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REVIEW

Allergen-Associated Immunomodulators: Modifying Allergy Outcome

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Abstract The prevalence of allergies is increasing since mid twentieth century; however the underlying causes of this increase are not fully clear. Understanding the mechanism by which a harmless protein becomes an allergen provides us with the basis to prevent and treat these diseases. Although most studies on allergen immunogenicity have traditionally focused on structural properties of the proteins, it is increasingly clear that allergenicity cannot be determined only based on structural features of the allergenic proteins. In fact, allergens do not encounter human facings as isolated molecules but contained in complex mixtures of proteins, carbohydrates and lipids, such as pollen grains or foods. As a result, attention has lately been directed to examine whether allergen-associated molecules exhibit immune-regulatory properties. The present review aims to illustrate some examples of how non-protein molecules accompanying the allergen can modulate allergic responses.

Keywords Immunomodulator · Allergen · LPS · Particles · Carbohydrates · Lipids

Abbreviations

AHR	Airway hyper-responsiveness
APC	Antigen-presenting cell
BMDCs	Bone marrow-derived dendritic cells
CE	Combinatorial extension
CD	Cluster of differentiation
DC	Dendritic cell
FATCAT	Flexible structure alignment by chaining aligned fragment pairs
GlcNAc	*N*-Acetylglucosamine
Ig	Immunoglobulin
IL	Interleukin
IMP	Immunomodulatory protein
LPS	Lipopolysaccharide
MR	Mannose receptor
nsLTP	Non-specific lipid transfer protein
ODN	Oligodeoxynucleotide
OVA	Ovalbumin
PALMs	Pollen-associated lipid mediators
PAMPs	Pathogen-associated molecular patterns
PR	Pathogenesis-related
Th	T helper type
TLR	Toll-like receptor
TM	Template modeling

Introduction

Allergies are type I immune-mediated hypersensitivity reactions that most commonly affect skin, airway and gut mucosa (e.g., the interface between organism and environment), when antigens able to induce immunoglobulin (Ig)E synthesis come into contact with the human facing (Traidl-Hoffmann et al. 2009). Two phases are distinguished in the development of allergies: sensitization and effector phase. During the past decades, myriads of information regarding the effector phase have been produced, whereas less is known about the sensitization phase. In this phase, antigen-presenting cells (APCs) take up and process the antigen producing peptides that are transported to the plasma membrane associated with the major histocompatibility complex II. The complexes on APCs are recognized

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by T cells, which differentiate into a T helper type 2 (Th2) subset. The specific recognition of the allergen on APCs and an appropriate cytokine environment (i.e. interleukin (IL)-4, IL-5, IL-13) are essential for Th2 responses.

The prevalence of allergic diseases has increased in the last decades, and they currently affect around 30 % of the Western population, but the causes of this increase still remain to be determined (Platts-Mills and Woodfolk 1997). The hygiene hypothesis proposes that the rise in allergic diseases is due to excessive cleanliness during early stages of life, although other factors such as air pollution, exposure to irritant chemicals, decreased frequency of breast feeding, and changes in dietary habits may also account for this increase. The immune system at birth is immature and skewed towards Th2-like cytokine production. Certain stimuli, such as infections, can help immunological development towards a healthy balance of Th1 and Th2 responses. In the absence of these stimuli, i.e., children living in relatively "sterile" urban environments, the immature Th2-like pattern of cytokine production persists, leading to an increased risk of asthma and other atopic diseases (Frei et al. 2012; Gern and Busse 2002).

Yet this hypothesis does not explain at the molecular level why some proteins are more allergenic than others (Frei et al. 2012; Lack 2012). Although the characterization of relevant allergens has led to improved clinical management of allergies, the knowledge of the mechanisms of sensitization and reaction to different allergenic sources is generally inadequate and incomplete.

