



The multiple roles of mite allergens in allergic diseases

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Purpose of review

Mites are the most worldwide spread allergens and relevant causative of respiratory allergies. Life cycle, component allergens, biological activity and immunogenicity are discussed in depth.

Recent findings

It is now known that mite allergens are able to stimulate the innate immune system through different receptors, for example, TLRs and PARs. The activation of the cells in the airway mucosa is followed by type 2 polarizing cytokine production in predisposed individuals. This complex network plays a pivotal role into the promotion of Th2 differentiation.

Summary

This is a comprehensive review regarding all the mite allergens known so far, including their location within dust mites, composition, biological activities and binding receptors relevant to the fate of the immunological response.

Keywords

adjuvant, allergen immunotherapy, allergens, component-resolved diagnosis, house dust mites

INTRODUCTION

The first evidence that dust might be involved in the genesis of asthma came in 1698 from the manuscript 'A treatise of the Asthma' by Sir John Floyer, who postulated that asthmatic patients should avoid damp air, dust and bad smell and should get out of bed as soon as possible in order to sit in 'clean air' [1]. More than 200 years later, it was questioned that dust itself was the cause of asthma, or rather something contaminating the indoor environment. The experiment by van Leeuwen in 1923 demonstrated that house dust asthmatic patients could be cured by living at high altitude even in the presence of abundant dust, whilst their respiratory symptoms could be elicited again when exposed to the dust of their own homes [2]. Only in 1964 and 1967, physicians and biologists altogether could clarify the taxonomy of the so-called house dust mites (HDM) and demonstrate them as the real source of the 'house dust allergens' (Fig. 1) [3]. From then on, HDM have grown more and more in their importance for allergic diseases, because of their ubiquitous nature, so much to be found in the Space Station [4].

In this review, we offer a synthetic and schematic representation of the most important 'house dust allergens', focusing on their biochemical structure,

biological activity and interaction with the immune system.

LIFE CYCLE AND GEOGRAPHY OF HOUSE DUST MITES

HDM life cycle is of great interest because it is strictly dependent on the habitat in terms of humidity, temperature and food supply (Fig. 2). In each stage different potential allergens are released. In addition, life cycles are different in the different families of HDM. For instance, pyroglyphid have six stages (egg, prelarva, larva, protonymph, tritonymph and adult) with glycyphagoid and acaroid missing the prelarva stage. Each stage takes roughly 6–8 days to be completed, with a total life span of 65–150 days. Humidity,

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KEY POINTS

- The diffusion of house dust mites is explained by their adaptability even in disadvantageous environmental conditions.
- Proteases (group 1 allergens) are the pivotal actors of allergenicity as able to disrupt the tight junctions among airway epithelial cells and modify the chemical structure of surfactants.
- Interaction between mite allergens and innate receptors (e.g. PAR2 and TLR4) promotes allergic type 2 responses in predisposed individuals.
- House dust mites live in a complex microenvironment that constitutes the so-called bacteriome, able to enhance their allergenicity.

temperature and food supply are pivotal for the population dynamics [5] but few studies account for the seasonal variations of HDM in real life and at different latitudes whereas most of the data come from controlled laboratory experiments or empirical observations (Fig. 2) [6]. In general, 75% relative humidity and 23–30 °C temperature result in great proliferation. Extreme temperatures and lower humidity rates are lethal or deeply decrease feeding and reproduction, but nymph stages present quiescent, immotile and desiccation-resistant behaviors so that HDM can overcome long periods of extreme conditions. Thus, few hours of adequate humidity are sufficient to increase the population again [6]. As so resistant, HDM have colonized most of the globe (Fig. 3) [7].

