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Recent Developments in Understanding the Mechanisms of Food Allergy

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Abstract

Purpose of review: The prevalence of food allergy (FA) is rising globally. This review will discuss recent discoveries regarding the immunologic mechanisms that drive the initial sensitization and allergic response to food antigens, which may inform prevention and treatment strategies.

Recent findings: Tolerance to food antigens is antigen-specific and promoted by oral exposure early in life and maternal transfer of immune complexes via breast milk. Immunoglobulin G (IgG) can inhibit both the initiation and effector phases of allergic responses to food antigens in mice, and high levels of food-specific IgG4 are associated with acquisition of tolerance in humans. Disruption of the skin barrier provides a route for food sensitization through the actions of mast cells, type 2 innate lymphoid cells (ILC2s) and IL-33 signaling. Regulatory T cells (Tregs) promote acquisition of oral tolerance, although defects in circulating allergen-specific Tregs are not evident in children with established food allergy. Certain microbes can offer protection against the development of IgE and food allergic responses, while dysbiosis increases susceptibility to FA.

Summary: Tolerance to food antigens is antigen-specific and is promoted by oral exposure early in life, maternal transfer of immune complexes, food-specific IgG, Tregs, an intact skin barrier, and a healthy microbiome.

Keywords

Food allergy; tolerance; IgG4; sensitization; T regulatory cell; skin barrier; antigen specificity; commensal microbiota

INTRODUCTION

Food allergy (FA) affects millions of adults and children around the world. A population-based study in Australia recently found that the prevalence of challenge-confirmed IgE-mediated FA was 11% at 1 year of age and 3.8% at 4 years of age [1]. While food antigens are normally tolerated by the immune system, certain individuals develop food antigen-

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specific IgE antibodies, thus becoming “sensitized”. Subsequent exposure to the food can result in crosslinking of antigen-specific IgE bound to the high affinity IgE receptor FcεR1 on mast cells and basophils, leading to the release of inflammatory mediators that produce the symptoms of an allergic reaction, which in severe cases can be fatal [2,3].

Recent work in mice and humans has shown that disruption of the skin barrier increases the likelihood of sensitization to food antigens [4–6], while oral exposure results in the differentiation of regulatory T cells (Tregs) that promote tolerance [7–10]. The balance between IgE and other immunoglobulin classes, including IgG, additionally influences the response to food antigens [11–13]. As first suggested by David Strachan with the hygiene hypothesis decades ago, microbiota may also play a central role in food allergy pathogenesis [14]. Several studies have shown that commensal microbiota and their metabolites can protect against sensitization to food antigens [15,16]. Ongoing research focuses on identifying factors that promote dysbiosis as well as specific microbes and microbial products that may be effective in preventing and/or treating FA. This review will focus on recent studies informing the mechanisms underlying susceptibility to food allergy and the pathways that lead to the development of this common disease.

ROLE OF IMMUNOGLOBULINS AND THEIR RECEPTORS IN THE IMMUNE RESPONSE TO FOOD ANTIGENS

Oral exposure to food antigens normally results in antigen-specific immunological tolerance to the food, defined as a failure of the immune system to mount an inflammatory response upon subsequent exposure. Indeed, the Learning Early About Peanut allergy (LEAP) study showed that infants at high risk for developing peanut allergy (due to eczema or egg allergy or both) were protected if they introduced peanut into their diet early in life compared to those who followed strict avoidance [17*,18]. Despite the fact that peanut antigens share homology with other common food allergens including tree nuts and sesame, early introduction and tolerance to peanut had no preventative effect on the development of other food allergies, asthma, or rhinoconjunctivitis, nor did early exposure help resolve eczema or egg allergy [17*].

