lymphopoietin (TSLP). NOD-like receptors (NLRs) sense cytoplasmic PAMPs and DAMPs. Some NLRs are core components of inflammasomes, protein complexes involved in generating the proinflammatory cytokines IL-1 β and IL-18. Inflammasomes are triggered by Der p 1, Api m 4 (bee), and *Ambrosia artemisiifolia* pollen extracts. Surfactant associated proteins (SP), found in the alveoli of the lungs, bind inhaled glycosylated

allergens via a carbohydrate recognition domain. Der p 1 and Der f 1 degrade SP-A resulting in increased degranulation of mast cells and basophils triggered by these allergens.

In addition, other cells of the innate immune system, such as epithelial cells, function as a physical barrier whose tight junction proteins are degraded by proteases including Der p 1 and Act d 1 (kiwi). Following allergen contact, epithelial cells produce TSLP, IL-25, and IL-33 and instruct dendritic cells to induce T_H2 responses. Dendritic cells bridge innate and adaptive immunity and polarize the T helper cell response (Bublin et al. 2014; Gomez-Casado et al. 2013; Kitzmuller et al. 2015). Polarization toward a T_H2 response in dendritic cell-T cell cocultures has been shown for Bet v 1 (birch pollen) and Pru p 3 (peach) when cells were derived from allergic donors. iNKTs recognize lipids presented by CD1d (Salio et al. 2013) and secrete IL-4, -5 and -13 when presented with lipids from Brazil nut or sphingomyelin from milk. Codelivery of certain lipids and potentially allergenic proteins can determine the outcome of the sensitization process.

In summary, allergic sensitization is a multifactorial process that is influenced by a protein's biological and molecular features and by the interaction pathway/s with the immune system. The innate immune system plays a fundamental role in shaping the response to potentially allergenic proteins. Proteins can manifest their allergenicity through interaction with Toll-like-, C-type lectin-, NOD-like-, and PARs (present on epithelial cells and dendritic cells) or with surfactant proteins (present in soluble form). Moreover, lipids or glycans (directly bound by allergens, present in the allergen source, or originating from microbial contaminations) can also modulate the immune response of predisposed individuals by interacting with the innate immune system.

6.7 Representative Allergen: House Dust Mite

Hypersensitivity to (HDM; *Dermatophagoides* sp.) allergens is one of the most common allergic responses, affecting up to 85 % of asthmatics (Thomas et al. 2010). HDMs are of paramount importance in all but a few regions of the world, where they do not survive due to aridness, extreme cold, or high altitude (Thomas 2010). Sensitization to indoor allergens is the strongest independent risk factor associated with asthma. Additionally, >50 % of children and adolescents with asthma are sensitized to HDM. IgE-binding studies have found that while a wide range of mite proteins can elicit antibodies most induce low or sporadically detectable titers. The main species that cause allergic sensitization are *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*. The most abundant, *D. pteronyssinus*, is essentially the only species found in Australia and the United Kingdom, whereas mixed species are found elsewhere except for the *D. farinae*-rich regions of central and northern Korea, northern Italy, and the high-latitude areas of eastern USA, where mites are found in low numbers. The allergens from these species cross-react extensively so species specificity cannot be determined by skin test.

Only three allergens of *D. pteronyssinus* bind IgE from most people at high titers, Der p 1 and 2 and the recently recognized Der p 23 (Weghofer et al. 2013). The allergens Der p 4, 5, 7, and 21 each elicit IgE antibodies in 30–50 % of mite-allergic subjects and collectively, and sometimes individually, induce titers of a magnitude considered important for the induction of disease. The group 1 and 2 allergens can be readily detected in dust and proprietary HDM extracts made from mites cultured in optimized allergen-producing conditions. The distribution of other allergens in the environment is largely unknown and frequently cannot be detected in proprietary extracts. The evolutionary conservation of the amino acid sequence of tropomyosin Group 10 makes them a potential source of cross-reactivity with allergens from a wide range of species. In most regions of the world, however, they only induce IgE in about 10 % of mite-allergic subjects. The possibility that the biochemical functions of the allergens might help promote their allergenicity has been discussed, especially the cysteine protease activity of Der p 1, the lipopolysaccharide binding activity of Der p 2, and the chitin-binding of Der p 23, but this remains unproven. *Blomia tropicalis*, a glycyphagoide mite found with *D. pteronyssinus* in some tropical and subtropical environments, provides another source of allergens, where Blo t 5 and Blo t 21 are the major allergens and Blo t 2 is a minor one (Thomas 2010).