ALLERGENS OF HOUSE DUST MITES

Standardized names for allergens have been established by WHO/International Union of

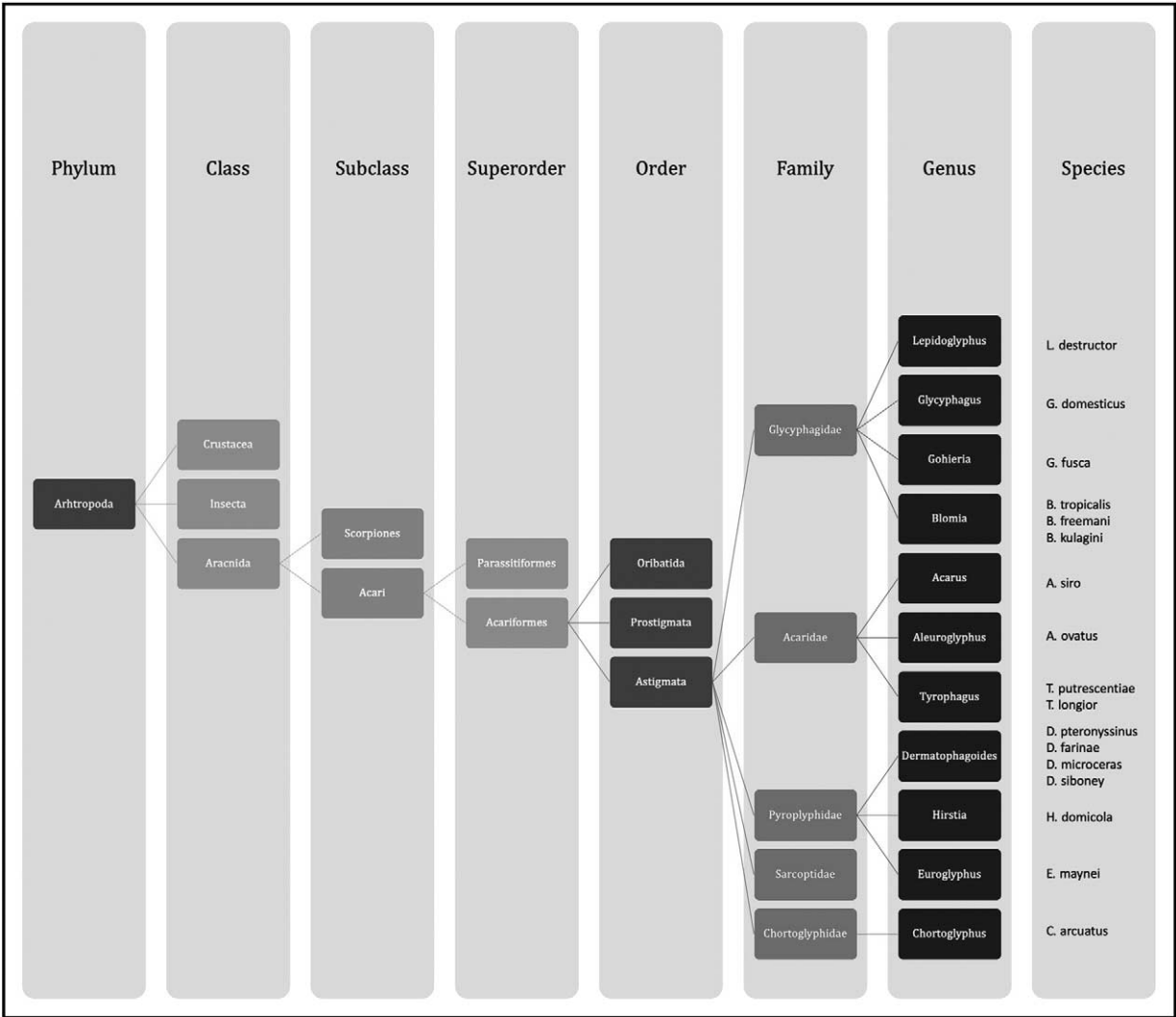


FIGURE 1. Taxonomy of house dust mites.