Recent studies have provided insight into the mechanisms responsible for antigen-specific tolerance induction during infancy. Female mice epicutaneously sensitized to the egg protein ovalbumin (OVA) conferred OVA-specific tolerance to their offspring via immune complexes (IC) transferred to the neonate via breastmilk and, less efficiently, in utero [19**]. This protection required the neonatal crystallizable fragment receptor (FcRn), which is present on neonatal CD11c+ dendritic cells (DCs). Uptake of OVA-IgG immune complexes by these cells induced the formation of OVA-specific Tregs and prevented the development of OVA-specific IgE and anaphylaxis in the offspring [19**]. Importantly, human breastmilk from non-atopic mothers similarly contained OVA-IgG-IC, and feeding this milk to mice expressing humanized FcRn promoted induction of OVA-specific Tregs and tolerance to egg whites [19**]. Soluble FcεR1 may also have a role in negatively regulating IgE responses. Following FcεR1 cross-linking, human monocyte-derived DCs and murine mast cells secrete sFcεR1, which forms an immune complex with IgE [20*].

Soluble FcεR1 prevented IgE binding to cell surface FcεR1 and inhibited human basophil activation *in vitro*. Furthermore, pretreatment with recombinant sFcεR1 reduced the magnitude of anaphylactic shock in mice [20*]. These studies thus support a role for both FcRn and sFcεR1 in modulating the immune response to food antigens.

Growing evidence suggests that the balance between antigen-specific IgE and IgG antibodies is also important for acquiring natural tolerance to food. A recent study found that IgG, via the inhibitory IgG receptor FcγRIIb, inhibited both the initiation and effector phases of allergic immune responses. Administration of antigen-specific IgG prior to sensitization limited anaphylactic responses in antigen-challenged mice by blocking IgE:FcεR1 activation of mast cells and the production of IL-4 and IL-13, reducing the inflammatory response, and allowing for increased Treg polarization and decreased TH2 effector responses [21*]. Administration of allergen-specific IgG also enhanced the efficacy of oral desensitization in mice with established FA by promoting Treg expansion [21*]. IgG4 in humans has also previously been shown to block allergic responses and promote tolerance [18,22–24]. The epitope diversity of IgE and IgG4 antibodies in children who outgrew cow's milk allergy was lower than in children with persistent disease, while the affinity of IgG4 was higher in the tolerant group and closer to that of IgE [25]. Similarly, children who were able to tolerate baked egg had a higher egg-specific IgG4/IgE ratio than children who reacted to all forms of egg [26].

ROLE OF THE SKIN BARRIER IN FOOD ALLERGY PATHOGENESIS

The dual exposure hypothesis posits that exposure through the skin promotes sensitization to foods, while oral exposure leads to tolerance [4]. In agreement with this theory, a history of preschool eczema was recently associated with IgE sensitization to food and aeroallergens, as well as polysensitization [27]. However, eczema per se may not be responsible. Children with a mutation in the filaggrin (FLG) gene, which encodes an epidermal protein important in skin barrier function, were also more likely to be sensitized to peanut but not other food or aeroallergens [27]. Although FLG mutations are a risk factor for eczema, the association with peanut allergy remained after controlling for coexistent eczema [28,29]. Interestingly, non-lesional skin of eczema patients with FA exhibited increased transepidermal water loss, decreased filaggrin breakdown products, and keratinocytes that were hyperproliferative and unable to terminally differentiate compared to eczema patients without FA [30*]. A GWAS study also found that challenge proven-FA was associated with FLG mutations, and in this case the association was not only with peanut allergy but with hen's egg and cow's milk allergy as well. Although the effect size was largest in children with eczema, a strong association was still present in the absence of eczema [31]. This study further identified a significant association of FA with single nucleotide polymorphishms (SNPs) in *SERPINB7*, which encodes a protein that is important for epithelial integrity and upper digestive tract function [31]. Moreover, variants in *SPINK5*, which encodes a protein important in epidermal shedding, have been associated with FA independent of eczema, and preliminary experiments suggested that these variants may cause increased skin barrier permeability [32]. Collectively, these studies support a role for skin barrier integrity in the pathogenesis of FA.

