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House Dust Mites and Allergy: Microbiological Overview

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Abstract: Background: House Dust Mites (HDMs) are various species of acariform mites found in association with dust in residences. They are tiny creatures, about a quarter of a millimeter long, that are documented to cause allergies. They Feed on dead human skin cells and prefer warm and humid conditions. Up to date, 39 allergens of the HDM genus Dermatophagoides have been documented by the Allergen Nomenclature Subcommittee of the World Health Organization (WHO) and the International Union of Immunological Societies (IUIS). They are named (Der p) or (Der f) after mite species (*Dermatophagoides pteronyssinus* or *Dermatophagoides farinae*), respectively and are numbered according to their chronological identification or homology to previously discovered allergens in other mite species. Recognizing the correlation between allergen sensitization and disease provides valuable information for the clinicians in prevention and treatment of allergic diseases related to HDM. HDM allergens are considered among the most prevalent perennial allergens that are difficult to eliminate. They are found to induce allergic inflammation in respiratory mucosa, cause nasal obstruction, and disturb sleep. The German Multicenter Allergy Study observed participants sensitized to HDM from birth until the age of 20 years and reported that early mite allergen sensitization during childhood was associated with polysensitization to mite and a higher risk to develop allergic rhinitis or asthma. In this review article we will give brief microbiological overview about House Dust Mites and Allergy.

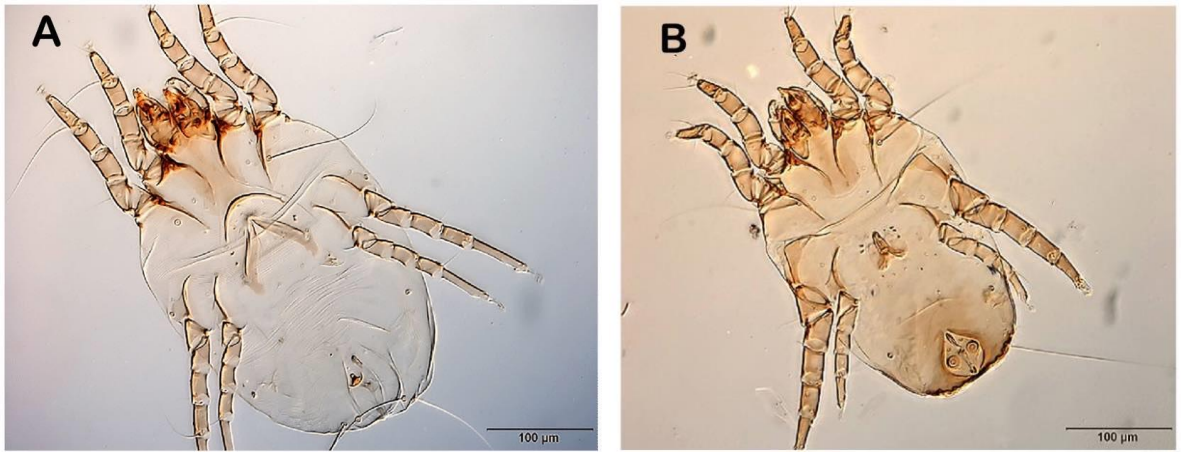
Keywords: *House Dust Mites, Allergy, Der p, Der f, Allergen, Allergic rhinitis*

Introduction

HDMs are various species of acariform mites found in association with dust in residences. They are tiny creatures, about a quarter of a millimeter long, that are documented to cause allergies. They feed on dead human skin cells and prefer warm and humid conditions [1].

The major allergenic species of HDMs are *Dermatophagoides pteronyssinus* (*D. pteronyssinus*), Figure (1), *Dermatophagoides farinae* (*D. farinae*), and *Euroglyphus maynei* (*E. maynei*) belonging to the phylum

Arthropoda, in the class Arachnida, subclass Acari and the suborder Astigmata. Within the suborder Astigmata, they belong to the family Pyroglyphidae. As illustrated in Figure (2) [2].



Figure(1): Microscopic pictures of *Dermatophagoides pteronyssinus*, female (A) and male (B) [2].

