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Review

The rise of food allergy: Environmental factors and emerging treatments

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ABSTRACT

Food allergy has rapidly increased in prevalence, suggesting an important role for environmental factors in disease susceptibility. The immune response of food allergy is characterized by IgE production, and new findings from mouse and human studies indicate an important role of the cytokine IL-9, which is derived from both T cells and mast cells, in disease manifestations. Emerging evidence suggests that route of exposure to food, particularly peanut, is important. Exposure through the skin promotes sensitization while early exposure through the gastrointestinal tract promotes tolerance. Evidence from mouse studies indicate a role of the microbiome in development of food allergy, which is supported by correlative human studies showing a dysbiosis in food allergy. There is no approved treatment for food allergy, but emerging therapies are focused on allergen immunotherapy to provide desensitization, while pre-clinical studies are focused on using adjuvants or novel delivery approaches to improve efficacy and safety of immunotherapy.

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1. Introduction

Food allergy is defined as "*an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food*" (Boyce et al., 2010) or as "*an adverse reaction to food in which immunologic mechanisms have been demonstrated*" (Muraro et al., 2014). This definition includes acute IgE-mediated type-I hypersensitivity reactions, such as hives, wheezing, or vomiting after exposure to common allergens such as peanut, milk, or egg. In addition, there are non-IgE-mediated food allergies that are characterized by delayed gastrointestinal reactions to foods, such as food protein induced enterocolitis syndrome (FPIES) or proctocolitis. Eosinophilic gastrointestinal disorders (EGID) are also commonly triggered by foods. This review will focus

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on IgE-mediated food allergy, which is the most common and best-understood category of food allergy. Readers are referred to recent reviews on the pathophysiology of FPIES (Berin, 2015) or EGID (Rothenberg, 2015). (See Table 1.)

Food allergy is increasing in prevalence (Savage and Johns, 2015) for reasons that are not yet clear. A rigorous population-based study utilizing food challenges to demonstrate food allergy showed that approximately one in 10 Australian children had a food allergy at one year of age (Osborne et al., 2011). Estimates in the US and Canada indicate a prevalence rate of 1 in 15 to 1 in 20 (Soller et al., 2012; Sicherer and Sampson, 2014). Factors such as hygiene and lack of exposure to microbial factors, composition of the intestinal microbiota, diet, obesity, Vitamin D, and environmental chemical exposure have all been proposed to contribute to this alarming rise in the rate of food allergy in countries with a Westernized lifestyle. This review will review recent advances in our understanding of the pathophysiology of food allergy, and identify new approaches for the treatment of food allergy.

2. Mechanism of anaphylaxis

IgE-mediated food allergy is triggered by allergen cross-linking of IgE bound to the surface of mast cells or basophils, as in a typical type I hypersensitivity reaction. The most severe manifestation of food allergy is anaphylaxis, which is an acute reaction affecting 2 or more organ systems that can be life threatening (Kim and Fischer, 2011; Muraro et al., 2014; Simons and Sampson, 2015). Although IgE-mediated activation of tissue mast cells and circulating basophils is thought to represent the major source of mediators that contribute to the pathology of anaphylaxis (Kalesnikoff and Galli, 2010), other cell types such as neutrophils and macrophages and other antibody isotypes such as IgG have been described to contribute to anaphylaxis (Jonsson et al., 2011; Tsujimura et al., 2008; Strait et al., 2002). The existence of these alternative pathways of anaphylaxis has not yet been described in humans.

Histamine correlates with anaphylaxis severity (Brown et al., 2013) and histamine receptor blockers are the first line treatment to relieve mild to moderate allergy symptoms. In addition, platelet-activating factor (PAF) shows a pivotal role as a mediator of anaphylaxis in mice (Arias et al., 2009) as well as in humans (Vadas et al., 2012), where levels correlate with anaphylaxis severity. PAF receptor antagonists, which inhibit the binding of PAF to the receptor, reduce mortality associated with anaphylaxis in animal models (Arias et al., 2009), and deficiency of PAF-AH (PAF acetylhydrolase), the enzyme that inactivates PAF, predisposed patients to severe anaphylaxis (Vadas et al., 2008), demonstrating the role of this pathway.