Additional evidence supporting a role for skin exposure in the development of FA comes from mouse models. Tape stripping and epicutaneous sensitization of mice effectively induced antigen-specific IgE and IgG and anaphylaxis after oral challenge [33], while oral exposure before epicutaneous sensitization protected against an anaphylactic reaction to oral challenge [34*]. Moreover, epicutaneous sensitization of mice required fewer antigen challenges to induce an allergic response than intraperitoneal sensitization [35]. Allergic reactions in epicutaneously sensitized mice could be exacerbated by chemical or mechanical damage of the skin barrier, or ameliorated by topical treatment with glucocorticoids [35]. Mice with skin barrier dysfunction as a result of heterozyous mutations in *Filaggrin* and Matt (*Tmem79*^{ma}) were also recently shown to be more susceptible to sensitization and anaphylaxis following epicutaneous exposure to food antigens, although concurrent cutaneous exposure to environmental allergens (*Alternaria alternata* or house dust mite extract) was required in this model [34*].

Recent murine studies have also provided insight into the cellular mechanisms by which a defective skin barrier contributes to FA, highlighting the importance of IL-33, mast cells, and type 2 innate lymphoid cells (ILC2s). Mechanical skin injury via tape stripping induced the expansion of mast cells and ILC2s specifically in the intestine [36*]. Accumulation of intestinal mast cells increased intestinal permeability and drove anaphylaxis to oral challenge after intraperitoneal sensitization [36*]. Following mechanical injury, keratinocytes produced IL-33, which acted on intestinal ILC2s in conjunction with IL-25 to induce IL-4 and IL-13 release and subsequent mast cell expansion [36*]. This process is illustrated in Fig. 1. Congruently, mice sensitized intradermally with TSLP and OVA also required IL-33 signaling in the skin in order for FA to develop. Deletion of IL-33 from epidermal keratinocytes or neutralization of IL-33 signaling systemically lessened the development of OVA-specific IgE, TH2 cytokine production, skin draining lymph node cellularity and allergic diarrhea [37]. Further supporting the important role of IL-33, mice sensitized intradermally with IL-33 and OVA developed oral and GI anaphylaxis symptoms when challenged [37]. Additional signaling for TH2 polarization comes from TSLP-induced basophils which accumulate in the inflamed skin and provide IL-4 [38]. Experimental therapies blocking IL-25, IL-33, or TSLP with monoclonal antibodies in mice effectively prevented the development of food allergy, but a cocktail of all three was required to suppress established food allergy [39*].

TREGs AND TOLERANCE TO FOOD ANTIGENS

Loss of function mutations in *FOXP3*, which encodes the Treg lineage-defining transcription factor, result in a failure to produce functional Tregs and consequent widespread lymphoproliferation, autoimmunity, and atopy, including FA, in both humans and mice [40,41]. More recently, patients with Wiskott-Aldrich syndrome (WAS), caused by loss of function mutations in the *WAS* gene, were found to have elevated total and food antigen-specific IgE levels and an increased prevalence of FA. A mouse model revealed that loss of *Was* in Tregs alone was sufficient to drive FA and Th2-type inflammation in the small intestine [42]. Impaired Treg activity and high levels of food antigen-specific IgE along with FA and enteropathy were also observed in patients with *DOCK8* mutations [43]. Undoubtedly, a failure of Tregs can be a driving force behind the development of FA;

however, the extent to which Treg dysfunction contributes to allergy development in the absence of a primary immunodeficiency remains less clear. In support of a role for Treg deficiencies in general FA, a large birth cohort study recently found that infants who developed FA by one year of age had lower percentages of Tregs among CD4+ T cells at birth relative to non-allergic infants [44]. However, this difference was slight (3.75% versus 4.41%) and visible only with exposure to labor, and no correlation between FA status and Treg percentages was found at 6 months or 12 months of age [44]. A small scale study also found a slightly lower Treg count (per μl of blood) in a group of 28 infants within days of an initial confirmed allergic reaction to cow's milk relative to non-allergic controls [45]. The percentage of Tregs among total CD4+ T cells was not different between the allergic and the control groups, which leaves open the question of whether the difference is in the Tregs themselves or the total CD4+ T cell population [45]. In mice, transfer of complexes of IgG and ovalbumin (OVA) from mothers to offspring via breast milk protected against future OVA sensitization by inducing Foxp3+ OVA-specific Tregs [19**]. While this represents a fascinating mechanism for induction of Tregs to prevent FA, many infants are fed formula that does not contain immune complexes and do not go on to develop food allergies, thus suggesting that this process may promote tolerance but is not required for its establishment.