While most studies have traditionally focused on defining structural properties of the proteins contributing to the activation of immune cells, and many efforts have been taken to identify aminoacid sequences that characterize an allergen, there is growing evidence that allergic sensitization cannot only be explained at the protein level. Therefore, attention has lately been directed towards examining whether associated molecules exhibit immune-modulatory properties. These molecules are in contact with the allergen or co-liberated from the allergen carrier and may influence the host response to the allergenic protein (Akira et al. 2006). They are not recognized as allergens but can act as potent inducers of IL-4-producing cells, which might then facilitate the development of an IgE-dominated immune response or, on the contrary, exert protective function from allergy development. In fact, some of the most prevalent allergens including Bet v 1 from birch pollen, and the lipocalin family can bind hydrophobic molecules that may exert immune-regulatory activities (Mattila and Renkonen 2009; Pacios et al. 2012).

The most important sources of allergens are wind-dispersed pollen grains from trees, grasses, and weeds, followed by excretions of house dust mites and cockroaches, fungal spores, animal dander and insect venoms. It is known that only a few protein families harbor the capacity to cause allergy (Hoffmann-Sommergruber and Mills 2009). A great number of allergens have intrinsic biological functions (proteases, trypsin inhibitors, calcium-binding proteins, lipid transfer proteins, etc.), which can contribute to allergenicity (Akdis 2006; Chapman et al. 2007b; Cortes et al. 2006; Tai et al. 2006); others such as Bet v 1, act as membrane-binding proteins, which might help to cross the mucosal barrier and facilitate access to APCs (Mogensen et al. 2007). A protein is characterized as an allergen when at least 5 % of the tested sera from allergic individuals produce specific IgE towards the allergenic source (Traidl-Hoffmann et al. 2009). However, no biochemical characteristics have been found defining a protein to be an allergen (Bredehorst and David 2001; Chapman et al. 2007a; Radauer et al. 2008). Roth-Walter et al. (2014a) hypothesized that allergens are proteins that share similar characteristics to human self proteins and, through still unknown mechanisms, these similarities make them capable of mounting Th2 responses.

Allergen-Associated Immunomodulators

Molecules co-released with allergens have been described to be able to modulate allergic responses in a number of studies. There are many examples of such immune-regulators contributing to the enhancement of allergic responses by inducing Th2 polarization, or exerting a preventative role, thus dampening allergic reactions. Allergen-associated molecules able to either promote or prevent allergic responses are the subject of this review. The characteristics and interaction with allergens of the most studied allergen immunomodulators are discussed below.

Intrinsic Allergen-Associated Immunomodulators

It is currently accepted that lipid binding is a common characteristic observed for several protein families that include allergens, such as Bet v 1-like proteins, non-specific lipid transfer proteins (nsLTPs), 2S albumins, secretoglobins, lipocalins, oleosins, and mite group 2, 5, and 7 proteins (Bublin et al. 2014). Additionally, some allergens are glycosilated proteins. The glycan fraction of these allergens may also contribute to their allergenicity. In this section, several examples of these intrinsic allergen-associated immunomodulators, and their impact on allergenicity are reviewed.

Lipocalins, Major Animal Allergens

Most animal-derived allergens belong to the lipocalin protein family (Virtanen 2001). Lipocalin allergens are

found in dander, saliva and urine, they disperse effectively and are widely present in indoor environments. Initially, lipocalins were characterized as transport proteins for hydrophobic molecules such as retinol, steroids, and pheromones, although they are currently known to be involved in many other biological functions, such as enzyme activity (Hilger et al. 2012).

Lipocalin allergens do not present any known physicochemical, functional or structural properties that would account for their allergenicity; thus, they cannot be distinguished from other lipocalin proteins based on structural properties (Virtanen and Kinnunen 2008). As lipocalins are known to carry small hydrophobic ligands in their internal ligand-binding site, it has been suggested that lipid binding may be a key characteristic for many allergens because lipids can directly activate innate immunity (Thomas et al. 2005). Although there is little data supporting the idea that lipocalin allergens would carry immunomodulatory substances favoring allergy, the hypothesis is no doubt worth further examination (Roth-Walter et al. 2014b).

