Review

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House Dust Mite Allergy in Korea: The Most Important Inhalant Allergen in Current and Future

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The house-dust mite (HDM), commonly found in human dwellings, is an important source of inhalant and contact allergens. In this report, the importance of HDM allergy in Korea and the characteristics of allergens from dust mite are reviewed with an emphasis on investigations performed in Korea. In Korea, *Dermatophagoides farinae* is the dominant species of HDM, followed by *D. pteronyssinus*. *Tyrophagus putrescentiae* is also found in Korea, but its role in respiratory allergic disease in Korea is controversial. The relatively low densities of mite populations and concentrations of mite major allergens in dust samples from Korean homes, compared to westernized countries, are thought to reflect not only different climatic conditions, but also cultural differences, such as the use of 'ondol' under-floor heating systems in Korean houses. HDM are found in more than 90% of Korean houses, and the level of exposure to HDM is clinically significant. About 40%-60% of Korean patients suffering from respiratory allergies, and more than 40% of patients suffering from atopic dermatitis, are sensitized to HDM. Mite allergens can be summarized according to their inherent auto-adjuvant activities and/or their binding affinities to the adjuvant-like substances: proteolytic enzymes, lipid binding proteins, chitin binding proteins, and allergens not associated with adjuvant-like activity. In general, allergens with a strong adjuvant-like activity or adjuvant-binding activity elicit potent IgE reactivity. In Korea, Der f 2 is the most potent allergen, followed by Der f 1. Immune responses are modulated by the properties of the allergen itself and by the adjuvant-like substances that are concomitantly administered with the antigens. Characterization of allergenic molecules and elucidation of mechanisms by which adjuvant-like molecules modulate allergic reactions, not only in Korea but also worldwide, will provide valuable information on allergic diseases, and are necessary for the development of diagnostic tools and therapeutic strategies.

Key Words: Allergen; allergy; house dust mite; Korea

INTRODUCTION

The house-dust mite (HDM) was first suspected as a source of allergen in 1928,[1] and has been recognized as an important cause of allergic disorders since 1968.[2,3] The relationship between house dust and HDM in bronchial asthmatics has been demonstrated using the skin reactivity test, bronchial provocation test, serologic test for mite-specific IgE and the basophil histamine release test.[3,4] Epidemiologic studies performed with the skin prick test showed that HDM is the most common cause of allergic diseases in Korea. In Korea, the rate of sensitization to HDM has been reported to be 27.9%-68.8% in patients with atopic dermatitis[5-10] and 40%-60% in patients with respiratory allergy, allergic rhinitis and asthma.[11-14] In a study of 431 allergic subjects in Seoul, about 60% were sensitized to HDM, regardless of their allergic symptoms.[15]

The rate of sensitization to HDM has increased with industrialization and the westernization of Korean lifestyles.[16,17] With the advent of molecular biological technology, proteins from various mite species responsible for the induction of allergic responses have been investigated. HDM produces various proteins that could elicit IgE-mediated immune responses, and some molecules may modulate the allergic reactions by their adjuvant-like characteristics or their affinity to adjuvant. However, it is not clear which allergenic substances of HDM are responsible for the increase in allergic disorders in Korea. Molecular characterization of these substances will provide new insight and new strategies for the development of immunotherapeutic tools to modulate the immune response.

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HDMS AND ALLERGEN LEVELS IN THE ENVIRONMENT

In house dust, five families of mites (Pyrogliphidae, Acaridae, Glycyphagidae, Chortoglyphidae and Chelyetidae) have been identified.[18] HDM belongs to the family Phyrogliphidae, and mites of the other families are collectively called storage mites. The term 'dust mites' refers to the mite species isolated from dust samples, regardless of their family; *i.e.*, HDM and storage mite (Figure).

In Korea, five species of mites (*Tyrophagus dimidiatus, Chibidania tokyoensis, Rhizoglyphus echinopus, Ornithonyssus nagayoi* and *Dermanyssus gallinae*) were reported from house dust samples for the first time in 1967.[19] Dust mites of allergenic importance (*Dermatophagoides fainae, D. pteronyssinus*, and *Tyrophagus putrescentae*) were first described by Cho and Houh in 1977.[20] Studies on the geographical distribution of dust mites in Korea confirmed *D. farinae* as the predominant species (65.3%), followed by *D. pteronyssinus* (20.6%) and *T. putrescentiae* (6.5%) among 7,257 mites collected.[21,22] Marked cross-reactivity between *D. farinae* and *D. pteronyssinus* extracts has been reported.[23]

