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The Innate Immune Response in House Dust Mite-Induced Allergic Inflammation

Jiu-Yao Wang*

Division of Allergy and Clinical Immunology, Department of Pediatrics, College of Medicine, National Cheng Kung University, Tainan, Taiwan

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Hypersensitivity to house dust mite (HDM; *Dermatophagoides* sp.) allergens is one of the most common allergic responses, affecting up to 85% of asthmatics. 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. Although allergen-specific $CD4^+$ Th2 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. This review highlights the HDM components that lead to activation of the innate immune response. Activation may due to HDM proteases. Proteases may be recognized by protease-activation receptors (PARs), Toll-like receptors (TLRs), or C-type lectin receptors (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.

Key Words: House dust mites; innate immunity; toll-like receptors; C-type lectin receptors; dendritic cells.

THE SWEET ENEMY IN THE MODERN HOME

"*the modern cultivated person sleeps in beds which are a mockery of all the rules of hygiene, … daily use through dust, fungal spores, bacteria, and from the effect of the damp bed warmth, an opulent breeding ground of fungi, yeasts, and harmful vermin, in beds… All the worse that for sure asthma is not the only illness to arise from mites…*"

-*Hermann Dekker, 1928.*[1]

As early as 1921 it was reported that many asthmatics had strongly positive skin tests to house dust.[2] The first attempt to purify allergens from house dust was unsuccessful.[3] In 1928, Dr. Dekker suggested that mites played an important role in allergy, but his evidence was unconvincing.[1] A breakthrough came in the mid-1960s, when Spieksma and Voorhorst established that there was a strong relationship between the number of dust mites and the allergenicity of house dust.[4] Using skin test reagents, it became obvious that there was a strong association between dust mites and asthma. In some areas, the association was so strong that 80%-90% of children with asthma had sensitivity to dust mite allergens.[5] In fact, early sensitization to perennial indoor allergens has been implicated in several recent reports as a major risk factor for a persistent type of respiratory allergic disease in childhood.[6,7]

THE GLOBAL ENDEMIC OF HDM ALLERGY

There is increasing evidence that exposure to indoor allergens is a causative factor for the development of asthma among persons who are genetically predisposed to mount IgE autoantibody responses.[8-10] Hypersensitivity to house dust mite (HDM) allergens is one of the most common allergic responses. Sensitization to indoor allergens is the strongest independent risk factor associated with asthma (odds ratios>10).[11] In fact, more than 90% of allergic asthmatic children are sensitive to *Dermatophagoides spp* (*D. pteronyssinus*, Derp and *D. farina*, Der f).[12] Reports from others also suggest that >50% of children and adolescents with asthma are sensitized to HDM.[11,13]

GEOGRAPHY OF HDM

Multicenter studies suggest that HDM are the most prevalent

Correspondence to: Jiu-Yao Wang, MD, D.Phil. (Oxon), Division of Allergy and Clinical Immunology, Department of Pediatrics, College of Medicine, National Cheng Kung University, No.138, Sheng-Li Road, Tainan 70428, Taiwan. Tel: +886-6-2353535; Fax: +886-6-2753083; E-mail: a122@mail.ncku.edu.tw
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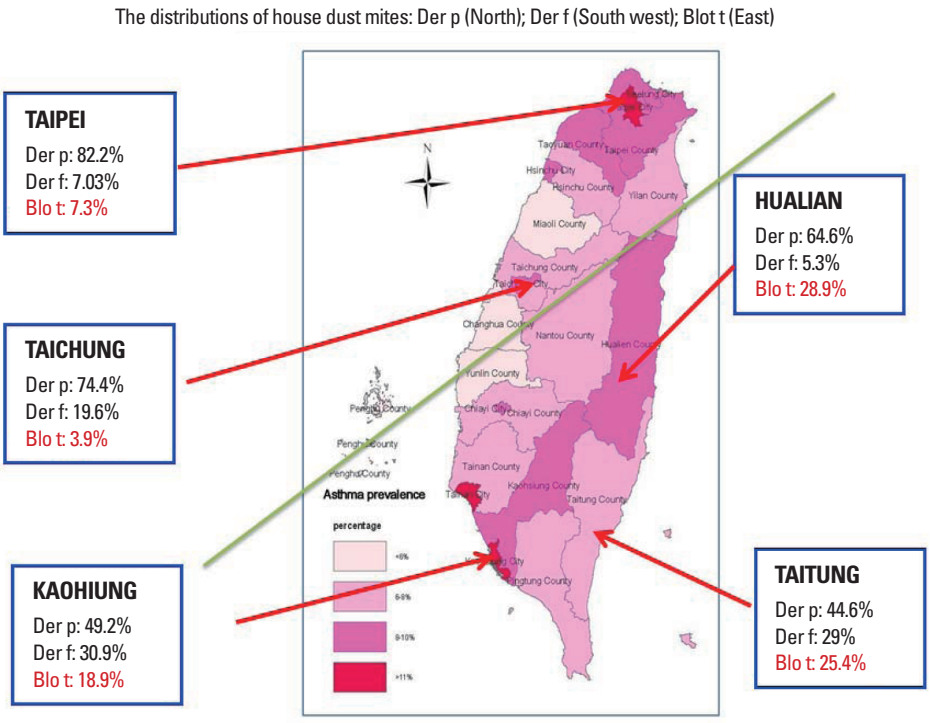

