House dust allergy and immunotherapy

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HDM allergy is associated with asthma, allergic rhinitis and atopic dermatitis. In many countries childhood asthma is predominantly found in HDM-allergic children with their probability of developing disease being proportional to their IgE antibody titers and the early development of Th2 responses. While the pathogenesis is complex and increasingly linked to infection the immunologically-based allergen immunotherapy and anti-IgE antibody therapy are highly beneficial. Immunotherapy could be a short-term treatment providing lifelong relief but the current regimens depend on repeated administration of allergen over years. Immunological investigations point to a contribution of responses outside the Th2 pathway and multiple potential but unproven control mechanisms. Over half of the IgE antibodies are directed to the group 1 and 2 allergens with most of remainder to the group 4, 5, 7 and 21 allergens. This hierarchy found in high and low responders provides a platform for introducing defined allergens into immunotherapy and defined reagents for investigation.

Introduction

HDM allergy is the most prevalent indoor sensitization. It is associated with atopic dermatitis, perennial rhinitis and asthma. Chronic atopic dermatitis, which afflicts 2% of people,[1] results from reduced skin barrier function, often caused by mutation of the filaggrin gene, acting in concert with immunological hypersensitivity to staphylococcal superantigens, self proteins, food allergens and aeroallergens.[2,3] House dust mite (HDM) allergy is found in half the patients[3] and immunotherapy produces symptom relief.[2] Rhinitis has been found to afflict 13% of USA children with 37% being persistent.[4] Seventy-five percent of the persistent rhinitis patients are atopic, most commonly to HDM and often develop asthma.[5] Asthma is the most important disease associated with HDM allergy with a significant mortality causing deaths in 0.25 per 100,000 subjects aged 5–35.[6] Worldwide about 5% of children have asthma, with prevalences ranging from 3% in the Asia-Pacific and Northern and Eastern Europe to near 10% in Oceania, Latin America and most English speaking countries and increasing in developing countries.[7] A population-based Melbourne study showed that in 1964 30% of asthmatic

children had persistent disease and 22% had severe persistent disease that was apparent before 3 years.[8] The latter patients on re-examination at 43 years retained their asthma and impaired respiratory function.[8] A contemporary Australian survey similarly found that 19.4% of adults and 29.7% of children with asthma had sought urgent medical care for exacerbation in the last 12 mo with 4 and 5% being hospitalised, half more than once.[9] Asthma accounts for 10% of hospital admissions for US children aged 1–14.[10] The direct medical costs there were reckoned at $18B (billion) annually (2004 US dollars) compared with 7.2–14.5B for chronic obstructive pulmonary disease, 16–21B for arthritis, 26B for depression and 20–90B for diabetes.[11]

Asthma and HDM Allergy

About 80% of asthmatics are allergic to indoor allergens.[12-14] HDM are the most prevalent source infesting most homes in Australia, New Zealand, UK and Western Europe, extensive regions of Asia and South America and temperate and subtropical regions of the US.[15] HDM do not predominate in arctic, cold continental climates, deserts and high altitude temperate regions. In the northeastern US cities cockroach and mouse allergy are prevalent aided by poor housing. The varying infestations of cockroach and HDM between the cities has been used to demonstrate that asthma occurs when the allergic sensitization is to the prevailing allergen.[16] Allergy to cats and dogs is more abundant in arctic northern Sweden[17] and allergy to fungi is prominent in deserts.[18] Indoor heating and air conditioning can however provide the humidity and temperature to support high infestations.[19,20] Pollens can be a major cause of seasonal asthma. Affected subjects only need to be sensitized to the pollen and there is little evidence for interactions with perennial allergens.[21]

Role of Allergy in Asthma

Just over half of people with the high titers of IgE HDM antibody develop asthma and it is rare in subjects with low titers.[22] These observations have been extended with longitudinal studies of unselected birth cohorts.[12,13] The Manchester cohort[12] showed that probability of developing asthma was proportional to log of anti-allergen IgE concentration with at 15% prevalence at about 0.35 IU/ml (0.87 ng/ml), the historic level of reliable IgE detection, and a prevalence of 60% at high titers. The results were similar when calculated with either the dominant HDM, or combined with cat and dog titers. Early detection of the antibody

increased the probability[13,23] as similarly shown for anti-HDM Th2 responses.[13,24] From this it can be expected that little correlation would be found in multi-center population studies comparing asthma and atopy, especially measured by skin test. There is sound evidence for antecedents to both the development of allergic sensitization and asthma especially with respect to infection. Many studies show increased viral[25,26] and suspected bacterial infection[27] in infancy and recent data show an early widespread deficiency in antibody responses to respiratory tract bacteria,[28] which indicates delayed immunological maturation.

