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Pathogenesis of Food Allergy in the Pediatric Patient

Stacy Chin · Brian P. Vickery

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Abstract In the US and other developed countries, food allergy is a growing epidemic in pediatric populations with a substantial impact on health-related quality of life. As such, there are great efforts underway to unravel the mechanisms of oral mucosal tolerance and to better define the factors related to host and allergen exposure that contribute to the aberrant immune response leading to sensitization and clinical food allergy. Although more research is needed to eventually develop targeted treatment and prevention strategies, this review highlights our current understanding of the pathogenesis of IgE-mediated food allergy.

Keywords Food allergy · IgE · Allergic sensitization · Dendritic cells · Pathophysiology · Oral tolerance · Pathogenesis · Pediatric

Introduction

Food allergy is an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given antigen [1]. It is a common, serious, and growing problem in developed countries. Whereas the immune system of all individuals recognized food antigens as foreign, patients with food allergy develop pathological immune responses and can rapidly experience harmful adverse symptoms upon re-exposure. Determining the precise prevalence of food allergy has been challenging since the most reliable indicator of food allergy, the double-blind, placebo-controlled food challenge (DBPCFC), is too difficult or time-consuming to employ in most prevalence studies. Self-reported survey data from the Centers for Disease Control and Prevention indicate that the current prevalence of food allergy in US children is approximately 4 %, an increase of nearly 20 % in the last decade [2]. A similar increase has been observed in methodologically rigorous studies from around the world [3, 4•], suggesting that the rise is not simply due to self-diagnosis or increased recognition.

While food allergy is often considered to result from a failure in oral tolerance, spontaneous clinical tolerance does develop in some food-allergic individuals. Although the process is not entirely clear, resolution tends to occur in allergen-specific patterns. For example, allergy to egg, milk, wheat, and soy is generally outgrown, whereas most patients remain allergic to peanut and tree nuts and must maintain life-long, strict elimination diets. Even so, it is a common scenario for a child to outgrow an early milk or egg allergy but not a peanut allergy [5]. Therefore, it appears that the pathophysiology of food allergy differs in antigen-specific ways even within the same patient.

Due to an inability to predict the risk of anaphylaxis or determine the eliciting dose threshold, avoidance remains the standard of care [1]; however, even in the most cautious patients, accidental ingestions frequently occur and are often undertreated [5, 6]. The inability to completely eliminate the possibility of anaphylaxis and the associated limitations in everyday activities are great sources of uncertainty and stress for affected families [7]. Over time, health-related quality of life is seriously eroded, to a greater degree than seen in other chronic diseases of childhood [8].

Consequently, great efforts are underway to better understand the mechanisms of oral tolerance and conversely what factors cause them to go awry [9]. While many details remain elusive, this review will cover our current knowledge of the

S. Chin
Department of Pediatrics, Division of Pediatric Allergy & Immunology, Duke University School of Medicine, Durham, NC, USA

B. P. Vickery (✉)
Department of Pediatrics, Division of Pediatric Allergy, Immunology, Rheumatology, and Infectious Disease, University of North Carolina School of Medicine, CB# 7231, Chapel Hill, NC 27599, USA
e-mail: bvickery@email.unc.edu

pathogenesis of IgE-mediated food allergy. To date, the majority of mechanistic evidence has been derived from animal models, but we will review the evidence for similar phenomena in humans and the relevant applications for clinical medicine where possible.