Fig. 1. The distributions of house dust mites, Der p, Der f, and Blot in the counties of Taiwan. Red shading indicates the prevalence of childhood asthma as determined by ISSAC.

source of indoor allergens in Europe,[14] USA,[15] Asia,[16,17] South America,[18] New Zealand,[19] Australia,[20] and Africa.[21,22] The distribution of house dust mites and their species vary around the world according to temperature and humidity.[23] A recent survey in Taiwan revealed that, along with *D. pteronyssinus* (Der p) and *D. farina* (Der f), the most common mite species in house dust fauna was *Blomia tropicalis* (Blo t).[24] As shown in Fig. 1, there is a significant difference in the distribution of Blo t in house dust between the northwest (3.9%-7.3%), which is cold and humid, and the southeast (18.9%-28.9%), which is hot and humid. Due to the high humidity, the majority of *Dermatophagoides* species were Der p. The prevalence of Der p in the north and south parts of Taiwan was not markedly different.

THE ALLERGIC IMMUNE RESPONSE TO HDM

Allergens derived from HDM have been recognized as an important cause of IgE antibody responses for more than 30 years. During allergen sensitization and provocation in allergen-induced inflammation, mite allergens break the anatomical barrier of the mucosal membrane and are processed by professional antigen presenting cells (APCs), such as dendritic cells or macrophages. APCs mature and present processed allergen peptides to resting naïve T cells in the draining lymph nodes. Activated T cells signal to APCs, particularly DCs, to produce Th2 cytokines, such as IL-3, IL-4. IL-5, and IL-13, which recruit, mature, and activate eosinophils. These cytokines induce isotype switching from IgG to IgE, leading to increased production of allergen-specific IgE that eventually binds to high affinity IgE receptors (FCεR1) in mast cells, basophils, and eosinophils. Therefore, subsequent encounters with the same allergen will result in degranulation of preformed granules from IgE-IgE receptor–complex-bound mast cells and basophils (immediate hypersensitivity phase), production of newly synthesized inflammatory mediators (late inflammatory phase), and a hypersensitivity response (chronic phase). The innate immune response may also play a role by being induced by the allergen itself.[25]

THE INNATE IMMUNE RESPONSE TO HDM

More than 20 HDM allergen groups that induce IgE antibodies in allergic patients have been defined based on sequence and functional homologies.[26] When these allergens contact the mucosal membrane, they may induce innate immune stimulation. We have demonstrated that extracts from dust mites (Der f) can directly activate innate immune cells such as alveolar macrophages (AMs),[27] and mast cells,[28] and can induce Th2 cytokine responses without previous *in vitro* or *in vivo* sensitization. Proteases in HDM may induce the innate immune response by binding protease-activation receptors (PARs), Toll-like receptors (TLRs), or C-type lectin receptors (CTRs), or they may function as molecular mimics (Fig. 2), as discussed below.

