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Allergy to House Dust Mites and Asthma

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ABSTRACT

House Dust mites are the most frequently encountered aeroallergens. Their role in sensitizing asthmatic patients was first reported in 1921, and the association of house dust mite allergy, asthma, and perennial rhinitis has been repeatedly corroborated. Asthma is a chronic respiratory disease that affects millions of people worldwide, and numerous scientific studies have shown that the prevalence of asthma is increasing. The most common dust mite species around the world include *Dermatophagoides pteronyssinus* (Dp), *Dermatophagoides farinae* (Df), *Euroglyphus maynei* (Em) and *Blomia tropicalis* (Bt). Over the past three decades, many important allergens from these species have been identified and characterized at the molecular level. The biological function of several house dust mite allergens has been elucidated, with many of them showing enzymatic activity. Mite allergens remain one of the most studied, since house dust mites are very common in tropical and subtropical regions of the world. Therefore, it is very important to include mite antigens in routine diagnostic and therapeutic strategies for allergy and asthma, particularly in areas where mite exposure and sensitization are high. Recombinant DNA technology, as well as other molecular biology and immunological techniques, have played a fundamental role in advances towards a better understanding of the biology of house dust mites and their role in allergic diseases. This kind of study also contributes to the understanding of the complex immunologic mechanisms involved in allergic reactions. The development of effective diagnostic and therapeutic approaches depends on the continuity of research of house dust mite allergens. The objectives of this review are to describe the most important aspects of house dust mite allergy and to acquaint the scientific community with the latest findings pertaining to house dust mite allergens.

Keywords: Allergy, Asthma, House dust, Mite, Mite allergens

INTRODUCTION

House dust mites have been shown to be important sources of indoor allergens associated with asthma and other allergic conditions. Allergy covers a wide range of symptoms or reactions to substances in our environment, many of which have not been shown to have any connection with immunology. There is now good evidence to suggest that chronic exposure of allergic individuals to foreign proteins in houses is an important cause of two major chronic diseases: asthma and atopic dermatitis (AD). Atopic allergy describes those symptoms or diseases that are epidemiologically associated with, and thought to be caused by, immediate hypersensitivity to common inhaled allergens. Allergy is an exaggerated or hypersensitivity reaction of the immune system to specific external substances called allergens, which are usually harmless to most people. Common causes of allergy include animal dander, house dust mites, foods, pollen, insects, and chemical substances. Allergy to house dust mites is a condition that affects millions of people around the world.

Domestic mites, the main source of allergens in house dust, produce potent allergens that are capable of inducing sensitization and respiratory and cutaneous diseases. The most common species belong to the families Pyrogyphidae, Acaridae, Glycyphagidae, Echymopodidae, Chortoglyphidae, Cheyletidae, and Tarsonemidae. These arthropods have a worldwide distribution. The most important species are *Dermatophagoides pteronyssinus*, (Figure 1), *D. farinae, D. siboney, D. microceras, Euroglyphus maynei, Acarus siro, Suidasia medanensis, Aleuroglyphus ovatus, Tyrophagus putrescentiae, Glycyphagus domesticus, Lepidoglyphus destructor, Blomia tropicalis, Chortoglyphus arcuatus, Cheyletus* spp., and *Tarsonemus* spp. Storage mites belong to a wide range of families, genera, and species and are found in stored grain, barns, hay, and straw. Exposure to these mites and their allergens can also occur in

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homes. Several species of storage mites have been identified in house dust worldwide. The term "domestic mites" applies to all mite species that can be found in the indoor environment and to which type I allergic sensitization has been demonstrated. In 1964, the role of a species of the genus *Dermatophagoides* in the etiology of bronchial asthma produced by the inhalation of house dust was proposed. Sensitization to domestic mites and asthma has since been recognized as a worldwide clinical problem. Cutaneous sensitivity to mite allergens has been demonstrated in 50% to 90% of asthmatic individuals. Several groups have identified nasal and bronchial reactivity in response to direct challenge with mite allergens in humans, supporting the idea that mite allergens play an important role in the pathogenesis of allergic respiratory diseases. Domestic mite extracts contain many allergens, which are grouped according to their homologies, or order of description. So far, approximately 19 groups of mite allergens have been characterized and/or sequenced.

Figure 1. House dust mite allergenicity. The various components of HDM, and their associated fecal pellets and dust, which activate the immune system to initiate an inflammatory response, are illustrated.

Source: Lisa G. Gregory and Clare M. Lloyd. Orchestrating house dust mite-associated allergy in the lung. Trends in Immunology September 2011, Vol. 32, No. 9 : 402 -411

Some common conditions caused by allergy to house dust mites include asthma, allergic rhinitis and conjunctivitis. Although allergy to house dust mites is not a direct threat to a person's life, asthma could become a serious condition that, if not properly treated, could lead to death due to respiratory complications. Asthma is a chronic respiratory disease, often of allergic origin, that is characterized by continuous or paroxysmal labored breathing accompanied by wheezing, bronchial constriction and inflammation, and often by attacks of coughing or gasping. The prevalence of asthma in the United States and other countries has been increasing during the last ten years [1, 2, 3]. Diverse studies suggest that exposure to house dust mite allergens may be a primary cause or a risk factor in the development of asthma, and that it can act as a trigger for the exacerbation of the symptoms [4, 5, 6, 7, 8]. A 2002 study by Terreehorst and collaborators with 325 atopic patients showed that 92% of the asthmatic patients and 85% of the patients with atopic dermatitis had a history of allergic rhinitis, and that there was a high prevalence of nasal symptoms associated with sensitization to house dust mites in these patients. These investigators conclude in their study that asthma and atopic dermatitis are highly associated with allergic rhinitis, and that allergic rhinitis is a risk factor for asthma [9]. Other epidemiology surveys have reported similar results [10]. The American Academy of Allergy, Asthma and Immunology reports up to 78% of asthmatic patients with nasal symptom and up to 38% of allergic rhinitis patients with asthma [11]. Allergic rhinitis is the inflammation of the mucous membrane of the nose as a result of exposure to an allergen. It is a very common condition not as serious as asthma, but very debilitating and with a negative impact in the quality of life of the affected person. Allergic rhinitis caused by house dust mites is perennial, with symptoms appearing continuously or intermittently all throughout the year. People with allergic rhinitis or asthma often have a family or personal history of atopy. Atopy is the increased tendency, with a genetic origin, to produce immediate hypersensitivity reactions usually mediated by immunoglobulin E (IgE) antibodies against normally harmless substances. Diverse scientific