The storage mite, *T. putrescentiae*, is the third most commonly found dust mite in Korean homes. However, its role in allergic diseases is controversial. IgE-binding components of *T. putrescentiae* were reported to be completely inhibited by *D. pteronyssinus* or *D. farinae* extracts.[24,25] A 16-kDa allergen, probably Tyr p 2, is the most potent, and is responsible for cross-reactivity with Der f 2 and Der p 2 in urban areas (Seoul).[25] However, studies conducted in rural areas of Sweden showed that inhabitants were exposed to high levels of *T. putrescentiae*, which is an important inhalant allergen with little cross-reactivity to *D. pteronyssinus*.[26]

Nationwide studies reflecting the regional differences between urban and rural areas of Korea are necessary to evaluate the importance of allergies against storage mites. *T. putrescentiae* is one of the most common allergens, and some patients suffering from perennial asthma in Daejeon were reported to be sensitized only to *T. putrescentiae*.[27] Sensitization to *T. putrescentiae* is also prevalent (19.5%) in allergic children in Seoul.[28]

Different procedures for mite collection and isolation from dust samples may result in different mite counts and allergen concentrations. Recently, a standard method for the investigation of dust mite density was suggested for use in objective and convenient field surveys.[29] The number of mites per unit area (1 m^2) collected in a given time (2 minutes) was measured using a house-hold vacuum cleaner equipped with a nonwoven fabrics.

Using the standard collection method, HDM allergens have been found in more than 85%-90% of houses in Korea. About one-third (31.2%) of dust samples from houses in Korea (mostly Seoul) contained more than 2 μg/g dust that consisted of mite group 1 allergen,[30] a known risk factor for sensitization and development of asthma (equivalent to 100 mites/g dust).[31,32] In 10% of dust samples from Korean homes, 10 μg/g of dust consisting of mite group 1 allergen was detected, which is known to be a major risk factor for the development of acute asthma

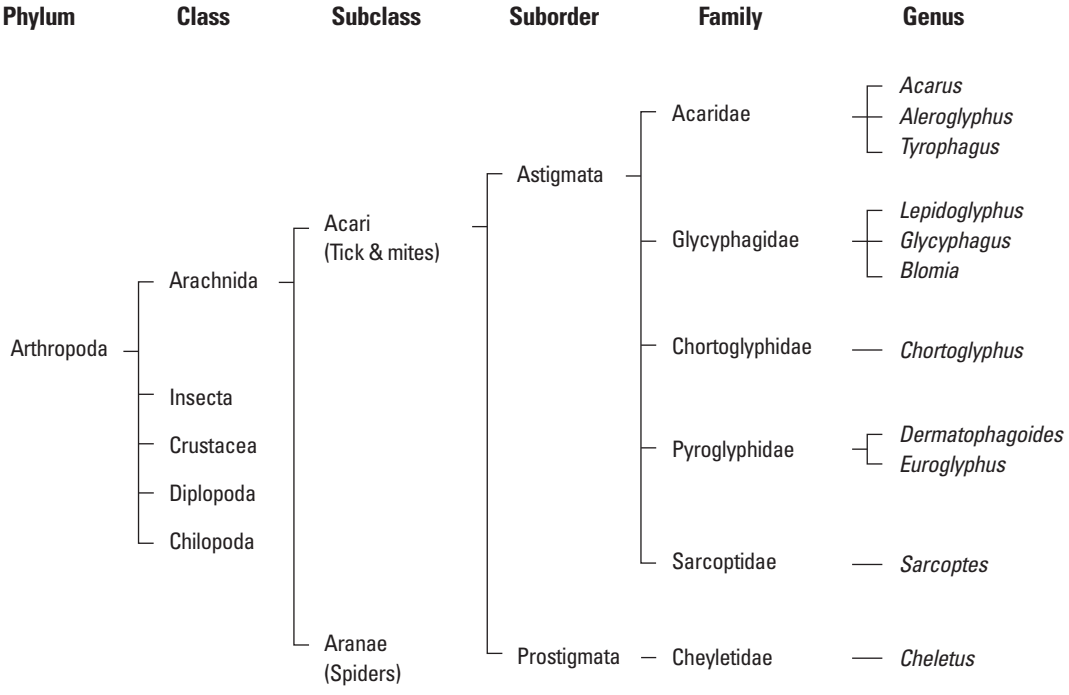

Figure. Classification of dust mites of allergenic importance.