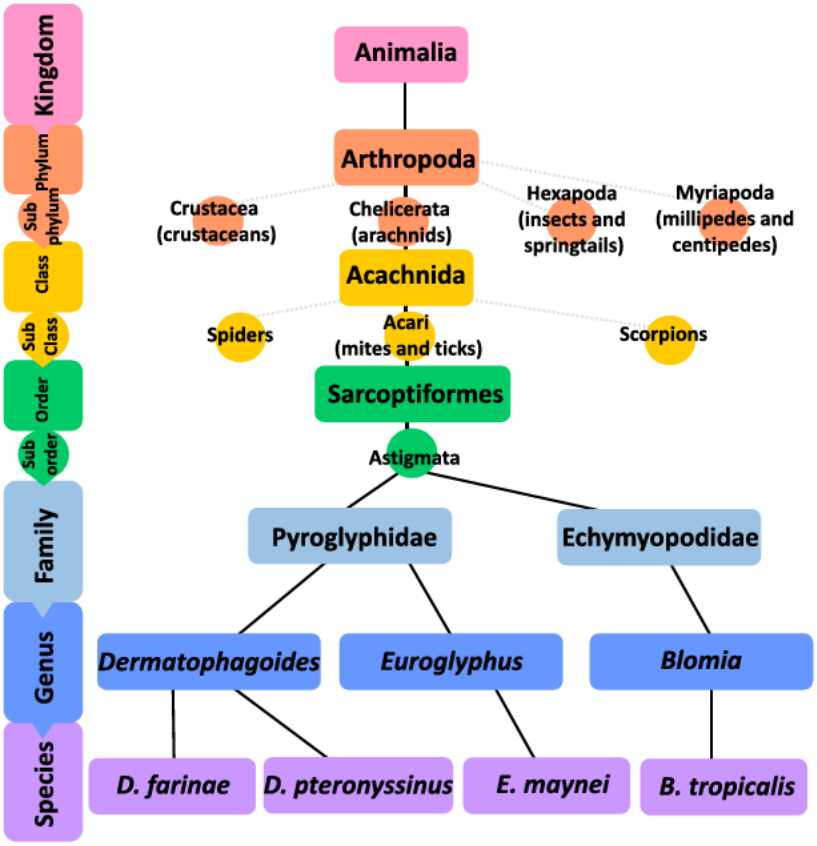


Figure (2): Classification and taxonomy of mite species [3].

Distribution of HDM species differs according to climate difference regarding humidity and temperature. They are found relatively allover the world except for Anarctic and Arctic due to the extremely low humidity and temperature. The ideal humidity for HDM growth is above 50 %, while the ideal growth temperature is between 18 and 24 ◦ C [3].

It is well known that the most essential factor affecting mite growth is the humidity level. The mite growth is proportional to the indoor humidity level, which is affected by seasonal changes in outdoor humidity. The highest concentration of mites is found during the seasons with the highest interior humidity level [4].

The HDM species *D. pteronyssinus* and *D. farinae* are adapted to different climate and can survive in the cold Scandinavian countries as well as in dry countries as Iran and Saudi Arabia. Yet, the ideal climate for HDMs is that of tropical and subtropical countries, where *D. pteronyssinus* and *D. farinae* can be found in most homes [5].

In Egypt, Dermatophagoides farina and *Dermatophagoides pteronyssinus* are reported as the most prevalent species. They are found with high density and high prevalence in areas with very low economic standard and with high relative humidity. Moreover, many studies documented that HDM sensitization in Egypt is mainly associated with asthma and allergic rhinitis [6]. Houses may host millions of HDMs in their pillows, mattresses, furniture, mats, and curtains. They feed on decomposing human skin cells in the dust. HDMs are incapable of stinging or penetrating human skin but their fecal pellets and bodies fragments are the core of their allergy [7]. House dust mites' numbers and allergen levels are high in mattresses and the new mattresses can accumulate clinically significant levels of mite allergen within 4 months. In old mattresses where many generations of dust mites accumulate, high levels of allergenic waste can be detected [8].