The Interesting Case of Bet v 1

Bet v 1 from the pathogenesis-related (PR)-10 family is the major allergen of birch pollen. The PR-10 protein fold creates a large hydrophobic pocket that could carry many ligands including flavonoids, cytokinins and fatty acids. There are several isoforms of Bet v 1 displaying 95 % aminoacid sequence identity and almost identical tertiary structures; however, one difference is that they have different binding profiles (Kofler et al. 2012; Smole et al. 2010). Bet v 1 is able to bind and associate with lipid membranes (Mogensen et al. 2002). It undergoes structural rearrangements when binding to phospholipid vesicles (Mogensen et al. 2007) thus very likely releasing any bound natural ligand (Bublin et al. 2014). Recently, the natural ligand of the main isoform of Bet v 1.0101 has been described to be the flavonoid glycoside quercetin-3-*O*-sophoroside (Seutter von Loetzen et al. 2014), which requires both the glycan and the lipid for binding. This ligand might affect the allergic sensitization process when released after contact with lipid membranes to perform its possible role in signal transduction (Agati et al. 2013).

Quercetin is a flavonoid that can bind iron molecules and act as an iron chelator. In relation to this, one recent report has suggested that Bet v 1 may behave as a lipocalin-like protein (Roth-Walter et al. 2014a). In this work, Bet v 1 was able to skew the immune system depending on its iron-loaded state, as it has been described for lipocalin proteins. Bet v 1 mounted a Th2 response when presented uncomplexed to the immune cells. However, when applied in a complex with iron-siderophore, Bet v 1 Th2-skewing potential was inhibited.

This publication has been the matter of intense debate within the scientific community. In the work by Roth-Walter et al. (2014a), the structural relation between Bet v 1 and lipocalin 2 was analyzed by three different methods (FATCAT, CE and TM-Align), one of which allows the introduction of a limited number of twists in the protein structure (FATCAT). Both structures were, although weakly, significantly related by the three methods used. However, neither the topology nor the sequence of the compared proteins were analyzed raising the possibility that although these proteins share significantly related structures, they may not belong to the same protein family.

Plant Lipid Transfer Proteins

Non-specific lipid transfer proteins (nsLTPs) have been identified as allergens in a wide range of plant foods, including fruit, vegetables, nuts, and cereals. There are several important food allergens included in this protein family such as those from peach (Pru p 3), and chestnut (Cas s 8); aeroallergens, such as Par j 8 from *Parietaria judaica* pollen, and olive Ole e 7, and the skin sensitizer Hev b 12 from latex (Egger et al. 2010).

The name of these proteins arises from their ability to bind different types of lipid molecules and enhance their transfer between membranes (Salcedo et al. 2007). The inner cavity contained in the nsLTP fold can accommodate a broad range of lipids including fatty acids, fatty acyl-CoA, phospholipids, glycolipids, hydroxylated fatty acids, and prostaglandin B2 due to its high plasticity (Douliez et al. 2000; Pacios et al. 2012; Sy et al. 2003). Li et al. (2013) described that medium-chain but not long chain triglycerides could promote allergic sensitization and anaphylaxis to co-administered peanut proteins in mice by affecting absorption and stimulating a Th2 response. Thus, molecules carried by these allergens may play a role in the induction of allergic sensitization.

Ligands transported by allergenic LTPs can contribute to the activation of innate immune cells, although there is little experimental evidence of this (Yeats and Rose 2008). Tordesillas et al. (2013) showed that the peach nsLTP Pru p 3 could cross the monolayer formed by Caco-2 epithelial cells through the endocytic pathway by means of lipid rafts and caveolar endocytosis. The authors also reported that the lower transport rate of a hypoallergenic peach nsLTP was associated with significantly lower expression of Th2-related cytokines compared with Pru p 3 (Tordesillas et al. 2013). Although it was not addressed in this work, the molecule transported by Pru p 3 may account for its allergenicity and may help the allergen to get into contact with immune cells underlying the epithelial cell layer. There is no doubt that the transport and interaction of this allergen with the gut-associated immune system deserves further study.