Table 1
Glossary of food allergy related terms.

Term	Definition
IgE-mediated food allergy	Adverse reaction to a food source mediated by the cross-linking of specific IgE bound to mast cells and basophils through FcεRI.
Non-IgE mediated food allergy	Adverse reaction to a food source that is not mediated by IgE. Symptoms are typically delayed (hours) and are thought to be cell mediated.
Anaphylaxis	Acute, systemic reaction that can occur within minutes of exposure and includes symptoms such as vomiting, skin rash, rapid and weak pulse, abdominal pain, swollen throat, trouble breathing or swallowing, diarrhea, chest tightness.
Sensitized	Having positive IgE to the allergen, with or without symptoms
Allergic	Sensitized individual with allergic symptoms to the allergen
Th2	T helper cells producing IL-4 and IL-13
Tfh	T helper cells homing to lymph node follicles (and identified as CXCR5+) and enabling B cell isotype switching
Treg	Regulatory T cell, mostly commonly a CD4+ T cell expressing the transcription factor Foxp3
Epithelial cytokines	TSLP, IL-33, IL-25 are epithelial-derived cytokines that can promote the generation of Th2 cells
Allergen-specific immunotherapy	Prolonged treatment consisting in the administration of increasing amount of a specific allergen to reduce symptoms. It can be applied by different routes:
SLIT	Sublingual immunotherapy: the allergen is given as drops under the tongue.
OIT	Oral immunotherapy: the allergen is administered orally.
EPIT	Epicutaneous immunotherapy: the antigen is applied on the skin using a patch or similar device.
Desensitization	Clinical non-responsiveness while antigen-specific immunotherapy is maintained
Clinical tolerance	Sustained clinical non-responsiveness to food allergen after discontinuation of therapy

3. Immune profile of food allergy

Despite the fact that IgE plays a central role in the pathogenesis of food allergy, measurement of food-specific IgE is not diagnostic in isolation. Quantification of food-specific IgE antibody levels in serum can identify patients in the pediatric population who are highly likely (>95%) to experience clinical reactions to egg, milk, peanut or fish, as recently reviewed (Chokshi and Sicherer, 2016). However lower levels poorly discriminate between those who are sensitized versus allergic. Detection of IgE reactivity against components of food (for example the protein allergen Ara h 2 in peanut or Cor a 14 for hazelnut) improves specificity (Klemans et al., 2015; Beyer et al., 2015; Eller and Bindslev-Jensen, 2013). Ara h 2 is digestion-resistant and can trigger systemic reactions while Ara h 8 is cross-reactive with birch pollen allergens (and can result in positive IgE to peanut in birch pollen-allergic individuals), is susceptible to digestion, and does not trigger systemic reactions. IgE levels against whole peanut extract would not discriminate between IgE to these two allergens with differing potential to trigger reactions. Antibody isotypes other than IgE, such as IgG and IgA, are not predictive of food allergy. However, ratio of egg white allergen-specific IgE/IgG4 has been shown to be better than IgE levels alone in predicting clinical reactivity to egg (Okamoto et al., 2012; Caubet et al., 2012).

For the production of IgE antibodies, B cells require help from allergen-specific T cells producing IL-4, either Th2 or T follicular helper (Tfh) cells. T cells from allergic patients display a uniquely Th2 cytokine production profile (Prussin et al., 2009). IL-9 production from a T cell subset distinct from those producing IL-5 was recently reported to differentiate between children with peanut allergy and children with peanut sensitization (Brough et al., 2014). In addition, it was recently reported in mice that a population of intestinal mast cells express IL-9, promote experimental food allergy in an IL-9-dependent manner, and are dependent on Th2 cells for their development (Chen et al., 2015). Furthermore, the authors showed that in patients with food allergy, duodenal biopsies had elevated expression of genes associated with the mast cell signature (IL-9, IL-13, chymase, and tryptase). Thus innate events in the intestinal tissue may be critical for linking systemic Th2-skewed adaptive responses to symptoms.