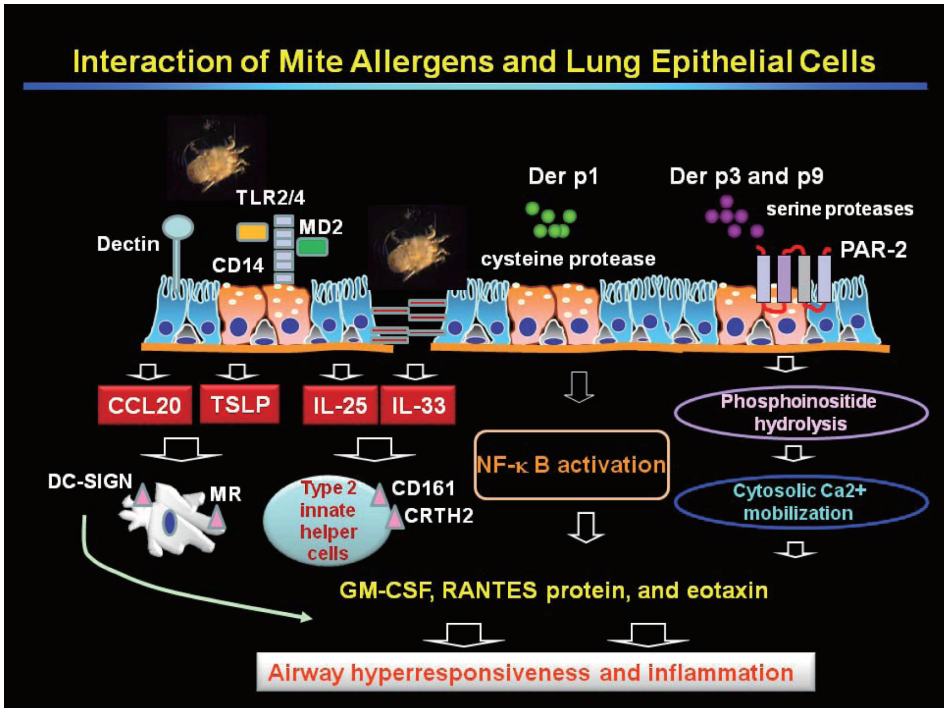

Fig. 2. Activation of innate immune cells and the cell surface receptors; toll-like receptor 4 (TLR4), protease activation receptor 2 (PAR2), and C-type lectin receptor (CTR), by house dust mite (HDM) allergens in airway epithelium.

THE PROTEASE ACTIVITY AND PAR ACTIVATION IN HDM ALLERGY

HDMs and their fecal pellets contain several proteolytic enzymes. Group 1 allergens are cysteine proteases that share sequence identities with the catalytic sites of the plant enzyme papain. Groups 3, 6, and 9 are serine proteases,[29,30] which account for 79% of the proteolytic activity in house dust.[31] Proteolytically active allergens can down-regulate the anti-protease-based lung defenses in mucosa, leading to enhanced tissue damage and immune activation. Der p 1 and Der f 1 can degrade airway α1-antitrypsin inhibitor, resulting in dysregulation of human neutrophil chemotaxis.[32] Previously, we found that pulmonary surfactant proteins A (SP-A) and D (SP-D) secreted from alveolar type II cells, which belong to the innate immune defense in the lung, are able to bind to Der p extracts[33] and prevent Der p allergen-induced histamine released from mast cells in sensitized patients.[34] These two mite cysteine proteases can inactivate SP-A and SP-D (collectins), which have significant functions in the innate defense mechanism against pathogens. Collectins also facilitate the recognition of aero-allergens, and protect against and resolve allergen-induced airway inflammation.[35,36]

Der p 1 triggers the breakdown of the epithelial barrier through proteolytic cleavage of tight junction proteins occludin and zonula occludens-1 (ZO-1).[37,38] This increase in the permeability of the bronchial epithelium can facilitate allergen presentation by airway DCs in subepithelial tissues.[38] Der p 1 downregulates IDO expression in DCs from HDM-sensitive subjects with asthma, which explains the loss of tolerance to HDM allergens.[39] Proteolytically active Der p1 also induce airway epithelial cells, skin keratinocytes, DCs, eosinophils, basophils, and macrophages to secrete large amounts of proinflammatory, pro-Th2 cytokines, such as TSLP and IL-33, as well as chemokines to recruit inflammatory cells to the damaged epithelium.[40]

Group 3 (Der p 3) and 9 (Der p 9) mite allergens are serine proteases that can increase vascular permeability and detach epithelial cells.[30] Although the receptors for these proteases have not yet been characterized, it is probable that the primary response is due to activation of cell surface protease-activated receptors (PARs) or similar molecules in the airways. This would induce leukocyte infiltration and amplify the response to allergens.[41]

PARs are receptors activated by proteolytic cleavage of their extracellular N-terminus. Signaling through PARs (G protein-coupled receptors) involves the cleavage of an extracellular region of the receptor by proteases to reveal a tethered-ligand sequence capable of auto-activating the receptor.[42] Protease inhibitors already in clinical use for the treatment of endogenous protease release-related diseases, such as acute pancreatitis, may have some beneficial effect in the inhibition of proteolytically active allergen-induced airway inflammation. In fact, we have found that gabexate mesylate (FOY) and nafamostat mesylate (6-amidino-2-naphthyl p-guanidinobenzoate dimethane

sulfonate [FUT]), which are non-antigenic synthetic inhibitors of trypsin-like serine proteases that have been used in the treatment of pancreatitis and disseminated intravascular coagulation, are able to alleviate mite allergen-induced airway hyperresponsiveness and inflammation in the allergic asthma mouse model.[43] Moreover, a monoclonal blocking antibody (Wan 108) against Der p 1 developed by our group can not only interfere with IgE antibody binding to Der p1 by steric hindrance, but can inhibit the cysteine protease activity of Der p 1. Intra-peritoneal injection of Wan 108, can also prevent and treat mite allergen-induced airway inflammation in sensitized and allergen-challenged mice.[44] Hence, anti-protease inhibitor antibodies or other targeted therapies may be used in the future to treat allergic diseases.