Several recent studies have focused on identifying and characterizing antigen-specific Tregs in the context of FA and tolerance. Our group identified peanut-specific Tregs in peripheral blood of peanut allergic and non-allergic children based on their upregulation of CD137 after stimulation with crude peanut extract (CPE). We found no difference in the frequency of peanut-specific Tregs in peanut allergic and non-allergic children of school age or at one year of age [46*]. Peanut-specific Tregs from peanut allergic and non-allergic individuals were comparable in percent methylation of the Treg specific demethylated region of *FOXP3*, a marker of Treg stability, and in their ability to suppress division of CD4+ peanut-specific effector T cells [46*]. Interestingly, we did find significant differences in cytokine production and homing molecule expression by CD4+ peanut-specific effector T cells isolated from allergic and non-allergic individuals, suggesting that differences in the effector T cell response rather than the Treg response may be responsible for driving allergy development. A previous study of aeroantigen-specific T cells similarly concluded that the frequency, gene expression profile, suppressive function, and sequence diversity of the T cell receptor were comparable among birch-specific Tregs from birch allergic and non-allergic individuals, while the birch-specific conventional T cell response differed greatly [47]. Other groups have identified antigen-specific Tregs based on upregulation of CD154 on FOXP3+CD25+CD127- cells after 18 hours of stimulation. Using this method, the frequency of egg-reactive Tregs and peanut-reactive Tregs was not different between individuals reactive or tolerant to these foods, although the researchers noted that IL-2 production by antigen-specific conventional T cells could also drive CD154 expression on Tregs at this time point [26,48]. Removal of Tregs increased the amount of IL-5 and IL-9 in the supernatant of PBMCs cultured with peanut extract in healthy controls but not peanut allergic individuals, which suggests that Tregs may normally prevent release of these cytokines in healthy individuals, although the total amount of these cytokines still appeared higher in the allergic group [48]. One caveat of all these studies is that they were done using peripheral blood, and while food antigen-specific T cells can circulate, a large fraction likely

remain in the small intestine [10,49]. Unfortunately, biopsies of the small intestine are much more difficult to obtain, and identification of antigen-specific Tregs using activation markers is technically challenging due to the higher baseline level of T cell activation in the gut.

Finally, several groups have assessed the Treg compartment following treatment for allergy. In mice, epicutaneous immunotherapy of mice sensitized to OVA resulted in the differentiation of OVA-specific CD4+LAP+Foxp3- cells that homed to the gut and protected against mast cell degranulation following oral challenge [50]. In humans, the results have been mixed; while some groups have found an increase in the number and function of food-antigen reactive FOXP3+ Tregs after oral immunotherapy (OIT) [51], others have found no difference, [52,53] or even a decrease in antigen-specific FOXP3+ T cells [54]. Together, these studies suggest that while Tregs play an important role in establishing tolerance to food antigens, there are many other cell types involved in the development and resolution of allergy, and Treg dysfunction may not be the driving force behind the majority of food allergies.