Glycoproteins and N-Linked Glycans

N-Linked mannose glycans, which are common in plant but not in mammalian glycoproteins, have been described as non-protein Th2 inducers (Ilchmann et al. 2010; Royer et al. 2010; Shreffler et al. 2006). N-Glycans are able to bind IgE and can induce maturation of activated APCs, with the production of pro-inflammatory cytokines, such as IL-6, IL-8 and IL-10 (Altmann 2007). In previous studies by our group, Act d 2, the thaumatin-like protein and one of the major allergens of kiwi, was reported to contain a N-glycan fraction (Garrido-Arandia et al. 2014). The N-glycan fraction of Act d 2 was shown to induce maturation of APCs and triggered the production of IL-6 and IL-10 cytokines by these cells, but could not activate peripheral blood mononuclear cell proliferation (Garrido-Arandia et al. 2014). The mechanism by which the N-glycan fraction is recognized by dendritic cells (DCs) is well understood. Many of the C type lectin-like receptors that are found on DCs function as antigen uptake receptors, including mannose receptor (MR; CD206), DCSIGN (CD209), and DEC-205 (CD205) (Altmann 2007).

Royer et al. (2010) showed that the MR, a C type lectin expressed by DCs, recognizes various glycoallergens from diverse sources and is involved in promoting allergic responses to a major house dust mite allergen in vitro. They later investigated the potential role of MR in allergic responses to Fel d 1, a secretoglobin and major cat allergen (Emara et al. 2011). In this study they discovered that, unlike other glycoallergens, recognition of Fel d 1 by MR is mediated by the cysteine-rich domain, which correlates with the presence of sulphated carbohydrates in natural Fel d 1. To study the role of MR in allergic sensitization to Fel d 1 in vivo, they used MR-deficient mice sensitized with cat dander extract and observed that Fel d 1 produced significantly lower levels of total IgE, Fel d 1-specific IgE and IgG1, compared with wild-type mice. They concluded that MR might play a pivotal role in allergic sensitization to airborne allergens in vivo.

Concluding Remarks

Intrinsic allergen-associated molecules such as glycans, hydrophobic ligands, lipids or iron-chelators are able to modulate allergic responses, either by promoting (as in the case of Fel d 1 or Pru p 3) or by preventing them (as demonstrated for Bet v 1). Undoubtedly more research is needed to characterize the implication of these non-proteinaceous allergen-associated molecules in allergic reactions.

Extrinsic Allergen-Associated Immunomodulators

In addition to the discussed intrinsic allergen-associated immunomodulators, there exist allergen-extrinsic factors that can also influence the outcome of allergic responses. These molecules are pathogen-associated molecular patterns (PAMPs) able to trigger specific receptors expressed on the membrane of immune cells. These molecules may exert both immunosuppressive and immunostimulatory activities.

Toll-Like Receptors Ligands

Toll-like receptors (TLRs) are receptors for conserved microbial structures that play a critical role in the initiation and skewing of adaptive immune responses by APCs (Iwasaki and Medzhitov 2004). In humans, up to eleven members of TLRs have been identified (Zhang et al. 2004). Trompette et al. (2009) stated: "Exogenous antigen presentation by APCs in the absence of direct TLR stimulation generally leads to tolerance". On the contrary, upon stimulation of TLRs, inflammatory cytokines are produced to directly activate the adaptive immune system. The effects of natural TLR ligands were detected in the farming environment in support of the hygiene hypothesis. Children exposed to animal sheds, and thus to higher endotoxin concentrations and unprocessed milk consumption, were protected from the development of atopic disorders such as asthma (von Mutius 2010). Even, the susceptibility of children to developing allergies was significantly reduced when the mother had contact with a farming environment during pregnancy (Diesner et al. 2012; von Mutius 2010).