Food allergy is commonly referred to as a failure of oral tolerance, a systemic state of antigen-specific immune suppression that is mediated by regulatory T cells. However, there is little information on the role of Tregs in food allergy. In mouse models, administration of Tregs can suppress food allergy (Burton et al., 2014). Furthermore, in mice genetically susceptible to food allergy there is an impairment of Treg function, and evidence of Th2 reprogramming such that Tregs contribute to Th2 cytokine production rather than suppress it (Noval Rivas et al., 2015). This was also observed in peripheral blood of subjects with milk allergy (Noval Rivas et al., 2015), supporting the hypothesis that food allergy is a failure of regulatory T cells.

4. Emerging evidence for the role of the skin in food allergy

There is growing evidence pointing to the skin as the main site of sensitization to food allergens, particularly peanut. The majority of patients with peanut or tree nut allergy experienced their first reaction the first time that the food was knowingly ingested, so previous

sensitization to the allergen has been proposed to occur in utero, through breast-milk, or by another route of exposure, such as topical exposure. Ezcema is a risk factor that strongly associated with food allergies (Martin et al., 2015). Infants presenting with eczema were 11 times more likely to present peanut allergy and 6 times more likely to have egg allergy, suggesting that alteration of the skin barrier facilitates contact with the allergen. Moreover, mutations in filaggrin, a protein essential to maintain skin barrier, have been associated with increased risk of food allergy (Brown et al., 2011).

High levels of environmental exposure to peanut due to household consumption during infancy have been related with sensitization (Fox et al., 2009). There is a positive correlation between high peanut consumption and the presence of peanut proteins in the house dust (Brough et al., 2013; Trendelenburg et al., 2013), which has also been shown for other allergens including fish, milk or egg (Bertelsen et al., 2014). These peanut dust proteins are biologically active and able to activate immune system cells (Brough et al., 2013). In addition, the use in infants of preparations containing peanut oil has been associated with peanut allergy (Lack et al., 2003) and the same association has been found between wheat allergy and exposure to wheat protein in facial soap (Fukutomi et al., 2014). Immune profiling of allergen-responsive T cells also supports the hypothesis of skin priming. T cells from peanut-allergic individuals that expressed the skin-homing marker cutaneous lymphocyte antigen (CLA) had increased proliferation to peanut compared to those expressing β7, one component of the α4β7 gastrointestinal-homing molecule (Chan et al., 2012). Similarly, CD4 + T cells from peanut-allergic individuals that were reactive to the peanut allergen Ara h 1, identified using Ara h 1-specific tetramers, expressed the skin-homing marker CCR4 but low levels of β7 (Delong et al., 2011). These homing receptor studies are supportive of the concept of skin priming.

Although environmental peanut exposure has been postulated as a risk factor for food allergies, exposure to allergens via the skin does not by default lead to sensitization. For example, mice exposed to milk or soy allergens by topical application only develop sensitization when exogenous adjuvants are co-administered (Dunkin et al., 2011; Tordesillas et al., 2014). Staphylococcal enterotoxin B (SEB), which is found to be produced by bacteria colonization lesional skin in patients with atopic dermatitis (Boguniewicz and Leung, 2010), can promote topical sensitization to foods in mice (Tordesillas et al., 2014). Other factors that promote sensitization through the skin include damage, such as that caused by tape stripping that models damage induced by scratching in eczema. Some allergens can induce sensitization in the absence of any exogenous adjuvant or damage. Peanut or tree nuts can induce sensitization when applied topically on the skin without any external adjuvant, which in the case of peanut was shown to be due to intrinsic adjuvant activity (Tordesillas et al., 2014).

