ALLERGY

Allergic mimicry

Why do particular innocuous environmental proteins act as allergens in susceptible hosts? It has been suggested that the protease activity of some allergens might be important, but clear mechanistic explanations of allergenicity are still lacking. Now, Karp and colleagues have shown that the main house dust mite allergen, Der p 2, acts as a functional homologue of MD2 (a lipid-binding, Toll-like receptor 4 (TLR4) signalling co-factor) to drive airway inflammation in a TLR4-dependent manner; they suggest that this mimicry could be an underlying mechanism of allergenicity.

MD2 binds lipopolysaccharide (LPS), TLR4 and the co-factor CD14, and is essential for LPS recognition and the initiation of TLR4 signalling. Recent studies have shown that Der p 2 has structural homology with MD2, so the authors sought to determine whether they also share functional homology. Using an *in vitro* system, the authors showed that Der p 2 could reconstitute LPS-induced TLR4 signalling in cells that lack MD2 and also could enhance the response in the presence of MD2. Further analysis showed that Der p 2 directly interacts with TLR4, CD14, MD2 and LPS.

The ability of Der p 2, which was purified from house dust mites and contained low levels of LPS, to activate cells in the absence of MD2 in a TLR4-specific manner indicated that an LPS–Der p 2 complex might mimic the TLR4-activating properties of the LPS–MD2 complex. Indeed, recombinant Der p 2 that is devoid of any LPS was inactive in the functional assays. However, recombinant Der p 2 in the presence of low levels of LPS — which alone were insufficient to activate TLR4 — stimulated TLR4-dependent cytokine production.

In an airway sensitization model, the presence of low levels (<1 ng) of LPS has been shown to induce tolerance, whereas slightly higher levels (100 ng) of LPS drive T helper 2 (T_H2)-type immune responses. Airway sensitization and challenge with Der p 2 in the presence of an extremely low level (0.026 pg) of LPS induced airway T_H2-type inflammation in wild-type and MD2-deficient mice but not in TLR4-deficient mice.

So, these data show that the main house dust mite allergen mimics the function of MD2 and can facilitate TLR4 signalling and airway T_H2-type inflammation under conditions of low levels of ambient LPS exposure that normally would induce tolerance. Given that many allergens, including Der p 2, are members of the MD2-like lipid-binding protein family and that more than 50% of major allergens are lipid-binding proteins, such mimicry could also underlie the allergenicity of these allergens.

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ORIGINAL RESEARCH PAPER Trompette, A. *et al.* Allergenicity resulting from functional mimicry of a Toll-like receptor complex protein. *Nature* 7 Dec 2008 (doi:10.1038/nature07548)