THE ROLE OF TLR ACTIVATION AND MOLECULAR MIMICRY IN HDM ALLERGY

The contribution of the TLR4 signaling pathway to HDM allergy was confirmed by the absence of common allergic asthma symptoms in mice deficient in MYD88, TLR4, and IRF3.[45,46] Previously, we reported that the differential reactivity of two mouse alveolar macrophage cell lines, MH-S (BALB/c strain, $CD14^{high}$/$TLR4^{high}$), and AMJ2-C11 (C57BL/6 strain, $CD4^{low}$/$TLR4^{low}$), to Der p could be ascribed to their relative TLR4 expression levels.[47] LPS and Der p induced different levels of NO in each cell line. We hypothesize that these different responses depended on the expression of CD14/TLR4 complexes.

In addition, pretreatment of macrophages with SP-D inhibited NO production from Der p and LPS-stimulated alveolar macrophages.[47] Recent data also showed that TLR4 expression in lung epithelium, but not on DCs, is essential for the development of a robust HDM-specific Th2 inflammatory response.[48] More importantly, TLR4 activation in the airway epithelium by HDM combined with small amounts of LPS induced pro-Th2 cytokines such as TSLP, GM-CSF, IL-25, and IL-33 (Fig. 2). These new findings place epithelial cells in a pivotal position in the development of allergic inflammation though the activation of the TLR4 signaling pathway.

Molecular mimicry is a dominant immunostimulatory effect in the HDM allergen Der p 2. Der p 2 mimics the activity of its fellow ML-domain protein, MD-2, by presenting lipopolysaccharide to TLR4, resulting in the activation of inflammatory genes. In addition, Der p 2 presented with lipopolysaccharide-induced enhanced type 1 allergic sensitization of mice, even when they were deficient in MD-2.[49] MD-2 mimicry allows Der p 2 to serve as a self-adjuvant to enhance its allergenicity. Recombinant Der p 2 also stimulates airway smooth muscle cells in a TLR4-independent manner but triggers the MyD88 signal pathway through TLR2.[50]

We have found that mice repeatedly exposed to mite extracts or the mite component, Der p 2, induced significant NGF production in bronchoalveolar lavage fluid (BALF), activation of AMs and mast cells, and induced eosinophilic infiltration, goblet cell hyperplasia, and hyperplasia of peri-bronchial smooth muscles.[51]

THE ROLE OF CLR ACTIVATION IN HDM ALLERGY

DCs are the first line of defense in many mucosal membranes. DCs sample their environment using a plethora of receptors, such as C-type lectin receptors (CLRs), scavenger receptors, and TLRs, which increase their internalization efficiency and deliver information regarding the presence of danger signals. DCs also play a role in the induction and re-elicitation of Th2-mediated inflammation in allergic diseases.[52,53] However, the molecular processes underpinning these events have remained elusive. In particular, little information is available regarding the mechanism used by DCs to recognize and internalize allergens and how these processes lead to Th2 cell polarization.

The mannose receptor (MR), a C-type lectin, is a multifunctional endocytic receptor on DCs with two distinct lectin activities mediated by its extracellular region.[54] The cysteine-rich (CR) domain recognizes sulfated sugars, whereas mannose (together with fucose and N-acetylglucosamine) recognition is mediated by the multiple C-type lectin-like carbohydrate recognition domains (CTLDs). MR mediates internalization of diverse allergens from mite (Der p 1 and Der p 2), dog (Can f 1), cock-roach (Bla g 2), and peanut (Ara h 1) through their carbohydrate moieties.[55] Silencing MR expression on monocyte-derived DCs reverses the Th2 cell polarization bias driven by Der p 1 allergen exposure through upregulation of IDO activity.[55]

Another DC C-type LTR is dendritic cell-specific intercellular adhesion molecule 3-grabbing non-integrin (DC-SIGN). DC-SIGN recognizes carbohydrate structures on pathogens and self-glycoproteins.[56] We found that HDM (Der p)-sensitive subjects exhibited decreased expression of DC-SIGN, increased endocytosis, and impaired differentiation of monocyte-derived DCs (MDDCs). Der p allergen may modulate the differentiation and function of MDDCs via interaction with DC-SIGN, a C-type lectin receptor in the mature DCs. Our data indicate that immature MDDCs internalized Der p allergen through DC-SIGN and, after maturation, promoted Th2 polarization of naïve $CD4^+$ T cells (Fig. 3).[57]

Although Der p 1 can specifically cleave CD40 and DC-SIGN, resulting in a downregulation of Th1 polarization or tolerance through the reduction of IL-12p70 and extracellular thiol production (CD40 cleavage),[58,59] our results show that Der p directly binds to DC-SIGN and is pinocytosed into an intracellular compartment in DCs. Downregulation of DC-SIGN on the surface of DCs, which was not due to the protease activity of HDM, will bias DCs towards a Th2 response. DC-SIGN may be important in mediating the innate immune response in DCs when in contact with Der p allergen.

