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IgE and T-cell responses to house dust mite allergen components

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ABSTRACT

Using the terminology for *Dermatophagoides pteronyssinus*, IgE responses to house dust mites have been shown to be mostly directed to the serodominant Der p 1, 2 and 23 allergen components with mid -tier responses to Der p 4, 5, 7 and 21 that are made by 30–50% of subjects with titers proportional to those of the serodominant specificities. This pattern can be seen to evolve in childhood and although responses to minor allergens appear to contribute little to the total IgE they are at least markers for a greater propensity to develop disease. While Der p 23 is a component that induces prevalent IgE responses, sometimes in the absence of responses to Der p 1and 2, not all studies have found high titers so further investigation is needed. From limited knowledge adult onset IgE responses might have a different pattern that is not so centered on Der p 1 and 2. Responses that induce under 3.5 IU/ml of IgE antibody are not usually associated with disease and should be examined for cross reactivity expected from IgE responses to other allergens and antigens of infectious agents. Scabies that has 40% endemicity in some regions and is spread by immigration can give rise to high-titer binding that can be recognized by component resolved diagnosis. Recent studies with synthetic peptides representing allergens and non-allergenic HDM proteins now offer new research avenues on HDM induced immune responses, including the ability to use peptides representing the serodominant allergens as defined reagents for long overdue reproducible T-cell investigations.

1. Introduction

The recent progress towards compiling an exhaustive list of the IgE binding house dust mite (HDM) components is not only valuable for investigations in different geographic regions but as shown for Der p 21(Weghofer et al., 2008) and 23 (Weghofer et al., 2013) and Der f 35 (Fujimura et al., 2017) has added significantly to the knowledge of HDM allergy in well-studied populations. Responses to these relatively recently recognized components have been shown by gravimetric measurements and comparative titrations to contribute significantly to the total IgE binding and Der p 21 is a cross-reactive determinant for allergy to *Blomia tropicalis* (Tan et al., 2012). It is however important to appreciate that HDM sensitization is not constituted by random responses to different components (Thomas, 2015; Thomas, 2016) and that the size of IgE response is critical for the association with allergic disease. Titers of less than 3.5 IU/ml (10 times 0.35 IU/ml) of IgE antibody are strongly associated with a life untroubled by allergy (Simpson et al. 2005; Crane et al., 2012). Western immunoblotting has detected over 30 IgE-binding entities in HDM extracts (Tovey and Baldo,1987) but most of it was focused on seven important components. In keeping with this although extracts made from whole mite cultures and washed mite bodies had differences in binding to minor components they were quantitatively equally able to cross inhibit IgE binding to each other. Studies using purified components and quantitative measurements have similarly identified 7–8 components that account for most of the known IgE binding to HDM extracts as well as a distinctive pattern of IgE binding (Thomas, 2015; Thomas, 2016) that is different for childhood and adult onset sensitization (O'Brien and Thomas, 1994) and from current determinations not always directly related to the specificity of T-cell responses (Oseroff et al., 2016). The term serodominant will be used here instead of a major allergen because the latter has become attached to a definition based on a 50% prevalence without a consideration of the amount of antibody or its contribution to the overall response.

2. Childhood sensitization

The serodominance of the group 1 and 2 allergen components (Trombone et al., 2002) was evident from the first analyses of the IgE binding components of children. IgE antibodies to Der p 1and 2 contributed 50–60% of the IgE binding in 95% of children in Australia (Hales et al., 2006) and was the dominant combination in 78% of children in Singapore (Kidon et al., 2011) noting that some of this population were also sensitized to *B. tropicalis*. Further Hales et al. (2006) found that Der p 4, 5, and 7, that each bound IgE in 30–50% of subjects, were mid-tier components accounting for much of the residual

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IgE binding and binding with titers proportional to the combined titers to Der p 1 and 2. The contribution of the IgE binding to Der p 3, 8, 10 and 20 was insignificant and this was unsurprising from absorption assays of IgE binding to HDM extracts (Weghofer et al., 2005). Although with lower prevalences and an equivalent contribution from Der p 3, Kidon et al. found the same mid-tier components and the expected mid-tier response to the then recently discovered Der p 21 (Weghofer et al., 2008).

Recent microarray studies have corroborated these observations and added the peritrophin-like allergen Der p 23 that bound IgE with similar prevalence to Der p 1and 2 and was the dominant IgE binding component in 5% of asthmatics (Resch et al., 2015). The pattern has been replicated across Europe and in Canada, USA and Japan and for the *D. farinae* allergens (Batard et al., 2016) but the titer of binding to the group 23 components was variable and mostly lower. The proportional relationship of the IgE binding of the mid-tier and serodominant components can be seen in the heat maps for individual patients shown by Resch et al. (2015) except for one low responder. The IgE binding of atopic but non-asthmatic subjects had the same pattern as that of asthmatics but with lower titers and fewer detectable responses ((Resch et al., 2015). A result that could have been emphasized was that, as inferred from binding to extracts, children with high binding to serodominant and mid-tier components did not necessarily develop asthma. Although the clinical history of subjects in the allergic rhinitis sample examined for IgE binding to components by Mueller et al. (2016) was not reported in detail, and the IgE titers to all allergens were very low, the higher-titer responses showed the Der p 1, 2 and 23 dominance described for asthma. There was a heterogeneous response in the very low responders that might have been from the cat-allergic subjects included in the panel and since a high proportion bound the glutathione-*S*-transferase, Der p 8, could include cockroach cross reactivity (Mueller et al., 2015).