- **Epidemiology and Global Impact of HDM:**

HDMs are considered one of the most prevalent indoor allergens. They are documented to be associated with numerous allergic diseases, especially perennial allergic rhinitis and allergic asthma. They are found worldwide and HDM allergies are reported to affect approximately 65–130 million, about 1–2 %, of the global population [9].

- **HDMs and Allergy:**

Up to date, 39 allergens of the HDM genus Dermatophagoides have been documented by the Allergen Nomenclature Subcommittee of the World Health Organization (WHO) and the International Union of Immunological Societies (IUIS) as illustrated in table (1). They are named (Der p) or (Der f) after mite species (*Dermatophagoides pteronyssinus* or *Dermatophagoides farinae*), respectively and are numbered according to their chronological identification or homology to previously discovered allergens in other mite species [10].

Table (1): HDM allergens, *Dermatophagoides pteronyssinus* (Der p) and *Dermatophagoides farina* (Der f):

Group	Biological function	MW (kDa)	Der p	Der f	% IgE binding	Clinical importance
1	Cysteine protease	24	x	x	64–100	High
2	ML domain lipid-binding protein	14	x	x	63–100	High
3	Trypsin	28	x	x	7–97	Low
4	Alpha-amylase	57	x	x	28–74	Medium
5	Unknown	15	x	x	30–40	Medium
6	Chymotrypsin	25	x	x	41–65	Low
7	Lipid-binding protein	22	x	x	30–40	Medium
8	Glutathione S-transferase	27	x	x	4–96	Low
9	Serine protease	24	x	x	92	Low
10	Tropomyosin	33	x	x	2–81	Low
11	Paramyosin	103	x	x	7–82	Low
13	Fatty-acid binding protein	15	–	x	6	Low
14	Apolipophorin	190	x	x	2–84	Low
15	Chitinase	61	x	x	8–70	Low
16	Gelsolin	53	–	x	47	Low
17	EF hand binding protein	53	–	x	35	Low
18	Chitinase-like protein	49	x	x	38–63	Low
20	Arginine kinase	40	x	x	7–44	Low
21	Unknown	15	x	x	30–40	Medium
22	Unknown	17	–	x	Unknown	Low
23	Peritrophin	8	x	x	70–86	High
24	Troponin C	18	x	x	11	Low
25	Triosephosphate isomerase	27	x	x	75	Unknown
26	Myosin	18	x	x	25	Unknown
27	Serpin	48	–	x	42	Unknown
28	Heat shock protein 70	71	x	x	68	Unknown
29	Peptidyl-prolyl cis-trans isomerase	18	x	x	40	Unknown
30	Ferritin	20	x	x	40	Unknown
31	Cofilin	17	x	x	30	Unknown
32	Pyrophosphatase	34	x	x	40	Unknown
33	Tubulin	44	x	x	25	Unknown
34	Enamine-imine deaminases	16	–	x	70	Unknown
35	Unknown	14	–	x	50	Unknown
36	Unknown	23	x	x	40	Unknown
37	Petrotrophic-like protein	30	x	x	20–30	Low
38	Bacterial lytic enzyme	15	x	–	70	Unknown
39	Calcium-binding protein	18	–	x	10	Unknown

Allergen with high relevance: with high allergenic activity and high IgE biding frequency.
Allergen with medium relevance: with high allergenic activity but medium IgE biding frequency.
Allergen with low relevance: with low allergenic activity and low IgE biding frequency.

1. Classification of *D. pteronyssinus* allergens:

a. Allergens with high relevance:

Group 1, 2 and 23 allergens of *D. pteronyssinus (*Der p 1, Der p 2, Der p 23) are identified as major allergens because of their high allergenic activity and high IgE binding frequency [11]. All these three major allergens were found to cause severe allergic symptoms and are, thus, of major clinical significance. Furthermore, it has been reported that childhood sensitization to HDM begins with the development of IgE antibodies to these three allergens [12].

Group 1 allergen (Der p1) was the first HDM allergen identified and the first one to be cloned in 1988. It can be found in large amounts in present in fecal pellets from *D. pteronyssinus* and about 80–90% of all HDM allergic patients are sensitized to group 1 allergens [13].