Although allergen-specific CD4⁺ T_H2 cells orchestrate the HDM allergic response through induction of IgE directed toward mite allergens, activation of innate immunity also plays a critical role in HDM-induced allergic inflammation (Wang 2013). Previously, we have found HDM components that lead to activation of the innate immune response (Wang et al. 1996, 1998; Chun-Keung et al. 1996; Chen et al. 2003; Yu and Chen 2003; Liu et al. 2005; Ye et al. 2011; Huang et al. 2011). This activation could be due to HDM proteases. Proteases may be recognized by protease-activated receptors (PARs), TLRs, or CTRs, or act as a molecular mimic for PAMP activation signaling pathways. Understanding the role of mite allergen-induced innate immunity will facilitate the development of therapeutic strategies that exploit innate immunity receptors and associated signaling pathways for the treatment of allergic asthma.

References

- Bohle B, Zwolfer B, Heratizadeh A, Jahn-Schmid B, Antonia YD, Alter M, et al. Cooking birch pollen-related food: divergent consequences for IgE- and T cell-mediated reactivity in vitro and in vivo. *J Allergy Clin Immunol*. 2006;118:242–9.
- Brennan PJ, Brigl M, Brenner MB. Invariant natural killer T cells: an innate activation scheme linked to diverse effector functions. *Nat Rev Immunol*. 2013;13:101–17.
- Bublin M, Eiwegger T, Breiteneder H. Do lipids influence the allergic sensitization process? *J Allergy Clin Immunol*. 2014;134:521–9.
- Chapman MD, Wünschmann S, Pomés A. Proteases as Th2 adjuvants. *Curr Allergy Asthma Rep*. 2007;7:363–7.
- Chen CL, Lee CT, Liu YC, Wang JY, Lei HY, Yu CK. House dust mite *Dermatophagoides farinae* augments proinflammatory mediator productions and accessory function of alveolar macrophages: implications for allergic sensitization and inflammation. *J Immunol*. 2003;170:528–36.