Providing a new perspective, Posa et al. (2017) showed that the evolution of responses to the components paralleled their IgE binding hierarchy. Children first showed antibodies to Der p 1, 2 and 23 and then progressed to anti-mid-tier responses binding Der p 4, 5, 7 and 21 with responses to the minor components Der p 11, 14, 15, 18 and clone 16 not becoming apparent until 5–6 years. Responses to the mid-tier components did not affect the propensity of the children to develop asthma but it was increased two-fold for children who had responses to serodominant, mid-tier and minor components. It might be that responses to the dominant and mid-tier are part of a single pathway of sensitization as shown by the frequent correlation of their responses (Hales et al., 2006; Hales et al., 2013) while the minor allergens sensitize via a different pathway that interacts for disease. It has already been reported that the IgE titers to the chitinase- and chitin binding-like components Der p 15 and 18 correlate well with themselves but not with those to the serodominant and mid-tier components (Hales et al., 2013). Alternatively subjects that respond to poorly stimulating allergens might just have a greater propensity to develop disease. Although interesting it needs to be appreciated that the subjects that bound all three groups of components (Posa et al., 2017) only constituted 18.5% of the children that developed asthma. Hales et al. (2006) examining antibodies to Der p 1, 2, 3, 4, 5, 7, 8, 10 and 20, found children admitted to the emergency department for asthma exacerbations did not have a broader recognition of allergens than children with stable asthma indicating that only some minor components might contribute to disease. The properties and denomination of the allergens examined during the evolution of disease in children are shown in Table 1.

Table 1
House dust mite allergen components in the development of childhood asthma[a].

Serodominant	
Group 1	Cysteine protease (that requires the addition of reducing agents to extracts for activity)
Group 2	ML domain protein with characteristic lipopolysaccharide binding
Group 23	Non-chitin binding peritrophin-like protein
Mid-tier	
Group 4	Alpha amylase
Group 5	Coiled-coil bundle of unknown function
Group 7	Bacterial permeability increasing/lipid binding protein homologue
Group 21	Homologous to group 5
Minor	
Der p 11	Paramyosin is an unstable allergen. Amongst minor IgE binding associated with enhanced development of asthma
Group 14	Large lipid transport proteins susceptible to degradation producing IgE binding peptides. amongst minor IgE binding associated with enhanced development of asthma
Group 15	Chitinase-like proteinamongst minor IgE binding associated with enhanced development of asthma
Group 18	Chitin binding domain containing amongst minor IgE binding associated with enhanced development of asthma
Clone 16	Unspecified recombinant protein amongst minor IgE binding associated with enhanced development of asthma

[a] Developmental evolution as described by Posa et al. (2017).

3. Newly reported IgE binding components

The International Union of Immunological Societies/World Health Organization (IUIS/WHO) allergen nomenclature subcommittee assigns a name to a protein if it is tendered that it binds IgE antibodies from sera of five subjects allergic to HDM regardless of titer. Since IgE production is part of normal immune responses, even those of healthy children to bacterial antigens (Hales et al., 2012), and responses to allergens can provide collateral help for IgE production to bystander antigens (Eisenbarth et al., 2004), it would not be surprising to find low IgE responses to many mite proteins. Accordingly newly denominated IgE-binding proteins need to be assessed with quantitative measurements and comparisons with other components for their contribution to allergic responses. As detailed elsewhere (Thomas, 2016) such assessments have yet to materialize for many of the newly-described *D. farinae* components and not only do many discrepancies need to be resolved but a recent proteomic analysis failed to detect IgE or IgG binding to most of the allergens designated Der f 24–30 (Oseroff et al., 2016). This might have been due to the particular extract however the accompanying analysis of T-cell responses to peptides representing these components also showed little reactivity indicating a need to identify the extent of the binding or regional differences. A newly described IgE binding protein that warrants corroboration is Der f 35 found to have quantitatively similar IgE binding as Der f 2 and like the group 2 components is a ML domain protein (Fujimura et al., 2017). Further analysis of the group 11 paramyosin allergens are indicated from the finding of a high frequency in atopic dermatitis but not asthma patients (Banerjee et al., 2015) and its recently described binding by sera from clinically undefined adolescent and adult patients (Conti et al., 2017). The latter study also found from immunoblotting that Der p 14 was frequently reactive. Both these allergens are members of the minor allergen panel used by Posa et al. (2017) but both need the production of authentically structured recombinant proteins or the isolation of stable natural components since IgE antibodies to other allergens are highly dependent on conformation (Greene and Thomas, 1992). The high IgE binding titers measured to recombinant fragments of Der f 14 in Japanese patients continue to point the importance of this component (ElRamlawy et al., 2018), which was also one of the strongest inducers of T-cell responses (Oseroff et al., 2016).

4. Cross reactivity

The cross reactivity of the group 10 and 20 components with their tropomyosin (Fernandes et al., 2003) and arginine kinase (Binder et al. 2001) homologues in other arthropods is especially implicated in shellfish allergy. Tropomyosin however only induces IgE in a small percentage of HDM-sensitized subjects (Hales et al., 2006; Resch et al.,