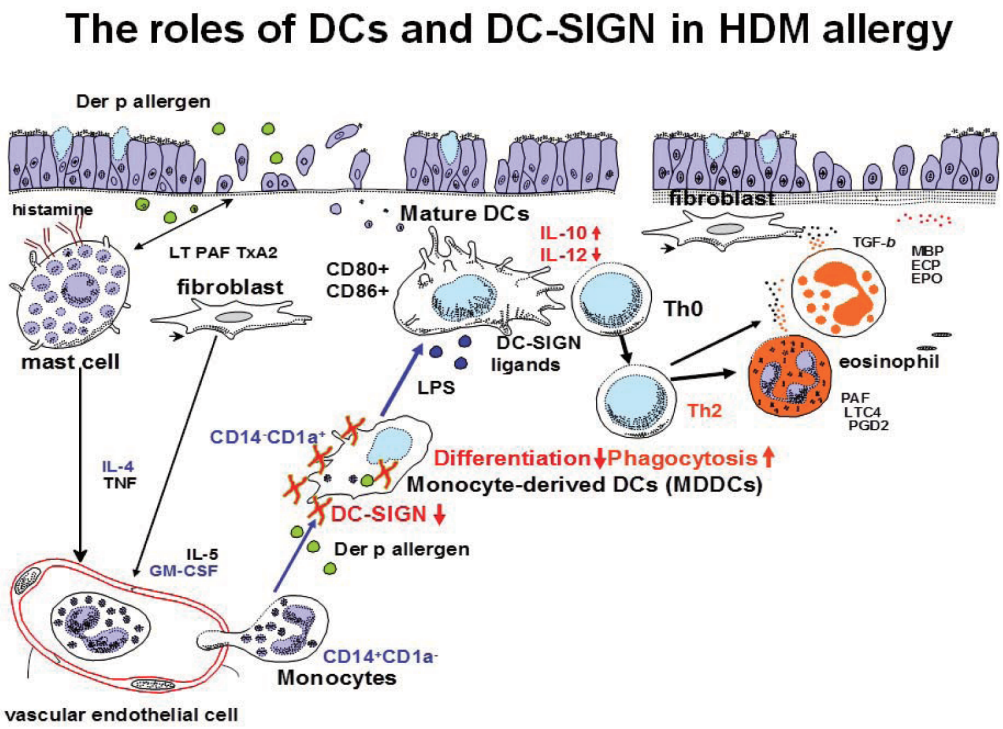

Fig. 3. The role of DCs and DC-SIGN in HDM allergy. Decreased expression of DC-SIGN and more immature phenotypes in MDDCs from Der p-sensitive asthmatic patients may partially explain the enhancement of the Th2 response associated with HDM-related allergies. In addition, Der p can modulate differentiation and maturation of monocyte-derived DCs through DC-SIGN binding and downregulation of its expression, which may result in an aletred polarization activity, leading to the Th2 cytokine immune response.

CONCLUSIONS

Type I IgE-mediated hypersensitivity reactions initiated by HDM allergens occur after their recognition by APCs such as dendritic cells (DCs). Recognition leads to Th2 cell differentiation, IgE Ab production, and mast cell sensitization and triggering. Initiation of the allergen response may involve multiple innate immunity receptors on mucosal membranes. Previously, we have demonstrated that extracts from dust mites (Der f) can directly activate innate immune cells, such as alveolar macrophages and mast cells, and can induce Th2 cytokine response without previous *in vitro* or *in vivo* sensitization. Recent studies have suggested that allergen-induced DC activation and inflammation may involve TLRs and/or CLRs on antigen-presenting cells.

Using alveolar macrophage cell lines derived from different genetic backgrounds, we found that lipopolysaccharides (LPS) and Der p elicited different responses, and that this was dependent upon the level of expression of the CD14/TLR4 complex. Protease activity in HDM allergens may cause direct damage to the epithelium that leads to production of pro-Th2 cytokines; for example, TSLP, CCL20, IL-25, and IL-33.