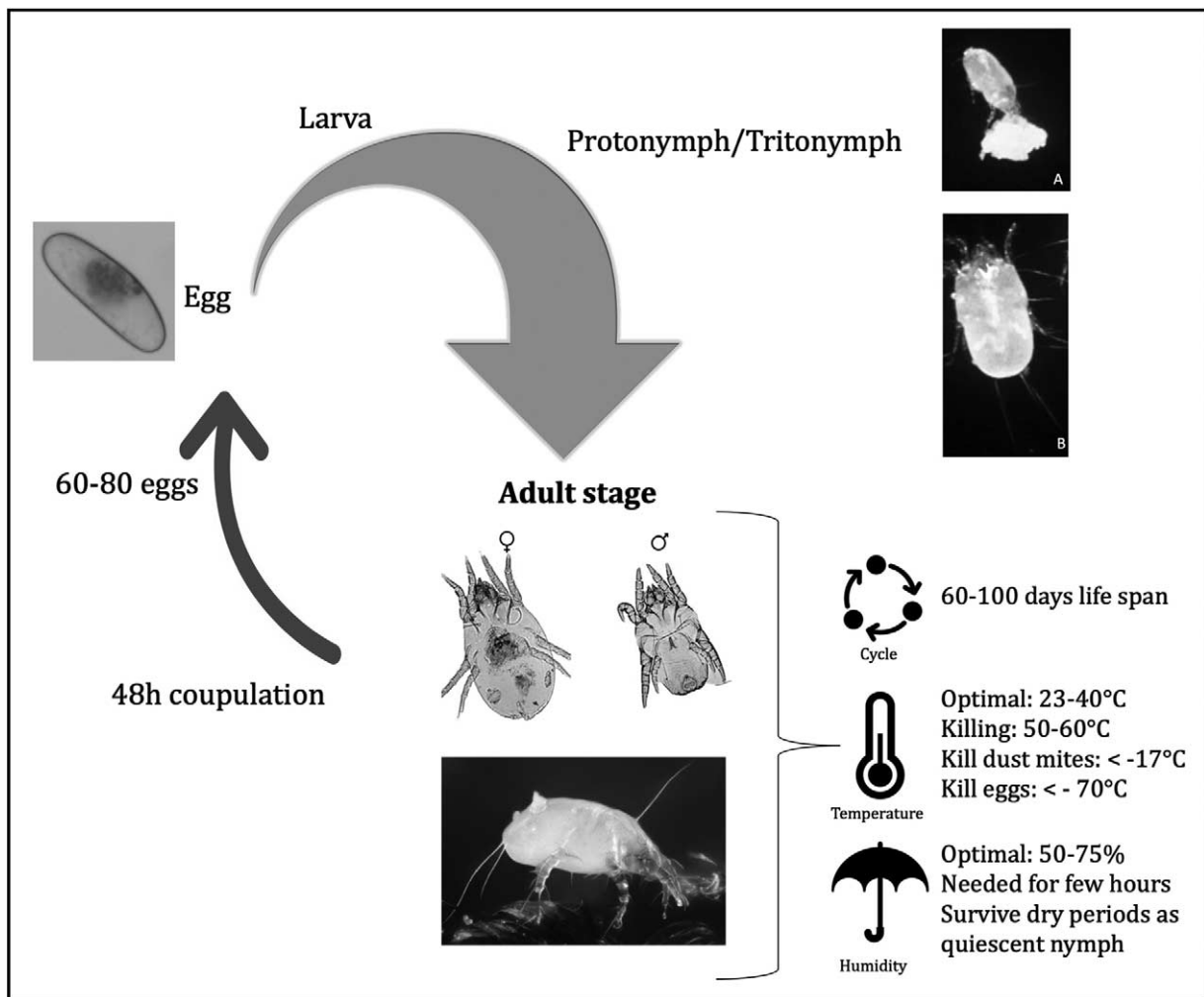


FIGURE 2. Life cycle of *Dermatophagoides pteronyssinus* and environmental conditions influencing maturation. (a) Representation of the protonymph/tritonymph maturation stage, compared with (b) adult. Images courtesy of Council for Agricultural Research and Economics (CREA) – Research centre for Plant Protection and Certification (DC), Firenze, Italy; e-mail: dc.firenze@crea.gov.it.

Immunological Societies and are accessible from www.allergen.org, a website that is constantly up to date. Structural biology and biochemical properties of HDM-related allergenic molecules are resumed in Table 1 [8–12,13^{***}].

