

“Molecular and biochemical properties of storage mites

Dr. Enrique FERNÁNDEZ-CALDAS

Clinical Professor of Medicine

University of South Florida, College of Medicine, Division of Allergy and Immunology;

Tampa, Florida

Scientific Director Inmunotek S.L., Madrid, Spain

Email: efcaldas@immunotek.com

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Summary

In recent years, the allergological importance of different mite species not belonging to the family Pyroglyphidae has been demonstrated. These mites, commonly named storage mites, include *Lepidoglyphus destructor*, *Glycyphagus domesticus*, *Tyrophagus putrescentiae*, *Acarus siro*, *Aleuroglyphus ovatus*, *Suidasia medanensis* and *Thyreophagus entomophagus*. Several allergens from these species have been purified, sequenced and cloned. Many of these allergens have shown sequence homology and a biological function similar to those previously described in *Blomia tropicalis* and the *Dermatophagoides* spp. The main allergens described in storage mites include fatty acid binding proteins, tropomyosin and paramyosin homologues, apoliphorine like proteins, alfa-tubulines and other, such as group 2, 5 and 7 allergens, which definitive biological function has not been described yet. Besides the purification and characterization of allergens, the allergenicity of other species such as *Acarus farris*, *Austroglycyphagus malaysiensis*, *Blomia kulagini* and *B. tjobodas*, *Cheyletus eruditus*, *Chortoglyphus arcuatus*, *Gohieria fusca*, *Thyreophagus entomophagus* and *Tyrophagus longior* has been investigated. Research has also been conducted to identify allergens in parasitic mites, such as *Psoroptes ovis*, *Sarcoptes scabiei*, *Varroa jacobsoni*, *Diplaegidis columbae* and *Hemisarcoptes cooremani*. The allergenicity of mites present in agricultural environments has been investigated. Crossreactivity studies have also been performed to elucidate to what extent all these mites share common, or species specific epitopes. Herein we

present a comprehensive review of the allergenicity of mite species which have been implicated in human respiratory and/or dermatological diseases.

Introduction

From the early 1960s, much literature has been published concerning the taxonomy, biology, immunochemistry and control of mites implicated in allergic reactions. Numerous species have been described that are the source of allergens capable of sensitizing and inducing allergic symptoms in sensitized and genetically predisposed individuals. Allergic diseases that can be triggered by mite allergens include allergic rhinoconjunctivitis, asthma, atopic dermatitis and other skin diseases.

The most studied species, because of its abundance and allergenic importance, is the group of the house dust mites, which belong to the family Pyroglyphidae, especially *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae* and *Euroglyphus maynei*. Other species of this group, such as *Dermatophagoides microceras*, *Dermatophagoides siboney* and *Gymnoglyphus longior*, are also considered allergenic, although their study is more limited. Other genera from the Pyroglyphidae family present in house dust are *Hirstia* and *Malayoglyphus*. House dust mites are commonly present in human dwellings, where they thrive on human dander. They are especially abundant in mattresses, sofas, carpets, and blankets.

In recent years, many mite allergens have been purified, sequenced, and cloned (Table 1). Many of these allergens have enzymatic activities, such as those described in *Dermatophagoides* spp. An important group of mites, referred to as “storage mites,” comprises mainly members of the Acaridae and Glycyphagidae families. Besides their allergenic importance, these mites also have an economical significance, because they can destroy large crops of grains and other stored products. Currently, all mite species present in the home environment and capable of inducing IgE-mediated sensitization are called “domestic mites”¹. However, the name “storage mites” is still used to designate mite species found in house dust that do not belong to the family Pyroglyphidae. Approximately, 150 storage mite species are known², although only approximately 20 can be considered to be important from an economic and sanitary perspective. From this group, the most studied species is *B. tropicalis*, due to its abundance in tropical and subtropical regions of the world, and *L. destructor*, because of its frequent presence in barns. Other storage mite species are present in relatively small quantities in human dwellings (mattresses and carpets), although they can be found in larger quantities in kitchen floor dust, cupboards, and pantries. In some

cases, and especially in humid homes, these species can also be found in mattress dust, although their preferred habitat is stored food. They can be an important plague with economical consequences and cause occupational respiratory allergies in farmers and other occupationally exposed individuals. The most important genera are *Lepidoglyphus* (Glycyphagidae), *Glycyphagus* (Glycyphagidae), *Acarus* (Acaridae), *Tyrophagus* (Acaridae), *Aleuroglyphus* (Acaridae), *Suidasia* (Suidasidae), *Chortoglyphus* (Chortoglyphidae), and *Cheyletus* (Cheyletidae).