studies propose the atopy concept as the basis for a connection among allergic conditions such as atopic dermatitis, allergic rhinitis, asthma and conjunctivitis. Allergic conjunctivitis is the inflammation of the conjunctive membrane of the eye caused by airborne allergens that invade it, and atopic dermatitis is the inflammation of the skin as a result of a hypersensitive reaction. The onset of allergic rhinitis and asthma usually occur during childhood, adolescence or early adulthood. Symptoms may decrease in older people, but more often persist throughout their lifetime [9, 11]. Allergic and asthmatic people have to deal with their conditions in a daily basis, seeing their energy and productivity levels negatively affected and, therefore, their overall daily performance as well [12, 13]. Moreover, these conditions require scheduling frequent visits to their allergists and doctors, often having to take time from school and work. Allergic rhinitis and asthma may also influence adversely over other common activities such as sleeping, learning and social interactions [14]. Therefore, not only is the physical state of the person adversely affected but the emotional well-being as well.

BIOLOGY OF HOUSE DUST MITES

House dust mites belong to the phylum Arthropoda (i.e., animals with external skeletons and jointed limbs), subphylum Chelicerata, class Arachnida, order Acari, and sub-order Astigmata (lacking specialized respiratory organs) [15, 16]. Contrary to what some people might believe, house dust mites are not closely related to insects, which belong to subphylum Uniramia. The morphology and physiology of house dust mites differ greatly from those of insects. For this reason, common insecticides used successfully to kill insects are ineffective for controlling house dust mite populations [17]. These microorganisms usually measure between 0.1 to 0.6 mm, so they are not visible to the unaided eye, for proper identification at least 10X magnification lens are necessary. Their bodies are oval-shaped and creamy to translucent white, and they have eight legs. The reproduction of house dust mites is sexual, with mating of a male and a female. The life cycle of house dust mites starts with the fertilized female laying a couple of eggs per day. Six-legged larvae hatch from the eggs and remain active for some time, then shed their integuments and become eight-legged resting protonymphs. The protonymphs also shed their integuments and become larger active tritonymphs.

Finally, the tritonymphs undergo another shedding of skin developing into active adult mites [18, 19, 20]. The period of time of this developmental cycle is uncertain, fluctuating from 2 to 6 weeks. The number of eggs a female may lay is also unclear, but it is estimated between 40 to 100 eggs over a six-week lifespan. Adult house dust mites may live between 2 to 5 months, depending on the environmental conditions. These microorganisms feed mainly from skin scales shed by humans and their pets, which are colonized by fungi, yeasts and bacteria, although they may also take advantage of other organic detritus that accumulates in homes. Competing or predating interactions between house dust mites and fungi are not clearly defined, but it was traditionally thought that fungi enhance rates of mite population increase [21]. Therefore, an approach considering fungi as a biotic factor for the control of house dust mites seems of little relevance yet. However, more research is necessary in this area and in the possibility of competitive interactions among different species of house dust mites. Proteins found in the metabolic waste products excreted in the feces by these microorganisms are the cause of the allergic reaction to them. A floating dust cloud seen in the light when dealing with bed clothing and similar materials may contain such waste products. House dust mites inhabit areas and items of the house, as well as the workplace, that comply with their survival requirements, such as carpets, curtains, mattresses, pillows, soft toys, books, and other pieces of upholstered furniture. Common house dust mites such as *Blomia tropicalis* (Bt) and *Dermatophagoides pteronyssinus* (Dp) are inevitably found in every household, predominantly in areas of the world with high relative humidity (>45%) and warm temperatures, between 65 to 85 F. House dust mites satisfy their requirement of water by taking up vapor from the surrounding air and that is why many scientists suggest maintaining a low humidity indoors as a measure to reduce the allergen levels in houses. A study in India revealed that the population of mites during the summer was lower than the rainy season of September to October and the winter [22]. In this study, the investigators concluded that the extremely high temperatures of the summer season, the low relative humidity (around 25%) and the lack of rain were unfavorable environmental conditions for the growth and thriving of mites. They also found that the number of house dust mites present in the beds was higher than that of floor dust in most of the homes, concluding that it is probably due to the association of these mites with the human habitat. Moreover, they observed that old and humid houses with poor ventilation were more favorable for the survival of house dust mites in comparison with newer and well ventilated houses.

These findings of seasonal variation, house dust mite concentrations and type of dwelling were directly proportional to the severity of allergic attacks in different groups of allergic and asthmatic patients studied simultaneously. In another study of 1997 with asthmatic patients sensitized to house dust mites, the investigators found that changes in airway hyperresponsiveness and other immunological parameters are associated with allergen exposure and seasonal variations [23]. They found that there was a tendency to higher concentrations of house dust mite allergens during autumn than in spring.

In correlation with this finding was the interesting observation that in the sensitized patients the airway hyperresponsiveness and the concentrations of serum total IgE and house dust mite specific IgE were also higher in

autumn. Humidity was also higher during autumn compared with spring. Certain measures can be followed to control these microorganisms at home. For example, washing fabrics at least weekly in very hot water and using acaricides can kill dust mites. Frequent dry and wet vacuum cleaning helps, although most allergist will recommend getting rid of carpets as well as other similar home items. Putting special covers to mattresses and pillows and using mechanical ventilation systems or air conditioning in the house are also recommended measures.