EFFECTS OF MITE EXTRACTS AND MITE-PURIFIED ALLERGENS ON THE AIRWAYS

Many studies have described the biological activities of HDM extracts and purified HDM allergens on airway innate immune cells. However, commercially available preparations of HDM extracts contain approximately 95% lyophilized mites with 5% ‘contaminating’ fecal pellets, which are not specified in their microbial compounds. HDM extracts administered *in vivo* intranasally or intratracheally in naïve mice resulted in Th2-type response, airway hyperresponsiveness and remodeling [14,15]. HDM

extracts were also able to increase permeability of the bronchial mucosa and to promote the release of a plethora of pro-inflammatory cytokines/chemokines (IL-6, IL-8, MCP-1, GM-CSF and IL-1) by activated airway epithelial cells [16,17]. These latter events are largely dependent on the proteolytic properties of mite allergens as discussed below.

Dust mite particles contain two main categories of active components on airway epithelial cells: proteolytic enzymes, interacting with protease-activated receptors (PARs), and pathogen-associated molecular patterns (PAMPs), acting on pattern recognition receptors (PRRs) with the consequence of alarmin production (TSLP, IL-33, IL-25) together with other Th2-promoting epithelium-derived cytokines [18^{***}].

In human airway epithelium and smooth muscle PAR1, PAR2, PAR3 and PAR4 are expressed both in asthmatic and normal individuals [19^{***}]. Similarly to



FIGURE 3. Global distribution map of *Dermatophagoides pteronyssinus* (Der p), *Dermatophagoides farinae* (Der f), *Euroglyphus maynei* (Eur m) and *Blomia tropicalis* (Blo t). Created with www.mapchart.net.

the epithelial cells in other barrier tissues, airway epithelial cells (AECs) express various PRRs, including Toll-like receptors (TLRs), RIG-I-like receptors (RLRs) and NOD-like receptors (NLRs) [20]. In particular, selected TLRs can be expressed in a tissue-specific manner and protein expression may not be detected despite the presence of TLR mRNA: nasal AECs express TLR1-10 mRNA but only TLR3-4 protein; tracheal/bronchial AECs express TLR1-10 mRNA and proteins but TLR8; lung AECs express TLR1-2 and 4-6 mRNA and only TLR2-4 and TLR2-5 proteins [21]. Human airway smooth muscle cells (HASMCS) express functional TLR2, TLR3, TLR4, TLR7 and NOD1 [22].

Further, the adjuvant activity of microbial compounds contained in fecal pellets may contribute to amplify the Th2-biased response.

The amount of all the effects of the single HDM allergens on the airway immune cells are detailed in Table 1.

PROTEOLYTIC ACTIVITY OF HOUSE DUST MITE ALLERGENS

Proteolytic digestive enzymes are placed in the peritrophic membrane of HDM fecal pellets and their activity is highly relevant for mite allergenic potential. Group 1 allergens belong to the cysteine protease family (Table 1) with Der p 1, a papain-like cysteine protease, as the most extensively studied,

and major allergen of *Dermatophagoides pteronyssinus*. Its enzymatic activity leads, directly and via proteinase-activated receptor 2 (PAR2) activation, to the disruption of the epithelial barrier, reduction of lung clearance, reduction of Th1 polarization and increase in Th2 response.

The activity of HDM protease allergens is largely because of their binding to PARs, G protein-coupled receptors expressed on the cell surface able to auto-activate after the proteolytic cleavage of their extracellular region [23]. PARs activation shows different effects: production and release of cytokines, chemokines and growth factors by epithelial cells indirectly leading to the dysfunction of the mucosal barrier; degranulation of eosinophils and mast cells; proliferation of fibroblasts and smooth muscle cells; cysteinyl leukotriene production by bronchial epithelial cells in allergic asthmatics [24]. PAR2 expression is increased on the airway epithelium of asthmatic patients compared with healthy individuals. Moreover, in uncontrolled asthma, severity and enlargement of airway smooth muscle parallel the expression of PAR2 and PAR2-ligands [25].

