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The Immunology of Food Allergy[1]

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Abstract

Food allergies represent an increasingly prevalent human health problem and therapeutic options remain limited, with avoidance being mainstay despite its adverse effects on quality of life. A better understanding of the key immunological mechanisms involved in such responses will likely be vital for development of new therapies.

This review outlines the current understanding of how the immune system is thought to contribute to prevention or development of food allergies. Drawing from animal studies as well as clinical data when available, the importance of oral tolerance in sustaining immunological non-responsiveness to food antigens, our current understanding of why oral tolerance may fail and sensitization may occur, as well as the knowledge of pathways that may lead to anaphylaxis and food allergy–associated responses are addressed.

Introduction

Within the clinical realm of allergy, food allergy is receiving an increasing amount of attention, mirroring its increasing prevalence both nationally and internationally. Current estimates put food allergy as affecting up to 15 million people within the United States (1). Therapeutically, these patients are dependent on a difficult avoidance approach with injectable epinephrine as a life-saving option in case of accidental exposure. This has been shown to significantly affect quality of life (2), and recent advances in understanding the mechanisms behind food allergy have been fueled by the desire to develop improved therapies.

In considering such mechanisms, we propose to focus on three processes that may be important: oral tolerance, sensitization to food allergens, and anaphylactic reactivity to these food allergens. Finally, an emerging concept of “non-responsive tolerance”, where anaphylactic reactivity does not occur or is lost despite evidence for IgE-associated sensitization will be highlighted.

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1. Oral Tolerance

Oral tolerance to egg proteins was first described over 100 years ago (3). This natural phenomenon, where ingested food proteins do not elicit a specific immune response, is also observed in humans (4), but the necessary mechanisms still remain unclear. Despite gastrointestinal enzymes degrading food and the physical barrier of the intestinal mucosa, immune surveillance of food antigens and establishment of tolerance mechanisms are clearly occurring. Several reviews have addressed possible routes of antigen sampling and presentation (5-7), including sampling by dendritic cells (DCs) across the epithelial layer; presentation by M cells or goblet cells to DCs; or soluble antigen directly traversing the epithelium through paracellular or transcellular routes.

Key cells seem important for oral tolerance and the maintenance of regulatory ($FoxP3^+$) T cell (Treg) populations. $CD11c^-CD11b^+F4/80^+$ macrophages exhibit an anti-inflammatory gene signature and produce IL-10 (8). Additionally, two distinct subsets of tolerance-associated $CD11c^+$ cells reside in the intestinal lamina propria, expressing either CX_3CR1 or CD103 (9). CX_3CR1 KO mice show diminished IL-10 production and Treg populations as well as a lack of oral tolerance in a food allergy model (10). In contrast, $CX_3CR1^+CD103^-$ cells have been implicated in intestinal inflammation (11).

Most evidence supports the role of $CX_3CR1^-CD103^+$ DCs in tolerance. These cells exhibit lymph-node homing where they activate naïve T cells (9, 12) and promote a $FoxP3^+$ Treg phenotype, a process requiring both transforming growth factor-beta (TGF-β) and retinoic acid (13-15). Retinoic acid imprints the gut-homing receptors CCR9 and $\alpha_4\beta_7$ onto both Tregs (16) and IgA-secreting B cells (17), an event that also seems to contribute to oral tolerance (16). $CD103^+$ DCs also utilize indoleamine 2,3-dioxygenase (IDO) for tolerance, and loss of IDO function drives T cells towards a Th1 or Th17 phenotype, limiting Tregs and oral tolerance (18). Recent findings also show that MUC2, a mucin secreted by intestinal goblet cells, supports the anti-inflammatory potential of these $CD103^+$ DC cells (19).

IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked) patients with mutations in the FoxP3 locus (20) develop severe food allergy as well as a plethora of other disorders, including autoimmunity, enteropathy, and atopic dermatitis (21), indicating the importance of Tregs in tolerance. FoxP3-mutant mice (scurfy) and DEREG mice, in which Tregs can be deleted upon diphtheria toxin treatment, have also been used to demonstrate the importance of Tregs in allergic responses (22, 23). Expression of CCR9 and $\alpha_4\beta_7$ on Tregs are necessary for tolerance, since these molecules support gut homing (10, 16). While previous reviews have summarized the effects of antigen concentration in oral tolerance (5, 6) (i.e., low doses drive Tregs, while high doses yield anergy and deletion of T cells (24)), most evidence points towards Treg-associated low-dose tolerance as being critical in food allergy. We previously showed that loss of oral tolerance to peanut was associated with diminished Treg responses but also that high-dose antigen feeding could overcome allergic responses (25).