Der p1 is a cysteine protease with a molecular weight of 24 kDa, which is produced as a proform and biologically activated by post-translational cleavage of the propeptide. This activation can be also achieved by self-cleavage of Der p 1 and its cysteine protease activity can also activate the other proteolytic HDM allergens Der p 3, Der p 6 and Der p 9 [14].

Der p1 protease activity was documented to disrupt the respiratory epithelial barrier by cutting the transmembrane molecules occludin and claudin, thus facilitating the allergen entry to the tissue. This disruption also allows allergens without protease activity to enter and hence enhances the sensitization to those allergens [15].

Group 2 allergens are found in the gut and feces of mites, and about 80–100% of HDM allergic patients are sensitized to group 2 allergens. Der p 2 has a molecular weight of 14 kDa and can induce inflammation by binding to lipopolysaccharide (LPS) and activating the Toll-like receptor 4 (TLR4) leading to activation of nuclear factor-κB (NF-κB) [16].

Der p 23, which is a peritrophin-like protein with 8 kDa molecular weight, was first identified as a new major *D. pteronyssinus* allergen by Weghofer, et al., in 2013. It can be found in mite fecal pellets. About 70–80% of HDM allergic patients are sensitized to Der p 23. It has been reported that it can directly activate the innate immune system, but still no data are available about its effect on the innate immune response [17].

b. Allergens with medium relevance:

The group 5, 7 and 21 *D. pteronyssinus* allergens (Der p 5, Der p 7, Der p 21) are identified as allergens of medium importance. They are found to have about 30% IgE-binding frequency, but they also have high allergenic activity [18].

Der p 5 and Der p 21 have a molecular weight of 15 kDa and can be found in the midgut epithelial cells and faeces of *D. pteronyssinus*. Their biological function is not well explained yet, however some studies assumed that they may stimulate respiratory epithelial cells by activating Toll-like receptors (TLR-2) dependent pathways [19].

Der p 7 has a molecular weight of 22 kDa. Its function is not fully understood yet, but it is shown to have structural similarities with LPS-binding proteins and may stimulate TLRs after binding LPS [20].

c. Allergens with low relevance:

According to the literature, the other allergens of *D. pteronyssinus* which are found only in the mite body but not in the feces, are only of minor importance as they show low allergenic activity and low IgE biding frequency. It has been reported that patients who react to allergens Der p 20 and Der p 37, suffer from asthma [21].

Der p 10, HDM tropomyosin, is detected by only about 10% of HDM allergic patients. It has a sequence homology to tropomyosin of other invertebrates (e.g., cockroaches, shellfish and mosquitoes). This results in a high cross-reactivity between them [22].

2. HDMs related allergic diseases:

Recognizing the correlation between allergen sensitization and disease provides valuable information for the clinicians in prevention and treatment of allergic diseases related to HDM [23].

In 1921, Kern reported that HDM sensitization is related to asthma. Since then, more studies have documented a strong association between exposure to HDM and allergic diseases such as rhinitis, conjunctivitis, asthma and atopic dermatitis, by inhalation to or contact with mite allergens [24,25,26].

a. Respiratory and ocular allergies:

HDM allergens are considered among the most prevalent perennial allergens that are difficult to eliminate. They are found to induce allergic inflammation in respiratory mucosa, cause nasal obstruction, and disturb sleep. The German Multicenter Allergy Study observed participants sensitized to HDM from birth until the age of 20 years and reported that early mite allergen sensitization during childhood was associated with polysensitization to mite and a higher risk to develop allergic rhinitis or asthma [27].

Using recombinant allergens, it was useful to link respiratory allergy and sensitization to certain HDM allergen molecules. Consequently, higher IgE levels to Der p 1 and Der p 23 were reported in HDM-allergic patients suffering from rhinitis and asthma. Recently, a study documented that sensitization to minor HDM allergens, Der p 20 and Der p 37, was associated with asthma, rhinitis and breathing problems [28].

In patients with preexisting asthma and dust mite susceptibility, exposure to mite allergens exacerbates bronchospasm and bronchial hyperresponsiveness, which decreases in mite allergen-free environments.

Symptoms in children with mite-sensitive asthma and abnormal lung function and bronchial reactivity in adults with mite-sensitive asthma correlate with their HDM allergen levels [8].