The administration of mAb W108, which inhibited IgE binding to the mite allergen epitope, to Der p-sensitize asthma mice alleviated allergen-induced airway inflammation and the reduced the Th2 cytokine immune response. These results suggest a target for the treatment of mite allergen-induced diseases and asthma. Therefore, understanding the role of mite allergen-induced innate immunity may facilitate the development of therapeutic strategies for the treatment of allergic asthma.

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REFERENCES

1. Dekker H. Asthma and Milben. Munch Med Wochenschr 1928; 515-16 (translated by Dekker H. Asthma and mites. J Allergy Clin Immunology 1971;48:251-2).
2. Kern RA. Dust sensitization in bronchial asthma. Med Clin North Am 1921;5:751-8.
3. Vannier WE, Campbell DH. A starch block electrophoresis study of aqueous house dust extracts. J Allergy 1961;32:36-54.
4. Voorhorst R, Spieksma FM, Varekamp H, Leupen MJ, Lyklema AW. The house dust mite (*Dermatophagoides pteronyssinus*) and the allergen it produces: identify with house dust allergen. J Allergy 1967;

39:325-39.
5. Thomas WR, Smith WA, Hales BJ. The allergenic specificities of the house dust mite. Chang Gung Med J 2004;27:563-9.
6. Shin JW, Sue JH, Song TW, Kim KW, Kim ES, Sohn MH, Kim KE. Atopy and house dust mite sensitization as risk factors for asthma in children. Yonsei Med J 2005;46:629-34.
7. Miraglia Del Giudice M, Pedullà M, Piacentini GL, Capristo C, Brunese FP, Decimo F, Maiello N, Capristo AF. Atopy and house dust mite sensitization as risk factors for asthma in children. Allergy 2002;57:169-72.
8. Tovey ER, Chapman MD, Platts-Mills TA. Mite faeces are a major source of house dust allergens. Nature 1981;289:592-3.
9. Boulet LP, Turcotte H, Laprise C, Lavertu C, Bédard PM, Lavoie A, Hébert J. Comparative degree and type of sensitization to common indoor and outdoor allergens in subjects with allergic rhinitis and/or asthma. Clin Exp Allergy 1997;27:52-9.
10. Thomas WR, Smith WA, Hales BJ, Mills KL, O'Brien RM. Characterization and immunobiology of house dust mite allergens. Int Arch Allergy Immunol 2002;129:1-18.
11. Gaffin JM, Phipatanakul W. The role of indoor allergens in the development of asthma. Curr Opin Allergy Clin Immunol 2009;9:128-35.
12. Wang JY, Chen WY. Inhalant allergens in asthmatic children in Taiwan: comparison evaluation of skin testing, radioallergosorbent test and multiple allergosorbent chemiluminescent assay for specific IgE. J Formos Med Assoc 1992;91:1127-32.
13. Cates EC, Fattouh R, Johnson JR, Llop-Guevara A, Jordana M. Modeling responses to respiratory house dust mite exposure. Contrib Microbiol 2007;14:42-67.
14. Heinzerling LM, Burbach GJ, Edenharter G, Bachert C, Bindslev-Jensen C, Bonini S, Bousquet J, Bousquet-Rouanet L, Bousquet PJ, Bresciani M, Bruno A, Burney P, Canonica GW, Darsow U, Demoly P, Durham S, Fokkens WJ, Giavi S, Gjomarkaj M, Gramiccioni C, Haahtela T, Kowalski ML, Magyar P, Muraközi G, Orosz M, Papadopoulos NG, Röhnelt C, Stingl G, Todo-Bom A, von Mutius E, Wiesner A, Wöhrl S, Zuberbier T. GA(2)LEN skin test study I: GA(2) LEN harmonization of skin prick testing: novel sensitization patterns for inhalant allergens in Europe. Allergy 2009;64:1498-506.
15. Arbes SJ Jr, Gergen PJ, Elliott L, Zeldin DC. Prevalences of positive skin test responses to 10 common allergens in the US population: results from the third National Health and Nutrition Examination Survey. J Allergy Clin Immunol 2005;116:377-83.
16. Leung R, Ho P. Asthma, allergy, and atopy in three south-east Asian populations. Thorax 1994;49:1205-10.
17. Li J, Sun B, Huang Y, Lin X, Zhao D, Tan G, Wu J, Zhao H, Cao L, Zhong N; China Alliance of Research on Respiratory Allergic Disease. A multicentre study assessing the prevalence of sensitizations in patients with asthma and/or rhinitis in China. Allergy 2009;64:1083-92.
