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Allergen-Specific Pattern Recognition Receptor Pathways

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Summary

Allergic diseases continue to plague modernized societies, underscoring the need to identify the molecular basis for the propensity of a small number of environmental proteins to provoke maladaptive, allergic responses. Recent data suggest that the ability of allergenic proteins to drive allergic responses in susceptible hosts is driven by their unique innate immune activating capabilities. Although the identification of allergen-specific pattern recognition receptors is in its infancy, studies to date have shown that allergens drive Th2-biased immune responses via directly engaging C-type lectin receptors (dectin-2, DC-SIGN, mannose receptor) on dendritic cells and/or mimicking toll-like receptor 4 signaling complex molecules expressed on airway structural cells. Elucidation of the specific innate immune pathways activated by allergens holds great promise in defining new therapeutic targets for the treatment of allergic diseases.

Introduction

The prevalence of allergic diseases had been increasing over the last few decades and it is estimated that 20% of the world's population is currently afflicted with one or more of these diseases [1]. Allergy is thought to result from maladaptive immune responses to ubiquitous, otherwise innocuous environmental proteins, referred to as allergens. Allergens, by definition, are environmental proteins, largely derived from complex living organisms (plants, fungi, insects, other mammals) that have the ability to elicit powerful T helper lymphocyte type 2 (Th2) responses, culminating in immunoglobulin E (IgE) antibody production (atopy) [2]. Although tremendous evidence points to the ability to elicit Th2 immune responses as a unifying feature of allergenic substances, the exact mechanisms by which these proteins drive aberrant Th2-polarized immune responses remains a mystery.

Based on the fact that allergens constitute only a small fraction of the antigens encountered by humans in their daily life and that those afflicted respond to the same allergens in the same manner, it has been proposed that there may be common structural motifs or conformational sequence patterns that underlie their allergenicity. Although our knowledge of the structure of allergens has greatly improved over the last few decades, much of the work in this area has focused on the elucidating the epitopes recognized by T and B cells. However, to date, there is no compelling evidence for common structural characteristics amongst the diverse T and B cell epitopes recognized in allergic responses [3]. Thus it

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appears doubtful that the presence of such B and T cell epitopes are sufficient to endow a protein with allergenic potential. Other factors such as the size, resistance to proteolysis, and enzymatic activity, have been suggested to play an important role in allergenicity. However, none of these factors have been consistently linked with allergenic potential. The current renaissance in the study of innate immunity has provided important insights into this question. Indeed, it has recently been proposed that allergens are linked by their ability to activate the innate immune system. In this review, we will discuss recent advances in our understanding of the diverse innate immune activating properties of allergens that appear to endow them with a propensity for driving Th2 immune responses-with a particular focus on their ability to activate pattern recognition receptor pathways.

TLR signaling pathways, lipid binding activity and allergic inflammation

In the late 1980's, Janeway and colleagues [4] put forth the paradigm that the innate immune system had evolved to recognize conserved molecular patterns referred to pathogen associated molecular patterns (PAMPs). This recognition would both initiate an immediate response from innate responding cells and set the stage for the ensuing adaptive responses. These PAMPs are recognized by the mammalian host through specific germ-line encoded pattern recognition receptors (PRRs) such as: Toll-like receptors (TLRs), NOD-like receptors (NLRs), RIG-I-like receptors (RLRs), and C-type lectin receptors (CLRs). PRR activation and instruction of antigen-presenting cells is a prerequisite for the initiation of immune responses, and as such presentation of exogenous antigens by dendritic cells to T cells in the absence of PRR stimulation leads to tolerance [5]. PRRs also play a role in determining the class of the adaptive immune response generated. Although tremendous progress has been made in identifying the spectrum of PRRs driving the activation of Th1 and Th17 immune responses, the identification of the exact receptors and pathways responsible for recognition of allergens and initiation of Th2-skewed immune responses has lagged behind.