Maintaining the relative humidity below 50% is a key factor for reducing dust mites levels [24, 25]. However, these and other meticulous control practices must be followed constantly and for indefinite time, an extremely difficult task for most people. Special mattress covers, acaricides, as well as other anti-allergen products to minimize contact with the dust mites can be expensive and not easily found in stores. These control methods should be used in combination and can have different effects in different homes. For example, the effectiveness of acaricides will depend on method of application, type of carpets and furniture, amount of dust in the house, and quality of post-treatment vacuum cleaning. Besides, control of these microscopic creatures has proven to be very difficult because they reproduce relatively rapidly. On the other hand, scientific studies have shown that asthmatic patients who are transferred to high altitudes or mite-free dwellings experienced reduced symptoms such as bronchial hyperactivity. Therefore, some scientists support dust mite avoidance measures as an effective alternative for controlling allergic diseases [26, 27]. *Blomia tropicalis* (Bt) belongs to the Glyciphagidae family. House dust mites in this family are characterized by numerous long dorsal setae (bristles), no dorsal shield, and no anal suckers. Their bodies are covered by minute papillae [28]. Members of the genus *Blomia* may be differentiated from other genera in this family because their legs lack a sub-tarsal scale present in the others, and also they have no claw. In addition, there are other subtle morphological differences among the species in this genus that allow differentiation of Bt from the other. These species are usually found in areas with very humid climate, such as the tropics and subtropics, including the island of Puerto Rico, although some of the members may be found in temperate regions [25, 26]. These mites have been traditionally referred to as "storage mites" or "stored products mites" because they have been found mainly in stored grain and flour, barns, hay and straw [27]. At the beginnings of scientific research with storage mites they were mostly associated with occupational allergic disease. Nevertheless, Bt and other Glyciphagid mites are also commonly found in homes nowadays, in rural and urban areas and therefore, are included in the "house dust mites" or "domestic mites" group [27]. The biology and ecology of Bt are the least studied among the major house dust mites. However, it has been found in several studies to be an important source of indoor allergens, mostly in the Southern hemisphere. Glycyphagid mites and most other common house dust mites have been also found in other habitats such as mammal and bird nests . This observation is not surprising considering that human habitats share certain characteristics such as heat, moisture and food availability with these other habitats that make them an ideal dwelling for mites. In a 1997 study in Puerto Rico, Bt was found as the second most common house dust mite with 31.6%, behind *Dermatophagoides pteronyssinus* with 45.6% [25, 26, 27].

DERMATOPHAGOIDES AND OTHER SPECIES

Dermatophagoides species of house dust mites belong to the family Pyroglyphidae and are the predominant ones in temperate and tropical regions of the world, including North America and Latin America. This genus is the most studied as it is evident in the scientific literature. Members of the Pyroglyphidae family are characterized by the presence of anal suckers, an anterior dorsal shield, and body with "fingerprint" pattern of striations and setae of variable length. The term "house dust mites" has been traditionally used to include mainly members of the Pyroglyphidae family that live permanently and almost exclusively in house dust. However, in the Second International Workshop on Mite Allergens and Asthma (1990) it was recommended to use the term "domestic mites" to include this family and also the Glycyphagidae family, to which Bt belongs [25, 26, 27]. Among the members of the Pyroglyphidae family, the most common are *Dermatophagoides pteronyssinus* (Dp) and *Dermatophagoides farinae* (Df), both with worldwide distribution. From the 49 species of Pyroglyphidae dust mites, 13 have been found in house dust while the others live mainly in bird nests or feathers. In Europe, Japan, North America, New Zealand and Australia the predominant Pyroglyphidae genera are *Dermatophagoides* and *Euroglyphu*s, which are closely related. In fact, Dp is the most commonly dust mite found in homes in Europe, followed by Df and *Euroglyphus maynei* (Em) [27, 29]. Em has also been found in Korea, China, India, New Guinea, and Southern United States. In Puerto Rico, Dp, Df and Em are the most common species of house dust mites, along with Bt from the Glyciphagidae family. Another species in this family that is being studied is *Dermatophagoides siboney*, which has been found also in tropical environments, including Cuba and Puerto Rico [25, 27, 28].

THE ROLE OF DUST MITES IN ALLERGIC DISEASES

Dust mites are the most frequently encountered aeroallergens in temperate climates. Their role in sensitizing asthmatic patients was first reported in 1921, and the association of house dust mite allergy, asthma, and perennial rhinitis has been repeatedly corroborated [30, 31]. Accordingly, the treatment of asthma and perennial rhinitis frequently includes immunotherapy with dust mite extract [32, 33]. In a 1967 study, dust mites of the *Dermatophagoides* genus were

identified as the single most important allergen in house dust. Mites are Arachnids (members of the spider family) with *Dermatophagoides farinae* the species encountered in North America and *Dermatophagoides pternoyssinus* common in Europe [34]. Presently, both species are found worldwide. The house dust mite life cycle includes three larval stages, and the total life span is about 3 months. Their principal habitat is fomites—carpet, fabric, upholstery, pillows and mattresses, and there are approximately 100 living mites in each gram of house dust. Their diet consists of human epidermal scale, animal dander, and trace nutrients. The more bare skin present in a home, the more dust mites are likely to be present in that environment. Because mites cannot take in fluids by mouth, however, their primary source of water is ambient water vapor. The upper humidity limit is constrained by the occurrence of mold growth, which can inhibit mite development, particularly at relative humidities above 88%. The survival of active adult mites is limited to 4 to 11 days at a relative humidity below 50% at 25°C. The most allergenic material is, in fact, mite fecal matter. The amount of fecal matter produced increases with increasing relative humidity, and the highest levels of allergens found in the environment usually correspond to optimal humidity conditions [35]. A 1992 study reported that home air conditioning, by reducing relative humidity, reduces the dust mite population as compared to homes without air conditioning or dehumidification. Der pI and Der pII are the major dust mite respiratory antigens, and importantly, they can persist in the environment long after the death of the mites [36]. Dust mite antigens also include other allergenic components such as acaridials, dialdehydes, cysteine proteases, trypsin, eicosapentanoic acid, and citral [37, 38].

House dust proteases exert profound effects on epithelial cells and promote allergic sensitization. These effects include disruption of intercellular adhesion, increased paracellular permeability, and initiation of cell death [39]. Allergen avoidance is recognized as an integral part of the management of patients with asthma along with antiasthma drugs and immunotherapy [40]. The National Institute of Environmental Health Sciences recently reported that over 45% of American homes have bedding with dust mite allergen concentrations that exceed the level necessary for allergic sensitization. They found that certain simple steps—allergen-proof mattresses and pillow covers, weekly laundering of other bedding, careful vacuuming and dry steam cleaning of bedroom carpets and upholstery—can significantly reduce the levels of dust mite allergens in bedrooms [41]. In addition, most studies have noted that when indoor humidity is kept below 50%, mite populations do not grow to significant levels.