GI Mucosal Immunity: Overview

The gastrointestinal tract, the largest immunologic organ in the body, is exposed to a constant barrage of exogenous antigens on a daily basis [10]. The mucosal immune system has evolved to inhibit responses to harmless antigens (e.g., commensal bacteria, food protein) while maintaining the ability to mount a vigorous protective response when faced with enteropathogens. Homeostasis between tolerance and immunity is therefore an active immune process. This intricate balance can be modified by several factors in the intestine and when disrupted can lead to a breach in oral tolerance and inappropriate allergic sensitization to food proteins. Remarkably, only a single epithelial layer separates this antigenic load from the lymphocytes, antigen presenting cells (APC), stromal cells and other immune cells in the lamina propria, which together comprise the mucosal-associated lymphoid tissue (MALT). Within the MALT, unique populations of dendritic cells (DCs) interact with dietary antigens and determine the fate of the resulting adaptive response, i.e., immunity versus tolerance [11]. In this context, immune tolerance is defined as the antigen-specific suppression of cellular or humoral immune responses. Normally, when the initial antigen exposure occurs through the GI tract, a robust T cell-mediated suppression develops called oral tolerance [12]; however, in 4–6 % of children, this mechanism appears to fail, leading to sensitization and elicitation. We will first consider several factors related to the host and the allergen exposure that may play a role in determining the nature of the immune response.

The Intrinsic Physical Properties of Food Allergens

Of the 12,000^{+} food protein families in existence, a relatively small number cause the majority of food allergies [5]. This fact suggests that the main food allergens – milk, egg, wheat, soy, peanut, tree nuts, fish, and crustacea – though diverse in origin, share common functional characteristics that confer allergenicity: (1) small molecular weight, (2) an abundant source of the relevant allergen, (3) glycosylation residues, (4) water solubility, and (5) resistance to heat and digestion. These properties are unique to food allergens, which unlike inhaled or contact allergens, must pass through the harsh environment of the digestive system. Following ingestion, processing of dietary proteins by salivary and gastric enzymes and gastric acid results in reduced immunogenicity, likely by the destruction of conformational epitopes. However, proteins with the above physicochemical properties resist this processing and have allergenic potential upon reaching the small intestine. Factors that disrupt normal digestion such as co-administration of antacids have been shown in animal models to result in a breakdown in oral tolerance induction [13].

Because food antigens are non-self proteins, all normal individuals will mount an immune response [14, 15]. However, once putative allergens survive the digestion process relatively intact, they must initiate a T_H2 response in order to result in IgE production and disease expression. While most of the focus in understanding the cellular and molecular basis of allergenicity has been on T and B cell epitopes, there is no compelling evidence for the presence of common structural characteristics [16]. Consequently, there has been renewed interest in studying the innate immune system and its activation by allergens [17]. In particular, recent studies have highlighted the emerging importance of the carbohydrate residues, which decorate glycosylated proteins and can act as adjuvants by influencing immunogenicity and T_H2 polarization [18]. This is not entirely surprising, given that the mucosal IgE system evolved to defend the host from intestinal metazoan parasites, which themselves are heavily glycosylated. Other potentially important features of food allergens include lipid binding as well as higher order macromolecular structures that may promote aggregation and influence transepithelial transport [19].

While some common food allergens may possess self-adjuvant activity promoting sensitization, other foods possess immunomodulatory effects to suppress sensitization. Isoflavones present in soy have recently been shown to hinder allergic sensitization in human DCs as well as protect against peanut allergy in a murine model [20]. Zhou and colleagues [21•] demonstrated that binding of sugar-modified antigen to the innate immune receptor SIGN-R1 (murine homolog to human DC-SIGN) could reduce the anaphylactic response to food allergen by inducing DCs to release IL-10 and to generate T-regulatory type 1 cells (Tr1). Thus, the specific modulatory effect of a given food antigen on innate immune cells could explain its allergenic potency. For example, peanut and soy proteins share extensive amino acid homology yet confer differing prevalence rates and symptom severity.

Onset of Sensitization: Genetics, Timing, and Environment

Genetics plays a clear role in mouse models in which certain strains have exaggerated T_H2 bias whereas others resist sensitization [22]. Likewise, familial aggregation in food allergy [23], high concordance rates of peanut allergy among monozygotic twins [24], and certain racial/ethnic

predilections [25] suggest that genetics plays a significant role in humans as well. Few genome-wide association studies of food allergy have been performed, and although polymorphisms in genes associated with food allergy have been found in single studies, the results have not been replicated in independent populations [26, 27]. Candidate gene approaches have been largely unsuccessful, with the exception being one case–control study suggesting increased risk of peanut allergy in 71 UK subjects with loss-of-function filaggrin mutations [28•]. While genetic susceptibility undoubtedly contributes to the onset of disease, the rise in prevalence is more rapid than genetics can explain, thus drawing attention to environmental factors. Increasing interest in epigenetic modifications may elucidate an important role for heritable gene-environment interactions in food allergy pathogenesis [29].