- Chun-Keung Yu, Lee Shiour-Ching, Wang Jiu-Yao, Hsiue Tzuen-Ren, Lei Huan-Yao. Early-type hypersensitivity-associated airway inflammation and eosinophilia induced by *Dermatophagoides farinae* in sensitized mice. *J Immunol*. 1996;156:1923–30.
- Cook DK, Freeman S. Allergic contact dermatitis to multiple sawdust allergens. *Australas J Dermatol*. 1997;38(2):77–9.
- Dai X, Sayama K, Tohyama M, Shirakata Y, Hanakawa Y, Tokumaru S, et al. Mite allergen is a danger signal for the skin via activation of inflammasome in keratinocytes. *J Allergy Clin Immunol*. 2011;127:806–14.
- Dall'Antonia F, Gieras A, Devanaboyina SC, Valenta R, Keller W. Prediction of IgE-binding epitopes by means of allergen surface comparison and correlation to cross-reactivity. *J Allergy Clin Immunol*. 2011;128:872–879.
- Dall'Antonia F, Pavkov-Keller T, Zangger K, Kellerc W. Structure of allergens and structure based epitope predictions. *Methods*. 2014;66(1):3–21.
- Dombrowski Y, Peric M, Koglin S, Kaymakanov N, Schmezer V, Reinholz M, et al. Honey bee (*Apis mellifera*) venom induces AIM2 inflammasome activation in human keratinocytes. *Allergy*. 2012;67:1400–7.
- Gomez-Casado C, Garrido-Arandia M, Gamboa P, Blanca-Lopez N, Canto G, Varela J, et al. Allergenic characterization of new mutant forms of Pru p 3 as new immunotherapy vaccines. *Clin Dev Immunol*. 2013;2013:385615.
- Hammad H, Lambrecht BN. Dendritic cells and airway epithelial cells at the interface between innate and adaptive immune responses. *Allergy*. 2011;66:579–87.
- Huang HJ, Lin YL, Liu CF, Kao HF, Wang JY. Mite allergen decreases DC-SIGN expression and modulates human dendritic cell differentiation and function in allergic asthma. *Mucosal Immunol*. 2011;4:519–27.
- Jahn-Schmid B, Radakovics A, Luttkopf D, Scheurer S, Vieths S, Ebner C, et al. Bet v 1142-156 is the dominant T-cell epitope of the major birch pollen allergen and important for cross-reactivity with Bet v 1-related food allergens. *J Allergy Clin Immunol*. 2005;116:213–9.
- King TP, Hoffman D, Lowenstein H, Marsh DG, Platts-Mills TA, Thomas W. Allergen nomenclature. *Int Arch Allergy Immunol*. 1994a;105:224–33.
- King TP, Hoffman D, Lowenstein H, Marsh DG, Platts-Mills TA, Thomas W. Allergen nomenclature. *Bull World Health Organ*. 1994b;72:797–806.
- King TP, Hoffman D, Lowenstein H, Marsh DG, Platts-Mills TA, Thomas W. Allergen Nomenclature. *J Allergy Clin Immunol*. 1995;96:5–14.
- Kitzmüller C, Zulehner N, Roulias A, Briza P, Ferreira F, Fae I, et al. Correlation of sensitizing capacity and T-cell recognition within the Bet v 1 family. *J Allergy Clin Immunol*. 2015;136:151–8.
- Liu CF, Chen YL, Chang WT, Shieh CC, Yu CK, Reid KB, Wang JY. Mite allergen induces nitric oxide production in alveolar macrophage cell lines via CD14/toll-like receptor 4, and is inhibited by surfactant protein D. *Clin Exp Allergy*. 2005;35:1615–24.
- Llanchezian R, Joseph CR, Rabinarayan A. Urushiol-induced contact dermatitis caused during Shodhana (purificatory measures) of Bhallataka (*Semecarpus anacardium* Linn) fruit. *Ayu*. 2012;33(2):270–3.
- Marsh DG, Goodfriend L, King TP, Lowenstein H, Platts-Mills TA. Allergen nomenclature. *Bull World Health Organ*. 1986;64:767–74.
- Radauer C, Bublin M, Wagner S, Mari A, Breiteneder H. Allergens are distributed into few protein families and possess a restricted number of biochemical functions. *J Allergy Clin Immunol*. 2008;121:847–52.
- Radauer C, Nandy A, Ferreira F, Goodman RE, Larsen JN, Lidholm J, Pomés A, Raulf-Heimsoth M, Rozynek P, Thomas WR, Breiteneder H. Update of the WHO/IUIS allergen nomenclature database based on analysis of allergen sequences. *Allergy*. 2014;69:413–9.
- Rosmilah M, Shahnaz M, Patel G, Lock J, Rahman D, Masita A, Noormalin A. Characterization of major allergens of royal jelly *Apis mellifera*. *Trop Biomed*. 2008;25(3):243–51.
- Salio M, Ghadbane H, Dushek O, Shepherd D, Cypen J, Gileadi U, et al. Saposins modulate human invariant Natural Killer T cells self-reactivity and facilitate lipid exchange with CD1d molecules during antigen presentation. *Proc Natl Acad Sci USA*. 2013;110(49):E4753–61.