Several studies demonstrated a doubling of the risk of asthma in mite sensitized children with each doubling of mite allergen in their bed, and other studies of children with parental atopy showed an association between exposure to high levels of mite allergen in infancy and the development of asthma at age 7 [29].

The occurrence of ocular symptoms with HDM allergy has been reported. A study on patients with AR from various sources, including dust mites, indicated that the majority also had ocular involvement including pruritus, tearing, conjunctival injection, and eyelid edema [30].

Moreover, patients with a history of dust mite-reactivity and AR exhibit persistent inflammatory cell infiltrates in the nose and eyes, even in the asymptomatic stage. Dust mite allergy can also cause conjunctivitis in the spring, with symptoms peaking in wet months and elevated dust mite levels [29].

b. Atopic Dermatitis:

The association between HDMs and atopic dermatitis was first observed about 30 years ago, when a correlation was observed between the number of HDMs and the presence and severity of atopic dermatitis in patients. Such observations do not indicate a causal direction, as the increase in mites may simply be the result of increased desquamation in patients providing additional food to dust mites [29].

HDM proteases can degrade skin function. Furthermore, they act on human keratinocytes by releasing pro-inflammatory cytokines and activating pyrin domain–containing-3 (NLRP3) inflammasome of the innate immune system. Chitin also initiates innate immune responses in keratinocytes, sensed by TLR2, and induces chemokine release and expression of TLR4 in patients with atopic dermatitis [31].

3. Mechanism of HDM respiratory allergies:

a. Effect of HDM allergens on toll like receptors (TLR) and innate immunity:

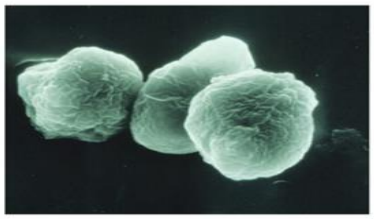
Several components of HDM particles act as pathogen associated molecular pattern (PAMPS) that bind to pattern recognition receptors (PRRs) on antigen-presenting cells, including epithelial and dendritic cells. These PRRs recognize PAMPS as belonging to non-self and are able to induce a Th2-directed IgE- immune response, Known PAMPS in HDM feces and body include chitin, mite DNA and endotoxin [32].

Certain HDM allergens activate receptors such as TLRs and protease-activated receptors (PARs) to generate leukocyte infiltration, cysteinyl leukotriene-mediated hypertrophy of bronchial smooth muscle and amplifying the response to allergens. [33].

Mite and bacterial DNA is unmethylated and thus acts as PAMPS activating TLR-9. Endotoxin (LPS, in mite feces, aided by the homology of Der p2 to the LPS-binding portion of TLR-4, acts as a ligand to TLR-4 receptors on pulmonary epithelial cells, resulting in the release of epithelial-derived Th-2 promoting cytokines including thymic stromal lymphopoietin, IL-25 and IL-33, and leading to airway inflammation and bronchial hyper-reactivity [34]. figure (3)

A

Component	PAMP/DAMP activity
Der p 1	Cysteine protease
Der p 2	MD2 analog (TLR4 co-receptor)
Der p 23	Peritrophin-like
Mite DNA	TLR9 agonist
Bacterial DNA	TLR9 agonist
Endotoxin	TLR4 agonist, MD2 analog
Chitin	TLR2 agonist, dectin 1 agonist
β-glucan	TLR2 agonist, dectin-1 agonist



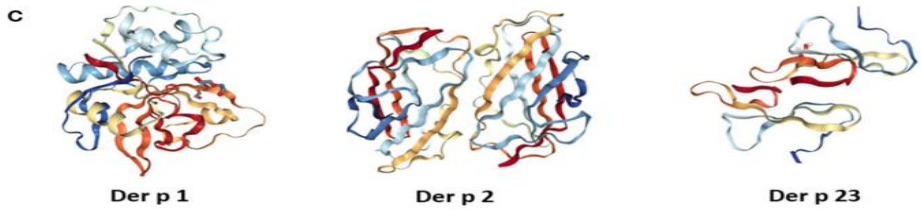


Figure (3): Major HDM allergic components in fecal particles. A, list of relevant allergic molecules, their PAMPS and DAMP. B, 3D image of fecal particles. C, Molecular structure of major HDM allergens [34].

b. Proteolytic effect of HDM allergens on epithelial barrier:

HDM allergy is an IgE-mediated type I hypersensitivity reaction to dust mite allergenic proteins from mite fecal pellets and mite bodies. Upon inhalation of mite fecal pellets or mite bodies, their allergens encounter the airway epithelium. The airway epithelium cells are connected by tight junctions (TJ), which are considered the main regulators of epithelial permeability [35].