DUST MITES AND ATOPIC DERMATITIS

The ubiquity and allergenicity of the dust mite should make it suspect as another possible trigger for exacerbations of the eczematous itchy skin of some atopics. In addition, dust mites have the capability of acting as irritants contact haptens, and IgE antigens on the atopic- impaired, epidermal barrier layer. A 1932 paper reported that patients with atopic eczema improved when they were placed in a dust-free environment, a finding confirmed subsequently by many investigators [42, 43, 44, 46]. A 1982 study reported positive patch test results when patients with AD were patch tested to purified allergen [47]. A PubMed (Medline) search listed almost 60 articles addressing the role of patch testing patients with AD. All but one of these papers support a positive correlation (16–92% positivity) between dust mites and their putative role as a trigger for exacerbations of AD [48]. Despite this overwhelmingly supportive literature there still remains significant skepticism, primarily among dermatologists, regarding the relevance of these findings to the overall management of patients with AD—perhaps as an antithetic reaction to the zealous support voiced by so many allergists toward the role of aeroallergens in AD.

More recently, other investigators have tested patients with AD for dust mite contact sensitivity, and all have similarly reported positive results in a subset of patients [49, 50, 51, 52]. The variability in the number of positive patch test results in patients with AD in different studies probably results from different testing techniques used by each investigator. The major flaws in these studies have been the lack of standardized dust mite patch-test material, patient selection bias, and a lack of uniformity in testing. While the lyophilized Der p1 and Der p2 aqueous material used for skin prick testing was used by all the early investigators, many of the later investigators (this author included) have been using a protocol utilizing mite whole body material [53, 54, 55, 56].

HOUSE DUST MITE ALLERGENS

The Allergen Nomenclature Sub-Committee, International Union of Immunological Societies (World Health Organization) establishes guidelines for the identification of a molecule as an allergen [57]. Only allergens with a frequency of IgE reactivity above 5% will be included in the nomenclature. Also, an allergen may be classified as a "major" or a "minor" allergen depending on whether more or less than 50% of the patients tested reacted with the corresponding allergen specific IgE in the given system. Of course, there are inherent factors that impose some uncertainty to the determination of IgE prevalence such as choice of test system, criteria for selection of patients, geographic region, environmental conditions and others. Therefore, researchers are encouraged to perform their analysis with a substantial number of patients whenever possible. The Sub-Committee recommends analyzing the defined component for allergenic activity with at least 20-30 human sera from highly allergic individuals [58].

During the past three decades it has been well demonstrated by different scientific investigations that allergens

from house dust mites constitute a major etiologic factor of allergies and asthma in many countries around the world [59]. Extensive studies have been conducted in search of a better understanding of the biological, chemical and structural properties of dust mite allergens as well as other factors that might be influencing or determining their allergenicity. Thanks to advances in molecular biology technology, the biological function and structural properties of many allergens have been elucidated, although many investigations with allergens are still in progress or are yet to be undertaken. Although the biological function of allergens has not been shown to be the only or the main responsible factor for their allergenicity, it may facilitate the immunological milieu required for specific sensitization toward an allergen or enhance the ability of the protein to trigger an IgE antibody response. For example, scientists have observed that allergenic molecules with enzymatic activity, such as cysteine proteases, irritate the mucosal surface facilitating their own processing The best characterized allergens of house dust mites are those in group 1, which have been identified as cysteine proteases. One of the most studied allergens from this group, Der p 1, seems to enhance allergenicity by several mechanisms such as increasing the permeability of the respiratory mucosa, enhancing antigen processing, promoting IgE synthesis, and augmenting TH2 cell responses [60]. Der p 1 was shown to cleave the low affinity receptor for IgE, CD23, and this action seems to disrupt the negative feedback regulation of IgE synthesis mediated by this receptor [61]. However, enzyme function is not essential to trigger IgE responses, as other types of biological functions have been found for several allergens from house dust mites and other sources. Other proteins from house dust mites that have shown to be allergenic include group 3 allergens which are serine proteases, group 4 (Der p 4) with amylase activity, group 6 allergens (Der p 6) identified as chymotrypsin-like proteases, group 10 as a tropomyosin (a structural protein), group 13 as a fatty acid binding protein, and allergens from the groups 2, 5, 7, and 12, all with unknown biologic function [62, 63]. The sensitizing dose of an allergen has been debated in several studies, but in the Indoor Allergens and Asthma: Report of the Third International Workshop it was established as 2 mg allergen/g of dust (100 mites/g). The structural stability of allergens may also play an important role in the allergic response toward them, as has been shown in some studies where IgE epitopes have been altered or the three-dimensional structure of the protein has been split. Allergens have different structures and are classified in different protein families according to their biological function, suggesting that there may be few or no common structural features or intrinsic properties between allergens making them allergenic. However, it seems that there is an important connection between biological function, structural integrity and IgE binding capacity for an individual allergen to keep its allergenicity [64]. Other factors cannot be ruled out as participants of the sensitization and the allergic reaction toward an allergen, such as genetic predisposition or defects in the regulation of IgE responses of the individual, other possible adjuvants such as hormones, bacterial and viral infections, and the route and degree of exposure. In view of these implications, recombinant allergens altered by site-directed mutagenesis to remove IgE epitopes may represent a valuable tool for further research and more effective allergen immunotherapy.

IMMUNOLOGICAL MECHANISM OF HOUSE DUST MITE ALLERGY

The development of allergy starts when the individual is in contact with the allergen for the first time and becomes hypersensitive to it. When the allergen invades the mucous membrane of the nasal passages an immediate allergic response occurs (Figure 2). The most accepted mechanism indicates that the allergen is presented to T helper-2 (TH2) lymphocytes by antigen presenting cells (APC), and the TH2 cells respond by releasing cytokines such as interleukin-4 (IL-4) and interleukin-5 (IL-5) which attract inflammatory cells to the airways, such as the mast cells, basophils, and eosinophils. TH2 cells activate B cells of the immune system, which produce a specific antibody, IgE, which is overproduced in subsequent allergic reactions. IgE antibodies attach to membrane receptors in mucosal mast cells and activate them. The allergen binds those antibody molecules causing the release of mast cell granules to the outside of the cell. These granules contain chemical inflammatory substances such as histamine and leukotrienes, which trigger the array of symptoms that comprise the allergic reaction. At the same time, mast cells secrete IL-4, which stimulates B cells to produce more IgE. In chronic allergic asthma the allergen induces activation of submucosal mast cells in the lower air passages, leading to bronchial constriction and an increase in fluid and mucus secretions which make breathing more difficult. These phenomena are a result of a late-phase reaction, characterized by the continuous synthesis and release of chemical mediators such as cytokines and leukotrienes from the activated mast cells and eosinophils. Mast cells also secrete IL-5, which further stimulates eosinophils for their release of more inflammatory mediators. A similar late-phase reaction occurs in chronic allergic rhinitis [65, 66, 67, 68].