2. Sensitization

In food allergy, the immune response is clearly biased towards a Type 2 cytokine–associated phenotype. Why specific food antigens trigger this response remains unclear, although some food antigens possess the potential to stimulate innate immune responses. For example, the peanut allergen Ara h1 binds to CD209 on DCs (26), while milk sphingomyelin activates Type 2 cytokine responses from iNKT cells (27).

Changes in microbial flora have been associated with allergic sensitization, with several lines of evidence supporting protection by specific bacteria and their products, likely through sustaining intestinal Treg populations (Reviewed by Berin and Sampson (28)). Mice with decreased commensal bacteria colonies, which includes either germ-free or antibiotic-treated mice, exhibit increased food-allergen sensitivity (29), high serum IgE, and increased circulating basophils (30). Interestingly, mice with enhanced signaling through IL-4Rα who display profound allergic sensitization and anaphylaxis to food antigens (31) also exhibit an altered microbiota that can be normalized by Treg transfer (32). Consequently, the interaction of host immunity and commensal microbiota seems bidirectional, with host immune responses not just responding to bacterial presence but also shaping the bacterial flora towards that associated with pathology.

The critical mechanisms responsible for allergic sensitization are beginning to be elucidated. Generally in allergy, epithelial production of TSLP, IL-25, and IL-33 has become a key area of interest (33). However, a recent study of these cytokines using a cholera-toxin–driven oral peanut model showed that only IL-33 was required for sensitization (34). IL-33 can increase mucosal permeability (35) and promote Th2 skewing by DCs (36). Interestingly, while constitutive IL-33 expression occurs in epithelial cells, increasing evidence supports the potential for inducible expression by several immune cells, including DCs, that is sufficient for subsequent Th2 immunity, as has been shown in helminth infection and for IgG immune complexes (37, 38). However, the key producer of IL-33 in food allergy remains to be determined.

At the level of antigen presentation, several mechanisms that may participate in tipping the balance from tolerance to sensitization have been described. Binding of OX40 ligand to OX40, TIM4 to TIM1, and jagged to notch on DCs and naïve T cells, respectively, can regulate T cell differentiation from Treg towards Th2, as previously reviewed (39). Environmental interactions may drive this differentiation; for example, Staphylococcal enterotoxin B (SEB) can break tolerance and promote food allergy (25, 40), and has been shown mechanistically to induce TIM4 expression on DCs that is necessary for Th2 skewing (40). Th2-associated responses can also occur if Tregs are deleted (10), or become dysfunctional, as induced by SEB (41). In contrast, some innate signals may also protect against sensitization, since $TLR9^{-/-}$ mice have impaired IgE and IgA responses, resulting in reduced anaphylaxis to peanut (42).

Intestinal penetrance by allergens may also enhance allergic sensitization (43). On intestinal epithelial cells, IL-4 can induce upregulation of the low-affinity IgE receptor, CD23, which binds antigen-specific IgE and facilitates antigen uptake (44). This potential mechanism may explain why large or low-solubility antigens traverse the epithelium and elicit systemic

responses (45). Similarly, alterations in tight-junction integrity may allow antigen penetrance. For example, deficiency in the desmosomal intercellular adhesion molecule desmoglein-1 has been shown to elicit profound allergic responses (46), while its expression is reduced in tissues of patients with Eosinophilic Esophagitis (47).

Recent interest has also focused on the skin as a potential route for sensitization, since food allergy often associates with eczema in patients (1). Barrier integrity may also be important here, since filaggrin-deficient mice, which exhibit weak epithelial barrier function, become sensitized to proteins on the skin (48), and epicutaneous sensitization is sufficient to promote anaphylaxis upon oral challenge (49). While very few studies have defined specific genes associated with food allergy, it is interesting to note that mutations in desmoglein-1 (47) and filaggrin (50) as well as in TSLP (51) have been shown to be associated with food allergy or Eosinophilic Esophagitis in human cohorts, since these molecules all regulate skin homeostasis. However, it is unclear if these associations relate to food allergy or eczema, since these diseases are often coincident in children, and the number of genes associated with food allergy alone remains relatively limited (52).