(equivalent to 500 mite/g dust).[33] In 100 randomly selected domestic homes in Cheonan, Korea, an average of 7.46 and 10.2 μg/g dust was measured from floors and mattresses, respectively.[34] High levels of mite allergen were reported in Cheonan, which may indicate a geographical difference in mite allergen levels in Korea.

It would be interesting to perform a nationwide study to investigate the regional differences in mite allergen concentrations in house dust. A low sensitization rate to inhalant allergens including HDM (17.2% to *D. farinae* and 19.5% to *D. pteronyssinus*) in Gangwon area was reported,[35] whereas a high prevalence of sensitization to HDM has been described in other areas, such as Chungbuk (more than 50%)[36] and Busan (44.9% to *D. farinae* and 49.3% to *D. pteronyssinus*).[37]

The bedclothes and sewing dolls of Korean children were reported to have 3.24±0.50 and 3.43±0.30 μg/g dust of Der f 1.[38] A median of 250 ng/g dust of Der f 1 was detected in the settled dust samples from 34 classrooms of Korean primary schools, which is higher than those (median, <200 ng/g dust) from 23 classrooms in Sweden.[39] Common contamination of schools with mite allergens, along with cat and dog allergens, may contribute to sensitization of Korean pupils.

The distribution and seasonal variations of mite allergens in homes were measured by radioallergosorbent (RAST) inhibition.[40] The mite allergen concentrations increased from spring (May) to autumn (September), and decreased from late autumn to early spring (October to May).[30] This seasonal pattern is quite similar to a study performed in the US.[41]

Seasonal changes in the mite allergen concentrations in bedding, which reflect the natural exposure, can lead to concurrent changes in skin test reactivity and the presence of mite-specific IgE antibody in mite-asthmatic patients.[42] A correlation between the allergen concentration and specific IgE to the HDM allergen, Der f 1, was described in 2006.[30] The seasonal change in mite allergen levels in house dust can lead to concurrent changes in mite-specific IgG antibody levels, especially in the case of IgG4 in mite asthmatics;[43] however, the significance of IgG changes remains unknown.

Recently, enzyme-linked immunosorbent assays (ELISAs) locally produced in Thailand detected higher levels of Der f 1 from dust samples compared to a commercially available immunoassay kit (Indoor Biotechnology, UK).[44] Commercial two-site ELISA kits do not reflect the sequence polymorphism in a region. Therefore, it is thought that the mite allergen levels reported in Korea may have underestimated the actual allergen levels. Estimation of mite allergen level based on group 1 allergens is thought to be more reliable than that based on group 2 allergens because the amino acid sequences of group 2 allergens are more highly polymorphic, which hinders the precise determination of allergen level.[45]

Almost all Korean houses have 'ondol' heating, an under-floor heating system. Ondol removes house dust and provides hot and dry conditions when activated. Usually, bedclothes are stored inside furniture compartments during the daytime, and a bed is laid on the bedroom floor in the evening. Traditionally, Koreans do not have the mattresses or carpets that provide ideal habitats for HDM. These cultural and lifestyle differences may partly explain the dominance of *D. farinae* in Korean homes. In fact, a much lower mite and mite antigen density was detected in fine dust in Seoul, Korea, compared to those from Saitama prefecture, Japan, where climatic conditions are similar.[46] Since the use of mattresses and carpets is becoming more common in Korea, it will be interesting to measure the change in the mite population density and the concentration of mite allergens in Korean homes as these lifestyle changes occur. The influence of global warming on the HDM population density and its allergen level should also continue to be monitored.

Recently, it was suggested that there is a bell-shaped relationship between exposure and sensitization, rather than a linear relationship.[47] It was also suspected that reduced allergen exposure results in the failure to induce and maintain immune tolerance to common environmental allergens.[48]

HDMS IN ALLERGIC DISEASES

More than 60% of patients in Seoul that suffer from respiratory allergic symptoms are reported to be sensitized to HDM allergens.[15,49] HDMs were also found to be the most frequent cause of respiratory allergic diseases, and 40%-60% of Korean respiratory allergic subjects were reported to show positive skin test reactions to HDM extracts between 1983 and 1985.[11-14] In more recent studies, a sensitization rate to HDM of 17.2%-64.7% has been reported among respiratory allergic subjects, with some geographical differences as described above.[15,35-37,49] There is no significant difference in the rate of sensitization to HDM between patients suffering from rhinitis and asthma. The rate of sensitization to HDM has been reported to be 27.9%-66.7% in patients suffering from atopic dermatitis.[5-10] HDM allergic subjects are known to most commonly suffer from perennial rhinitis.[33] The rate of sensitization to HDM in children suffering from atopic diseases is reported to be very high. The percentage of HDM-positive asthmatic children increases with age. In particular, as a risk factor for asthma symptom, positive HDM sensitivity values were lower in children who were 0-3 years (53.5%) compared with those who were 4-7 years (68.9%) and 8-12 years (80.2%) of age.[50]