Allergens from *Lepidoglyphus destructor*

The most important storage mite species by distribution and abundance, excluding *B. tropicalis*, is *L. destructor*. At least 20 allergenic proteins have been identified in the extract of *L. destructor*.³ The major allergen Lep d 2, former Lep d 1, is a protein of 141 amino acids (aa) and molecular weight of 14-18 kDa by SDS-PAGE⁴. It is present in the digestive tract of the mite⁵. Lep d 2 has been cloned, sequenced and expressed as a recombinant protein (rLep d 2)⁶. This allergen possesses high IgE reactivity *in vitro*⁷ and *in vivo*⁸. Lep d 2 presents a high degree of polymorphism, with two distinct isoforms Lep d 2.01 and Lep d 2.02, differing in 13 aa. Lep d 2.02 has 2 variants and Lep d 2.01, 3; 2 of which (Lep d 2.0101a and Lep d 2.0101b) have identical aa sequences. The rest of variants differ only in a few aa. The frequency of these variants may differ between wild and cultured mites⁹.

Lep d 5 has been partially cloned and expressed. This partial clone of 110 aa and a molecular mass of 12.5 kDa is recognized by 9% of 45 sera from patients sensitized to *L. destructor*¹⁰. Two isoforms have been sequenced Lep d 5.02 with 171 aa and 19.5 kDa and Lep d 5.04 with 169 aa and 19.3 kDa. The allergen Lep d 7 has been sequenced and cloned, the calculated molecular mass is 22 kDa, without N-glycosylation sites. The recombinant protein rLep d 7 was recognized by the 62 % of the sera of *L. destructor* positive subjects. The biochemical function of the group 7 mite allergens is unknown and Lep d 7 does not shows significant homologies to proteins other than to the group 7 mite allergens¹⁰.

An allergenic protein homologous to tropomyosin Lep d 10, was identified as a allergen from a phage display cDNA library. The molecule of 284 aa is formed by 2 polypeptide chains. The sequence exhibits a prominent seven-residues periodicity. The IgE-binding frequencies of the recombinant Lep d 10 is estimated at 13% among subjects with IgE reactivity to mites and/or crustaceans¹¹.

The allergen Lep d 13 has been sequenced and cloned, his length is of 131 aa and the calculated molecular weight mass of 14.6 kDa. It is involved in the intracellular transport of

lipids, belonging to the family of fatty acid binding proteins. The recombinant protein rLep d 13 is recognized by approximately 13 % of the sera of *L. destructor* sensitized patients¹⁰.

Recently other allergens have been sequenced, included the proteases Lep d 3 (Uniprot: Q1M2L7); a glutathione-S-transferase Lep d 8 (Q1M2L6) and Lep d 12 (Q1M2L5)¹². A 39 kDa component of *L. destructor* extract was detected¹³. The allergenicity of this protein was established by monoclonal antibodies; 46,5 % of sera from farmers sensitized to *L. destructor* were positive to this allergen¹⁴. An α -tubulin was identified as a putative allergen from a phage display *L. destructor* cDNA library. The tubulin is the major constituent of the microtubules. The IgE-binding frequency to the recombinant allergen was 12% among subjects with IgE reactivity to mites and/or crustaceans¹¹.

Allergens from *Glycyphagus domesticus*

G. domesticus is a phylogenetically closely related species with *L. destructor*. A 15 kDa allergen, belonging to group 2, and termed Gly d 2, has been cloned and expressed as a recombinant protein. Gly d 2 shows a high degree of homology with Lep d 2. Three isoforms of Gly d 2 have been isolated; 16 out of 17 sera of sensitized patients recognized this recombinant protein¹⁵. Other proteins homologous to group 3 (Q1M2M8), 5 (Q1M2M7), 7 (Q1M2M5), 8 (Q1M2M4), 10 (Q1M2L8) and 13 (Q1M2M3) have also been sequenced in this mite species¹².