CpG-Oligodeoxynucleotides (CpG-ODNs) are ligands for the TLR9 that may play a role in the suppression of Th2 cytokine responses. In a mouse model of ragweed-induced allergic airway inflammation, the protective effects of CpG-ODNs were mediated by increasing levels of interferon (IFN)-γ (Th1 cytokine) (Sur et al. 1999). CpG-ODNs triggered IFN-γ by up-regulating the transcription factor T-bet and suppressing IL-5 in a dose-dependent manner. The higher expression of T-bet was associated with elevated allergen-specific IgG2a levels and a suppression of IgG1 and IgE titters (Kitagaki et al. 2002). The efficacy of CpG-ODNs has been mostly investigated in asthma. A combined treatment of CpG-ODNs with ragweed immunotherapy revealed an increase in IFN-γ/IL-4 mRNA ratio that was further followed by ameliorated clinical symptoms (Tulic et al. 2004). Interestingly a protective role for TLR9 in acute allergic airway diseases has been attributed since CpG administration inhibits allergic Th2 cytokine production (Vissers et al. 2004).

Ligands for TLR7 have been also investigated for therapeutic use for allergy. In a mouse asthma model, TLR7 ligand therapy ameliorated airway hyper-responsiveness (AHR) upon allergen challenge, inhibited both Th2 (IL-4, IL-5, IL-6 and IL-13) and Th1 (IL-12 and IFN-γ) cytokines and was associated with a reduction in IgE levels and an increase in IgG2a (Moisan et al. 2006). In the study by Quarcoo et al. (2004), a single application of resiquimod, a TLR7 ligand from the imidazoquinolamine family, significantly reduced lung infiltration of inflammatory cells, decreased AHR and Th2 cytokines, whereas the Th1 cytokines IL-12 and IFN-γ were increased.

Some examples of TLR ligands have been presented. Yet, the most studied TLR ligand is lipopolysaccharide (LPS) and it deserves its own paragraph.

LPS Lipopolysaccharides are large molecules found in the membrane of Gram-negative bacteria. They consist of a lipid A, also known as endotoxin, and a polysaccharide that contains an O-antigen able to induce immune responses. LPS has been described as the most potent stimulator of DCs, which may be necessary for the postnatal maturation of these APCs (Martinez 1999). The interaction of LPS and DCs is mainly mediated via the signaling pathway composed by the trimolecular complex CD14, MD-2 and TLR4 (Simpson and Martinez 2010; Ulevitch and Tobias 1995). The potential of LPS to stimulate APC maturation and influence the development of allergy is determined by timing, dose, and site of stimulation. In the context of the hygiene hypothesis, high levels of exposure to bacterial products such as LPS in early life are inversely correlated with the development of atopy and allergic disease (Braun-Fahrlander et al. 2002; Gehring et al. 2002; Riedler et al. 2001). High doses of LPS have been shown to protect against allergy induction by promoting Th1 responses while low doses favor a Th2 environment (Kim et al. 2007).

Notably, Trompette et al. (2009) described that the major house dust mite allergen, Der p 2, has structural homology with MD-2, the LPS-binding co-receptor interacting with TLR4. They showed that Der p 2 works as a functional homologue of MD-2 facilitating LPS-driven signaling through direct interactions with the TLR4 complex in the absence of MD-2. Accordingly, airway sensitization and challenge with Der p 2 led to experimental allergic asthma in wild-type and MD-2-deficient, but not in TLR4-deficient mice. These results suggest that Der p 2 promotes TLR4 signaling and, hence, presents intrinsic adjuvant activity (Trompette et al. 2009). This mechanism may underlie the phenomenon of allergenicity, i.e., intrinsic adjuvant activity provided by allergen-associated lipids may sustain the allergenicity of such proteins.