TJ is composed of several proteins including junction adhesion molecules (JAMs) and the transmembrane proteins (zona occludens-1 (ZO-1), occludin, claudins). The cleavage of these proteins in respiratory epithelial cells by HDM allergens with protease activity facilitates transepithelial allergens delivery and provokes a cascade of IgE overproduction by B cells [36].

The mite cysteine protease Der P1 and serine proteases Der P3, P6, and P9 are not only allergens, but also have direct epithelial effects. Previously, the action of proteases on epithelia was thought to be limited to disruption of tight junctions between epithelial cells that allow allergens to reach allergen-presenting dendritic cells [37]. In atopic asthma, dust mite proteases directly stimulate PARs in the bronchial epithelium of asthmatics, leading to hypertrophy of bronchial smooth muscle. There is a correlation between asthma severity, airway smooth muscle enlargement, and the expression of PARs and its ligands [38].

c. Role of T cell in HDM allergy:

Naive CD4+ T cells residing in the tissue are activated when encountering the allergen presented by dendritic cells (DCs). In the presence of T-cell receptor (TCR) stimulation, Thymic stromal lymphopoietin (TSLP) signaling in naive CD4 T cells promotes Th2 differentiation and proliferation by inducing IL-4 gene transcription and stimulating the DCs to mature into Th2-promoting subtypes (CD11c+ DCs) that attract Th2 lymphocytes and enhance survival of memory B-cells [39].

Moreover, cleaved CD40 on the surface of DCs interrupts the production of thiols by DCs resulting in decreased Th1 proliferation together with increased IL-6 secretion led to Th2 proliferation. Th2 cells are responsible for the hallmark allergic rhinitis (AR) cytokines production (IL-4 and IL-13) [40].

Th2 cytokines, such as IL-4, IL-5 and IL-13, are involved in regulating the Th2 immune response to allergens, the IgE production or the allergen-induced inflammation [41].

d. Role of B cell in HDM allergy:

B cells play a key role in the development of HDM allergy through the production of mite allergen specific IgE antibodies which bind to Fc ε RI receptors on resident effector cells such as mast cells and basophils residing. When the bound IgE antibodies encounter the same HDM allergen and cross-linking takes place, the effector

cells degranulate and all mediators such as histamine, cytokines/chemokines and lipid are released inducing inflammation [42].