Allergens from *Tyrophagus putrescentiae*

T. putrescentiae is one of the most important pest mite species on stored products. The presence of at least 14 allergens has been demonstrated in this mite species by means of crossed radioimmuno-electrophoresis¹⁶. The major allergen is a 16 kDa protein recognized by 80 % of sera from sensitized patients¹⁷. This allergen, Tyr p 2, has been cloned¹⁸, sequenced and expressed as a recombinant protein (rTyr p 2). This recombinant protein has demonstrated high IgE reactivity *in vitro*⁷ and *in vivo*⁸. Another allergen, Tyr p 13, homologous to fatty acid binding protein has also been identified, sequenced and cloned. The recombinant allergen was detected by 6.4 % of sensitized patients¹⁹. An α -tubulin has been identified as a putative allergen from a phage display *T. putrescentiae* cDNA library. The IgE-binding frequency of the recombinant allergen was 29.3% among subjects with IgE reactivity to mites and/or crustaceans²⁰. Recently, it has cloned the Tyr p 10 allergen which shows 64-94 % shared amino acid identity with other allergenic tropomyosins. This recombinant allergen was recognized by 12.5 % of sera from sensitized patients²¹.

Allergens from *Acarus siro*

A. siro belongs to the Acaridae family. A protein of 15 kDa homologous with several other fatty acid-binding proteins (FABPs) allergens was identified, isolated, cloned, sequenced and expressed as a recombinant protein. This allergen, Aca s 13, was recognised by 23% of the sera of patients sensitized to this mite²².

Allergens from other storage mites

Numerous IgE binding bands have been described with layer isoelectric focusing immunoblots in extracts of the brown legged mite *A. ovatus*. This species exhibits minimum to moderate crossreactivity with house dust mites²³. The most frequently detected allergens in the tropical mite, *S. medanensis* have molecular weights of 30-31, 24.5, 21, 47 and 58 kDa. Sui m 2, with a molecular weight of 15 kDa (Q2TUH5) has been described¹². There is a high degree of crossreactivity between *S. medanensis* and *B. tropicalis*, and *D. farinae*²⁴. Anaphylaxis after the ingestion of flour contaminated with this *S. medanensis* has been reported²⁵. The mite species *Th. entomophagus* has also been implicated in cases of anaphylaxis after the ingestion of contaminated flour²⁶.

Several bands are recognized in extracts of *C. arcuatus* by specific IgE of sensitized patients. The most predominant bands have between 14 and 25 kDa, between 30 and 45 kDa, and between 46 and 65 kDa. There is minimal crossreactivity between this mite species and *D. pteronyssinus*, and moderate with other storage mites²⁷. Recently, a tropomyosin allergen, putatively Cho a 10, has been cloned and sequenced from a *C. arcuatus* expression library. The homology between Cho a 10 and Der p 10 is 94 % and between Cho a 10 and Lep d 10 is 95 %²⁸. *Ch. eruditus* is a predator mite species frequently identified in house dust, especially in rural environments, where it feeds on storage mites. We have demonstrated the existence of numerous allergens by immunoblotting²⁹ with a prominent band at approximately 16 kDa. There is a variable degree of crossreactivity of this mite with the other domestic mites.

Allergens in other mites of allergenic importance

Several mite species are present in agricultural settings (horticulture), either as crop pests, or as a control tool (predator mites). The spider mites are main pests of fruit and horticultural crops, and are common sensitizing allergens that are related to the prevalence of allergic

diseases³⁰. Epidemiologic studies have also demonstrated high rates of sensitization in the surrounding population, which is not occupationally exposed to orchard trees³¹.

Major allergens with 10, 14, 19, 29, 67 and 75 kDa have been described by immunoblotting in extracts of the two-spotted spider mite *Tetranychus urticae*³². Another study, 7 dominant allergens were described in *T. urticae* and 3 in *Panonychus ulmi*, the apple spider mite with molecular weights of 33, 41 and 51 kDa. The specific IgE bindings against *T. urticae* and *P. ulmi* were partially inhibited by crude extracts from *D. pteronyssinus* and *T. putrescentiae*³³. In the case of the citrus spider mite, *P. citri*, two allergens of 24 and 35 kDa have been considered major allergens. The N-terminal amino acid sequences of these major allergens of the spider mites are not homologous with any characterized allergens³⁴.

Allergens of mites used as biological control agents against spider mites and other pests, such as the Phytoseiidae; *Phytoseiulus persimilis* and *Amblyseius cucumeris*, or the Dermanyssidae: *Hypoaspis miles* have been described^{35, 36}. These predator mites have species-specific as well as common antigens that are cross-reactive with *D. pteronyssinus*³⁷. Two allergens from *Hemisarcoptes cooremani*, a predator of scale insect, of 16 kDa and 19 kDa have been described. These allergens were not present in other astigmatid mites³⁸.