It is not well known what structural features or what functional properties of allergens confer them the capacity to modulate the immune response toward the TH2 cell activation, which stimulates an IgE response [69, 70]. However, although much research is still necessary, it has been observed that many common allergens share typical characteristics such as enzymatic activity, relatively low molecular weight (less than 60-70 kDa) and high solubility. Moreover, it has also been shown that factors extrinsic to the allergen are involved, such as genetic predisposition to overproduce IgE (atopy) and the particular immune response of the individual, the nature or degree of exposure to the allergen and other environmental factors [70, 71].

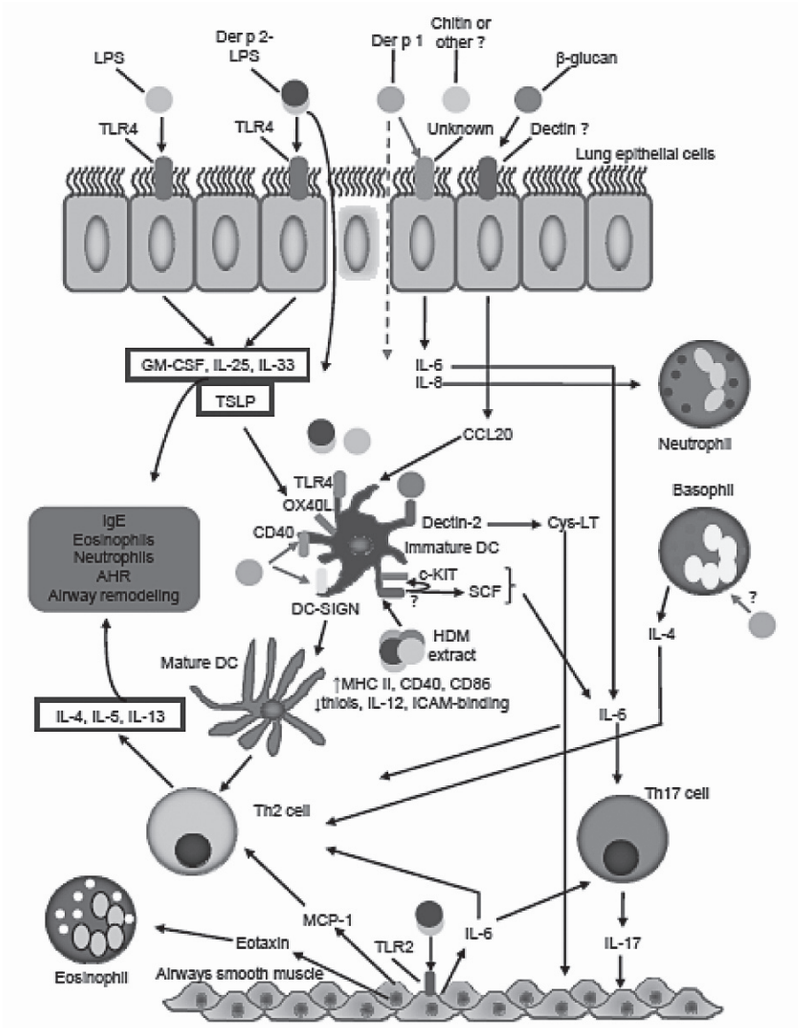

Figure 2. Proposed model for the innate initiation of the allergic response induced by HDM.

Der p 1 and the Der p 2-LPS complex, together with adjuvant-like contaminating molecules (including LPS, B-glucan or chitin), can activate unknown protease-sensitive receptors as well as PRR expressed by epithelial cells. Altogether, these stimulations lead to the production of chemokines and cytokines that not only attract and activate DCs but promote also an influx of inflammatory leukocytes to trigger eosinophilia, neutrophilia, airway remodeling and AHR. Thanks to the increasing permeability of the epithelial barrier following cleavages of tight junction proteins by Der p 1, submucosal DCs can be also directly activated by components of HDM. There is an immediate release of Cys-LT, potent mediators of bronchial smooth muscle constriction and IL-6. Activated DC will mature and migrate to mediastinal lymph nodes to present the allergen to naïve T cells. The cytokine milieu (notably TSLP, low IL-12 concentration) will drive the differentiation of naïve T cells into Th2 cells producing the cytokines IL-4, IL-5 and IL-13, the critical effectors of the salient features of asthma as the allergen- specific IgE antibody and the recruitment and activation of eosinophils. The presence of IL-6 will induce Th polarization skewing to Th17 cells which accentuate the airway pathology through notably the action of Th17 cytokines as IL-17 on the airway smooth muscles. TLR, Toll-like receptor; CCL, CC-chemokine ligand; GM□CSF, granulocyte/macrophage colony stimulating factor; TSLP, thymic stromal lymphopoietin; Cys-LT, cysteinyl leukotriene; SCF, stem cell factor; DC-SIGN, dendritic cell–specific intercellular adhesion molecule 3–grabbing nonintegrin; MCP-1, monocyte chemotactic protein-1.

Source: Alain Jacquet. New Insights into the Molecular Basis of the House Dust Mite-Induced Allergic Response The Open Allergy Journal 2009; 2: 38-44

The most common symptoms of allergic rhinitis and allergic asthma caused by inhaled house dust mite allergens include sneezing, itchy eyes, ears and nose, local edema, nasal secretions, nasal congestion, itchy palate and throat, cough, shortness of breathing, and wheezing.

ROLE OF IgE IN ANTIGEN PRESENTATION

The IgE/mast cell pathway, when first acknowledged, elucidated the mechanisms of anaphylaxis and the so called atopic diathesis—especially for respiratory symptoms [72]. However, dermatologic manifestations, namely eczematous skin lesions, could not be adequately explained by the IgE/mast cell flow of events.