Although food sensitization is often an early life event [30], it remains controversial whether allergic priming could occur in humans in utero [31–33]. Furthermore, manipulation of the maternal diet during pregnancy and/or lactation has demonstrated little protective effect on the development of food allergy [34, 35]. In mouse models, high-dose exposure to antigen in early life, even a single isolated dose, can produce lymphocyte anergy, whereas repeated, low-dose exposure induces tolerance through T-regulatory cell (Treg) development [36]. Emerging evidence in human disease suggests that exposure to the proper dose of antigen during this critical period in early life is important for the shaping of the appropriate immune response to foods. Several epidemiologic studies have implicated delayed weaning patterns in the increased prevalence of peanut allergy [37–39]. Similarly there is evidence that delayed introduction of cereals is associated with a higher risk of wheat allergy [40]. European and American feeding guidelines have recently been revised to reflect the position that insufficient evidence exists to support delayed weaning as a preventative strategy [1, 41, 42]. However, early introduction is not necessarily better, since mature immune regulation may require time [43]. Cow's milk is typically the first potentially allergenic exposure and yet is the most common food to which US children are allergic [5]. In addition, maternal peanut consumption during breastfeeding, but not pregnancy, was associated with peanut sensitization [44]. Defining the most appropriate time and dose for tolerance induction in humans is a great research need. Interventional studies are underway to investigate the importance of early life oral exposure in tolerance development.

The modern rise in food allergy has coincided with a concurrent upsurge in vitamin D deficiency (VDD). A hormone that binds nuclear elements and is known to affect both innate and adaptive immunity, VDD has already been linked to the development of atopic dermatitis [45] and recurrent wheeze [46], leading to the hypothesis that deficiency of this key environmental factor may also play a role in the pathogenesis of food allergy [47]. Supporting evidence includes the influential role of 1,25 $(OH)_2D$ in Treg development [48], microbiome diversity [49], and mucosal barrier maintenance and repair [50]. Recently, data from the National Health and Nutrition Examination Survey revealed that VDD was associated with higher levels of IgE sensitization to peanut and select aeroallergens in children and adolescents, but not adults [51•]. While too common to be individually responsible, VDD is another plausible contributing factor to the increasing prevalence of food allergy.

Route of Exposure

The coinciding increase in food allergy with dietary guidelines to delay introduction of allergenic foods has led to the hypothesis that sensitization may occur through non-oral routes. Given the high concurrence rates of food allergy among patients with atopic dermatitis, the skin is of particular interest; as previously noted, filaggrin mutations are thought to confer enhanced risk for peanut allergy. Household peanut consumption has been linked to an increased risk of peanut sensitization in children, independent of maternal peanut intake [38]. In addition, many children experience allergic reactions after their first known oral ingestion [52], suggesting sensitization through previous occult exposure. These observations suggest that oral exposure is tolerogenic by default, while exposure through other routes preferentially induces sensitization. Reinforcing this concept was the finding that UK children with positive oral food challenges to peanut were significantly more likely to have used eczema creams containing peanut oil than atopic or normal controls [31]. Studies of epicutaneous sensitization in murine models are conflicting regarding whether the skin is intrinsically pro-allergenic [53]. Interestingly, epicutaneous immunotherapy is being developed as an experimental treatment for food allergy [54, 55]. In the sections that follow, we will review the mechanisms in the gut that may determine whether a food exposure results in allergy or tolerance.