Bronchial challenge with major HDM allergens produces early and late phase asthma symptoms[29] but the converse, allergen avoidance, has done little to alleviate asthma.[30,31] The only outcome from a 5-y intervention study was to reduce the incidence of asthma emergencies by 10%.[31] Asthma symptoms can be improved by moving to high altitude havens but they are also diminished for non-atopic asthmatics and could be due to a number of environmental and lifestyle benefits.[32] The historical avoidance study showing improved respiratory function for HDM-allergic patients hospitalised for two months[33] remains uncorroborated and uncontrolled. The introduction of predatory mites to greenhouses for pest control has provided a controlled environment where the asthmatic symptoms can be clearly linked to mite exposure although the similarity to HDM-associated disease needs to be established.[34]

Injections of the humanized anti-IgE monoclonal antibody omalizumab produce favorable clinical outcomes for asthmatics. In a US trial the beneficial effects were highest for cockroach-allergic children living in cockroach infested houses and HDM-allergic children living in HDM infested houses consistent with abrogating specific IgE-allergen interactions.[35] The reduction of serum IgE by itself does however reduce the IgE receptors and activation state of a variety of cells including dendritic and mast cells.[36]

Immunotherapy

Subcutaneous allergen immunotherapy administers a series of 20–30 injections over several months with progressively increasing doses followed by maintenance injections of the highest dose every 6–8 weeks for 2–5 y. Such therapy with HDM extracts has shown efficacy in well-controlled trials. As an example the trial of Pifferi et al.[37] reduced the exacerbations of asthma in children from 8 to 2 per year, β-blocker usage from 40 to 20 d, corticosteroid use from 20 to 5 d and normalized bronchial hyperreactivity. Similar degrees of benefit have been reported for allergic rhinitis[38] and HDM-allergic atopic dermatitis patients.[39] A recent review showed more favorable outcomes for immunotherapy for asthma than pharmacotherapy.[40]

Many but not all double blind placebo controlled trials have demonstrated similar efficacy for sublingual immunotherapy.[41,42] Of studies noted for not showing efficacy one had a large and variable placebo effect[43] and another not only examined patients with few symptoms but instigated HDM avoidance and optimisation of corticosteroid treatment for controls.[44] A recent study that produced favorable immunological outcomes without affecting medication use[45] examined patients with very low IgE antibody titers so perhaps the treatments are better with more obvious allergy. It has been shown that HDM-allergic subjects seeking treatment as adults had a heterogeneous pattern of IgE responses compared with children.[46]

It has been reported that HDM immunotherapy in children reduces the development of sensitizations to new allergens such pollen.[47,48] This however has not always been found[49] and if it does occur in adults requires long-term treatment.[50] This specificity spreading has important implications for the benefit expected from immunotherapy, with major allergens and whether or not children should be preferentially targeted.

The mechanism for the action of immunotherapy remains conjectural. Given that the treatments use extracts that differ in allergen content and contain unknown immunomodulators[51] it may vary. Additionally T-cell assays are not only frequently conducted with undefined extracts but with different protocols including the addition of cytokines such as IL-2 and IL-7 that can bypass control points. Reviews of the complex literature on the mechanism favor an early induction of T regulatory cells including Foxp3+ cells, IL-10-producing Tr1-like cells and so-called Th3 cells producing transforming growth factor (TGF)-β).[52,53] The T-cell changes occur quickly so as investigated with pollen, the prolonged treatment that is required might restore an IgG/IgE balance that competes with allergen-IgE interactions or negatively signals via FcγR. Despite many experimental inconsistencies it can be concluded that HDM immunotherapy does increase the ability of T cells to make IL-10 and TGF-β[52,54] and does induce IgG to the major HDM allergens[52] Investigations directed specifically at HDM associated asthma are critical because symptoms caused by non-specific triggers acting on inflamed airways[55] are more prominent than symptoms directly evoked by allergen exposure, which occur for pollen allergy.