Yet, few would deny the existence of a small subset of patients, who associated exacerbations of their eczema with recognized IgE triggers such as foods, animal dander, mold, and even pollens [73]. Was elevated IgE in eczema patients merely an epiphenomenon, an indicator of other concurrent atopic disease or did it in fact play a role in inducing AD lesions? It is only recently that IgE receptors have been found not only on mast cells, but also on Langerhans cells and other dendritic antigen- presenting cells of atopic individuals, and it is this finding that has led to studies ultimately showing a direct role for IgE in AD pathogenesis [74, 75].

Dendritic antigen-presenting cells have been shown to be necessary for initiating and controlling the immunologic response to pathogens present at the interface with the environment [76]. They have a significant capacity to take up and process antigens in this location, but their ability to prime T cells is limited until they undergo phenotypic changes and become effective immunostimulatory cells. Maturation of dendritic cells occurs as they migrate to regional lymph nodes. They begin to express coreceptors and elaborate chemokines that enhance their ability to present antigen to T cells. The high-affinity IgE receptor (Fc_RI) that on mast cells facilitates the release of inflammatory mediators plays a different role on Langerhans cells. In AD lesional skin, Langerhans cells expressing Fc_RI are present in higher numbers than in the skin of nonatopics; these cells have been shown to be essential in the sensitization phase of AD.5 Moreover, the presence of Fc_RI_ Langerhans cells bearing IgE molecules is a prerequisite for provoking eczematous lesions in aeroallergen patch tests in atopic patients [77]. We now understand that activated Th2 cells are the effector cells for the early stages of AD, and similarly activated Th1 cells account for the later phases [78]. Thus, we now have a rational mechanism for the chronicity of AD (in a subset of patients) triggered, and then maintained by IgE antigens which include aeroallergens such as dust, animal danders, etc. The second deterrent to appreciating the putative role of contactants as triggers of AD is that an additional diagnosis, such as allergic contact dermatitis, is not sought once atopy is recognized. Moreover, atopic patients are considered by many clinicians to be less prone to sensitization by contact allergens. On the contrary, atopic patients are indeed sensitized just as frequently to contactants as their nonatopic counterparts under many circumstances [79]. In fact, numerous reports document that they react equally to most common allergens, eg, fragrances, rubber accelerators, lanolin, formaldehyde, and others [80, 81]. Nickel is the most common contact allergen with equal frequency in atopic and nonatopic subjects [82]. Most recently, allergy to topical corticosteroids has been increasingly reported in individuals with AD because of the frequent use of such agents on the impaired epidermal layer of these patients. Nonfluorinated corticosteroids are especially likely to cause this type of reaction [83]. The possibility of corticosteroid allergy should be suspected clinically when there is worsening of eczema at corticosteroid-treated sites.

CLINICAL AND LABORATORY TESTS FOR DETECTION OF ALLERGEN SPECIFIC IgE ANTIBODIES

Allergy Skin Tests

Immediate hypersensitivity skin tests are used to identify specific IgE sensitization [84]. The skin is marked for testing with a panel of appropriate allergens for the patient, selected on the basis of the clinical history and knowledge of the allergens commonly found in the locality. Positive and negative comparator tests using histamine and saline can be performed to prove that the skin is capable of demonstrating a positive reaction and to prevent the interpretation of false-positive results occurring as a result of dermatographism. A drop of allergen solution is placed onto the skin at each mark, and a fresh fine sterile needle or lancet is used to gently prick the skin through each drop, introducing a minute volume of allergen solution into the dermis. After 10-15 minutes the results are interpreted by reference to the control tests. Provided that there is no wheal response to the negative control, the presence of a raised wheal at the site of the allergen skin prick test of 3 mm or greater in diameter indicates the presence of IgE antibodies specific to that allergen. Taken in conjunction with the clinical history, the results of skin prick testing can confirm a diagnosis of IgE-mediated disease and identify causal allergens. Skin prick tests are particularly reliable for inhalant allergens. However, the variations in reaction between tests and testers limits its use with experienced personnel. Intracutaneous tests are used in some geographical areas and for some suspected allergens, e.g., drugs. The method is more sensitive than the skin prick test but carries more risk of systemic reactions and often gives false positive reactions. The method may be indicated when allergen extracts are not strong enough to give positive skin prick test reactions.

Radioallergosorbent tests (RAST)

The discovery of IgE allowed the development of immuno-assays for IgE and IgE-antibodies, enabling direct and objective measurement of the extent and specificity of the immune response [85, 86]. In RAST, allergens are linked to paper discs or polyurethane caps (CAP - RAST) and are reacted with the individual's serum. Binding of IgE specific to that allergen is detected by the use of an enzyme linked anti-human IgE antibody in a colorimetric reaction. Results of RAST testing show a very good corelation between the presence of IgE antibody in serum and positive skin and provocation tests, as well as symptoms of allergy. Positive RAST results to a specific allergen demonstrate specific IgE sensitization but are not proof that the allergen is the cause of clinical symptoms.

The measurement of allergen specific IgE antibodies in serum is of similar diagnostic value to that of skin tests but has a much higher reproducibility and is not influenced by ongoing symptoms or treatment, eg, antihistamines or anti-inflammatory therapy. In some instances, especially in food allergic individuals where, in rare cases, even skin prick testing with minute amounts of allergen might cause an anaphylactic reaction, RAST using blood samples is a safe method to determine levels of specific IgE antibodies. RAST is also the test of choice for individuals who have widespread eczema, which precludes skin prick testing.

Approximately 500 different allergens are now available for RAST-based allergy diagnosis [58, 59, 60]. In addition to classical pollen, dander and food allergens, drugs, occupational chemicals and recombinant allergens are available. The general availability of well standardized in-vitro allergy tests has greatly improved the quality of allergy diagnosis.

The use of extracts allows the identification of the source of the allergen but not the specific molecule to which the patient is allergic to, nor the determination of IgE levels against a particular allergen. Current diagnosis and treatment of dust mite allergy is mainly based on the use of crude mite extracts. A more effective approach would be to make a diagnosis and design a therapy according to the patient's allergen reactivity profile. This approach would allow the identification of the specific mite allergenic components causing the disease and the measurement of IgE levels against them. It is in this scenario that the design and availability of recombinant allergens play a fundamental role.