18. Fernández-Caldas E, Baena-Cagnani CE, López M, Patiño C, Neffen HE, Sánchez-Medina M, Caraballo LR, Huerta López J, Malka S, Naspitz CK. Cutaneous sensitivity to six mite species in asthmatic patients from five Latin American countries. J Investig Allergol Clin Immunol 1993;3:245-9.
19. Sears MR, Burrows B, Herbison GP, Holdaway MD, Flannery EM. Atopy in childhood. II. Relationship to airway responsiveness, hay fever and asthma. Clin Exp Allergy 1993;23:949-56.
20. Peat JK, Tovey E, Toelle BG, Haby MM, Gray EJ, Mahmic A, Woolcock AJ. House dust mite allergens. A major risk factor for childhood asthma in Australia. Am J Respir Crit Care Med 1996;153:141-6.
21. Perzanowski MS, Ng'ang'a LW, Carter MC, Odhiambo J, Ngari P, Vaughan JW, Chapman MD, Kennedy MW, Platts-Mills TA. Atopy, asthma, and antibodies to Ascaris among rural and urban children in Kenya. J Pediatr 2002;140:582-8.
22. Addo-Yobo EO, Custovic A, Taggart SC, Craven M, Bonnie B, Woodcock A. Risk factors for asthma in urban Ghana. J Allergy Clin Immunol 2001;108:363-8.
23. Thomas WR. Geography of house dust mite allergens. Asian Pac J Allergy Immunol 2010;28:211-24.
24. Tsai JJ, Yi FC, Chua KY, Liu YH, Lee BW, Cheong N. Identification of the major allergenic components in Blomia tropicalis and the relevance of the specific IgE in asthmatic patients. Ann Allergy Asthma Immunol 2003;91:485-9.
25. Jacquet A. The role of the house dust mite-induced innate immunity in development of allergic response. Int Arch Allergy Immunol 2011;155:95-105.
26. Thomas WR, Hales BJ, Smith WA. House dust mite allergens in asthma and allergy. Trends Mol Med 2010;16:321-8.
27. 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.
28. 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.
29. Cunningham PT, Elliot CE, Lenzo JC, Jarnicki AG, Larcombe AN, Zosky GR, Holt PG, Thomas WR. Sensitizing and th2 adjuvant activity of cysteine protease allergens. Int Arch Allergy Immunol 2012;158:347-58.
30. Stewart GA, Boyd SM, Bird CH, Krska KD, Kollinger MR, Thompson PJ. Immunobiology of the serine protease allergens from house dust mites. Am J Ind Med 1994;25:105-7.
31. Chapman MD, Wünschmann S, Pomés A. Proteases as Th2 adjuvants. Curr Allergy Asthma Rep 2007;7:363-7.
32. Kalsheker NA, Deam S, Chambers L, Sreedharan S, Brocklehurst K, Lomas DA. The house dust mite allergen Der p1 catalytically inactivates alpha 1-antitrypsin by specific reactive centre loop cleavage: a mechanism that promotes airway inflammation and asthma. Biochem Biophys Res Commun 1996;221:59-61.
33. Wang JY, Kishore U, Lim BL, Strong P, Reid KB. Interaction of human lung surfactant proteins A and D with mite (Dermatophagoides pteronyssinus) allergens. Clin Exp Immunol 1996;106:367-73.
34. Wang JY, Shieh CC, You PF, Lei HY, Reid KB. Inhibitory effect of pulmonary surfactant proteins A and D on allergen-induced lymphocyte proliferation and histamine release in children with asthma. Am J Respir Crit Care Med 1998;158:510-8.
35. Wang JY, Reid KB. The immunoregulatory roles of lung surfactant collectins SP-A, and SP-D, in allergen-induced airway inflammation. Immunobiology 2007;212:417-25.
36. Deb R, Shakib F, Reid K, Clark H. Major house dust mite allergens Dermatophagoides pteronyssinus 1 and Dermatophagoides farinae 1 degrade and inactivate lung surfactant proteins A and D. J Biol Chem 2007;282:36808-19.
37. Wan H, Winton HL, Soeller C, Taylor GW, Gruenert DC, Thompson PJ, Cannell MB, Stewart GA, Garrod DR, Robinson C. The transmembrane protein occludin of epithelial tight junctions is a functional target for serine peptidases from faecal pellets of Derma-