Similar to Der p 2, the cat secretoglobin Fel d 1 was demonstrated by Herre et al. (2013) to enhance signaling through TLR4 and TLR2. In contrast to Der p 2, Fel d 1 does not act by mimicking MD-2, but it does bind to LPS. They also show that the dog lipocalin allergen Can f 6 has similar properties to Fel d 1, despite being from different protein families. Both Fel d 1 and Can f 6 substantially amplified LPS/TLR signaling in macrophage-like cells. These proteins are proposed to belong to a group of allergen immunomodulatory proteins (IMPs) able to enhance innate immune signaling and promote airway hypersensitivity in asthma. They act by directly binding LPS or other PAMPs and transferring them to TLRs in a mechanism that is CD14-dependent. Therefore, Herre et al. (2013) conclude that lipid binding is a common property of allergen IMPs.

These two studies (Herre et al. 2013; Trompette et al. 2009) exemplify how the interaction of allergens and LPS influence the outcome of the allergic response by mutual immune-modulation.

Beta Glucan and Chitin

Beta-(1,3)-D-glucan (β-glucan) is a glucose polymer present in fungal cell walls, which, due to its proposed immunomodulatory effects, is regarded as a biological response modulator (Novak and Vetvicka 2008). β-Glucan in house dust has been associated with reduced wheeze in infants and young children in some populations (Iossifova et al. 2007). However, Maheswaran et al. (2014) found that home β-glucan exposure at school age is a risk factor for atopic asthma, and that the higher prevalence of AHR in urban adolescents may be a consequence of this home exposure during childhood. The exposure to β-glucan, a ligand for the C type lectin receptor Dectin-1, induces DCs to prime Th17 cells. Th17 cells are essential against pathogenic fungi, and as a consequence of their activation the induction of allergy is reduced. However, activation of Th17 cells may trigger inflammatory responses (Mintz-Cole et al. 2013). Cardone et al. (2014) demonstrated that β-glucan activates the transcription of genes bridging innate and adaptive immunity in human DCs via IL-1 and inflammasome-mediated mechanisms. Yet, IFN-γ interferes with this pathway of β-glucan-activated DCs and promotes Th1 responses with increased release of IFN-γ and IL-22. The characterization of these molecular networks provides new targets for the modulation of immune responses to β-glucan (Cardone et al. 2014).

Chitin is a β-1,4-linked homopolymer of *N*-acetylglucosamine (GlcNAc), and an essential polysaccharide of the cell wall of all fungi. It is also found in the skeleton of insects, crustaceans and nematodes. It is thus a potential component of human diets containing insects, nematodes or crustaceans. This polymer has been described to modulate immune responses depending on several factors such

as particle size, route of administration and dose, that led to some controversies in the literature (Alvarez 2014; Bueter et al. 2013; Muzzarelli 2010). A recent study by Wagener et al. (2014) reported that fungal chitin acts concentration dependently as a pro- and anti-inflammatory stimulus both in vitro and in vivo. Small-sized particles of chitin (<40 μm), which are the most commonly found in the host natural environment, mainly stimulated IL-10 secretion at low doses, while induced tumor necrosis factor (TNF) secretion at higher concentrations, according to previous observations (Muzzarelli 2010). However, chitin was also able to promote Th2-associated inflammation, which is central to the pathogenesis of allergy and asthma (Reese et al. 2007; Van Dyken et al. 2011). Da Silva et al. (2009) reported that medium-sized (40–70 μm) particles promote TNF and IL-17 production in a TLR2- and dectin-1-dependent manner, whereas small-sized particles stimulate TNF and IL-10 production via TLR2, dectin-1 and the MR signaling. Although TLRs, the MR and dectin-1 modulate chitin-mediated responses, there is not a clear demonstration of direct binding (Lee et al. 2011).

Chitin can be phagocytised by myeloid derived cells. Several receptors binding chitin or chitin-oligosaccharides have been identified including FIBCD1, expressed by lung and gut epithelial cells (Schlosser et al. 2009; Thomsen et al. 2011); ReGIII, a soluble C type lectin (Cash et al. 2006); NKR-P1, an activating receptor on rat NK cells (Semenuk et al. 2001), and galactin-3 (Seetharaman et al. 1998). In addition, some human chitinases are constitutively expressed by macrophages and epithelial cells lining the lung and the gut. Deregulation in the expression of these proteins has been linked to inflammatory and allergic diseases (Vega and Kalkum 2012).

