World Allergy Congress 2014

Postgraduate Course 20: Immunotherapy Track – New Developments in House Dust Mite Allergy

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House Dust Mite Allergens: From Fecal Particles to Molecular Determinants for Antibody Binding

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Learning Objectives:

- To become familiar with the intrinsic properties (structure and function) of the most important dust mite allergens, and their contribution to allergenicity.
- To understand the strategy for analyzing antigenic determinants of dust mite allergens, and its application for the design of hypoallergens for immunotherapy.

Dust mite allergy is the most prevalent among asthmatic patients worldwide. It affects up to 85% of asthmatic children and is a risk factor for emergency room admission with asthma [1,2]. Prolonged inhalation of low doses of allergens over months or years by genetically predisposed individuals leads to IgE antibody production. In the early 1980s, the importance of fecal particles from these arachnids as a major source of allergens was discovered [3]. The first dust mite allergen Der p 1 was purified from *Dermatophagoides pteronyssinus*, the most common species around the world, especially in temperate areas [4]. Since then, a large number of mite allergens have been identified. The allergen database approved by the World Health Organization and International Union of Immunological Societies (WHO/IUIS) Allergen Nomenclature Sub-committee lists up to 33 groups of allergens from nine different mite species (www.allergen.org). Allergens from groups 1 and 2 are immunodominant and show a

prevalence of sensitization of approximately 80% among asthmatic children. They account for more than 50% of total house dust mite specific IgE reactivity in mite allergic patients. Groups 4, 5, 7 and 21 contain midpotency allergens [5]. Molecular cloning of these allergens has led to their association with functional groups of proteins. Some mite allergens are digestive enzymes, in agreement with their presence in fecal particles. These include group 1, which are cysteine proteases, and groups 3, 6 and 9, which are serine proteases. A large body of evidence reports that the proteolytic activity of these allergens contributes to their allergenicity. Cleavage of proteins involved in tight junctions (such as occludin), and receptors (PAR-2, CD23, CD25) facilitates the access to the lung and the immunologic processes that result in IgE (and IgG) antibody production, respectively [6,7].

Here, we report recent developments made possible by the determination of the three-dimensional structure of mite allergens. These include Der p 1/Der f 1, Der p 2, Der p 5 and Der p 7, alone or in complex with antibodies [8-12]. Group 2 allergens are lipopolysaccharide (LPS)-binding proteins reported to activate the innate immune system in mice through Toll-like receptors (TLR) 4 in the presence of LPS. Der p 2 mimics the function of the structurally similar protein myeloid differentiation factor (MD-2) [13]. Similarly, the structure of Der p 7 resembles the LPS-binding protein involved in TLR4 activation. A function involved in activation of innate immunity has been suggested for this allergen [12]. Der p 5 contains three helices connected by short loops [11]. In the crystal, this allergen forms a dimer that creates a large hydrophobic cavity that could be a ligand-binding site, as occurs for many other allergens like Bla g 1, Fel d 1 and lipocalins [14-16]. Lipid adjuvants can strongly influence the innate immune response and subsequently skew the adaptive response toward allergy [14].

Molecular determinants of mite allergens have recently been analyzed by determining the X-ray crystal structures of allergens in complex with monoclonal antibodies (mAb) that inhibit IgE antibody binding. The structures of complexes of Der p 1 with the specific mAb 5H8 and 10B9, as well as the structures of Der p 1 or Der f 1 in complex with the cross-reactive mAb 4C1, have been determined [9,17]. These structures revealed in detail the amino acids involved in allergen-antibody interaction, and the

molecular basis of specificity and cross-reactivity between both allergens. Site-directed mutagenesis analysis based on these structures led to the production of modified allergens with reduced IgE antibody binding [18]. The significance of these studies is that determination of the intrinsic properties of the allergens, structure and function, combined with the analysis of the antigenic surface of these allergens, will enable the design of molecules with defined three-dimensional structure, reduced IgE reactivity and retained T cell epitopes, for production of hypoallergens for allergy vaccines.

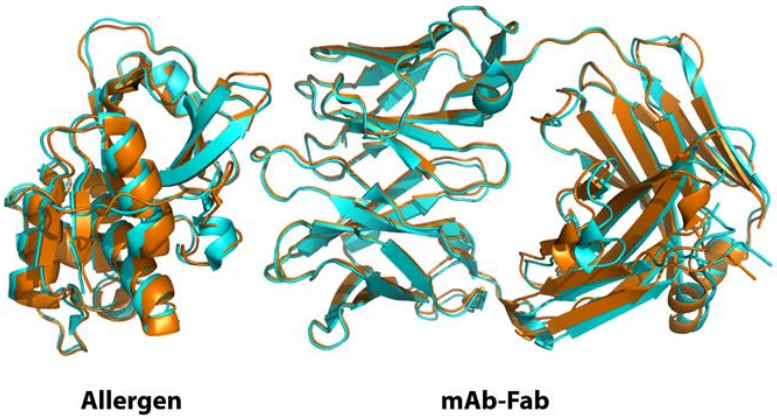

Figure. X-ray crystal structures of natural Der p 1 and Der f 1 in complex with a fragment of a mAb that inhibits IgE antibody binding (cyan and orange, respectively). The structures show the molecular basis of cross-reactivity between both dust mite allergens, and a conformational epitope which overlaps with an IgE antibody binding site [9].

References

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