Immunotherapy is an important approach to the treatment of HDM allergy. However, large-scale studies of their efficacy and mechanism have not been performed. Notably, immunotherapy of monosensitized patients showed improved allergic indices compared with polysensitized patients.[51] Successful immunotherapy depends not only on carefully controlled treatment, but also on the careful selection of subjects.

ENVIRONMENTAL CONTROL IN HDM STUDIES PERFORMED IN KOREA

Simple employment of allergen-impermeable covers is thought to be an effective allergen avoidance measure. Vapor-permeable water-proof fabric bedding covers did not decrease HDM allergen levels in bedding.[52] Selected use of an allergen-impermeable cover was reported to significantly reduce exposure to allergens from bedding dust and had clinical benefits.[53] Interventions that achieve substantial reductions in dust mite load may reduce clinical symptoms. However, isolated use of a mite-impermeable bedding cover is not thought to offer general benefits.[54]

HDM species were detected in air conditioner filters,[55] and air cleaners with electrostatic filters were shown to remove the mite allergen effectively.[56] Airborne mite allergens were also measured during normal domestic activity.[57] Airborne Der f 1 levels (14.0 pg/m^3) were significantly correlated with those in bedding samples. However, the role of air cleaners in the removal of airborne HDM allergen remains controversial. Regular laundry with mechanical washing machines proved effective for removing HDM allergens from bedding and clothes.[58] Water temperature (>60°C) is critical for killing HDM in clothes or bedding samples during mechanical laundry.[58]

HDM ALLERGEN: RELEVANT ALLERGENIC COMPONENTS IN KOREAN PATIENTS

A total of 32 IgE-reactive proteins have been shown to be allergenic among the 51 antigens identified by crossed immunoelectrophoretic analysis (CIE).[59-61] Of over 30 protein bands in a *D. farinae* extract, a 14-15-kDa protein allergen, which is probably a group 2 allergen, was found to be the most potent by electroblotting.[60]

Twenty-four groups of mite proteins have been officially listed as allergens by the allergen nomenclature subcommittee (available from: www.allergen.org). It is necessary to compare the allergenicity of these allergens and evaluate their clinical relevance in Korean patients.

Presentation of exogenous antigens by antigen-presenting cells (APCs) in the absence of direct Toll-like receptor (TLR) stimulation generally leads to immune tolerance or anergy. Adjuvants, of which many are derived from microbes, are thought to activate the innate immune system by displaying a pathogen-associated molecular pattern. Effector T cell responses to APCs are efficiently generated when TLR ligands are present in the phagosome. TLR ligands could be derived from commensals and pathogens within HDM as well as the host (allergic patients). Allergic responses to these allergens can be modulated by the concomitant administration of adjuvant-like substances.[62] Therefore, dust mite allergens can be classified according to the presence of inherent adjuvant-like activity or their affinity to adjuvant substances in mite extract. The following sections summarize the allergens from dust mites that are of allergenic importance with respect to their adjuvant-like activities.

Allergens with proteolytic activities

Protease activity is an important property of allergens.[63] Allergens from mite groups 1, 3, 6, and 9 were identified as cysteine protease, trypsin, chymotrypsin, and collagenolytic serine protease, respectively (Table 1). Protease activities of these allergens can influence their allergenicity in various ways: (1) the

Table 1. Dust mite allergens with proteolytic activity

Group	Allergen	Biochemical identity	Molecular weight (kDa)	IgE reactivity (%)	Species
1	Der p 1	Cysteine protease	25	80-100	*Dermatophagoides pteronyssinus*
	Der f 1				*D. farinae*
	Blo t 1				*Blomia tropicalis*
	Pso o 1				*Psoroptes ovis*
3	Der p 3	Trypsin	25	16-100	*D. pteronyssinus*
	Der f 3				*D. farinae*
	Der s 3				*D. siboney*
	Blo t 3				*B. tropicalis*
	Tyr p 3				*Tyrophagus putrescentiae*
	Eur m 3				*Euroglyphus maynei*
	Lep d 3				*Lepidoglyohus destructor*
	Gly d 3				*Glycyphagus domesticus*
	Sar s 3				*Sarcoptes scabiei*
6	Der p 6	Chymotrypsin	25	40	*D. pteronyssinus*
	Der f 6				*D. farinae*
9	Der p 9	Collagenolytic serine protease	9	90	*D. pteronyssinus*