Innate immune responses in the skin are critical for promoting sensitization to foods. Tape stripping upregulates TSLP which acts on skin DCs to promote Th2 skewing (Han et al., 2014). Peanut exposure drives Th2 cell induction by inducing IL-33 production from keratinocytes, which subsequently modifies the phenotype of skin-draining dendritic cells through its receptor ST2 (Tordesillas et al., 2014). In models driven by adjuvants or skin damage, TSLP, IL-6, and IL-1β contribute to the generation of Th2 and Tfh cells (Noti et al., 2013; Tordesillas et al., 2014). Thus, multiple immune mechanisms by a variety of environmental triggers can lead to Th2 skewing and IgE production when allergen exposure occurs via the skin.

The dual exposure hypothesis of food allergy proposes that exposure through the skin promotes sensitization, while early exposure through the gastrointestinal tract is tolerogenic. This is supported by clinical findings that early consumption of food, such as peanuts, fish or wheat is associated with a lower incidence of food allergy (Du Toit et al., 2008; Kull et al., 2006; Poole et al., 2006). To directly assess the impact of early oral introduction, infants with eczema were randomized to ingest egg or placebo at 4 months of age (Palmer et al., 2013). There was a trend toward lower frequency of egg allergy in the group that received dietary egg. However, there was a high frequency of children already clinically reactive to egg at 4 months. Early introduction of dietary peanut was tested in the LEAP (Learning Early about Peanut Allergy) study (Du Toit et al., 2015). Introduction of peanut in the diet of infants at high risk for peanut allergy (beginning at ages 4–11 months) was associated with a dramatically reduced frequency of peanut allergy compared to avoidance. To determine if this clinical response was consistent with sustained immune tolerance, subjects strictly avoided peanut for a year before being *re*-evaluated for peanut allergy. Results showed a sustained protection from peanut allergy in those who had ingested peanut early in life (Du Toit et al., 2016). Expanding the early dietary introduction to a general population and including 6 foods (EAT study) showed no significant effect in an intention-to-treat analysis, but did show a suppression of peanut and egg allergy in a per-protocol analysis. The investigators reported that compliance in introducing all 6 foods was poor, indicating that introduction of a diverse set of foods in early life may not be a simple task (Perkin et al., 2016). The tolerogenic response to foods encountered through the gastrointestinal route in early life is consistent with the concept of oral tolerance, which is a state of antigen-specific systemic unresponsiveness that is mediated by Tregs educated by a tolerogenic population of gastrointestinal DCs (Berin and Shreffler, 2016). See Fig. 1 for a schematic illustrating the site-dependent hypothesis of food allergy and tolerance.

5. Role of the intestinal microbiota in susceptibility to food allergy

Epidemiologic factors protective against food allergy includes having older siblings and pet exposure in early life (Peters et al., 2015). Pet ownership is associated with a high microbial diversity in the home environment (Fujimura et al., 2010) and administration of dust from pet-owning home into mice was shown to be protective against experimental asthma (Fujimura et al., 2014). The early life colonization of the gastrointestinal tract by bacteria important for normal immune development is also affected by factors including mode of delivery and dietary intake, which have been shown to alter risk of food allergy.

The fetal gut is believed to be sterile, although several reports have described meconium (first infant stool) microbiota composition, suggesting that microbial colonization may begin already in utero (Moles et al., 2013; Gosalbes et al., 2013). The four major bacteria phyla in the intestine (Actinobacteria, Bacteroides, Firmicutes, and Proteobacteria) have been found in meconium. Experimental studies in pigs indicate that the establishment and development of a normal gut microbiota and immune system require continuous microbial exposure during the first months of life, and that can be compromised by excessive hygiene (Schmidt et al., 2011). It has been suggested that the composition and diversity stabilize and reach the level of adult microbiota within the first three years of life (Yatsunenko et al., 2012).