HDMs also contain other allergens with proteolytic activity, a 'triad' of trypsin-like, chymotrypsin-like and collagenolytic-like serine proteases belonging to the groups 3, 6 and 9, respectively (Table 1). Their activity depends on the enzymatic activity of Der p 1, which represents their primary activator. Der p 3, 6 and 9 proteases are thus able to promote

Table 1. Allergen nomenclature according to WHO/International Union of Immunological Societies

Group	Mite species	Localization in mites	Biochemical	Biological activity	Prevalence	IgE-binding frequency	Effect on the immune system
1	Der p 1 Der f 1 Blo t 1	Gut (feces)	Cysteine protease	Proteolysis	Major	80%	1. Promotion of Th2 polarization 2. Increased permeability 3. Degranulation 4. Smooth muscle proliferation and airway remodeling
2	Der p 2 Der f 2 Blo t 2	Gut (feces) Other cells	MD-2-like lipid-binding protein	Lipid binding (including LPS)	Major	80%	1. TLR2 and TLR4 activation 2. Promotion of Th2 polarization
3	Der p 3 Der f 3 Blo t 3	Gut	Trypsin	Serine protease	Major or minor	16-100%	1. Increased permeability 2. Degranulation 3. Smooth muscle proliferation and airway remodeling 4. PAR activation
4	Der p 4 Der f 4 Blo t 4	Gut (feces)	Amylase	Glycoside hydrolase	Minor	40–46%	Unknown
5	Der p 5 Der f 5 Blo t 5	Gut (feces)	Unknown	Hydrophobic binding	Major or minor	50–70%	1. Possible TLR activation 2. Promotion of Th2 polarization
6	Der p 6 Der f 6 Blo t 6	Gut (feces)	Chymotrypsin	Serine protease	Minor	40%	1. Promotion of Th2 polarization 2. Increased permeability 3. Degranulation 4. Smooth muscle proliferation and airway remodeling 5. PAR activation
7	Der p 7 Der f 7 Blo t 7	Unknown	Similar to LPS-binding protein/bactericidal permeability increasing family	Hydrophobic binding	Major or minor	50%	1. Possible TLR activation 2. Promotion of Th2 polarization
8	Der p 8 Der f 8 Blo t 8	Other cells	Glutathione-S-transferase	Glutathione transferase	Major	20–40%	Unknown
9	Der p 9 Der f 9 Blo t 9	Other cells (feces or bodies)	Collagenolase	Serine protease	Major	90%	1. Promotion of Th2 polarization 2. Increased permeability 3. Degranulation 4. Smooth muscle proliferation and airway remodeling 5. PAR activation
10	Der p 10 Der f 10 Blo t 10	Muscle cells	Tropomyosin	Muscle protein	Minor	50–95%	1. Interaction with impaired dectin-1 and subsequent IL-33 secretion Responsible for shrimp cross-reactivity
11	Der p 11 Der f 11 Blo t 11	Muscle cells	Paramyosin	Muscle protein	Major or minor	80%	Unknown Major allergen in atopic dermatitis
12	Der p 12 Blo t 12	Other cells	Chitinase	Unknown	Major or minor	50%	Unknown Not present in WHO/IUIS Allergen Nomenclature
13	Der p 13 Der f 13 Blo t 13	Other cells (bodies)	Fatty acid-binding protein	Lipid transfer	Minor	10–20%	1. Possible TLR activation 2. Promotion of Th2 polarization
14	Der p 14 Der f 14 Blo t 14	Other cells (bodies)	Vitellogenin/apolipoprotein-like	Large lipid transfer	Major	90%	1. Possible TLR activation 2. Promotion of Th2 polarization through induction of IL-4 and IL-13 production
15	Der p 15 Der f 15	Gut (feces or bodies)	Chitinase	Family 18 of glycosyl hydrolases	Major	70%	1. Promotion of Th2 polarization
16	Der f 16	Other cells	Gelsoline, viline	Lipid-binding microtubule regulator	Minor	50%	Unknown

Table 1 (Continued)