ROLE OF COMMENSAL MICROBIOTA IN THE DEVELOPMENT OF FOOD ALLERGY

The dramatic rise in FA in recent years is hypothesized to result from alterations in the microbiome secondary to frequent antibiotic use in early infancy, an increased rate of Caesarean births, a Westernized diet, and higher rates of formula feeding [55–57]. Studies of germ free (GF) mice have shown that commensal microbiota protect against the development of FA and food antigen-specific IgE; elevation of serum IgE occurs spontaneously in GF mice and increases with age [58**]. The increase in IgE can be attributed to a response to antigens found in mouse chow since feeding GF pups an antigen free diet (AFD) protected against IgE elevation [58**]. The gut associated lymphoid tissue (GALT) of GF mice contained increased numbers of IL-4 producing T follicular helper cells (TFH), a subclass of CD4+ T cells that regulate memory B cell and plasma cell differentiation, that were critical for the elevated IgE phenotype (Fig. 1) [58**]. TFH cell numbers were slow to recover in adult GF mice after TFH depletion, and adult mice produced fewer TFH cells than younger mice when they were switched from an AFD to normal mouse chow. These data suggest that the majority of food antigen-specific TFH cells are generated in early life, rather than replenished with new cells throughout life, which again emphasizes the importance of immune conditioning during early life [58**]. IgE levels remained high in GF mice even after depletion of TFH cells or heavy irradiation, suggesting that IgE levels are maintained by long-lived IgE producing plasma cells and making TFH cells a poor target to reduce IgE levels in FA patients [58**]. Interestingly, while GF mice produced higher levels of OVA specific IgE following sensitization compared to conventionally colonized mice, they were protected from systemic allergic responses [59]. Both at baseline and after sensitization, GF mice had reduced number of mast cells and mast cell protease 1 (MCPT1) levels, and these mast cells were less mature and had reduced functionality compared to conventional mice [59].

Atopic individuals have an altered microbiota signature, raising the question as to whether the composition of the microbiome can be manipulated to protect against allergic disease [15]. Fecal samples taken from cow's milk allergic (CMA) and healthy volunteer (HV) infants had 58 operational taxonomic units (OTUs) that were differentially abundant, and the HV group contained significantly more OTUs that were potentially protective [60**]. GF mice colonized with microbiota from CMA infants anaphylaxed after oral sensitization and challenge, and had significantly higher levels of serum IgG1, IgE, and mMCPT-1 compared with HV microbiota colonized mice, which were protected from anaphylaxis [60**]. *Anaerostipes caccae* was enriched in the ileum of HV colonized mice, and monocolization of GF mice with *A. caccae* protected against anaphylaxis and type two immune responses following sensitization and challenge [60**]. A similar study found that stool from children with egg allergy or sensitization had a significantly different microbiome composition with greater alpha diversity and community richness and increased abundance of phyla *Firmucutes* and *Verrucomicrobia* compared to healthy controls [61]. After adjusting for age, eczema severity, breastfeeding, and antibiotic usage, the microbiota of children with egg allergy was enriched for genera *Ruminocuccus* and *Lactococcus*, while *Leuconostoc* was enriched in that of HV [61]. In the egg sensitized group, after adjusting for age and race, the microbiota was enriched for the genera *Roseburia* and *Faecalibacterium* [61]. In contrast, a different study found no difference in microbial diversity comparing allergic or sensitized patients to controls when they grouped all food allergies together [62]. Looking at specific genera, *Haemophilus*, *Dialister*, and *Clostridium* were associated with food sensitization, while *Citrobacter*, *Oscillospira*, and *Lactococcus* were associated with FA, and *Dorea* was associated with both FA and sensitization [62]. Thus, two studies found that egg allergy or FA in general were associated with enrichment of the genera *Lactococcus* [61,62]. Comparing patients with FA, food sensitization, or controls, 6 OTUs, all within genus *Bacteroides*, were positively associated with sphingolipid metabolites, food sensitization, and invariant natural killer T cell (iNKT) activation [63]. It was hypothesized that α-galactosylceramide, a sphingolipid that is likely produced by *B. fragilis*, contributes to the increased iNKT cell activation in food sensitized patients and may have a protective effect [63]. Athough less well-studied, additional evidence suggests that the skin microbiome may also have a modulating effect on FA susceptibility. In the LEAP study, children with *S aureus* skin colonization were more likely to develop peanut allergy and have persistent egg or peanut allergy independent of eczema severity [64].