The allergenic specificity of immunotherapy has rarely been addressed. Allergen specific immunological changes have occasionally been reported[56] but so have non-specific changes[57] and few studies have examined clinical specificity. Some certainty that benefit is obtained by specifically modifying adaptive immune responses would both help elucidate the mechanism of immunotherapy and focus on effective strategies. There is evidence for the clinical specificity of ragweed immunotherapy. When treated with ragweed extract, subjects with dual ragweed and grass pollen allergy showed reduced symptoms during the ragweed but not the grass pollen season.[58] Contrarily however sublingual immunotherapy of dual birch and grass pollen allergic patients with single allergen extracts reduced symptoms during the pollination season of both allergens[59] although it was more effective for the homologous allergen. A recent publication of 30-y old data showed a crossover study where immunotherapy for HDM and grass allergy showed specificity at the level of conjunctival challenge.[60] The translation of this into clinical specificity for natural exposure would be critical. The repeated administration of an allergen that induces cascades of inflammatory responses including pleotrophic cytokines may well have widespread pharmacological actions. Indeed patients that had

received subcutaneous allergy immunotherapy showed, over a 10-y study period, lower mortality, less heart disease and less autoimmune disease.[61]

Immune Responses in HDM Allergy

Immune responses to HDM are marked by IgE antibody, Th2-type T-cells[13,24] and the Th2 associated chemokines, macrophage derived chemokine (MDC, CCL22) and thymus and activation regulated chemokine (TARC, CCL17).[62] The general principles for Th2-type hypersensitivity apply[63] albeit molded to HDM allergy.[64] As reviewed there are no consistent associations of HDM allergy or immune responses with major histocompatibility genes.[64]

T cells from HDM-allergic subjects when stimulated with the major allergens make strong in vitro proliferative responses but there is extensive overlap with the size of the responses from non-HDM-allergic patients with high IgE immunoglobulin levels and to a lesser degree with cells from non-atopic subjects.[65] T-cell precursor frequencies determined with HDM extracts have shown 2–5-fold more precursors in HDM-allergic than non-allergic subjects with frequencies typically around 0.05%.[64] Such frequencies are similar to those found in pollen allergens[66] and even for non-allergic subjects are high. The frequency for naive subjects to exotic proteins has been reported as 0.001%[67] and the post vaccination frequency for Hepatitis B capsid antigen as 0.02%.[68] Wambre et al. using tetramer technology to measure frequencies directly from the blood recapitulated the high anti-Der p 1and Der p 2 CD4 frequencies of 0.01–0.06% for HDM allergic subjects but, being at about the limit of detection, tetramer staining cells from non-allergic were only found after in vitro expansion.[69]

Responses to HDM allergens were central to the discovery of Th1-Th2 polarization in humans[70,71] but feedback from IL-4 in the extended in vitro cultures systems used probably suppressed IFN-γ responses. Responses found in shorter-term cultures stimulated with HDM allergens[72] and extracts[73] showed larger contributions of IFN-γ. Increased IFN-γ release by both CD4^{+} and CD8^{+} T-cells from allergic adults was then found for responses to Der p 1[74] and then for children where there was a positive association with bronchial hyper-reactivity.[75,76] Botturi et al. now report that peripheral blood mononuclear cells from asthmatics respond to purified lipopolysaccharide (LPS)-free Der p 1 by generating more IFN-γ producing T cells than cells from healthy subjects[77] and the recent comparison of tetramer staining of T-cells from HDM and birch-pollen allergic patients showed that in comparison to Bet v 1-binding cells, HDM-allergen-binding cells displayed a wide range of cytokines including IFN-γ.[69] There are reports indicating that T-cell from asthmatics with protracted HDM sensitization may have reduced IFN-γ[78,79] but there is growing realization of a contribution of Th1 responses to the pathogenesis of allergic disease.[63,64]

