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How do allergens sensitize?

Comment les allergènes sensibilisent-ils ?

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Abbreviations

pattern recognition receptor
 innate lymphoid cell
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 serum amyloid A
 formyl-peptide receptor
 dendritic cell
 lipocalin 1
 major urinary protein
 phospholipase A2
 domain myeloid differentiation factor 2-related lipid recognition domain
 suppressor of tumorigenicity 2
 non-specific lipid transfer protein

Various views on why the allergic immune response has evolved have been expressed including the toxin hypothesis, the danger theory and the allergic host defense model [1]. The exponents of these views agree that it is a common misconception to regard all allergens as generally harmless environmental substances or to think of the allergic immune response as a mistargeted response. Quite on the contrary, recent studies of several types of allergens have shown that they trigger specific molecular mechanisms resulting in the initiation of type 2 immune responses.

Certain allergens interact with specific innate pattern recognition receptors (PRRs). Dectin-1 is a C-type lectin receptor that binds

β -glucans and carbohydrates present in fungal cell walls, some bacteria and plants. It was first shown in a mouse model that dectin-1 also binds invertebrate tropomyosins, proteins that are ubiquitously present in the environment [2]. In mice with intact dectin-1 and in healthy humans, signaling through dectin-1 expressed by alveolar epithelial cells inhibits IL-33 secretion and recruitment of IL-33 producing innate lymphoid cells (ILCs) thus suppressing the development of an allergy to inhaled tropomyosins. However, in asthmatic and chronic rhinosinusitis (CRS) patients binding of house dust mite tropomyosin leads to an elevated IL-33 production. The authors identified a single nucleotide polymorphism in the dectin-1 gene locus that is associated with an impaired dectin-1 function and results in skewing of the immune response towards type 2 immunity.

The soluble PRR serum amyloid A (SAA) is an acute-phase protein that binds to the bacterial outer membrane protein A which shares structural homology with the house dust mite allergen Der p 13, a fatty acid binding protein. SAA1, produced locally by airway epithelial cells, can interact with group 13 arthropod allergens resulting in the dissociation of hexameric SAA1 into dimers and monomers [3]. These interact with the formyl-peptide receptor 2 (FPR2) which results in a robust release of IL-33 and a subsequent activation of ILC2s and dendritic cells (DCs). The SAA1-FPR2-IL-33 axis was also upregulated in nasal epithelial cells from CRS patients who also exhibited an increased SAA1 hexamer dissociation. The allergenic lipocalins Can f 1 from dog and Fel d 4 from cat, but not their non-allergenic human counterparts Lcn-1 and MUP, upregulated the expression of the N-formyl-peptide receptor 3 (FPR3) in DCs treated with these lipocalins [4]. The authors showed that

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lipocalins colocalized with FPR3 in endosomes and that binding of allergenic lipocalin-derived peptides prevented the upregulation of IL-12 in human DCs resulting in a Th2 skewing of naïve T cells.

Other allergens disrupt the integrity of cell membranes (e.g. phospholipases A2, defensins) triggering the release of the alarmin IL-33 or they degrade connective tissues (hyaluronidases). Bee venom phospholipase A2 (bvPLA2/Api.m 1) hydrolyzes membrane phospholipids to release lysophospholipids which induce the release of IL-33 via the disruption of these membranes [5]. Bee venom PLA2-induced group 2 ILCs and primary Th2 responses which were dependent on the ST2 receptor, the specific primary receptor for IL-33.

Proteases present in aero-allergen sources such as fungi, house dust mite and pollen, can directly process full-length IL-33 into its mature form thus activating ILC2s to produce large amounts of the type 2 cytokines IL-5 and IL-13 [6]. This IL-33-based protease sensing mechanism might have an important role in the rapid and efficient activation of ILC2s. IL-33 can be released from cells independently of the activity of external proteases as is the case for the PLA2-induced release, or due to the damage of the epithelial barrier.

Furthermore, many allergens are associated with lipid ligands (e.g. ML-domain proteins, members of the PR-10 family [7], lipocalins, non-specific lipid transfer proteins/nsLTPs) that activate PRRs of the innate immune system which in turn modulate adaptive immune responses. The natural lipid ligand of the peach nsLTP Pru p 3 is a derivative of camptothecin linked to phytosphingosin. The immunological activity of this lipid ligand resides in the phytosphingosine part and is mediated by CD1d which leads to the maturation of monocyte-derived DCs and the production of higher levels of IgE than Pru p 3 alone, thus the lipid ligand acts as an adjuvant [8].

In summary, although more and more details become known about the molecular mechanisms of allergic sensitization, very few studies on why only susceptible individuals raise a specific allergic

immune response have come forward so far. These studies indicate that genetic susceptibility is based on altered signal processing and mutations of PRRs [2,3].

Disclosure of interest

The author declares that he has no conflict of interest.

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