Given the growing evidence that dysbiosis contributes to the pathogenesis and potential rise in FA, there has been increasing interest in identifying factors that contribute to alterations in the microbiota. A recent study found that children who received histamine H2 receptor antagonists (H2Ras), proton pump inhibitors (PPI), or antibiotics during infancy, all of which can alter the gut microbiome, had an increased risk for all FA along with specifically cow's milk, peanut, or egg allergy [65*]. Moreover, PPIs and H2RAs had a dose-dependent effect on the risk of FA, but this was not significant for antibiotic use [65*]. A variety of dietary components can also alter the gut microbiome in a manner that affects susceptibility to FA [66]. Mice fed a high fat diet (HFD) developed obesity and exhibited more severe systemic food allergic reactions, increased mast cell accumulation in the intestine and greater intestinal permeability compared to mice fed conventional chow [67*]. Mice fed a

HFD also exhibited an altered microbiota signature that could be transmitted to GF mice and was conserved over time despite switching the recolonized mice to a standard chow diet [67*]. Moreover, the transmitted microbiota conferred increased food allergic responses and susceptibility independent of an obese phenotype [67*]. Additional studies suggest that specific food components and metabolites produced by commensal bacteria in the gut, including non-digestible-oligosaccharides (NDOs) and short-chain-fatty-acids (SCFAs), can impact food allergy development and severity [66,68,69]. Pretreatment with NDOs slightly reduced IgE-mediated basophil degranulation in blood from peanut allergic patients *in vitro* [70]. SCFAs, including propionate, acetate, and butyrate, are derived from food products such as dairy or fermented from fiber by intestinal bacterial, and their abundance is affected by diet, breastfeeding, and family size [69]. FA and other atopic diseases were less likely to occur in children with the highest levels of butyrate and propionate, whereas high acetate levels were only protective for food sensitization and allergy [69]. Butyrate supplementation of mice during pregnancy and weaning led to an increased percentage of Tregs in the lungs and protection from airway inflammation [69]. Lastly, while general food diversity in early life is protective against allergic diseases, cheese consumption was specifically identified to reduce the risk for food allergy and atopic dermatitis, potentially due to its microbial diversity or relatively high content of SCFAs [71]. Collectively, these studies underscore the importance of environmental factors, including medications and diet, in shaping the microbiome in a manner that influences an infant's risk of developing FA.

CONCLUSION

Oral exposure to food antigens during infancy promotes antigen-specific tolerance that is further supported by immune complexes present in breast milk and the pro-tolerogenic activities of IgG. In contrast, exposure to food antigens via a disrupted skin barrier leads to food sensitization and allergy as a result of the inflammatory actions of ILC2s, mast cells, and IL-33. While Tregs clearly promote tolerance, children with FA do not exhibit defects in circulating antigen-specific Tregs. Commensal microbiota and their metabolites influence susceptibility to FA and are a likely pathway by which environmental factors influence the risk of FA. In the future, strategies to prevent FA may focus on limiting disruption of the skin barrier, encouraging early colonization with commensals that support a tolerogenic response, and promoting early introduction of allergenic foods. In established FA, targeting allergen-specific T effector cells and long-lived IgE secreting plasma cells may be more effective than attempts to expand antigen-specific Tregs.

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KEY POINTS

- Tolerance to food antigens develops early in life through ingestion of food and maternal transfer of immune complexes.
- Disruption of the skin barrier either through disease, genetics, or mechanical injury provides a route of sensitization to food antigens through the action of mast cells, ILC2s, and IL-33 signaling.
- Deficiencies in Tregs are associated with an increased prevalence of allergic disease, although the frequency and function of food-specific Tregs in children with established FA is similar to healthy controls.
- Environmental factors including diet, H2R antagonists, and antibiotics can promote dysbiosis and increase the risk of FA, while healthy infants may harbor microbes that are protective.