- Thomas WR. Geography of house dust mite allergens. *Asian Pac J Allergy Immunol.* 2010;28:211–24.
- Thomas WR. Innate affairs of allergens. *Clin Exp Allergy.* 2013;43:152–63.
- Thomas WR, Hales BJ, Smith WA. House dust mite allergens in asthma and allergy. *Trends Mol Med.* 2010;16:321–8.
- Varga A, Budai MM, Milesz S, Bácsi A, Tózsér J, Benkő S. Ragweed pollen extract intensifies lipopolysaccharide-induced priming of NLRP3 inflammasome in human macrophages. *Immunology.* 2013;138:392–401.
- Vieths S, Scheurer S, Ballmer-Weber B. Current understanding of cross-reactivity of food allergens and pollen. *Ann NY Acad Sci.* 2002;964:47–68.
- Wang Jiu-Yao. The innate immune response in house dust mite-induced allergic inflammation. *Allergy Asthma Immunol Res.* 2013;5:68–74.
- Wang Jiu-Yao, Kishore Uday, Lim Boon-Leong, Strong Peter, Reid Kenneth BM. Interaction of human surfactant proteins A and D with mite (*Dermatophagoid ptyrosinissus*) allergens. *Clin Exp Immunol.* 1996;106:367–73.
- Wang Jiu-Yao, Shieh CC, You PF, Lei HY, Reid KBM. The inhibitory effect of pulmonary surfactant protein A and D on allergen-induced lymphocyte proliferation and histamine released in asthmatic children. *Am J Respir Crit Care Med.* 1998;158:510–8.
- Wasserman SI. Approach to the patient with allergic or immunologic disease. In: Goldman L, Schafer AI, editors. *Cecil Medicine.* 2012.
- Weghofer M, Grote M, Resch Y, Cassel A, Kneidinger M, Kopec J, et al. Identification of Der p 23, a peritrophin-like protein, as a new major *Dermatophagoides pteronyssinus* allergen associated with the peritrophic matrix of mite fecal pellets. *J Immunol.* 2013;190:3059–67.
- Ye YL, Wu HT, Lin CF, Hsieh CY, Wang JY, Liu FH, Ma CT, Bei CH, Cheng YL, Chen CC, Chiang BL, Tsao CW. *Dermatophagoides pteronyssinus* 2 regulates nerve growth factor release to induce airway inflammation via a reactive oxygen species-dependent pathway. *Am J Physiol Lung Cell Mol Physiol.* 2011;300:L216–24.
- Yu CK, Chen CL. Activation of mast cells is essential for development of house dust mite *Dermatophagoides farinae*-induced allergic airway inflammation in mice. *J Immunol.* 2003;171:3808–15.

Author Biography



Dr. Jiu-Yao Wang, Ph.D. is now a Distinguished Professor of Pediatrics and Director of the Allergy and Clinical Immunology Research (ACIR) center at National Cheng Kung University Medical Center, Tainan, Taiwan. After clinical residency and subspecialty training in pediatric allergy, clinical immunology and rheumatology at the National Taiwan University Hospital, Taipei from 1984 to 1987, he was appointed as Lecturer (1989), Associate Professor (1992), and Professor (2000) at the College of Medicine, National Cheng Kung University, Tainan, Taiwan. He obtained his Doctor of Philosophy (D.Phil.) degree from the MRC Immunochemistry Unit, University of Oxford, United Kingdom in 1996. For more than 25 years, Dr. Wang's lab has been focused on the study of the genetic, environmental, and immunological factors involved in the innate immunity of allergic

and asthmatic children in Taiwan. These studies have produced more than 110 SCI journal papers that have been cited more than 2000 times. He has received several academic awards, including the 37th Ten Outstanding Young Persons in Medical Research Award (1999) sponsored by Taiwan Junior Commercial Chamber, Taiwan, and Gold Medal of K.T. Li Foundation for the Development

of Science and Technology (2014). He has been the president of the Taiwan Academy of Pediatric Allergy, Asthma, and Clinical Immunology (TAPAACI), Board Member and Congress Chair of the 2013 Asian Pacific Academy of Allergy, Asthma and Clinical Immunology (APAAACI), and currently serves as a National Delegate and Board Member of the Educational Council of the World Allergy Organization (WAO).