Several parasitic mite species, belonging to various families and genera, are in frequent contact with humans and domestic animals. A classic example is *Sarcoptes scabiei*, the itch mite, which causes skin lesions and IgE-mediated sensitization in parasitized individuals^{39, 40, 41}. Allergens homologous to serine proteases (group 3)⁴², glutathione-S-transferases (group 8)⁴³, paramyosin (group 11)⁴⁴ and apolipoprotein⁴⁵ have been identified. Ticks (Ixodida) belonging to the families Ixodidae and Argasidae have several proteins in their saliva that can induce IgE-mediated reactions after biting. Several cases of anaphylaxis after tick bites have been reported⁴⁶. The allergenic composition of these mites has been analyzed⁴⁷, and an important allergen of *Argas reflexus*, the European pigeon tick, has recently been cloned. Arg r 1 is a protein belonging to the lipocalin family⁴⁸. In the case of the paralysis tick *Ixodes holocyclus*, an allergen of 28 kDa from the salivary gland has been identified⁴⁹. Other allergenic proteins with molecular masses of 51, 38, 35 kDa from *I. pacificus*, *I. ricinus*, *Haemaphysalis punctata* and *Rhipicephalus* sp. have been described.

^{50, 51, 52, 53}

Other parasitic mites that have been involved in allergic reactions in humans are the bee parasite *Varroa jacobsoni*, with an allergenic protein of 13 kDa⁵⁴ and the feather mite of domestic birds *Diplaegidia columbae* with 20 IgE-binding components ranging from 22 to 200 kDa⁵⁵.

Crossreactivity of mite allergens

Crossreactivity is a common feature among mite allergens, especially in those from taxonomically related species. There has been considerable progress in the study of the molecular characteristics and crossreactivity of mite allergens. Mite-allergic individuals may be sensitized by various species. This could be, in part, due to crossreactivity of common allergenic determinants. Originally, crossreactivity was studied using whole extracts and radioallergosorbent test (RAST) inhibition techniques. More recently, purified native or recombinant allergens, epitope mapping, and T-cell proliferation techniques have been used⁵⁶. Small peptides, with eight to 15 amino acids, are known as allergenic determinants, or epitopes, and are responsible for specific IgE binding and, to a large extent, of crossreactivity between different allergens. It is now evident that crossreactivity studies are highly dependent of the serum pools used and if the patients are mono- or polysensitized to different mite allergens.

The allergenicity of the house dust mite *D. pteronyssinus*, *D. farinae*, and *E. maynei* is well documented, but the extent to which their allergens are unique or cross-react with mite allergens of other genera has not been completely delineated. The allergenic crossreactivity between *L. destructor* and *B. tropicalis* was initially demonstrated by specific IgE inhibition studies using whole allergen extracts. Puerta *et al.*⁵⁷ demonstrated a greater degree of crossreactivity between *B. tropicalis* and *L. destructor* than between *B. tropicalis* and *Dermatophagoides* spp. The participation of group 2 in the crossreactivity between these two species has also been suggested³. The sequence identity between Lep d 2 y Gly d 2 is high (79 %), but only 40 % to Tyr p 2 and Der p 2¹⁵. However, the crossreactivity among group 2 allergens from storage mites, *L. destructor*, *T. putrescentiae*, and *G. domesticus* is high, whereas there is only limited cross-inhibition between Der p 2 and the non pyroglyphid mite allergens¹⁵. This lack of crossreactivity between Der p 2 with and the group 2 of storage mites is a result of the multiple aa substitutions across the surface⁵⁸. Other studies have shown limited crossreactivity between *D. pteronyssinus*, *L. destructor* and *T. putrescentiae*^{59,60}, but others have reported a greater crossreactivity between *Dermatophagoides* and *T. putrescentiae*⁶¹. A low degree of crossreactivity between *D. pteronyssinus* and *A. siro* and *T. putrescentiae* was described in one study, whereas crossreactivity between *L. destructor* and *A. siro* was high⁶².