Immunoregulatory IL-10 producing cells are increased after immunotherapy[52] and after repeated bee stings[80] but natural control of inhalant allergy by IL-10 is unclear,[81,82] especially for HDM where increased IL-10 production is found in responses of allergic subjects to allergens[75,77,83] and extracts,[82,84,85] including highly purified LPS-free Der p 1.[77] This might be the concomitant production of effector and regulatory responses since Heaton et al. showed an inverse relationship between the size of skin test responses and IL-10 production.[75] However for non-allergic children IL-10 production was associated with bronchial hyper-reactivity.[75] Matsumoto et al. somewhat differently found that allergic adults with high IL-10 responses produced high late phase reactions on allergen challenge.[85] Since the dependence of IL-10 production on other endogenously-produced or added cytokines has been shown for allergen stimulation,[86] approaches other than in vitro culture seem urgent. Indeed Hayden et al. showed that T cells from HDM-allergic subjects with IL-10 gene polymorphisms associated with low expression, produced normal amounts of IL-10 in in vitro assays but had increased Th2 cytokine release indicating in vivo regulation.[87]

T regulatory cells under investigation[53,63] are the IL-10-producing Tr1-like cells, the Th3-type that produces TGF-β and nTregs (CD4^{+} CD25^{+} Foxp3^{+} cells mostly derived in the thymus). Considerable plasticity of their phenotypes are apparent, with changes induced by the cytokine milieu, and with activated effector T cells also being CD25^{+}Foxp3^{+}. Der p 1-specific CD4^{+}CD25^{+}Foxp3^{+} with in vitro suppressor functions have been generated by extended in vitro culture with allergen but from both nonatopic and HDM allergic individuals.[88] Botturi et al. also found no defect of CD4^{+}CD25^{+}Foxp3^{+} cells in HDM-allergic subjects with or without Der p 1 stimulation.[77] Going further, increased expression of HDM-extract-induced Foxp3 transcripts has been demonstrated from CD4^{+}CD25^{+} cells of infants with atopic dermatitis[89] and increased numbers of nTregs have been demonstrated in asthmatic children.[90] The latter showed low HDM-induced expression of Foxp3 and suppressor activity but this was shown to be due to an action of TNF-α in the in vitro cultures, which like for IL-10 shows the importance of experimental design.

IL-17 is of interest because of its neutrophilic chemotactic activity and because lung neutrophilia is frequently found in asthma exacerbation and in severe asthmatics. Increased IL-17 producing cells have been found in biopsies of asthmatics but with[91] and without[92] a correlation with neutrophilia. An enhanced ability of T-cells from HDM-allergic asthmatics to make IL-17 following in vitro HDM-extract stimulation has been reported[93] and the isolation of a small number of CD4^{+} T-cells with the Th17-associated CD161 marker able to produce IL-17 and IL-4 has been reported from for HDM-allergic asthmatics but not from non-allergic subjects.[94] The cells also produce IL-5, IL-8, IL-9, IL-13, IL-21 and IL-22 all of which could participate in the pathogenesis of this disease. It is likely that these observations will be extended with further study but to date Th17 cells more obviously participate in experimentally-induced murine pulmonary allergic eosinophilia than inhalant allergy of humans.

People allergic to HDM make IgE antibodies that reach titers of 100–200 ng/ml or more.[12,13,95] The antibodies are detectable in nearly half of HDM-allergic children by 2 y of age and increase to adult titers at 5 y.[13] Non-sensitized children rarely show antibody above 0.35 IU/ml (0.87 ng/ml). Fifty–sixty

Table 1. Important House Dust Mite (D. pteronyssinus) Allergens

Tier	Denomination	Structure/function
Major*	Der p 1	Cysteine protease
	Der p 2	ML-domain lipid binding protein
Mid Tier**	Der p 4	α-Amylase
	Der p 5	Protein of unknown function comprised of a bundle of coiled coils
	Der p 7	LPS binding bactericidal permeability increasing protein (LBP/BPI)
	Der p 21	Paralogue of Der p 5