Measurement of total IgE, not IgE antibodies, in serum, secretion or on cell surfaces is of little diagnostic value. The reason is that mitogenic factors in viruses (e.g., Cytomegalovirus - CMV), bacteria (e.g., *Staphylococcus*), helminths (e.g., *Ascaris, Schistosoma*) and adjuvant factors in air pollution (e.g., cigarette smoke, and diesel exhaust) stimulate the production of IgE molecules without initiating any allergen specific IgE-sensitization. However, production of IgE-antibodies will increase the total IgE level slightly and thus an increased total-IgE in cord blood is a high sensitivity but low specificity predictor of allergy.

TREATMENT OF HOUSE DUST MITE ALLERGY

During the past ten to fifteen years, scientists have been investigating new approaches to the treatment of house dust mite allergy. A variety of medications for minimizing allergy symptoms are currently available. However, these medications have to be taken indefinitely and many of them can cause side effects such as drowsiness, which affects the patient's daily performance. Other more effective and non-drowsy medications have to be prescribed and can also be very expensive. Control and avoidance measures at home have to be followed aggressively, and implementation of these practices can be very difficult.

This treatment literally reduces your sensitivity to the house dust mite. Desensitising injections (extracts) contain a small quantity of house dust mite. The body defends itself by producing protective antibodies. If enough are produced in the body, the next time you come in contact with house dust mites they will protect you. Not unlike immunisation.

Immunotherapy

Immunotherapy, or hyposensitization, with dust mite allergens is another common preventive therapeutic approach [87]. The patient is injected over a period of 1-4 years with increasing doses of the mite extract until reaching a maintenance dose, starting once a week and reducing the frequency to one or two injections a month depending on the patient's response [88, 89]. The aim of this procedure is to gradually induce tolerance to the mite allergens in the patient's immune system. Scientific studies have shown that immunotherapy is an effective treatment, but also indicate that the precise mechanisms involved in immunotherapy are still unclear. Some studies have shown that after the immunotherapy there was a down-regulation in the overall allergen-specific production of inflammatory cytokines such as IL-4, IL-5 and interferon-gamma (IFN-g) [90]. Proposed mechanisms include the switching of the allergic immune reactivity from a TH2-type response to a TH1-type (i.e. immune deviation), peripheral T cell unresponsiveness (anergy), or possibly deletion of allergen-reactive lymphocytes (Figure 3). Immunotherapy can be expensive, but it has the advantage of being aimed at the cause of the allergy and not only the symptoms, and thereby can eliminate or reduce dramatically the allergic reaction. It has been documented through extensive studies that immunotherapy may be one of the best therapeutic strategies for dust mite allergy. However, it has been observed that the use of dust mite extracts may involve some disadvantages. One of them is the possibility of anaphylaxis (severe life-threatening allergic reaction),

although this is apparently minimized with the application of very small doses over a long period. Additionally, in mite extracts it is difficult to standardize mixtures of allergenic and nonallergenic components, including proteins, carbohydrates and nucleic acids [91, 92]. The quality of the extract is influenced by several factors such as the extraction procedure and storage conditions. Certain allergens may not be well represented or may even be degraded during the preparation of the mite extract.

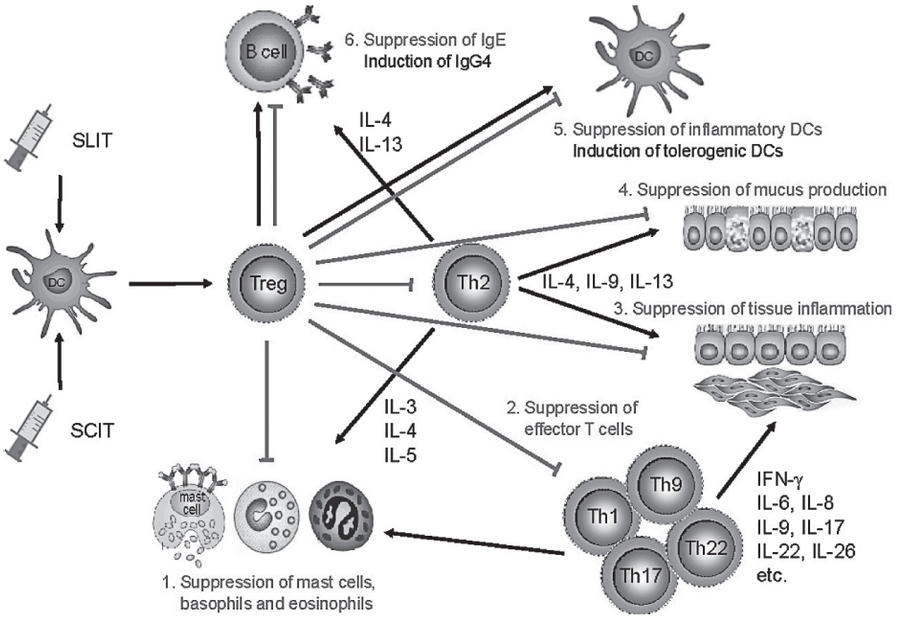

Figure 3. Mechanisms of allergen-specific immunotherapy and the role of regulatory T cells in allergic diseases. An allergen is taken up by regional dendritic cells leading to the induction of regulatory T cells. These cells suppress allergic responses directly and indirectly by the following mechanisms. 1. Suppression of mast cells, basophils and eosinophils. 2. Suppression of effector T cells. 3. Suppression of inflammatory cell migration to tissues and tissue inflame-mation. 4. Suppression of mucus production. 5. Suppression of inflammatory dendritic cells and induction of tolerogenic dendritic cells. 6. Suppression of allergen-specific IgE and induction of IgG4 from B cells.

Source: Fujita *et al*. Clinical and Translational Allergy 2012, 2:2
http://www.ctajournal.com/content/2/1/2

Allergy medications

The first treatment for controlling dust mite allergy is avoiding dust mites as much as possible. When you minimize your exposure to dust mites, you should expect to have allergic reactions that are less often or less severe. However, it's impossible to completely eliminate dust mites from the environment, hence the need of medications to control symptoms [93]. One of the following medications is needed to improve nasal allergy symptoms [94, 95].