The most well studied family of PRRs in allergic inflammation is the TLR family. Epidemiological studies have consistently reported an inverse correlation between high levels of bacterial products such as LPS in the ambient environment during very early life and the subsequent development of atopy and allergic disease [6-8]. It has been postulated that such exposures drive counter-regulatory immune responses in the developing immune system [9]. On the other hand, controlled human challenge studies have shown that LPS exposure of sensitized individuals can exacerbate existing disease [10]. Although the mechanisms underlying this apparent paradox are not entirely clear, the complexity of the responses to TLR agonists may be due to several factors including the array of TLR receptors activated by complex allergens (TLR9 vs. TLR4), their relative abundance, and the timing of exposure during the life of the individual. For example, TLR9 stimulation clearly prevents and inhibits the development of experimental allergic inflammation at all doses [11, 12], whereas TLR2 and TLR4 pathway stimulation has been shown to both drive [13, 14, 15] and inhibit [16, 17] the development of Th2-mediated allergic inflammation in experimental mouse models. Bottomly and her colleagues [14] have shed some light on this complexity, demonstrating that the impact of TLR4 stimulation on allergic inflammation is highly dependent upon the dose of TLR4 agonist. Specifically they showed that co-exposure to the normally tolerizing antigen (OVA) and high concentrations of LPS (100ug) induced Th1 immune responses (likely a regulatory response), whereas lower concentrations of LPS (100 ng) drove TLR4-dependent, Th2-polarized inflammatory responses. Although these studies provided a plausible explanation for the LPS dose effects observed in epidemiological studies, they did not explain how stimulation through the same receptor could result in two distinct biological outcomes. To address this issue, Tan and colleagues [18] examined allergic responses in a series of bone marrow chimeric mice expressing TLR4

in specific compartments. They show that strong (high dose LPS) TLR4 signaling always results in a Th1 response, despite the fact that high LPS stimulation of mice expressing TLR4 only in the stromal compartment drives Th2 responses, as a result of the dominant influence of the hematopoietic cell compartment under these conditions. Surprisingly, they found that at low LPS levels, mice expressing TLR4 only in the stromal compartment did not mount Th2 or Th1 immune responses. However, when mice that had competent TLR4 signaling in both the stromal and hematopoietic compartments were exposed to low levels of LPS +OVA, they mounted Th2 immune responses suggesting that once a threshold level of TLR4 stimulation is reached in the stromal compartment, Th2 responses ensue. The authors propose that the ability of stromal cells (presumably epithelial cells) to drive Th2 responses is likely through their ability to secrete TSLP and to promote the maturation of Th2-inducing dendritic cells that express the Notch-ligand Jagged-1, but not the Th1-inducing ligand, Delta-4. As other groups have shown that co-exposure of DCs with LPS and helminth antigens is associated with higher expression of Jagged-1 relative to Delta-4 suggests that this may be an important molecular signature of TLR4-mediated Th2 immune responses [19]. In contrast to Tan's findings, another group [15] showed that stromal cell TLR4 signaling was sufficient to drive Th2 immune responses when mice were exposed to dust mite extracts containing low levels of LPS, suggesting that the dust mite extracts might contain endogenous TLR4 agonists which shift the dose response of the stromal compartment to TLR4 stimulation into the Th2-inducing range.

A recent study has provided a compelling mechanism by which endogenous components of dust mites may drive TLR4 signalling. Based on the recent discovery of a structural homology between Der p 2, one of the major house dust mite allergens, and MD-2, a member of the lipid-recognition (ML) domain family of proteins, which is the LPS-binding member of the TLR4 signaling complex [20, 21], Trompette and colleagues [22] asked the question whether Der p 2 and MD-2 exhibited functional homology as well. Indeed, they reported that Der p 2 facilitates TLR4 signaling through direct interactions with the TLR4 complex, reconstituting LPS-driven TLR4 signaling in the absence of MD-2 and facilitating such signaling in the presence of MD-2. Importantly, they showed that the *in vitro* functional and biochemical activity of Der p 2 mirrors its *in vivo* allergenicity—Der p 2 drives experimental allergic asthma in a TLR4-dependent manner, retaining this property in mice with a genetic deletion of MD-2. Although the exact mechanism by which Der p 2 activation leads to Th2 skewing is unknown, it has been shown to induce the production of several mediators important in DC activation in a bronchial epithelial cell line (BEAS2B) including granulocyte-macrophage colony-stimulating factor, IL-6, and IL-8 [23]. Moreover, it can both recruit and activate APCs in the surrounding tissues through its induction of ICAM-1 on airway epithelial cells. Collectively, these studies suggest that exposure to naturally occurring components of complex allergens under low ambient levels of bacterial product exposure such as those associated with increasing rates of aeroallergy in the urban, Westernized world may shift the TLR4-response curve from the tolerizing into the Th2-inducing range through their ability to directly activate the TLR4 signaling complex on stromal cells in the airways (presumably the airway epithelium). This is of particular interest, as human airway epithelial cells are reported to express TLR4, but little to no MD-2, under homeostatic conditions [24].