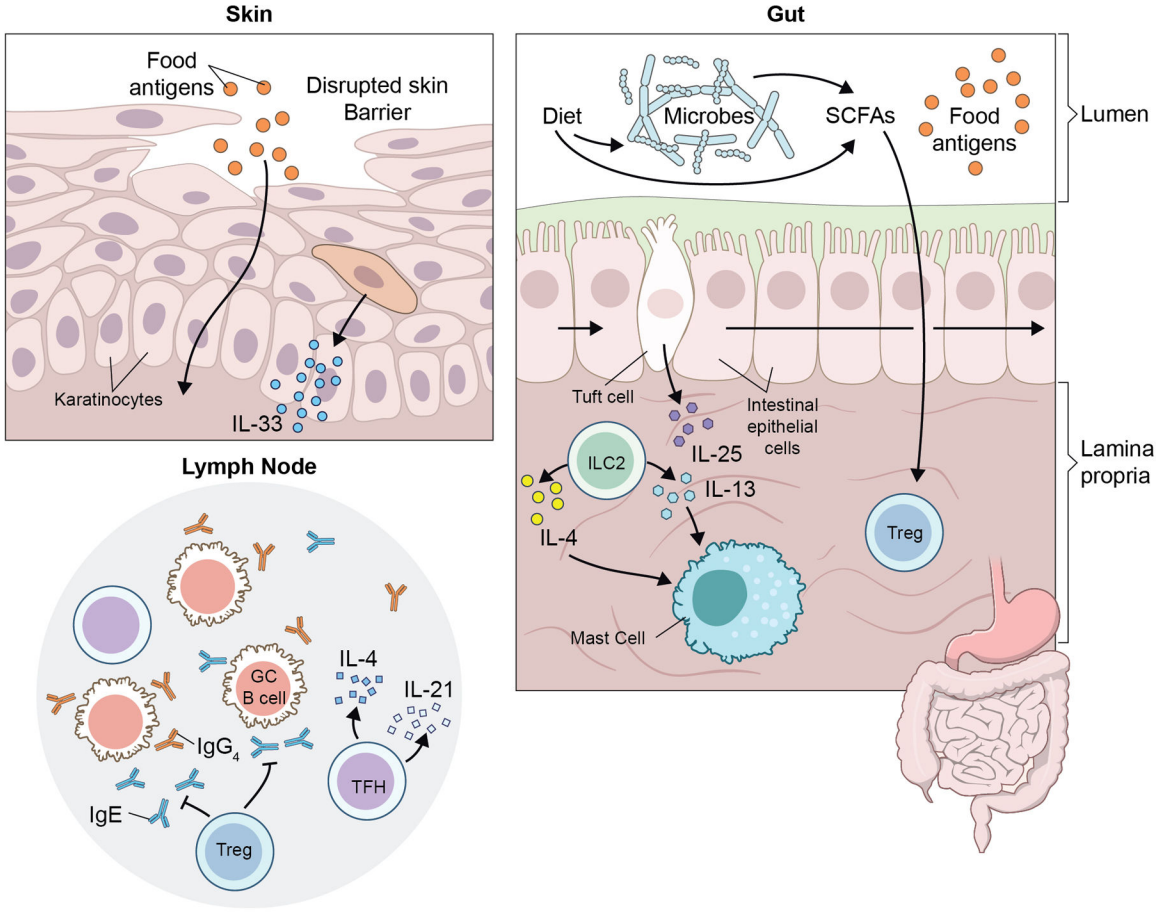

Figure 1.

Barrier integrity and environmental factors affect tolerance and sensitization to food antigens. Disruption of the skin barrier leads to increased sensitization to food allergens and keratinocyte production of IL-33. IL-33 can then act in conjuction with Tuft cell derived IL-25 to activate ILC2s in the gut to recruit mast cells, resulting in an increased allergic response. Diet and metabolites produced by commensal microbiota can affect induction of food antigen-specific Treg and Tfh, and thus allergic sensitization. Tfh direct class switching of food-reactive B cells in the germinal center to either protective IgG4 or pro-allergic IgE.