* Major allergens Der p 1 and 2 collectively bind 50–60% of anti-HDM IgE antibody of HDM allergic subjects. ** Mid-tier allergens Der p 4,5,7 and 21 each bind IgE in 50% of HDM allergic subjects and collectively account for ca 30% of anti-HDM IgE antibody

percent of the IgE is directed to the major group 1 and 2 allergens and titers to these allergens correlate very closely with those to HDM extracts.[95,96] Most of the remaining binding can be accounted for by binding to the mid-tier group 4,5,7 and 21 allergens,[95,97-99] which typically bind IgE in 40–50% of subjects with the titers being proportional to those to Der p 1 and 2.[95] Children recruited from the hospital emergency room, including those with persistent asthma, have slightly higher titers than asthmatics recruited from the community but with the same allergen binding profile and proportionality.[95,100] Thus except for the paucity of data for the unstable group 11 and 14 allergens and for severe persistent asthmatics, it can be concluded that HDM allergic subjects in most populations make IgE responses to a small number of allergens with a predicable hierarchy (**Table 1**). The titers do not correlate with the amount of protein produced by the HDM.[101] The group 1 and 2 allergens are the 31st and 41st most abundant proteins while the weak group 13 allergen is the 13th most abundant protein, the non-allergenic ferritin the 21st, with the usually poor allergens tropomyosin and arginine kinase being 23rd and 29th.

As first shown with HDM extract[102] and Der p 1,[103] IgG antibody responses to HDM allergens are largely restricted to sensitized people,[95,104,105] and mostly to the major and mid-tier allergens.[95] Both IgG1 and IgG4 antibodies are found with IgG1 titers proportional to the abundance of this isotype. Overall the prevalence and titers of children are higher than for adults except for low titers of children presenting to the emergency department[95] and even lower titers for children with severe and persistent asthma.[100] Results reporting high IgG titers in non-allergic subjects can, in the case of Tame et al.,[106] be explained by the use of a recombinant fusion construct with bacterial protein and for Smith et al. by comparing responses of subjects in a high-altitude low HDM environment. All titers there were low and since absolute titers were not estimated it is likely they were within background variations.[107] The IgG1 titers of 15 000 ng/ml that can be reached in sensitized subjects[95] are as high as those found against bacterial antigens[28,108] and only slightly less than anti-viral antibody titers.[109] They accordingly have the potential for mediating the degree of biological activity attributed to anti-microbial antibodies.

Reports of negative associations of IgA antibodies and asthma[104,105] and their presence in non-allergic subjects indicate a protective effect. In contrast however IgA antibodies have been associated with eosinophilic rhinitis in HDM-sensitized patients.[110] The resolution of these discrepancies would be useful given that increased IgA has been shown to indicate successful pollen immunotherapy.[111]

House Dust Mite Species

The most important HDM are *Dermatophagoides pteronyssinus* and *D. farinae* with *D. pteronyssinus* being the most widespread. As reviewed[15] they are found worldwide their growth being dependent on relative humidity and temperature. *D. pteronyssinus*, which outcompetes *D. farinae* in humid regions, is dominant in Australasia, Asia, South America and maritime western and southern Europe. It is essentially the only HDM for Australia, New Zealand and England. *D. farinae* is increased in continental regions of Europe but most countries have mixed populations. There are however micro-variations, an interesting one being the dominance of *D. farinae* in Italy where research is commonly conducted with *D. pteronyssinus*. In northern America the western maritime regions are biased to *D. pteronyssinus* although Los Angeles and Vancouver have both species. The mid western regions that have few HDM have *D. farinae* and this bias continues to the northeast extending to Toronto. For Asian countries that conduct frequent HDM research, Japan and many regions of China have mixed populations, Singapore has *D. pteronyssinus*, Thailand has mainly *D. pteronyssinus*, Taiwan has a *D. pteronyssinus* bias and Korea, except for southern coastal regions, has *D. farinae*.

It should be noted that skin tests with allergen extracts cannot attribute sensitization to a particular species. The allergens are cross-reactive and the allergen content of different extracts of the same species varies. The sequences of *D. pteronyssinus* and *D. farinae* allergens usually have 80–85% sequence identity so both cross reactivity and species specificity would be expected. For example a third of subjects in Japan, where both species exist, had twice the IgE binding to Der p 1 compared with Der f 1[112] and the ability to absorb IgE binding to Der p 1 with Der f 1 varied from 15–100%. In Virginia, USA with more exposure to *D. farinae* there were 10-fold differences in the group 1 allergen binding for some individuals.[113] The group 2 allergens were more cross-reactive in Japan[112] and Virginia.[114] In *D. pteronyssinus*-biased Taiwan, Der p 7 has been found to bind three-times more IgE than Der f 7 showing high species specificity.[115] Extensive inter-species T-cell cross reactivity to group 1 and 7 allergens were found for subjects in Western Australia where few *D. farinae* are