Microbiome: The Good with the Bad

A critical influence on the mucosal immune response is the microbial stimulation provided by the enteric flora, which by adulthood number approximately 100 trillion in the large intestine [56]. Within hours of birth, bacteria colonize the neonatal GI tract and begin interacting with the MALT; this probably represents the primary stimulus for proper postnatal immune development, since germ-free mice have disorganized and poorly developed mucosal and secondary lymphoid structures. In the absence of a microbial flora, these animals have impaired antibody responses and do

not develop oral tolerance [57]. More recently, a birth cohort study following high-risk children through 6 years of age demonstrated that the bacterial diversity of intestinal flora was inversely associated with the risk of allergic sensitization to foods and aeroallergens, peripheral blood eosinophilia, and allergic rhinitis [58•]. However, reduced bacterial diversity was not associated with an increased risk of asthma or atopic dermatitis in the first 6 years of life. Other studies have identified specific differences in the flora of allergic and nonallergic children [59, 60]. This suggests that although intestinal microbial colonization is required for proper immune development, certain microbes may play a significant role in skewing the immune response toward allergic sensitization, possibly by suppressing the general biodiversity and creating an environment that enhances the development of allergic disease. Interestingly, a group of investigators has recently linked a decline in environmental biodiversity with a decline in the biodiversity of skin flora in atopic individuals [61], possibly explaining why urban populations are disproportionately affected by allergic disease.

The critical information provided by the microbiome is interpreted through signals from innate pattern recognition receptors (PRR) such as toll-like receptors (TLRs), which play an important role in intestinal homeostasis [62], in the genesis of Tregs [63] and on the outcome of allergic disease [64]. Recently, differences in TLR-mediated microbial responses at birth and over time were found between allergic and nonallergic children, with the latter demonstrating age-related increased responsiveness to these recognition pathways [65•]. Additionally, investigators have identified specific microbial products (i.e., polysaccharide A from *Bacteroides fragilis*) that interact with TLRs and promote downstream induction of Tregs, modulating intestinal inflammation in mouse models of experimental colitis [63]. This differs from the general consensus that TLR4 pathways are both necessary and sufficient for the development of allergen-driven T_H2 immune responses in the airway [66, 67]. The intricacy of the innate signaling pathways has made identifying the specific microbial signal(s) that is/are most important in determining the immune response to food antigen in humans particularly challenging. This is evidenced by the overall disappointing results of probiotic trials on the prevention and treatment of allergic disease [68]. However, new deep-sequencing technologies that focus on the unique 16 s ribosomal subunit of bacterial RNA rather than culture-based methods are allowing investigators to identify previously unknown organisms [69].

Mucosal Barrier: First Line of Defense

The "first-line" features of mucosal defense include mucin oligosaccharides and antimicrobial peptides that serve to prevent luminal antigens from interacting with the MALT entirely. Secretory IgA also binds to luminal antigens preventing absorption (i.e., "immune exclusion"). However, its specific importance has been controversial since it appears that cellular mechanisms can compensate for impaired immune exclusion [70, 71]. If a potential allergen penetrates these initial physical factors, the intestinal epithelium itself acts as a barrier to sequester luminal antigens from the MALT, and leakiness of this barrier has been postulated to result in allergic sensitization. Structural integrity of the intestinal epithelium is conferred by adherens junctions and tight junctions, but it may take years for complete developmental maturation of the gut barrier in healthy children [72]. In mice, the permeability of this barrier is further influenced by environmental exposures that result in changes in gene expression and phosphorylation of tight junction proteins such as occludins, claudins, and JAM-ZO1 proteins, which in turn are associated with changes in intestinal mast cells and allergic sensitization [73, 74].

Interestingly, examination of the lactulose/mannitol ratio in urine revealed that food-allergic infants had increased intestinal permeability when compared to healthy children [75]. Even following a minimum 6-month period of allergen avoidance, the intestinal permeability in food-allergic children remained increased. Further evidence linking intestinal epithelial barrier dysfunction and food allergy comes from studies in patients who developed food allergy after solid-organ transplantation while taking calcineurin inhibitors. While initially assumed to result from the transfer of sensitized donor lymphocytes, it is now theorized that medication-induced decreases in cellular ATP altered the integrity of junctional complexes, resulting in increased intestinal permeability [76].