To determine if early life microbiota could influence the development of food allergy, a prospective study assessed fecal microbial composition by 16S rRNA sequencing at 3 and 12 months of life and compared infants with and without food sensitization (Azad et al., 2015). Low fecal microbial richness at 3 months preceded food sensitization as measured at 12 months, whereas concurrent richness at 1 year was not associated with food sensitization (Azad et al., 2015). Enterobacteriaceae were overrepresented while Bacteroidaceae were underrepresented in food sensitized infants. Bacteroidaceae have been described as a dominant feature of a mature intestinal microbiota, and therefore these findings suggest a delayed maturation of the food allergic microbiota. These findings were consistent with previous studies where low microbial diversity in early infancy (1 week and 1 month, respectively) was found to predict atopic dermatitis (Wang et al., 2008; Abrahamsson et al., 2012), and suggest that the composition of microbiota in early life contributes to susceptibility to food allergy.

Cross-sectional studies comparing the intestinal microbial composition of food allergic to healthy subjects have also been performed. Fecal

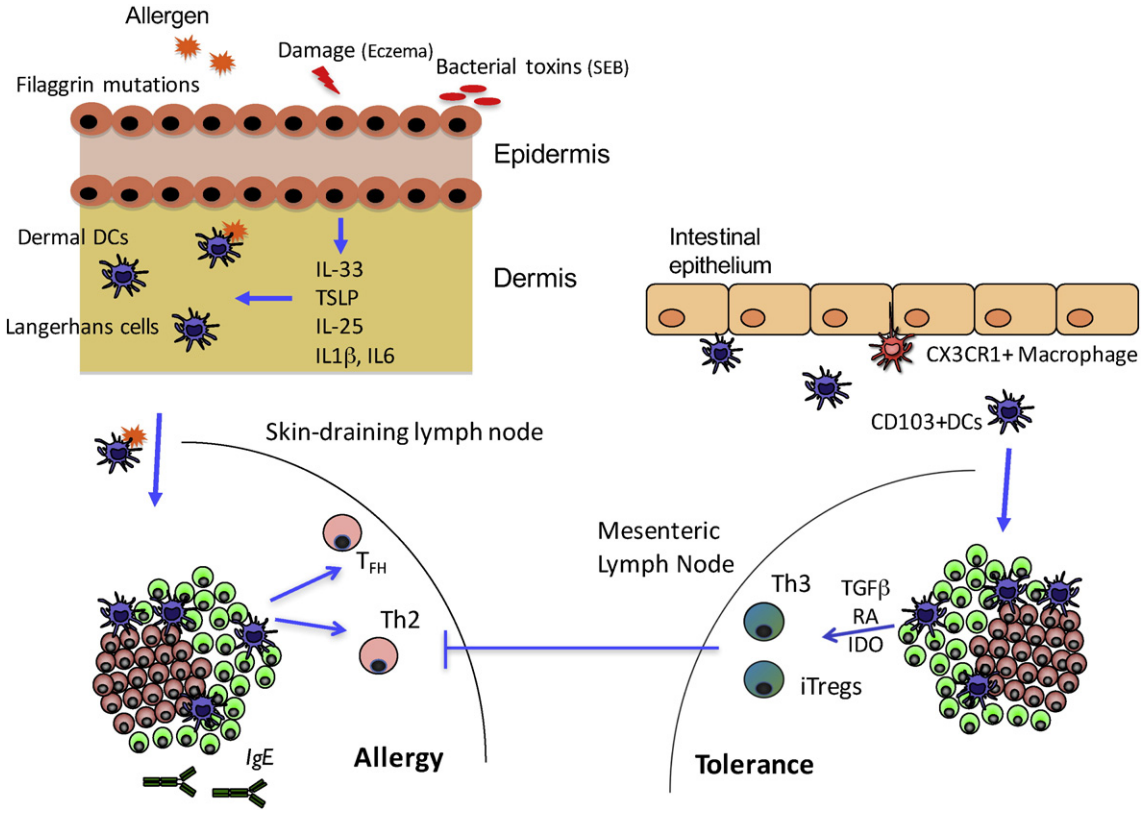

Fig. 1. Allergen exposure through the skin in the presence of skin damage, filaggrin mutation or bacterial toxins (SEB) promotes sensitization. Depending on the nature of the allergen and adjuvant, epithelial cells produce cytokines that instruct dendritic cells on the skin. They transport the antigen to the skin-draining lymph nodes, where Th2 and T follicular helper (Tfh) cells are generated and promote IgE class-switching. Antigen exposure by oral route leads to tolerance. CX_3CR1+ macrophages sample antigen from the lumen and transfer it to CD103 + DCs that transport the antigen to the mesenteric lymph nodes and promote the induction of Tregs. Oral tolerance can prevent the development of sensitization through the skin.

microbial composition was assessed using 16S rRNA sequencing to study differences between children with food allergy ($n = 17$ with IgE-mediated food allergy, $n = 17$ with non-IgE-mediated food allergy) and healthy controls ($n = 45$) (Ling et al., 2014). There was no difference in microbial diversity between groups. Subjects with IgE-mediated food allergy had increased levels of *Clostridium* sensu stricto and *Anaerobacter* and decreased levels of *Bacteroides* and *Clostridium XVIII* (Ling et al., 2014). Levels of *Clostridium* sensu stricto also correlated with levels of IgE. Hua et al recently reported findings from the publically available American Gut Project (Hua et al., 2016). Of 1879 participants (primarily adult, mean age 45 years), 2.5% self-reported allergy to peanuts, 3.2% to tree nuts, 2.6% to shellfish, and 9.1% to other foods. There was a marked reduction in microbial