proteolytic activity of mite allergens can cause disruption of the epithelium, allowing access of allergens to antigen-presenting cells[64-66]; (2) Der p 1 can cleave immunomodulators such as CD23 (low-affinity IgE receptor) and CD25 (α-subunit of IL-2 receptor)[67]; (3) trypsin-like group 3 allergens can activate complement and kallikrein, causing liberation of kinins and activated complement[68,69]; (4) protease allergens are known to elicit inflammatory reactions by activating protease-activated receptor-2[70]; (5) protease activity can release inflammatory cytokines independent of PAR-2 activation[71]; and (6) cysteine protease, possibly Der p 1, has been shown to activate and recruit basophils to the draining lymph nodes and stimulate production of Th2-inducing cytokines, including IL-4 and thymic stromal lymphopoietin (TSLP), suggesting an important role for protease in Th2 differentiation.[72] The mechanisms by which dust mite proteases might promote allergic responses were reviewed by Smith and Harper.[73] Recently, it has been suggested that cysteine protease activity could be an adjuvant for Th2 responses against both themselves (Der p 1) and bystander antigens (Der p 2), even in the absence of another adjuvant.[74] It is possible that there are proteolytic enzymes other than these protease allergens in mite extracts, which may affect allergic responses through induction of inflammatory reactions, regardless of IgE reactivity.[75]

Allergens with affinities to lipids

Lipid-binding properties are important characteristics of allergens.[76,77] Group 2, 13, and 14 allergens are associated with lipid-binding activity (Table 2). Der f 2 showed stronger IgE reactivity than Der f 1 in Korean mite-allergy patients.[78-80] Der p 2 and Der f 2 were localized in the midgut and fecal pellets of the mite, indicating that these are associated with the digestive system.[81,82] Jeong et al.,[82] suggested that Der f 2 plays a role in preventing microbes from penetrating the mite epithelia. However, the exact function of Der f 2 and Der p 2 in mites is not yet clear. Der p 2 can bind lipopolysaccharides, subsequently reconstituting and amplifying TLR4 signaling.[83] This observation suggests that the intrinsic adjuvant-like activity of allergens can enhance their allergenicity. Der p 2 is known to activate respiratory epithelial cells and induce secretion of granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-6, IL-8, monocyte-chemotactic protein-1 (MCP-1) and macrophage inflammatory protein-3α (MIP-3α), which is regulated by nuclear factor-κB (NF-κB) and mitogen-activated protein kinase (MAPK).[84] Der f 2 was shown to activate transcription factor-2, and subsequently induce activation of phospholipase D1 and expression of IL-13 in human bronchial epithelial cells.[85]

Der f 2 and Der p 2 of Korean HDM have frequent polymorphisms in their amino acid sequences,[86] which affect their affinities to human specific IgE and monoclonal antibodies.[45,87-89]

Lipids may play a role in triggering of immune reactions by activation of $CD1^+$ dendritic cells and restriction of T lymphocytes.[90] The size of the lipid vesicle entrapped by macrophages is reported to determine the pattern of cytokine production by T helper cells.[91] Vesicles with a mean diameter of less than 155 nm were shown to induce a Th2 response, whereas vesicles with a mean diameter larger than 225 nm induced Th1 responses. These reports suggest that the lipid-binding properties of allergens affect its allergenicity.

Allergens from mite groups 13 and 14 are thought to have lip-

Table 2. Dust mite allergens with lipid binding properties

Group	Allergen	Biochemical identity	Molecular weight (kDa)	IgE reactivity (%)	Species
2	Der p 2	Niemann-Pick C2 homologue	14	80-100	*D. pteronyssinus*
	Der f 2				*D. farinae*
	Blo t 2				*B. tropicalis*
	Tyr p 2				*T. putrescentiae*
	Lep d 2				*L. destructor*
	Gly d 2				*G. domesticus*
	Aca s 2				*Acarus siro*
	Sui m 2				*Suidasia medanensis*
	Pso o 2				*P. ovis*
13	Blo t 13	Fatty acid binding protein	15	10-23	*B. tropicalis*
	Tyr p 13				*T. putrescentiae*
	Lep d 13				*L. destructor*
	Gly d 13				*G. domesticus*
	Aca s 13				*A. siro*
14	Der p 14	Vitellogenin-apolipophorin like	177	90	*D. pteronyssinus*
	Der f 14				*D. farinae*
	Pso o 14				*P. ovis*

id-binding properties. Group 13 allergens are homologous to fatty-acid-binding proteins,[92,93] and group 14 allergens show some homology with apolipophorin and vitellogenin. The allergenicity of Der f 14 might have been underestimated because it is not water soluble.[94] Fujikawa et al.[95] reported that the allergenicity of Der f 14 is greater than that of Der p 2. Furthermore, Der f 14 is highly susceptible to proteolytic degradation, and the fragments so generated could be more allergenic than the intact protein.[96]