Increasing evidence suggests that the mucosal epithelium is more than simply an inert physical barrier. Epithelial cells express MHC class II molecules and thus may act as nonprofessional APCs that lack conventional co-stimulatory molecules, thus favoring anergy or tolerance [77]. In addition, factors derived from the gut epithelium are generally believed to condition the DCs in the stroma, dampening immune responses and promoting gut homeostasis [78]. One such factor is retinoic acid (RA), which in combination with TGF-β is essential for the differentiation of Treg-inducing DCs [79]. Another factor constitutively expressed by the gut epithelium is thymic stromal lymphopoetin (TSLP). TSLP is an IL-7 like cytokine that can activate expression of OX40L on DCs and drive T_H2 differentiation. Although TSLP has demonstrated a regulatory role in the gut by limiting deleterious T_H1 and T_H17 inflammation in models of helminth infection and colitis [80], other studies have shown that TSLP amplifies T_H2 responses directly from $CD4^+$T cells and is required for allergic inflammation although not for sensitization or tolerance [81]. Furthermore, a recent study illustrated that TSLP promotes systemic basophilia, resulting in increased T_H2 cytokines and IgE [82].

Innate Immunity: Dendritic Cells Set the Stage

If food proteins survive digestion and evade luminal defenses, they will be detected by APCs in the MALT in the context of signals provided by the commensal flora. In this way, a complex interplay of all aforementioned factors (i.e., antigen character, dose, timing, and innate immune stimulation) will determine the immune response to an ingested food protein through the same final common pathway: by directly or indirectly influencing the APC. Mucosal DCs are probably the most critical determinant of allergic sensitization versus tolerance in naïve individuals, largely because of their location and their capacity to receive and interpret environmental signals, which lead to a specific immune response. These DCs can encounter ingested antigen in one of three ways: by extending dendrites through the paracellular space between epithelial cells to sample luminal contents, by directly interacting with the epithelial cells, and by taking up antigen in Peyer's patch, specialized lymphoid tissue that is immediately adjacent to microfold cells [83]. The properties of the antigen itself–particulate versus soluble– to a certain extent determine the route of exposure.

One of the more recent advancements fostering our understanding of oral tolerance is the characterization of two critically important and developmentally distinct subsets of intestinal DCs that can be discriminated by the cell surface expression of either CD103 or CX3CR1 [84, 85]. Of these two populations, only $CD103^+$DCs are able to migrate from the lamina propria to the mesenteric lymph node (MLN); thus, the $CX3CR1^+$ cells (which are $CD103^-$) are more appropriately categorized as intestinal macrophages. After acquiring antigen, $CD103^+$DCs migrate from the lamina propria to the MLN in a CCR7-dependent manner (Fig. 1) [86]. These specialized DCs express the enzyme retinaldehyde dehydrogenase 2, which converts the vitamin A metabolite retinal to RA. In the presence of TGF-β, which is also produced by $CD103^+$DC, RA can promote the differentiation of naïve T cells within the MLN into Foxp3-expressing Tregs. Moreover, the $CD103^+$DC uses RA to imprint naïve T cells with the gut homing markers integrin