richness and alpha diversity (i.e. number of taxa) in those self-reporting peanut or tree nut allergy compared to those without peanut or tree nut allergy. There were also significant differences in beta diversity (i.e. composition of the microbiota) in those with peanut or tree nut allergy. In contrast to the previous study, there were increases found in *Bacteroides* in those with peanut or tree nut allergy. The compositional differences found were not unique to food allergy, and were also associated with seasonal allergies. As with any cross-sectional design, it is not possible to assess causation between changes in microbial composition and food allergy.

It has been demonstrated that commensal bacteria regulate the production of IgE. Germ-free mice have increased levels of IgE, and colonization of germ-free mice with a diverse microbial population during a critical window early in life suppresses IgE and prevents mice from development of food allergy (Cahenzli et al., 2013). There is evidence that a difference in microbial composition can increase susceptibility to food allergy. Mice genetically susceptible to food allergy exhibit a specific gut microbiota signature capable of transmitting disease susceptibility (Noval Rivas et al., 2013). In this study, the authors showed that food allergy-prone mice with a gain-of-function mutation in the IL-4 receptor a-chain (*Il4raF709*) are susceptible to oral sensitization with OVA. OVA-sensitized *Il4raF709* mice exhibited a specific intestinal microbiota signature, which could be transferred to germ free mice by oral administration of fecal pellets. Recipient mice then developed susceptibility to food allergy (Noval Rivas et al., 2013). Commensal organisms that are protective against development of food allergy have been identified. Indigenous *Clostridium* species promoted Treg cell accumulation in the large intestine of mice, and inoculation of either mouse or human Clostridia strains attenuated disease in a mouse model of food allergy (Atarashi et al., 2011; Atarashi et al., 2013). Similarly, selective colonization of germ free mice with a clostridia-containing microbiota protected against sensitization to peanut (Stefka et al., 2014). In addition to Clostridium species, other bacterial strains have also been identified to induce Tregs in the gastrointestinal tract (Faith et al., 2014). The protective effect of commensal organisms has been shown to be regulated by metabolic products, such as short chain fatty acids (Smith et al., 2013), suggesting that factors such as high fiber diet that also promote short chain fatty acids may have a similar protective effect. Although the focus of studies to date has been on the composition of the intestinal microbiota, the skin also hosts an underappreciated commensal microbiota that regulates the immune tone of the skin (Naik et al., 2015) and may contribute to food allergy.