Chitin-binding proteins

Chitin, an abundant polysaccharide, is an important exoskeleton component of arthropods. Mites shed their chitin coats for growth, and recently, chitin was identified as a common constituent of house dust samples.[97] Interestingly, acidic mammalian chitinases were identified in human beings, even though humans do not metabolize chitin. Chitinase was found to play an important role in the pathogenesis of asthma.[98,99] Allergens from mite groups 5, 12, 15, 18, 21, and 23 are thought to bind to chitin (Table 3). Der f 15 shows homology with insect chitinases (family 18 of the glucohydrolase superfamily).[100] Group 18 allergens are also homologs of chitinase, and contain two putative chitinase catalytic domains.[101,102] The function of group 5 allergens is elusive. Secondary structure prediction and NMR analysis showed a pattern of heptad repeats, which might be associated with polymerization.[103,104] Blo t 21, which has a high sequence identity with group 5 allergens of *Dermatophagoides* spp., was localized in the midgut epithelium and fecal pellets,[105] implying that mite group 5 and 21 allergens may be involved in the formation of the peritrophic membrane envelope comprised of a protein matrix and chitin fibrils. Structural analysis by molecular modeling approaches revealed that group 5 and 21 allergens could dimerize and form a large hydrophobic cavity, which could be involved in the binding of hydrophobic ligands.[106] Der p 23 also shows some homology with peritrophin A, whose function is also associated with chitin binding. Group 12 allergens, Blo t 12[107] and Led d 12 (AY293744), show limited homology to a peritrophic membrane-binding protein from the moth cabbage looper, *Trichoplusia ni*, and Der f 15.

Allergens not associated with adjuvant-like activity

Some groups of mite allergens are not known to be associated with adjuvant-like activity. However, some of these have been described as potent allergens. These may be bystander allergens or could have an unidentified adjuvant-like function. This group of allergens is subclassified into muscle and non-muscle proteins for convenience.

Muscle proteins derived from dead debris could be inhaled and ingested with mite-contaminated food.[108] Allergens from mite groups 10, 11, and 24 are muscle proteins (Table 4). Tropomyosin (mite group 10 allergens), paramyosin (mite group 11 allergens), and troponin C (mite group 24 allergens) are known to be allergenic.

Tropomyosins are the most important food allergens of shellfish and mollusks, such as shrimp, lobster, crab, oyster and squid. The amino acid sequences of invertebrate tropomyosins are highly conserved and they can cause cross-reactivities.[109] However, dust mite tropomyosins are thought to contribute a limited degree of dust mite cross-reactivity due to their low IgE reactivity.[110] Furthermore, tropomyosin is a major concern regarding neo-sensitization in patients with mite immunotherapy.[111]

Paramyosin is a ubiquitous protein found in invertebrate muscle. A high frequency of IgE binding was reported for Der f 11, Der p 11 and Blo t 11 (67%-80%).[112-114] The amino acid sequences of mite paramyosins are highly conserved and might be cross-reactive. Paramyosin, an important parasite antigen, is a target for vaccine development.[115] Parasite paramyosin may affect the cross-reactivity of mite paramyosin. However, mite paramyosins were found to be easily degraded and present in the allergen extract at less than 1 μg/mL.[116]

Troponin C, a mite group 24 allergen, was recently described as an allergen from *T. putrescentiae*.[117] Interestingly, the IgE reactivity of Tyr p 24 was dependent on the Ca^{2+} concentration. It showed a limited degree of cross-reactivity with Bla g 6, the

Table 3. Dust mite allergens with chitin binding property

Group	Allergen	Biochemical identity	Molecular weight (kDa)	IgE reactivity (%)	Species
5	Der p 5	Unknown	15	50-70	*D. pteronyssinus*
	Blo t 5				*B. tropicalis*
	Lep d 5				*L. destructor*
	Gly d 5				*G. domesticus*
12	Blo t 12	Unknown	14	50	*B. tropicalis*
	Lep d 12				*L. destructor*
15	Der f 15	Chitinase	63	70	*D. farinae*
18	Der f 18	Chitinase-like	60	60	*D. farinae*
21	Der p 21	Unknown		<95	*D. pteronyssinus*
	Blo t 21				*B. tropicalis*
23	Der p 23	Unknown	14		*D. pteronyssinus*

cockroach troponin C (68.2% identical). The allergenicity of troponin C from HDM has not been investigated.