tophagoides pteronyssinus. Clin Exp Allergy 2001;31:279-94.
38. Wan H, Winton HL, Soeller C, Tovey ER, Gruenert DC, Thompson PJ, Stewart GA, Taylor GW, Garrod DR, Cannell MB, Robinson C. Der p 1 facilitates transepithelial allergen delivery by disruption of tight junctions. J Clin Invest 1999;104:123-33.
39. Maneechotesuwan K, Wamanuttajinda V, Kasetsinsombat K, Huabprasert S, Yaikwawong M, Barnes PJ, Wongkajornsilp A. Der p 1 suppresses indoleamine 2, 3-dioxygenase in dendritic cells from house dust mite-sensitive patients with asthma. J Allergy Clin Immunol 2009;123:239-48.
40. Gregory LG, Lloyd CM. Orchestrating house dust mite-associated allergy in the lung. Trends Immunol 2011;32:402-11.
41. Reed CE, Kita H. The role of protease activation of inflammation in allergic respiratory diseases. J Allergy Clin Immunol 2004;114:997-1008; quiz 1009.
42. Adams MN, Ramachandran R, Yau MK, Suen JY, Fairlie DP, Hollenberg MD, Hooper JD. Structure, function and pathophysiology of protease activated receptors. Pharmacol Ther 2011;130:248-82.
43. Chen CL, Wang SD, Zeng ZY, Lin KJ, Kao ST, Tani T, Yu CK, Wang JY. Serine protease inhibitors nafamostat mesilate and gabexate mesilate attenuate allergen-induced airway inflammation and eosinophilia in a murine model of asthma. J Allergy Clin Immunol 2006;118:105-12.
44. Dai YC, Chuang WJ, Chua KY, Shieh CC, Wang JY. Epitope mapping and structural analysis of the anti-Der p 1 monoclonal antibody: insight into therapeutic potential. J Mol Med (Berl) 2011;89:701-12.
45. Phipps S, Lam CE, Kaiko GE, Foo SY, Collison A, Mattes J, Barry J, Davidson S, Oreo K, Smith L, Mansell A, Matthaei KI, Foster PS. Toll/IL-1 signaling is critical for house dust mite-specific helper T cell type 2 and type 17 [corrected] responses. Am J Respir Crit Care Med 2009;179:883-93.
46. Marichal T, Bedoret D, Mesnil C, Pichavant M, Goriely S, Trottein F, Cataldo D, Goldman M, Lekeux P, Bureau F, Desmet CJ. Interferon response factor 3 is essential for house dust mite-induced airway allergy. J Allergy Clin Immunol 2010;126:836-44.e13.
47. 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.
48. Hammad H, Chieppa M, Perros F, Willart MA, Germain RN, Lambrecht BN. House dust mite allergen induces asthma via Toll-like receptor 4 triggering of airway structural cells. Nat Med 2009;15:410-6.
49. Trompette A, Divanovic S, Visintin A, Blanchard C, Hegde RS, Madan R, Thorne PS, Wills-Karp M, Gioannini TL, Weiss JP, Karp CL. Allergenicity resulting from functional mimicry of a Toll-like receptor complex protein. Nature 2009;457:585-8.
50. Chiou YL, Lin CY. Der p2 activates airway smooth muscle cells in a TLR2/MyD88-dependent manner to induce an inflammatory response. J Cell Physiol 2009;220:311-8.
51. 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.
52. Kuipers H, Lambrecht BN. The interplay of dendritic cells, Th2 cells and regulatory T cells in asthma. Curr Opin Immunol 2004;16:702-8.
53. MacDonald AS, Maizels RM. Alarming dendritic cells for Th2 induction. J Exp Med 2008;205:13-7.
54. Gazi U, Martinez-Pomares L. Influence of the mannose receptor in host immune responses. Immunobiology 2009;214:554-61.
55. Royer PJ, Emara M, Yang C, Al-Ghouleh A, Tighe P, Jones N, Sewell HF, Shakib F, Martinez-Pomares L, Ghaemmaghami AM. The mannose receptor mediates the uptake of diverse native allergens by dendritic cells and determines allergen-induced T cell polarization through modulation of IDO activity. J Immunol 2010;185:1522-31.
56. Shreffler WG, Castro RR, Kucuk ZY, Charlop-Powers Z, Grishina G, Yoo S, Burks AW, Sampson HA. The major glycoprotein allergen from Arachis hypogaea, Ara h 1, is a ligand of dendritic cell-specific ICAM-grabbing nonintegrin and acts as a Th2 adjuvant in vitro. J Immunol 2006;177:3677-85.
57. 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.
58. Ghaemmaghami AM, Gough L, Sewell HF, Shakib F. The proteolytic activity of the major dust mite allergen Der p 1 conditions dendritic cells to produce less interleukin-12: allergen-induced Th2 bias determined at the dendritic cell level. Clin Exp Allergy 2002;32:1468-75.
59. Furmonaviciene R, Ghaemmaghami AM, Boyd SE, Jones NS, Bailey K, Willis AC, Sewell HF, Mitchell DA, Shakib F. The protease allergen Der p 1 cleaves cell surface DC-SIGN and DC-SIGNR: experimental analysis of in silico substrate identification and implications in allergic responses. Clin Exp Allergy 2007;37:231-42.