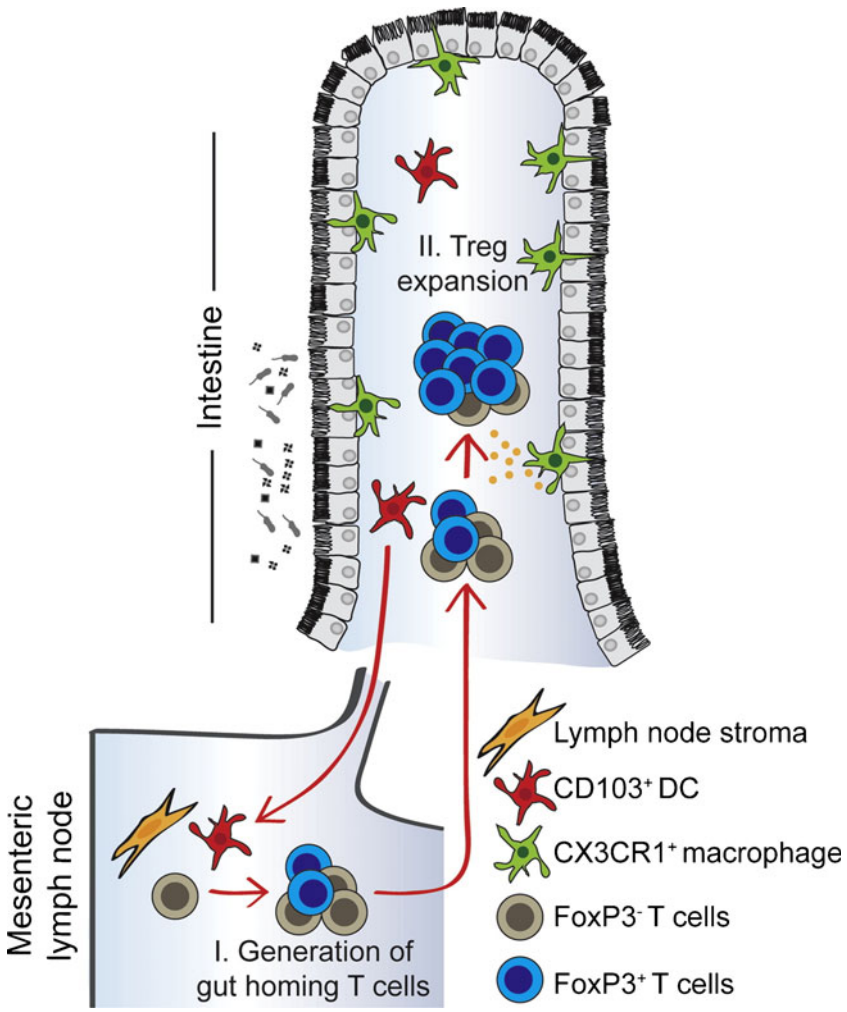

Fig. 1 After taking up antigen in the lamina propria, $CD103^+$ dendritic cells (DCs) migrate to the mesenteric lymph node. $CD103^+$DCs present antigen to naïve T cells that are induced to differentiate into FoxP3-expressing T-regulatory cells (Tregs) and imprinted with α4β7 and CCR9. After homing back to the gut, $CX3CR1^+$ ($CD103^-$) cells secrete IL-10 to allow for local expansion of Tregs and induction of oral tolerance. (*Adapted from* Hadis et al. [89•]; copyright 2011, Elsevier; with permission)

α4β7 and chemokine receptor CCR9. Further contributing to their tolerogenic capabilities, $CD103^+$DCs also express the enzyme indoleamine 2,3 dioxygenase (IDO), which serves to inhibit the generation of T-effector cells by metabolizing tryptophan and producing toxic byproducts [87]. Inhibition of IDO abrogates the development of inducible $Foxp3^+$Tregs in vitro and prevents the development of oral tolerance in vivo [88]. This finding along with defective oral tolerance in CCR7-deficient mice suggests that $CD103^+$DCs are critical to the induction of oral tolerance. Recently, two studies [89•, 90] definitively established that α4β7, CCR9 expressing $Foxp3^+$Tregs are required for oral tolerance. Using DEREG mice that selectively express the diphtheria toxin receptor on $Foxp3^+$ cells, investigators demonstrated the reversal of oral tolerance following ablation of $Foxp3^+$T cells with diphtheria toxin after antigen feeding. While $CD103^+$DCs are essential to oral tolerance induction, intestinal $CX3CR1^+$ macrophages are necessary to sustain local tolerance induction [89•]. This subset of DC expands $FoxP3^+$ Tregs in the lamina propria, produces IL-10, and clears bacteria that breach the epithelial barrier. Exploiting the inherently tolerogenic characteristics of $CD103^+$DC – for example, by targeting delivery of a specific antigen, could represent a potential treatment modality in the future, although a much greater understanding of their biology is first needed.