found[116] although studies with synthetic peptides showed those representing Der p 1 induced more responses than the homologous Der f 1 peptides.[117] Should immunotherapy be tailored to the sensitizing species? There are no direct comparisons but the efficacies reported using *D. pteronyssinus* in *D. farinae*-infested Italy[37,118] have been similar to those from England using *D. pteronyssinus* for *D. pteronyssinus* sensitization[38] and in South Korea with *D. farinae* for *D. farinae* sensitization[119] or mixtures of *D. pteronyssinus* and *D. farinae* in Italy.[120]

Blomia tropicalis

Blomia tropicalis from the superfamily Glycyphagoidea is as summarized[15] a HDM in some tropical and subtropical regions. It is the most abundant HDM in Singapore, Hong-Kong, Malaysia and the Philippines and is found in Taiwan and China where in Chengdu province 49% of patients had antibodies to the *B. tropicalis*-specific Blo t 5 allergen,[121] showing the need for more study in this populous region. It is the most prevalent HDM in Barbados and Puerto Rico and a minor HDM in Florida and Texas. *B. tropicalis* abound in tropical coastal areas of Brazil along with *D. pteronyssinus*[122] and show similar importance in Columbia and Peru but not in neighboring Ecuador and Venezuela. *B. tropicalis* allergens typically have 30–40% amino acid sequence identity with their *Dermatophagoides* spp homologs and little cross reactivity.[98] The tropomyosin and glutathione-S-transferase of *B. tropicalis* antigens cross-react with ascaris proteins limiting the usefulness of extracts in many tropical regions.[123]

Properties of Allergens

Knowledge of the structure and function of the important HDM allergens (**Table 1**) has been recently reviewed.[99] The group 1 allergens are cysteine proteases but contrary to popular perceptions only HDM have cysteine proteases as important allergens and the only common sources of inhalant allergens that have important serine protease allergens are *Penicillium* spp[124] Enhancement of allergenicity by cysteine proteases[125] has been proposed based on in vitro observations of the cleavage of immunological receptors and the weakening of intercellular barriers. Cysteine protease activity is however highly sensitive to oxidation and is not found in HDM extracts.[99] It is likely that as shown for the cleavage of toll like receptor (TLR)-3 by a parasite cysteine protease[126] that its action is endosomal. Extracellular fluid is oxidising and endosomes and lysosomes have a special cysteine transport mechanism to active the cysteine proteases that mediate many of their functions.[127]

The group 2 allergens are myeloid differentiation (MD) antigen-like lipid binding proteins (ML domain proteins). It has been proposed that Der p 2 has intrinsic adjuvanticity by mimicking the action of MD-2, which loads LPS unto TLR-4 to activate an innate inflammatory cascade. Der f 2 binds LPS with high affinity in a manner similar to MD-2[128] and the administration of Der p 2 complexed with LPS can induce Th2 responses in MD-2 knockout mice.[129] The poor allergenicity of Blo t 2[98] might be related to fact that it lacks key residues homologous to those used by MD-2 to bind TLR-4.[130]

The group 4 allergens are typical α-amylases and the group 7 allergens are structurally related to the LPS binding bactericidal permeability increasing protein (LPB/BPI proteins)[131] as well the related odorant binding proteins.[132] The major horse allergen Equ c 3 and the cat allergen Fel d 8 are also members of this family.[133] The group 5 and 21 allergens are related proteins that so far appear unique to mites and have no known function. Despite their obvious relatedness they only have about 40% sequence identity and it is not possible to tell which of the allergens called Blo t 5 and 21 are in fact homologous to Der p 5 or Der p 21. The crystal structure of Der p 5 shows a bundle of coiled coils[134] that can polymerise to create a cage with a hydrophobic cavity. The monomer structure agrees with that solved by NMR for Blo t 5[135] both of which differ in detail from that of Chan et al.[136] It could be speculated that the group 5, 7 and 21 allergens might bind molecules that resemble pathogen associated microbial patterns (PAMPS) and thus compete favorable for interactions with the innate immune system and that the group 4 amylase might similarly bind to carbohydrates or glycolipids.