3. Reactivity

The mechanisms of anaphylaxis—the hallmark of food-allergy reactivity—are generally biphasic: an acute reaction occurs immediately after allergen exposure, followed by a late-phase reaction several hours later. Symptoms occurring during the acute reaction are due to release of pre-formed mediators, while the late-phase response involves influx of inflammatory cells. Clinically, heterogeneity in responses is observed, with some patients experiencing either the acute or late-phase reaction, and others experiencing both the acute and late-phase reactions (53). In addition to clinical heterogeneity, anaphylactic responses can be elicited through multiple mechanisms.

Antibodies in Anaphylaxis—First shown in 1997 by Miyajima and colleagues (54), both IgE and IgG can play a role in anaphylaxis in the mouse. IgE functions via its high-affinity receptor, FcεRI, which is highly expressed on mast cells and basophils (55). FcεRI$^{-/-}$ mice do not respond in a passive IgE-mediated systemic anaphylaxis model (56) and have reduced responses in models of allergic diarrhea and food allergy (57-59). IgG has several receptors: the high-affinity FcγRI and FcγRIV, and the low-affinity FcγRIIB and FcγRIII. These receptors are all expressed on several cell types involved in anaphylaxis, including mast cells, basophils, neutrophils, and macrophages. Using a model of systemic anaphylaxis, Strait et al. showed that inhibition of FcγRII/III abolished temperature drops associated with shock in IgG-, but not IgE-, mediated anaphylaxis (56). Similarly, Jönsson et al. used knockout mice to show that FcγRIV is necessary for systemic anaphylaxis (60). While these pathways have been differentially defined using these passive models, both antibodies appear to participate in active food allergy: Arias et al. showed that IgE$^{-/-}$ and IgG$_1^{-/-}$ mice were only partially protected from peanut-induced anaphylaxis, but blockade of IgG$_1$ in IgE$^{-/-}$ mice completely abolished the response (61); similarly, FcRγ$^{-/-}$ mice, which lack the common chain for both the IgE and IgG receptors, were protected (62). Importantly, recent studies using humanized mice have supported the potential anaphylactic functions of IgG via human receptors (63).

Mediators of Anaphylaxis—Histamine, platelet-activating factor (PAF), and 5-hydroxytryptamine (5-HT, serotonin) are all sufficient to induce early-phase anaphylaxis (64, 65). Several groups have also looked at the necessity for each of these mediators in anaphylaxis, and there appears to be heterogeneity here also.

Histamine, produced from both mast cells and basophils, is a well-established mediator necessary for anaphylaxis (56, 66). In IgE-mediated systemic anaphylaxis, histamine synthesis as well as histamine H1 and H2 receptors are necessary for responses (66, 67), and blockade of these receptors is therapeutically beneficial in patients with acute allergic reactions (68).

Additionally, PAF and 5-HT have been shown to contribute to anaphylaxis (56, 58, 61-63). Several inflammatory cells make PAF, including macrophages/monocytes, mast cells, basophils, neutrophils, and platelets. While associated with platelet activation, PAF also influences vascular permeability, leukocyte recruitment, and leukocyte activation (69). Studies using models of allergic diarrhea, food allergy, or systemic anaphylaxis models have shown that responses may be due to either PAF and histamine (56, 61), or PAF and 5-HT (58, 63).

While other mast cell– and basophil-derived mediators have been implicated in food allergy, their role is less defined. These include other pre-formed mediators (e.g., tryptase, chymase, and heparin), lipid mediators (e.g., PGD_2, LTC_4, LTD_4, and LTE_4 (70)), and several cytokines. IgE activation of mast cells has the potential to generate several cytokines that have been shown to direct late-phase inflammation, including release of preformed TNF and synthesis of IL-33 (71, 72). TNF has been shown to be necessary for late-phase recruitment of neutrophils (71) as well as for a late-phase increase of PAF in the serum (73). The IL-33 receptor, ST2, is necessary for IgE-triggered tissue inflammation (72). IL-33 does not directly cause mast cell degranulation (74), but promotes expression of several cytokines and chemokines, including IL-6 and IL-13, from mast cells, as well as eosinophils (72, 75). Similarly, IL-9 can both stimulate and be produced by mast cells (76). IL-9 has been shown to be critical for the initiation and severity of food-associated anaphylaxis by promoting intestinal mastocytosis (77, 78).