Individuals allergic to the *Dermatophagoides* spp. may experience allergic symptoms after the consumption of crustacean and mollusks. Der f 10 and Der p 10 proteins with homology to tropomyosin from various animals are involved in the crossreactivity among

Dermatophagoides spp., mollusks, and crustaceans. The 36 kDa cross-reactive tropomyosin present in mites, various insects (chironomids, mosquito, and cockroach), and shrimp⁶³ is responsible for crossreactivity among different arthropods⁶⁴. In addition, a 25-kDa allergen present in several arthropod groups also seems to be involved in this crossreactivity.

Immunochemical studies have demonstrated that allergens from snails, crustaceans, cockroaches, and chironomids cross-react with house dust mite allergens. However, house dust mites are usually the primary source of sensitizing allergens.

The nematode *Anisakis simplex*, a common fish parasite, can act as a hidden food allergen, inducing IgE-mediated reactions. Allergic crossreactivity between this nematode and the domestic mites *A. siro*, *L. destructor*, *T. putrescentiae*, and *D. pteronyssinus* have been reported, in which tropomyosin seems to be involved. The clinical relevance of this crossreactivity needs to be further investigated⁶⁵.

The feather mite *Diplaegidia columbae* is a major source of clinically relevant allergens for pigeon breeders. The results of RAST inhibition experiments suggest that this feather mite cross-reacts with *D. pteronyssinus*⁵⁵. Arlian *et al.*⁶⁶ demonstrated that antigens of the parasitic mite *S. scabiei* cross-react with antigens of *D. pteronyssinus*. More recently, proteins with homology to different groups of mite allergens have been identified by molecular cloning in the parasitic mites *S. scabiei*⁴⁴ and *Psoroptes ovis*⁶⁷.

Conclusions

In this review article, we have included 25 mite species, excluding *B. tropicalis*, and the house dust mites to which allergenic properties have been ascribed. Several storage mite allergens have been purified, cloned and sequenced in recent years. However, the lack of studies using internationally standardized extracts of storage mites hampers, to a certain extent, the complete understanding and full analysis of the clinical significance of sensitization to these mite species. Concerning immunotherapy, only a few studies have demonstrated clinical efficacy using storage mite extracts. More studies are needed to fully delineate the characteristics of mite allergens to establish to what extent these allergens are common, or species specific. The use of recombinant allergens will help in the clinical diagnosis of patients who are sensitized to multiple mite species. There is now increasing evidence that a large proportion of mite allergens belong to a certain group of protein families and that some of these allergens can be considered as pan allergens. This list is increasing and in the upcoming years, the allergenicity of more species will be fully investigated. A genetic

predisposition and exposure to certain species seems to be a key factor for sensitization and the development of symptoms.

Table 1. Main allergens described in several storage mite species

		MW (kDa)	
Group 1	Pso o 1		Cysteine-protease
Group 2	Lep d 2, Gly d 2, Tyr p 2, Aca s 2, Sui m 2, Pso o 2	14	Unknown
Group 3	Der p 3, Der f 3, Der s 3, Eur m 3, Blo t 3, Lep d 3, Gly d 3, Sar s 3	24-31	Trypsin
Group 5	Lep d 5, Gly d 5	14-17	Unknown
Group 7	Lep d 7, Gly d 7	24-31	Unknown
Group 8	Lep d 8, Gly d 8	26	Glutathione-S-transferase
Group 10	Lep d 10, Gly d 10, Tyr p 10, Cho a 10, Pso o 10	33-37	Tropomyosin
Group 11	Pso o 11	98-110	Paramyosin
Group 12	Lep d 12	14	Unknown
Group 13	Blo t 13, Lep d 13, Gly d 13, Aca s 13, Tyr p 13	14-15	Fatty-acid binding protein
Group 14	Pso o 14	190	Apolipoprotein like protein
HSP-70	Der f, Blo t		Heat-shock protein70
α-tubulin	Lep d, Tyr p		Alpha-Tubulins
GST	Sar s		Glutathione-S-transferase
Paramyosin	Sar s		
Ssag1	Sar s		

Lep d: *Lepidoglyphus destructor*; Gly d: *Glycyphagus domesticus*; Aca s: *Acarus siro*; Tyr p: *Tyrophagus putrescentiae*; Sui m: *Suidasia medanensis*; Pso o: *Psoroptes ovis*, Sar s: *Sarcoptes scabiei*

Data from: www.allergome.com, www.allergen.org. Recombinant proteins from many gene sequences from www.allergome.com and www.allergen.org are not available yet, as the expression of these recombinant proteins has been performed.

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