The acquisition of $CD103^+$DC's unique tolerogenic properties likely requires a specific milieu of local conditioning factors provided by intestinal epithelial cells (IECs), commensal bacteria, and dietary constituents. The differentiation of $CD103^+$DC depends upon RA and TGF-β produced by the IECs [79]. Commensal bacteria such as *Bacteroides* and *Bifidobacteria* strains are capable of directly inducing monocyte-derived DC to acquire a tolerogenic phenotype [56]. Signaling through certain members of the CLR family (e.g., dectin-1, SIGN-R1) upon recognition of microbial glycans also leads to induction of oral tolerance [21•]. Depletion of vitamin A and tryptophan from the diet (the only source for these nutrients in mammals) hinders the tolerogenic effect of $CD103^+$DC by hampering their ability to generate Tregs and imprint gut homing receptors on lymphocytes [87].

Exactly what factors skew the $CD103^+$DC toward a non-tolerogenic phenotype or perhaps propagate a different proallergenic DC subset are not entirely clear. However, the potential pathways involved have been highlighted by experiments using adjuvants to orally sensitize mice [53]. Feeding of cholera toxin (CT) alters the migration of $CD103^+$DC from the lamina propria to the MLN and enhances their maturation, leading to enhanced T cell priming [91]. Upregulation of OX40L in the $CD103^+$DC was responsible for an increase in IL-4 and IL-13 by T-effector cells and for the sensitizing capabilities of CT [92]. Within the lamina propria, allergic sensitization was also associated with an increase in $CD11b^+$DC and relative decrease in the $CD103^+$DC subset [93], indicating that the phenotype of intestinal DC determines the immune response to antigen. While CT is unlikely to play a role in human food allergy, Staphylococcal enterotoxin B (SEB) is a toxin produced by some strains of *Staphylococcus aureus*. SEB is frequently found as a contaminant in the food supply and frequently produced by colonizing strains present on the skin of atopic dermatitis patients [94]. As an oral adjuvant in mouse models of sensitization, SEB has exhibited an ability to increase T_H2 cytokine expression and decrease TGF-β and Foxp3 expression in vitro [95]. Furthermore, SEB acts directly on DCs to upregulate TIM-4 expression, which drives T_H2 cytokine production in T-effector cells [96]. TIM-4 expressed on DCs and its ligand TIM-1 on T cells have been shown to be critical regulators of T_H2 differentiation in humans and mice [96, 97]. Similar to CT, TSLP-stimulated DCs act through OX40L to induce T_H2 cells and thus may serve as a natural adjuvant when expressed by IECs. Determining additional environmental factors that are capable of modulating molecules such as OX-40 L and TIM-4 on gastrointestinal DCs may identify factors potentially responsible for the steep increase in the incidence of food allergy in recent years.

If the DC-food allergen interaction fails to induce tolerance, the ensuing immune response proceeds through two phases: *allergic sensitization* and *elicitation*. Allergic sensitization involves T cell priming after DC activation, and the resultant T-helper-2 (T_H2) response is characterized by the production of interleukin-4 (IL-4), IL-5, and IL-13 from $CD4^+$T cells. This T_H2 response leads to B-cell IgE production, and this IgE binds to its high-affinity receptor on the surface of mast cells in the skin, gut, and respiratory and cardiovascular systems, arming them for reactivity upon re-exposure to allergen. The elicitation of classic allergic symptoms occurs within minutes after allergen exposure, when IgE-bound mast cells recognize the allergen and become activated [14].

Conclusions

Although food allergy affects 12 million Americans, it is remarkable that it is not more common considering the complexities of the mucosal immune system. Robust immunologic mechanisms involving both humoral and cell-mediated responses have evolved to maintain a homeostatic environment amidst the literally billions of antigens within the intestine. In order to incite the allergic cascade, an ingested protein must circumvent this tolerogenic system. Several interrelated factors such as genetic susceptibility and age of the host; antigen timing, dose, and route of exposure; enteric microbiome; and dietary constituents can influence the immune response toward oral tolerance or sensitization and clinical food allergy. More insight into these complex interactions will be essential to developing targeted treatments for food allergy and eventually primary prevention strategies.

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