Pathways of Anaphylaxis and Food Allergy—Largely from murine studies of passive sensitization models, mast cells, basophils, macrophages, and neutrophils have been shown to contribute to anaphylactic shock responses. Four distinct pathways of response seem to be possible—a “classic” pathway involving IgE, FcεRI, mast cells, and histamine; an “alternative” pathway mediated by IgG_1, FcγRIII, macrophages, and PAF (79); an IgG-basophil-PAF pathway (80); and an IgG-neutrophil-PAF pathway via FcγRIV activation (60).

In active sensitization models, IgE, FcεRI, and mast cells are responsible for inducing allergic diarrhea (58, 59). While both allergen-specific IgE and IgG antibodies are increased by sensitization, only FcεRI (58, 59), and not FcγRII/III (58), is required. Interestingly, the diarrhea response seems to be mediated by a combination of PAF and 5-HT. In contrast, the mast cell responses that are key in anaphylactic food allergy models (with contributions

from macrophages and basophils) occur via IgE- and IgG-dependent mechanisms requiring both histamine and PAF (57, 61, 81). Recently, the necessity for basophils in peanut anaphylaxis was also defined (82). Interestingly, the pathways to systemic anaphylaxis models may relate to the antigen dose required to trigger each mechanism, since small doses activate the classical pathway and large doses activate the alternative pathway (56).

4. Non-responsive Tolerance

Clinical studies have shown that the incidence of food allergen–specific IgE is ten times greater than the incidence of food allergy (83), suggesting an additional level of tolerance regulation above that of simply preventing immunological priming towards Th2 and IgE. Furthermore, in patients with Stat3 mutations leading to hyper-IgE syndrome, anaphylactic reactivity to food allergens is actually diminished (84). Recent work has shown that Tregs can suppress IgE-primed mast cell degranulation to antigen exposure via OX40/OX40 ligand interactions (85). In food allergy, we demonstrated that Treg transfer could suppress anaphylaxis and restore intestinal Th17 homeostasis by enhancing mast cell–derived IL-6 (41). Interestingly, this cytokine-mediated process was OX40-independent and instead mediated via TGF-β (41). Additionally, Tregs can downregulate FcεRI on mast cells in vitro (86). This emerging form of active tolerance—occurring despite the presence of an antigen-specific IgE–primed immune system—seems distinct from antigen desensitization, which is associated with internalization of FcεRI and IgE and altered Syk activation (87, 88).

Conclusions

Immunologically, food allergy is a disease with much left to determine. The mechanisms of tolerance, both in terms of what prevents most people from developing responses as well as why some individuals outgrow or never develop food allergies despite sensitization, remain unclear. Similarly, the environmental and genetic influences over sensitization are just becoming understood. Importantly, studies from animal models are showing that the mechanisms of anaphylactic reactions may well be heterogeneous in terms of routes of exposure, cell types involved, and the mediators responsible for symptoms. A better understanding of this heterogeneity will be crucial in developing future therapies.

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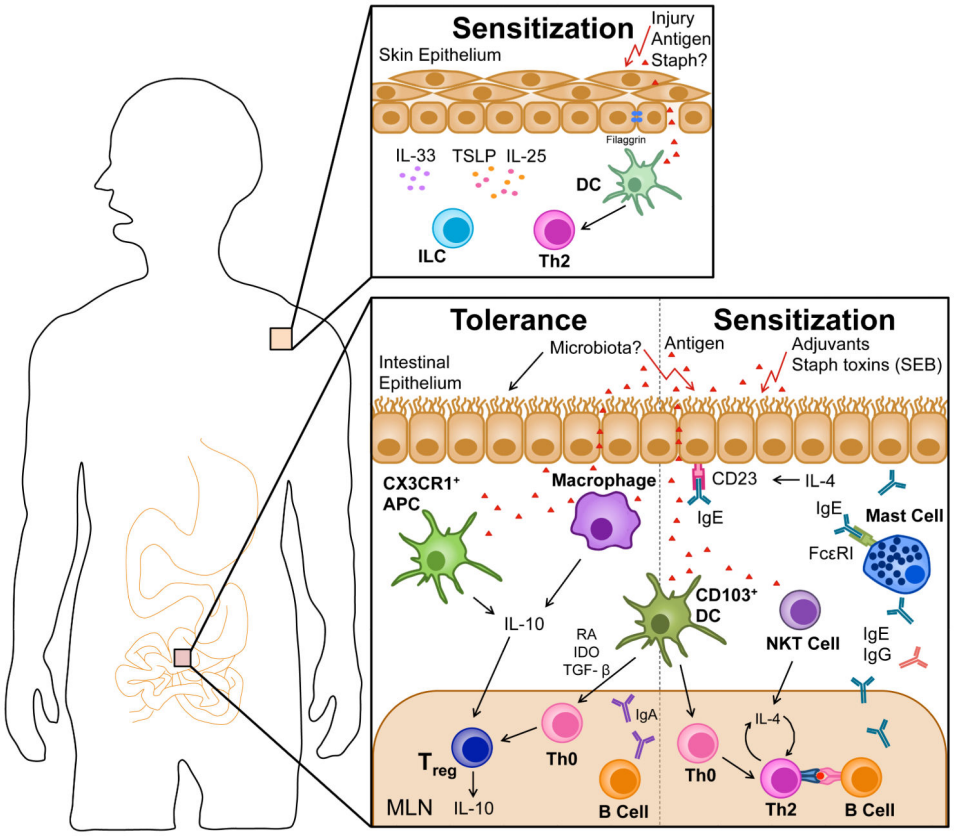