The effect of chitin as an adjuvant has been analyzed intranasally, orally and intraperitoneally. When given orally or intranasally in mice, chitin can ameliorate Th2-induced allergic response to *Dermatophagoides pteronyssinus* and ragweed (Shibata et al. 2000), an effect that may be partially explained by chitin-mediated inhibition of T cell proliferation. Dubey et al. (2015) recently found that chitin used as a peritoneal adjuvant in a mouse model of *Aspergillus fumigatus* sensitization was able to increase the total IgE, specific IgE and IgG1 levels in serum. Yet the Th2 cytokines IL-4 and IL-13 in the lungs were significantly lower in this setting. However, another study showed that in a model of ovalbumin (OVA) sensitization the levels of the Th2 cytokines IL-4, IL-5 and IL-13 in bronchoalveolar lavage were enhanced when chitin was used as an adjuvant (Da Silva et al. 2010). The main difference between the two models (*A. fumigatus* and OVA) is that the fungal extract is a mixture of several proteins and enzymes that possess, on their own, the ability to activate the immune system.

Pollen-Associated Lipid Mediators

In respiratory allergic diseases, it is known that pollen grains release bioactive, pollen-associated lipid mediators (PALMs), which have pro-inflammatory and immune-modulatory effects on the immune cells.

Pro-inflammatory PALMs (e.g., oxylipins) attract and activate eosinophils and neutrophils, independently of the sensitization status of the donor. They act as adjuvants enhancing the inflammatory process (Behrendt et al. 2001; Eisenbarth et al. 2002; Plotz et al. 2004; Traidl-Hoffmann et al. 2002).

Another example of Th2 inducer PALMS are E1 phytoprostanes, which are autoxidation products of α-linolenate present in all plant tissues. E1 phytoprostanes represent the most prominent group in aqueous pollen extracts within the group of phytoprostanes, and seem to be involved in plant host defense (Karg et al. 2007). These compounds can inhibit DC production of IL-12 and Th1-type chemokines (Radcliffe et al. 2006) and increase the capacity of DCs to induce Th2 cell differentiation and recruitment (Gutermuth et al. 2007; Mariani et al. 2007). One mechanism that may account for this outcome is the suppression of LPS effect that results in the enhancement of the sensitization process. Kamijo et al. (2009) compared the effect of pollens from different plant species on murine bone marrow-derived dendritic cell (BMDC) responses. For that, BMDCs were stimulated with pollen extracts in the presence or absence of LPS. They observed a marked reduction of LPS-induced IL-12 and TNF-α production by murine BMDCs stimulated with birch and grass pollen extracts. A moderate reduction of LPS-induced cytokine production was observed for the other pollen extracts tested (Kamijo et al. 2009). This study is an example of allergen-associated immunomodulators interfering on one another immune stimulation.

Concluding Remarks

Pathogen-associated molecules such as LPS or chitin, and pollen mediators are allergen-extrinsic factors that released with the allergen carrier modulate immune responses that may result in the promotion or inhibition of allergic reactions. Not only are these molecules capable of interacting with the allergen, but to mutually interfering with one anothers immune-modulation by triggering TLRs and/or C type lectin receptors.

Conclusions

The molecules associated with allergens that exhibit immune-modulatory properties have attracted the attention of researchers and more and more information is currently

available on how immune-modulators influence the allergy outcome. TLR agonists, carbohydrates, lipids, and other compounds in contact with the allergen might influence the host response acting as Th2 inducers of allergic responses or, on the contrary, promoting Th1 pro-inflammatory responses and consequently dampening Th2 outcomes. These immunomodulators can alter the immune response at different levels by interacting with APCs, T cells or other immune cells, skewing both cellular and humoral responses. In this review, some of the most studied immunomodulators such as LPS, lipid ligands or glycans have been discussed. However, allergy is a complex process involving many players being the outcome of allergic responses largely influenced by determined environmental circumstances.

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