Group	Mite species	Localization in mites	Biochemical	Biological activity	Prevalence	IgE-binding frequency	Effect on the immune system
17	Der f 17	Other cells	EF-hand Ca ²⁺ -binding protein	Ca ²⁺ -binding protein	Minor	35%	Unknown
18	Der p 18 Der f 18 Blo t 18	Gut (feces or bodies)	Chitin binding	Noncatalytic chitinase-like	Major	55%	1. Promotion of Th2 polarization
19	Blo t 19	Gut	Antimicrobial peptide	Unknown	Minor	10%	Unknown
20	Der p 20 Der f 20	(bodies)	Arginine kinase	ATP maintenance	Minor	Unknown	Unknown
21	Der p 21 Der f 21 Blo t 21	Gut (bodies)	Group 5 homologue	Hydrophobic binding	Major	Unknown	1. Possible TLR activation
22	Der f 22	Feces or bodies	MD-2-like lipid-binding protein	Lipid binding (including LPS)	Unknown	Unknown	Unknown
23	Der p 23	Gut (feces or bodies)	Peritrophin	Chitin binding to stabilize feces	Major	74%	Unknown, homology with peritrophin-like domain
24	Der p 24 Der f 24	Other cells	Ubiquinol-cytochrome c reductase-binding protein	Electron transfer	Major	80–100%	Unknown
25	Der p 25 Der f 25	Other cells (feces or bodies)	Triosephosphate isomerase	Glycolysis	Major	46–54%	Unknown, but present in patients with airway allergy
26	Der f 26	Other cells (bodies)	Myosin alkali light chain	Ca ²⁺ -binding protein	Minor	29–100%	Unknown
27	Der f 27	Gut (feces or bodies)	Serpin	Serine protease inhibitors	Minor	34–100%	Unknown
28	Der f 28	Gut or other cells (feces or bodies)	Heat shock protein	Chaperone	Major	68%	Unknown
29	Der f 29	Gut or other cells (feces or bodies)	Cyclophilin	Peptidyl-prolyl isomerase	Major	70–85%	Unknown
30	Der f 30	Other cells (bodies)	Ferritin	Iron-binding	Major	60–65%	Unknown
31	Der f 31	Other cells (bodies)	Cofilin	Actin-binding protein	Minor	31–100%	Unknown
32	Der f 32	Other cells (bodies)	Secreted inorganic pyrophosphatase	Unknown	Minor	15–100%	Unknown
33	Der f 33	Other cells (bodies)	Alfa-tubulin	Microtubules	Minor	25–100%	Unknown
34	Der f 34	Unknown	Enamine/imine deaminase Troponin C Ca ²⁺ -binding protein	Hydrolase	Minor	68%	Unknown
35	Der f 35	Unknown	Aldehyde dehydrogenase	Oxydation	Major (?)	51%	Unknown
36	Der p 36 Der f 36	Unknown	Profilin	Unknown	Major (?)	42–60%	Unknown
37	Der p 37 Der f 37	Unknown	Chitin binding	Unknown	(?)	21–40%	Unknown
38	Der p 38	Unknown	Unknown	Bacterial lytic enzyme	(?)	45–77%	Unknown
39	Der f 39	Unknown	Troponin C	Ca ²⁺ -binding protein	(?)	9–86%	Unknown

Available at: www.allergen.org, last accessed 3 June 2019 and data from [8–12,13[■]]. IUIS, International Union of Immunological Societies; LPS, lipopolysaccharide; PAR, proteinase-activated receptor-2; TLR, toll-like receptor.

the release of pro-inflammatory cytokines and the disruption of the epithelial barrier [26]. Der p 3 was also recently shown to activate PAR4 leading to store-operated Ca^{2+} channels stimulation and mast cell migration [27].

HDM proteases follow three main pathways in the development of airway IgE-mediated disease:

A. Interruption of the epithelial barrier

Der p 1 directly cleaves tight junctions between epithelial cells, allowing allergens to reach allergen-presenting dendritic cells placed in the submucosa. Der p 1 proteolytic sites have been identified in the extracellular domain of plasma-membrane protein occludin and the adhesion protein claudin-1. Der p 3, 6 and 9 serine proteases perform their enzymatic action intracellularly on ZO-1 and occludin [26]. Finally, the in-vitro activation of PAR2 on airway epithelial cells by Der p 1 indirectly contributes to the disruption of epithelial barrier as inducing GM-CSF, IL-6 and IL-8 production and increasing permeability and extravasation of innate inflammatory cells [28].