The fact that the major dust mite allergen, Der p 2 is a molecular mimic of an endogenously-expressed mammalian lipid binding family member has several important implications for our understanding of allergenicity. As numerous other members of the MD-2-like lipid binding family are major allergens [25], the activation of innate immune pathways via lipid binding is likely to be a common feature of allergens. Indeed, the recently solved structures of several allergens including Der p 5 and Der p 7 suggest that they possess the propensity to bind hydrophobic compounds [26, 27]. Of note, Der p 7 has been shown to resemble the

LPS binding protein (LBP), and to bind to the lipopeptide polymyxin B from gram-positive bacteria [28]. More broadly, a wide range of allergens are lipid binding proteins—[i.e. lipid transfer proteins (peach allergen Pru p 3), steroid-like molecules (cat allergen Fel d 1), lipocalins (horse allergen Equ c 1, mouse allergen Mus m 1). Further studies are clearly needed to define the lipids naturally bound by these allergens, the receptors activated by such lipids, and the precise pathways of innate and adaptive immune responses driven by such activation.

The fact that Der p 2 is a target of the mammalian host immune response, taken together with the fact that high titers of anti-Der p 2 IgE mAbs are strongly associated with asthma risk [29], raises the real possibility that the mammalian homolog, MD-2 may also become a target of the host's own immune system. This is potentially a very important concept as many allergens are known to serve evolutionarily conserved biological functions (Der p 1, cysteine protease) and as such they are likely to be structural homologs of numerous mammalian proteins. Whether the human homologs are recognized by antibodies directed against their molecular mimics remains to be determined.

Carbohydrate Structures and Allergic Sensitization

Just as the mammalian immune system has evolved mechanisms to recognize bacterial proteins in association with pathogen-associated molecular patterns (PAMPs) that induce appropriate Th1 responses, recent studies suggest an important role for complex carbohydrates in driving Th2 immune responses to both parasites and allergens. In particular, fucosylated glucans are a diverse class of naturally occurring glucose polymers, which are widely expressed in the cell walls of fungi, helminths, pollens, and certain bacteria, but they are not found in mammalian cells. Evidence is emerging that these carbohydrates drive strong Th2-biased immune responses through their interaction(s) with a large array of C-type lectin receptors (CLRs). Most notably, the *Schistosoma* egg antigen lacto-*N*-fucopentaose III (LNFPIII) has been shown to promote Th2 responses *in vivo* in a fucose-dependent manner [30]. Subsequent studies have shown that LNFPIII conditions iDCs to drive Th2 differentiation via activation of a combination of CLRs, including dendritic cell-specific ICAM3-grabbing non-integrin (DC-SIGN), macrophage galactose-type C-type lectin receptor (MGL), mannose receptor (MR), which synergize with TLR4 pathways to drive Th2 immune responses [31]. In support of the requirement for stimulation through multiple CLR and TLR pathways, a recent study suggests that despite its ability to drive DC activation and Th2 responses *in vitro*, the interaction of parasite antigens with SIGN-R alone is not sufficient to drive immune responses to the parasite *in vivo* [32]. Collectively, these studies suggest that carbohydrate moieties are strong Th2 PAMPs, but that they likely work in tandem with other pattern recognition receptor pathways such as TLR4 to drive Th2 responses to multi-cellular organisms.

Support for a broad role for complex carbohydrates, in particular, β -glucans, in allergen-associated Th2 immune responses is emerging. Most notably, it has been reported that β -glucan structures present in the peanut glycoallergen Ara h 1 have Th2 inducing characteristics [33]. Specifically, native, but not deglycosylated, Ara h 1 was shown to activate human monocyte-derived dendritic cells and induce Th2-cytokine secreting cells. The induction of Th2 cytokines by Ara h 1 was mediated via the C-type lectin receptor, DC-SIGN. Consistent with a role for CLRs in allergen recognition, a variety of allergens including Der p 2, and Bermuda grass pollen (Cyn-dBG-60) are known to bind to and signal through the specific CLRs, DC-SIGN and L-SIGN [34]. Similarly, house dust mite extracts are known to drive epithelial chemokine production [35] and DC leukotriene production [36] through β -glucan and dectin-2 receptor-mediated pathways, respectively. *In vivo*, exposure to β -glucans drives the recruitment of eosinophils and lymphocytes into the mouse