Figure 1.

Within the intestine, unique populations of cells that include macrophages, CX3CR1^{+} APCs, or CD103^{+} dendritic cells (DCs) ensure maintenance of tolerance through driving development of IL-10–producing regulatory T cells (Treg) and IgA-secreting B cells. Critical signals for tolerance are provided by retinoic acid (RA), indoleamine 2, 3-dioxygenase (IDO), and TGF-β. Perturbation in these cells or mediators, through largely unknown signals, breaks tolerance and promotes allergic sensitization characterized by dominant Th2-biased responses and class-switching towards IgG and IgE. Evidence supports the roles for tissue-derived cytokines, particularly IL-33, in supporting these events, perhaps via activation of innate lymphoid cells (ILCs). Initiating signals for sensitization include intrinsic activities of food components on innate cells, such as NKT cells, and exposure to bacterial toxins, such as SEB. The intestinal microbiota may also influence the balance between tolerance and sensitization. Additionally, defective barrier functions at either the skin or intestine have been shown to facilitate sensitization to food allergens.

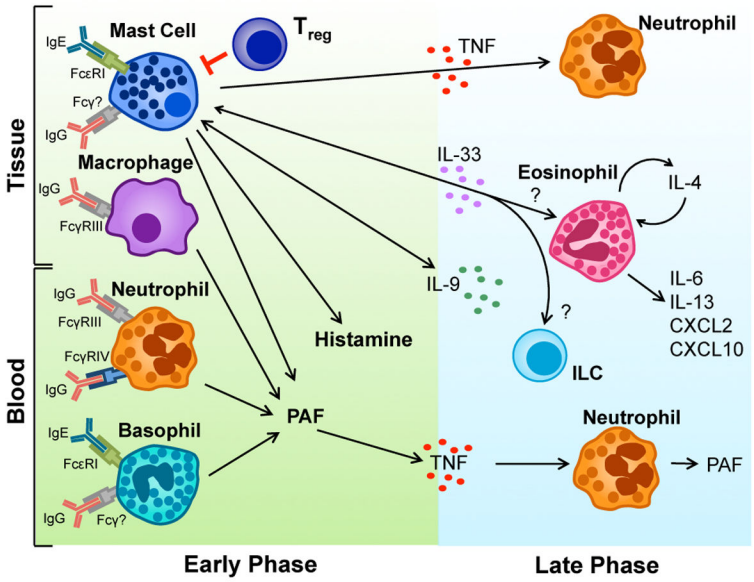

Figure 2.

Multiple pathways of anaphylaxis exist, mediated by either IgE or IgG and their respective Fc receptors. Within tissues, mast cell activation via IgE and FcεRI initiate early-phase responses mediated by histamine and PAF; this activation is actively regulated by Treg interactions. Macrophage activation by IgG may also represent an alternative pathway to PAF responses. Within the blood, neutrophil and basophil activation by either IgG or IgE presents additional pathways to generate these mediators if antigen becomes accessible. Kinetically slower, the release of preformed cytokines (TNF) or cytokines that are synthesized and then released (IL-33, IL-9) support localized tissue inflammation.