B. Reduction of lung clearance

Der p 1 and Der f 1 can cleave two lung surfactant proteins, SP-A and SP-D, crucially responsible of pathogen opsonization and phagocytosis. Pulmonary surfactant is also relevant for allergen clearance as able to bind allergens preventing their contact with dendritic cells [29].

C. Th2 polarization and augmented IgE production

Dust mite proteolytic enzymes act on biological mechanisms moving T-cell polarization towards the Th2 phenotype but also directly impact on IgE-production. Der p 1 triggers IL-6 production by epithelial cells inducing IL-4 expression and IFN- γ signaling inhibition, with the consequence of Th2 promotion. The Der p 1-surrogate papain can activate type 2 innate lymphoid cells (ILCs 2) in lung mucosa, representing the earliest source of Th2 cytokines, as an inducer of alarmins and other epithelial-derived cytokines [30]. Der p 1 is also able to cleave B-cells receptors, including the IL-2 receptor alpha subunit CD25. As IL-2 signal has a pivotal role for Th1 cells whereas Th2 cells receive proliferative signals from both IL-2 and IL-4, this cleavage moves the balance away from Th1 and towards a Th2 response. *In vitro*, Der p 1 can also cleave CD40, the co-stimulatory molecule expressed on APCs, reducing IL-12 with a lower production of IFN- γ and increased IL-4 [31].

The co-stimulatory molecule DC-SIGN (ICAM-grabbing nonintegrin on dendritic cells) and its receptor on APCs, DC-SIGNR, represent other targets of group 1 mite allergens. Their cleavage reduces the interaction between APCs and naïve T cells via ICAM-3 with preferential activation of Th1 signaling [32]. Finally, again *in vitro*, Der p 1 can block the negative feedback mechanism that involves IgE-binding to the low-affinity receptor for IgE CD23 by the selective cleavage of CD23 itself, thereby suppressing the feedback process designed to limit IgE synthesis [33].

TROPOMYOSINS: ALLERGENICITY AND HOMOLOGY WITH INVERTEBRATES

Tropomyosin is an alpha-helical protein found both in invertebrates and vertebrates that, assembled in coil-coiled pairs, plays a central role in the contraction of muscle and nonmuscle cells together with actin and myosin. Tropomyosin belongs to the group 10 HDM allergens (Der p 10, Der f 10, Blo t 10) with a binding frequency that varies from 50 to 95% [13²²,34]. The mechanism of its allergenicity still needs to be fully elucidated. Tropomyosins have been recently shown to bind the C-type leptin receptor Dectin-1, with the following induction of a Th1 response. However, allergic patients may present a defective expression of Dectin-1 linked to a *CLEC7A* polymorphism. In this group of patients, the exposure to HDM induces the production of a greater amount of IL-33, able to induce a strong type-2 response [35²²].

Due to its vital function for muscles, the sequence of tropomyosin is highly conserved throughout evolution and it is considered a pan-allergen [34]. Along with this, extensive homology and cross-reactivity between HDM and shellfish tropomyosins have been found [36]. Nonetheless, although tropomyosins are considered as the major allergens in shellfishes (e.g. Pen a 1), this is not true for HDM and isolate sensitization to Der p 10 is not frequent. Moreover, different sensitization patterns have been recorded in European versus Asiatic and, in general, tropical/subtropical countries [36,37]. In this context, it is difficult to assess the clinical relevance of tropomyosin positivity in epidemiological and clinical studies, neither is clear whether the primary sensitization occurs via inhalation or ingestion. Intriguingly, in Iceland, a region with no HDM but high-shrimp exposure from the diet, the majority of HDM-positive patients were sensitized to shrimps, without experiencing any clinical allergic picture (e.g. neither rhinitis nor food allergy) [38]. On the contrary, in Jews following a strict Kosher diet (no shellfish exposure) with HDM sensitization,

a high rate of shrimp sensitization was found at the same time [39].