airway [36] and enhances responses to co-delivered antigens (OVA), concomitant with enhanced lung expression of Th2 cytokines [37]. Another CLR, the MR has been shown to mediate the internalization of a diverse range of allergens (Der p 1, Der p 2, dog-Can f 1, cockroach-Bla g 2, peanut-Ara h 1) into monocyte-derived DCs through their carbohydrate moieties [38]. Moreover, silencing of MR expression on monocyte-derived DCs (MO-DC) reversed Der p 1-induced Th2 cell polarization. These findings taken together with previous studies showing that MR expression was higher in MO-DCs from allergic patients and that they took up Der p 1 more efficiently than did MO-DCs from healthy individuals suggests that alterations in glycoallergen recognition and DC activation may contribute to susceptibility to allergic diseases [39]. Along these lines, genetic variants in the mannose receptor gene (MRC1) have been shown to be associated with asthma in two independent and ethnically diverse populations (Japanese, African American) [40]. Although the study of the role of carbohydrates as Th2-inducing PAMPs is only in its infancy, collectively the data suggests that carbohydrate moieties contained in common allergens act as strong Th2 inducers via regulation of DC function through the integration of signals derived from engaging a variety of C-type lectin receptors and other PRRs such as TLR4. Identification of the exact carbohydrate moieties contained in common allergens, the CLR-signaling pathways they activate, and the pathways by which they drive aberrant Th2 immune responses is eagerly awaited.

Conclusions

Although allergens are a diverse group of molecules, it is becoming increasingly clear that their allergenicity likely resides in their ability to activate various innate immune pathways at mucosal surfaces. It is clear that we have only begun to scratch the surface of defining the universe of allergen associated patterns recognized by the mammalian immune system, and further studies are clearly needed to define the specific receptors or combination of receptors involved in their recognition, and the pathways by which they drive Th2-skewed immune responses (See specific issues that need to be addressed, Box 1). Furthermore, as healthy individuals do not mount Th2-immune responses to environmental allergens, despite similar exposures, there are likely functional variants in these receptors and/or their downstream signalling pathways that enhance the risk of developing allergic diseases. A better understanding of the molecular and cellular substrates of allergenicity holds tremendous promise for the development of preventive and therapeutic strategies to effectively block allergen recognition and the ensuing inflammatory cascade.

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Box 1**Insights into the role of allergen-activated pattern recognition receptor pathways in the pathogenesis of allergic diseases****What we know:**

1. Recent advances in our knowledge of the critical role of pattern recognition receptors in shaping adaptive immune responses has lead to the recognition that allergens contain specific lipid and carbohydrate ligands that directly engage and activate a variety of pattern recognition receptor pathways on dendritic cells and stromal cells which drive Th2-mediated immune responses.
2. There is a consensus that TLR4 pathways are necessary and sufficient for the development of allergen-driven Th2 immune responses depending on the strength of stimulus at the receptor, the timing of exposure relative to initial sensitization, and the cell types upon which the TLR4 is engaged.
3. The major dust mite allergen, Der p 2, drives Th2 immune responses through its ability to facilitate TLR4 signaling through direct interactions with the TLR4 complex, through its structural similarity to the mammalian lipid binding protein, MD-2, which is the LPS-binding member of the TLR4 signaling complex.
4. Carbohydrate moieties contained in common allergens (Ara h 1, Der p 2, Der p 2, Bla g 2, Can f 1) drive strong Th2 immune responses through engagement of a variety of C-type lectin receptors (MR, DC-SIGN, MR, dectin-2) on dendritic cells.
5. As complex allergens contain multiple biologically active components (i.e. house dust mite; Der p 1-Der p 14), the type of immune response that ensues is likely determined through the integration of downstream signals initiated by PRR ligation.

What we still need to know:

1. Studies are needed to define the pattern recognition receptor pathways (TLRs, CLRs, NLRs, RLRs) or combinations of receptor pathways mediating Th2-mediated immune responses to a broad range of allergens.
2. As many allergens are lipid-binding proteins, the lipids associated with lipid-binding allergens and the receptors and signaling pathways they engage need to be determined.
3. As carbohydrate ligands are strong Th2 stimulators, the precise carbohydrate moieties associated with allergens and the array of pattern recognition receptors and signaling pathways they engage need to be investigated.
4. Studies are needed to further determine the molecular and cellular mechanisms by which allergen engagement of PRRs such as TLR4, drive Th2 immune responses, instead of Th1 or Th17 responses.
5. It appears that allergens may be structural homologs of mammalian lipoproteins, which raises the question whether the immune responses directed against the exogenous proteins result in cross-reactivity with endogenous homologs?
6. Are allergic diseases associated with functional variants in conserved allergen-activated pattern recognition receptors or signaling pathways?

7. Which of these conserved pattern recognition receptor pathways will be the most tractable targets to prevent or treat allergic diseases.