Cross Reactive Allergens

The cross-reactivity of antibodies to the group 10 tropomyosin allergens with tropomyosins from disparate species is well known. The amino acid sequences of the tropomyosins of *D. pteronyssinus* and *D. farinae* are 98% identical and 96% identical to Blo t 10. Der p 10 and cockroach have 80% amino acid sequence identity and high cross reactivity.[137] IgE binding to the group is however usually rare and relatively weak.[95,138] Prevalent IgE binding has however been reported in Japan[139] and Zimbabwe.[140] It is not an incidental cross reactivity because the antibodies were only found in subjects with IgE antibodies to the major HDM allergens. Also HDM-allergic subjects in a tropical community known to have experienced helminthic infections have not shown Der p 10 binding[141] so it is an interesting puzzle. The group 20 arginine kinase allergens show high sequence conservation and thus a potential for cross reactivity. There is 75% and 80% identity to sequences of insects and crustaceans that have major inhalant[142] and food[143] arginine kinase allergens but the HDM arginine kinases do not appear to be important HDM allergens.[95,98,141]

Future for HDM Immunotherapy

The main medications for asthma are inhaled corticosteroids, long-acting β2-agonists and leukotriene modifiers.[144] They provide symptom relief and improve lung function but do not prevent exacerbations or the progression of disease in 10–20% of asthmatics[145] equivalent to 1–2% of most western populations. There is a problem of equal magnitude for poorly-managed controllable asthma[146] resulting in persistence and deteriorating lung function.[147] HDM reduction and avoidance procedures are ineffective or of little use,[30,31,148] despite being recommended in treatment guidelines. The clinical efficacy demonstrated for the current injection and sublingual protocols of immunotherapy,

combined with new knowledge of antigen presentation by the innate immune system, point to the possibility of developing of fast-acting effective first-choice immunotherapy. The ordered hierarchical profile of the importance of different HDM allergens, found in subjects with a wide spectrum of allergic disease, provides a platform for the use of defined allergen formulations. Using the successful immunotherapy with purified Amb a 1 for ragweed hypersensitivity[149] as guide it can now be deduced that only about 60% of the allergen load needs to be checked.[150] This can be met with the group 1 and 2 HDM allergens and, if required, increased by a selection from the group 4, 5, 7 and 21 allergens. Cognisance should also be taken of limitations of the current knowledge of T-cell function demonstrated by the inconsistency of experimental results. The employment of different investigative strategies would be logical as would replacing the use of unknown irreproducible extract reagents with pure allergens used in defined concentrations. The major allergens are obtainable from commercial sources,[54] and are being increasingly used. This along with the application of new techniques such as tetramers and functional genetic associations should produce outcomes closer to the in vivo events and provide clear avenues for new investigations. Consideration of the methods that might be used to monitor the effectiveness of the treatment brings this into sharp focus. Taking pollen immunotherapy as a precedent early monitoring of IL-10 production might be an indication that the therapy is on track. Treatment of pollen-allergic patients with low, ineffective, doses of allergen however still induces IL-10[151] so it might be limited to indicating potential if a correct dose was administered. In contrast to measuring IL-10 the level of CD4$^+$CD25$^+$Foxp3 regulatory cells do not consistently increase.[152] Increased IgA and IgG antibody associate with successful long-term immunotherapy but functional measurements are being explored for more relevance especially since anti-grass IgG declines on cessation of grass pollen immunotherapy while blocking antibody, measured by blocking of CD23 binding to antigen, persists.[153] The blocking of allergen-CD23 binding has provided a convenient functional assay that implies the possibility that the antibody might block antigen presentation to T cells but the functional significance needs further exploration because it has been found to correlate well with the ability of IgG antibodies to allergen induced basophil degranulation.[154] The blocking of CD23 presentation by IgG antibody was first described for HDM allergy[155] so it can be used for immunotherapy studies. Even for pollen immunotherapy however the immunological changes noted are not predictive of successful treatment[156] and should not be expected to occur for new innovative strategies of immunotherapy. The identification of immunological changes that mediate clinical improvement remains a major goal which might be best studied with new techniques that can track allergen-specific effects of in vivo allergen exposure at the cellular level.[157]

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