CHITIN-CLEAVING AND BINDING ACTIVITY

Chitin, a long chain polymer of an *N*-acetylglucosamine, is the major structural polymer in the cell walls of bacteria and fungi, shells of shellfish, exoskeleton of mites and cockroaches and nematodes sheath. Chitin plays a controversial role as a potent adjuvant regulating both innate and adaptive Th2, Th1 and Th17 immune responses. In mammals, chitinolytic activity has a defense purpose against pathogens but paralleled by self-damaging consequences when its activity is addressed against allergens. The role of chitinases and chitinase-like molecules has been investigated in Th2 inflammation and asthma. Chitinase expression is upregulated in allergic conditions taking part in tissue remodeling [40]. Further, in humans circulating levels of chitinase-3-like protein 1, also named YKL-40, correlate with asthma severity, thickness of the subepithelial basement membrane, and disease exacerbations [41]. However, few information is available so far for the groups of HDM allergens exhibiting chitinase or chitin-binding properties, namely groups 12, 15, 18 and 23. Among these, serum IgE against Der p 15 and Der p 18 are found at high frequency in humans, identifying them as potentially important HDM allergens. Der p 23 has been indeed identified as a major HDM allergen being recognized by more than 70% of HDM-allergic patients and showing high allergenic activity [42]. In this context, a clear association between hypersensitivity to Der p 23 and asthma prevalence has been recently demonstrated in patients monosensitized to HDM [43²²]. Data regarding this chitinase-like group are nevertheless controversial and currently it is hypothesized that they might play a role in the polarization of Th2 cells.

ADJUVANTICITY AND HOMOLOGY WITH TLR4 LPS-BINDING COMPONENT

The reason why some proteins act as allergens stimulating a type 2 immune-response, is still largely unknown. However, some foreign proteins are able to modify the innate immune response, a characteristic referred as adjuvanticity [44]. This concept has raised hypotheses to link the high allergenicity of some HDM proteins to their ability to influence the innate immune system in susceptible individuals. This is especially true for the group 2 allergens (Table 1) [45]. Der p 2 exhibits structural homology with MD-2 lipid-binding proteins and activates TLR4 signaling independently of the presence of

LPS, thus acting as an autoadjuvant. In this way, antigen-presenting cells become activated and induce a strong Th2 response initiating the allergic response in a mouse model of OVA-induced asthma [46].

Groups 3, 6 and 9 serine proteases are not limited to only disrupt tight junctions of epithelial cells. Eventually, these molecules may exert an adjuvant effect via PAR-2 on airway epithelial cells and other immune cells, thereby stimulating the production of thymic stromal lymphopoietin and favoring the type 2 response [45].

It is also relevant that HDMs live in a complex environment (i.e. house dust) that constitutes a large and various bacterial mixture, the so-called HDM bacteriome [47]. Endotoxin produced by these bacteria might act as adjuvant again through the TLR4 pathway, being able to either induce or suppress Th2 responses [48]. A brilliant example of this balancing property of endotoxin came from the observation of the unexpected differences in atopy prevalence, despite their genetically similar background, among Amish (7.2% sensitized individuals) and Hutterite families (33.3%). When the attention was turned on environmental exposures, both the two populations lived in a farm environment but only Amish avoided all modern technology. A six-fold level of endotoxin and a great difference in bacterial composition was found in Amish houses if compared with Hutterite's. In the OVA-induced mouse model of asthma, inhalation of house dust from Amish houses inhibited airway hyperresponsiveness, reduce eosinophilia and decrease OVA-specific IgE levels. The protective effect of Amish dust was abrogated in MyD88- and TRIF-deficient mice, thus confirming the role of TLR4-related activation [49²¹].

CONCLUSION

Mites are the most worldwide spread allergens and their multiple activities on the mucosal epithelial cells and innate immune receptors justify their aggressiveness in orchestrating the allergic response in predisposed individuals. The microenvironment in which mites live, soiled by their feces, contributes to the bacterial milieu, which greatly influences their final biological and allergy-inducing effect. The scientific ferment on this topic may have therapeutic implications, especially in the view of allergen-specific immunotherapy.

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