Some mite allergens, such as those from groups 4, 7, 8, 16, 17, and 20, are neither muscle proteins nor associated with any known adjuvant-like molecules (Table 5). For example, α-amylase is a group 4 allergen.[118,119] Interestingly, amylase inhibitors from cereals are known as important occupational allergens.[120] Insects and mites produce multiple isozymes against these dietary inhibitors.[121] It is worth noting that the amino acid sequences of amylases are highly conserved across the animal kingdom. Investigations of cross-reactivities between related species should be performed.

Little is known about the structure and function of group 7 allergens. Despite its abundance in the mite,[122] the group 7 allergen concentration in mite extract was low.[123] Group 7 allergen is glycosylated and easily degraded in extract.[124] The IgE binding frequency of group 7 allergens was reported to be 37%-67%.[125-127] Mite group 7 allergens are thought to be important molecules for the standardization of recombinant protein production.

The group 8 allergens, which are mu-class glutathione *S*-transferases (GSTs), play a role in detoxification.[128] Huang et al.[129] also described cross-reactivity between the mite and cockroach GSTs. However, Bla g 5, the cockroach GST, belongs to the sigma class.

Table 4. Dust mite allergens from muscle

Group	Allergen	Biochemical identity	Molecular weight (kDa)	IgE reactivity (%)	Species
10	Der p 10	Tropomyosin	35	<95	*D. pteronyssinus*
	Der f 10				*D. farinae*
	Blo t 10				*B. tropicalis*
	Tyr p 10				*T. putrescentiae*
	Lep d 10				*L. destructor*
	Gly d 10				*G. domesticus*
	Cho a 10				*Chortoglyphus arcuatus*
	Pso o 10				*P. ovis*
11	Der p 11	Paramyosin	100	80	*D. pteronyssinus*
	Der f 11				*D. farinae*
	Blo t 11				*B. tropicalis*
	Pso o 11				*P. ovis*
	Sar s 11				*S. scabiei*
24	Tyr p 24	Troponin C	18	11	*T. putrescentiae*

Table 5. Dust mite allergens without autoadjuvant or adjuvant binding activity

Group	Allergen	Biochemical identity	Molecular weight (kDa)	IgE reactivity (%)	Species
4	Der p 4	α-amylase	56	40-46	*D. pteronyssinus*
	Blo t 4				*B. tropicalis*
7	Der p 7	Unknown	24	50	*D. pteronyssinus*
	Der f 7				*D. farinae*
	Lep d 7				*L. destructor*
	Gly d 7				*G. domesticus*
8	Der p 8	Glutathione *S*-transferase	26	40	*D. pteronyssinus*
	Lep d 8				*L. destructor*
	Gly d 8				*G. domesticus*
16	Der f 16	Gelsolin	55	35	*D. farinae*
17	Der f 17	Calcium binding EF protein	30	35	*D. farinae*
20	Der p 20	Arginine kinase	20	25	*D. pteronyssinus*
Ungrouped		α-tubulin	51	12	*L. destructor*
					T. putrescentiae
		Heat shock protein 70	70	57	*D. farinae*
					B. tropicalis

There is a limited degree of cross-reactivity between sigma- and delta-class GSTs, even within the same species.[130] Cross-reactivities between the same GST class should be examined.

Der f 16, a member of the gelsolin/vollin family, and Der f 17, an EF-hand Ca^{2+}-binding protein, were identified by screening cDNA libraries.[131] Blo t 19 is known to have 76% homology with an antibacterial factor, ASABF, from *Ascaris suum*. However, no detailed information on these allergens has been published to-date.

Group 20 allergens consist of arginine kinase, an equivalent to the vertebrate creatine kinase. Der p 20 bound 40% of IgE antibody, although with a low titer.[132] Interestingly, the group 2 allergen of shrimp is also arginine kinase.[133] Invertebrate arginine kinases have a high homology (70%-80% identity), suggesting the possibility of cross-reactivity.