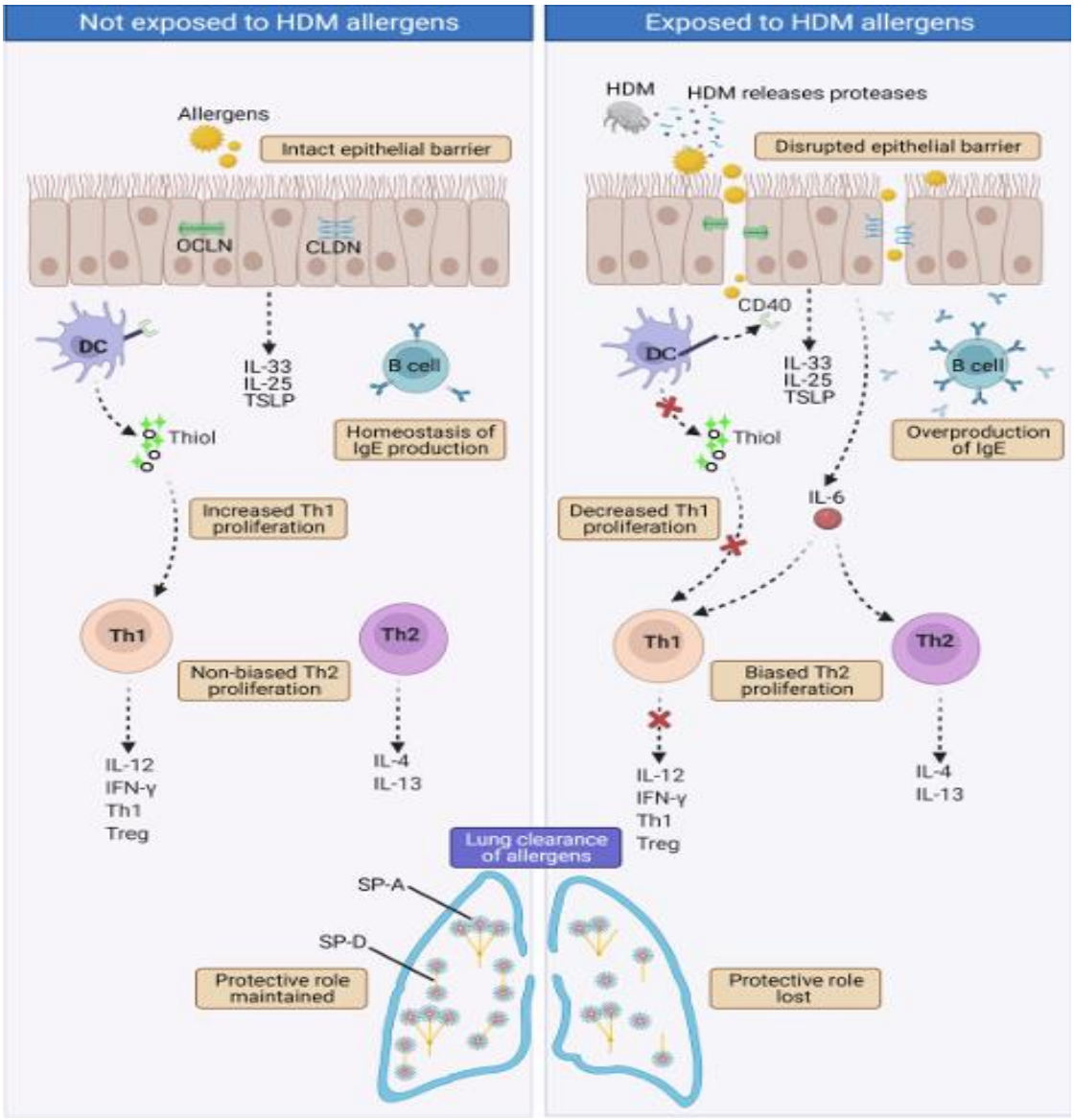
In physiological state, the IgE production level by B cells is controlled by a negative feedback mechanism which involves binding between IgE and CD23 (i.e., the low-affinity receptor for IgE FcεRII) resulting in downregulation of IgE production by B cell. However, in HDM sensitization Der p 1, disrupts this feedback mechanism by selective cleavage of CD23, resulting in IgE overproduction by B cells [8].

Sustained inflammation responses by continuous HDM allergens exposure results in airway remodeling with subepithelial fibrosis and epithelial desquamation in HDM allergic patients [43].

e. Dust mites as facilitators of polysensitization:

Atopy is an epithelial barrier disease and an immune disease. Thus, HDMs can promote sensitization to other allergens, both because of proteases that disrupt epithelial barriers in the skin, airways, or gut, and as adjuvants that polarize dendritic cells for Th2 responses [44].

Immunoglobulin E antibodies against a single antigen can enhance the formation of IgE against other antigens through the action of CD23 on epithelial and B cells, and at high-affinity receptors for IgE on basophils and mast cells. IgE responses can generally be enhanced by upregulating certain high-affinity IgE receptors (FcεRIs). HDMs may play an important role in the development of the 'atopic march' due to their large number of allergens, proteases and PAMPs [45]. Figure (4)



Figure(4): Mechanism of HDM respiratory allergies: DC(dendritic cell) IL(interleukin), IFN(interferon gamma), SP-A(surfactant protein A, SP-D(surfactant protein D) [45].

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