- Antihistamines reduce the production of an immune system chemical that is active in an allergic reaction. These drugs relieve itching, sneezing and runny nose. Prescription antihistamine tablets include fexofenadine (Allegra) and desloratadine (Clarinex). Azelastine (Astelin, Astepro) and olopatadine (Patanase) are prescription antihistamines taken as a nasal spray. Over-the-counter antihistamine tablets (Claritin, Zyrtec, others), as well as antihistamine syrups for children, also are available.
- Corticosteroids delivered as a nasal spray can reduce inflammation and control symptoms of hay fever. These drugs include fluticasone (Flonase), mometasone furoate (Nasonex), triamcinolone (Nasacort) and ciclesonide (Omnaris). Nasal corticosteroids provide a low dose of the drug and have a much lower risk of side effects compared with oral corticosteroids.
- Decongestants can help shrink swollen tissues in your nasal passages and make it easier to breathe through your nose. Some over-the-counter allergy tablets combine an antihistamine with a decongestant. Oral decongestants can

increase blood pressure and shouldn't be taken if you have severe high blood pressure or cardiovascular disease. In men with an enlarged prostate, the drug can worsen the condition. Talk to your doctor about whether you can safely take a decongestant. Over-the-counter decongestants taken as a nasal spray may briefly reduce allergy symptoms. The use of a decongestant spray for more than three days in a row can contribute to congestion.

- Cromolyn sodium prevents the release of an immune system chemical and may reduce symptoms. You need to use this over-the-counter nasal spray several times a day, and it's most effective when used before signs and symptoms develop. Cromolyn sodium doesn't have serious side effects.
- Leukotriene modifiers block the action of certain immune system chemicals. Your doctor may prescribe this prescription tablet, montelukast (Singulair). Possible side effects include headache. Less common side effects include abdominal pain, cough, dental pain and dizziness.

Other therapies

- **Nasal lavage** is the use of a saltwater (saline) rinse for your nasal passages. Your doctor may suggest a saline rinse to help lessen congestion, sneezing and postnasal drip. You can purchase over-the-counter saline sprays or nasal lavage kits with devices, such as squeeze bottles, to administer a rinse. You can make your own solution with 1/8 teaspoon (5 milliliters) of table salt in 8 ounces (237 milliliters) of distilled or purified water. Mix the ingredients together and store the solution at room temperature, and remix another batch after a week. Lavage your nose daily.

Lifestyle and home remedies

Avoiding exposure to dust mites is the best strategy for controlling dust mite allergy. While house dust mite cannot completely be eliminated from homes, their numbers can be reduced significantly by adopting the following instructions and measures [96, 97, 98].

- **Use allergen-proof bed covers**. Cover your mattress and pillows in dust-proof or allergen-blocking covers. These covers, made of tightly woven fabric, prevent dust mites from colonizing or escaping from the mattress or pillows. Encase box springs in allergen-proof covers.
- **Wash bedding weekly**. Wash all sheets, blankets, pillowcases and bedcovers in hot water that is at least 130 F (54.4 C) to kill dust mites and remove allergens. If bedding can't be washed hot, put the items in the drier for at least 20 minutes at a temperature above 130 F (54.4 C) to kill the mites. Then wash and dry the bedding to remove allergens. Freezing non washable items for 24 hours also can kill dust mites, but this won't remove the allergens.
- **Keep humidity low**. Maintain a relative humidity between 30 and 50 percent in your home. A dehumidifier or air conditioner can help keep humidity low, and a hygrometer (available at hardware stores) can measure humidity levels.
- Choose bedding wisely. Avoid bedcovers that trap dust easily and are difficult to clean frequently.
- Buy washable stuffed toys. Wash them often in hot water and dry thoroughly. Also, keep stuffed toys off beds.
- **Remove dust**. Use a damp or oiled mop or rag rather than dry materials to clean up dust. This prevents dust from becoming airborne and resettling.
- **Vacuum regularly**. Vacuuming carpeting and upholstered furniture removes surface dust — but vacuuming isn't effective at removing most dust mites and dust mite allergens. Use a vacuum cleaner with a double-layered microfilter bag or a high-efficiency particulate air (HEPA) filter to help decrease house-dust emissions from the cleaner. If your allergies are severe, leave the area being vacuumed while someone else does the dirty work. Stay out of the vacuumed room for 20 minutes after vacuuming.
- **Cut clutter**. If it collects dust, it also collects dust mites. Remove knickknacks, tabletop ornaments, books, magazines and newspapers from your bedroom.
- **Remove carpeting and other dust mite habitats**. Carpeting provides a comfortable habitat for dust mites. This is especially true if carpeting is over concrete, which holds moisture easily and provides a humid environment for mites. If possible, replace wall-to-wall bedroom carpeting with tile, wood, linoleum or vinyl flooring. Consider replacing other dust-collecting furnishings in bedrooms, such upholstered furniture, nonwashable curtains and horizontal blinds.
- **Air purifiers**. Air purifiers collect airborne dust in your home and can help with controlling dust if you also maintain vigorous cleaning practices. But purifiers won't remove dust mites because the mites are too heavy to remain airborne long enough to be filtered through an air purifier. Some dust mites may be airborne right after cleaning, but they quickly settle again onto surfaces.

- **Acaricides**. Various chemicals have been used to control mite populations. Products containing benzyl benzoate, benzoic acid, pyrethroids, and pirimiphos methyl, among others, are effective acaricides. Denaturating agents, such as tannic acid, reduce allergen levels in carpets but do not kill mites

CONCLUSION

It is clear that properties of the allergen dictate features of the immune response and therefore ensuing pathology. The complexity of HDM induces a multifaceted immune response involving both the innate and adaptive arms of the immune system, activated by enzymatic protease activity and ligand binding to C-type lectin, protease-activated and Toll-like receptors at mucosal surfaces in the lung. Until the immunologic aberrations of atopy can be interdicted, treatment of the clinical symptoms resulting from the activation of relevant effector cells remains essentially symptomatic. Namely, the sneezing of allergic rhinitis is quelled by antihistamines, which antagonize the effect of the histamine released by activated, atopic mast cells and basophils. Unfortunately, many afflicted atopics are only half-heartedly instructed to avoid the recognized triggers that initiate the inflammatory cascade that sets off their symptoms. Progress will probably come in a variety of directions, e.g. both in the design of regimes for reducing exposure and in new approaches to immunotherapy. The recognition and understanding of the contribution of innate and adaptive pathways might well lead to the development of new strategies for therapeutic intervention that will play a role in the future treatment of asthma and other allergic diseases.

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