Der f 22, recognized in the International Union of Immunological Societies (IUIS) official list of allergens (available from: www.allergen.org), is known to have some homology with mite group 2 allergen. However, no published data on mite group 22 allergen is available at present.

β-glucan derived from fungi has also been detected in house dust samples,[134] and is known to be associated with asthma symptoms.[135,136] However, none of the allergens identified to-date exhibited a relationship with β-glucan. It would be interesting to investigate the role of β-glucan in HDM allergy and characterize the molecules from mite species that are associated with β-glucan-like substances.

Additional proteins with IgE reactivity from dust mites have been described, although they are not included in the IUIS list, including hydrolase,[137] a heat shock protein-70 homologue,[138] α-tubulin,[139,140] a 39-kDa allergen of unknown function,[141,142] a 244-kDa allergen of unknown function,[143] and 79- and 93-kDa proteins from *L. destructor*.[144] Of these, the IgE reactivity of recombinant α-tubulin from Korean *T. putrescentiae* was investigated,[140] and the frequency of IgE reactivity was 29.3%. However, it is noteworthy for its highly conserved amino acid sequence among almost all known species.

Induction of various cytokines and chemokines by treatment with mite extract has been described in peripheral blood mononuclear cells and human monocytic THP-1 cells.[145,146] Identification of the molecules responsible for these observations is necessary.

Allergenic relevance of dust mite allergens in Korea

IgE immunoblotting showed some differences in IgE-reactive components among individuals,[60] and therefore, the development of personalized immunotherapeutic reagents might be beneficial.

A 15-kDa allergen, possibly belonging to group 2, was the most potent in terms of IgE-binding frequency and intensity in Korea.[147] Serum samples from 60% and 61% of patients who showed positive skin prick test responses to HDM extract were found to contain IgE specific for Der f 1 and Der f 2, respectively.[78] However, Der f 2 showed significant inhibition of specific IgE to HDM whole body extract, whereas Der f 1 did not at an inhibitory concentration (20 ng/mL). IgE responses to Der f 2 were also significantly higher than those to Der f 1 in children over 4 years of age.[80] IgE reactivity to Der f 1 and Der f 2 was higher in an atopic than a non-atopic group.[79] However, IgE to Der f 1 was more common in a group of asthma patients. This finding suggests a relationship between the properties of allergens and their allergic manifestation. Recombinant Der f 2 produced in *E. coli* is recognized by 90%-100% of serum IgE from Korean *D. farinae*-sensitized subjects (data not shown). Vaccination with DNA-encoding T cell epitopes of Der p 1 and Der p 2 effectively inhibits allergen-specific IgE synthesis and reduces cell infiltration in lung tissue in mice.[148] A mixture of DNA vaccines encoding mite group 1, 2, and 3 allergens had a protective effect in the murine model sensitized to HDM crude extract, indicating that these allergens play important roles in HDM allergy.[149] However, their effect in humans remains to be evaluated.

The recombinant mite tropomyosins, Der f 10 and Tyr p 10, showed 25% and 12.5% IgE-binding frequency to Korean mite-sensitized patients.[110] However, neither allergen significantly inhibited IgE binding to crude extracts. Recombinant fatty acid-binding protein, Tyr p 13, was recognized in 6.4% of sera from *T. putrescentiae*-sensitized subjects.[92] Recombinant Tyr p 13 was able to inhibit up to 61.9% of IgE reactivity to crude extract in serum. This suggests that minor allergens play an important role in some cases. For troponin C, Tyr p 24, a 10.6% IgE binding frequency was detected, but it did not significantly inhibit IgE reactivity to crude extract.[117] The frequency of IgE reactivity to recombinant α-tubulin from *T. putrescentiae* was 29.3%, although its titer was very low.[140] The allergenicities of the other groups of allergens in Korea have yet to be investigated.

CONCLUDING REMARKS

HDM is the most important inhalant allergen in Korea, and its exposure is also significant. More than 31 allergens have been reported to-date in HDM extracts, and IgE reactivity profiles to purified allergens vary in subjects from different countries.[150] In Korea, investigations of the sensitization profile of the entire panel of mite allergens, and comparisons among the relevant single allergens, are required. Additionally, future investigations will need to examine the mechanisms by which adjuvant-like activities modulate the innate immune response, subsequent to the allergic manifestation. Component-resolved diagnosis (CRD) is of growing importance for the diagnosis of allergic diseases,[151] and future studies will investigate the relationship between adjuvant-like activity and allergy symptoms. Development and production of therapeutic recombinant HDM allergens will facilitate CRD and immunotherapeutic approaches using selected molecules.[152]

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