6. Role of dietary factors

The relationship between diet during infancy (other than the allergenic food itself) and development of allergic diseases remains poorly understood. Exposure to an increased diversity of foods in early life is inversely associated with allergic diseases including food allergy (Roduit et al., 2014). But there are relatively few studies identifying specific dietary components that might be a risk for the development of food allergy.

Infants can be breast-fed, formula-fed, or experience the combination of both. The bacterial composition of the breast milk varies depending on maternal dietary habits, the genetic background, and demographic factors. Cessation of breastfeeding is a more significant factor in the composition of the intestinal microbiota than the introduction of solid foods (Backhed et al., 2015). In addition to modulating microbiota, breast milk is an immunologically complex solution that confers immunological protection when the infant's immune system is immature. Breast milk-derived immunomodulatory and protective properties have been linked to several components, including immunoglobulins, glycoconjugates and oligosaccharides, antioxidants and fatty acids, glutamine and dietary nucleotides, hormones, growth factors, and cytokines. There is a lack of unifying immune evidence on the impact of breastfeeding on development of food allergy (Matheson et al., 2012). Levels of immunomodulatory cytokines including those that modulate IgA production are different in the breast milk of mothers whose infants develop cow's milk allergy versus those who do not (Jarvinen et al., 2015). Furthermore, dietary cow's milk avoidance by mothers is associated with low cow's milk-specific IgA in breast milk, low cow's milk-specific IgG and IgA in infant serum, and development of cow's milk allergy in infants (Jarvinen et al., 2014). Reverse causation (changing of maternal diet or breastfeeding in response to symptoms in the infant) is a major confounding factor in studies of the role of breast milk on development of food allergy, and prospective studies are needed to determine causation.

Vitamin D deficiency is associated with food sensitization (Baek et al., 2014), as well as IgE-mediated food allergy (Allen et al., 2013). Infants from Australian-born parents with vitamin D insufficiency had increased likelihood of egg and peanut allergy (Allen et al., 2013). By contrast, elevated levels of vitamin D during pregnancy and at birth have been associated with high risk of food allergy (Weisse et al., 2013). The frequency of food allergy/anaphylaxis is higher at higher absolute latitudes where there is insufficient UVB intensity in the autumn and winter months for adequate vitamin D synthesis (Mullins and Camargo, 2012). Low vitamin D results in compromised barrier function, altered microbial composition of the gut, and together with effects on antigen presenting cells and T cells predisposes an individual to allergic responses to food allergens (Vassallo and Camargo, 2010).

Other dietary factors that suppress food allergy include aryl hydrocarbon receptor ligands, found in cruciferous vegetables such as cabbage, Brussels sprouts, and broccoli (Schulz et al., 2011). Ingestion of n−3 long chain polyunsaturated fatty acids (PUFA), and non-digestible oligosaccharides can also suppress food allergy in mice through induction of Tregs (Schouten et al., 2012; Van Den Elsen et al., 2013). Dietary factors may be directly immunomodulatory, or may suppress food allergy through modulation of the intestinal microbiota (Wu et al., 2011). See Fig. 2 for a schematic illustrating the role of microbiota and the diet in allergy and tolerance to foods.

7. Emerging treatments for food allergy

Currently the standard of care for food allergy is strict food avoidance and use of epinephrine injection pens for accidental exposures. As discussed in previous sections, prevention strategies can be highly effective but once allergy is established immune tolerance through intervention is difficult to achieve.

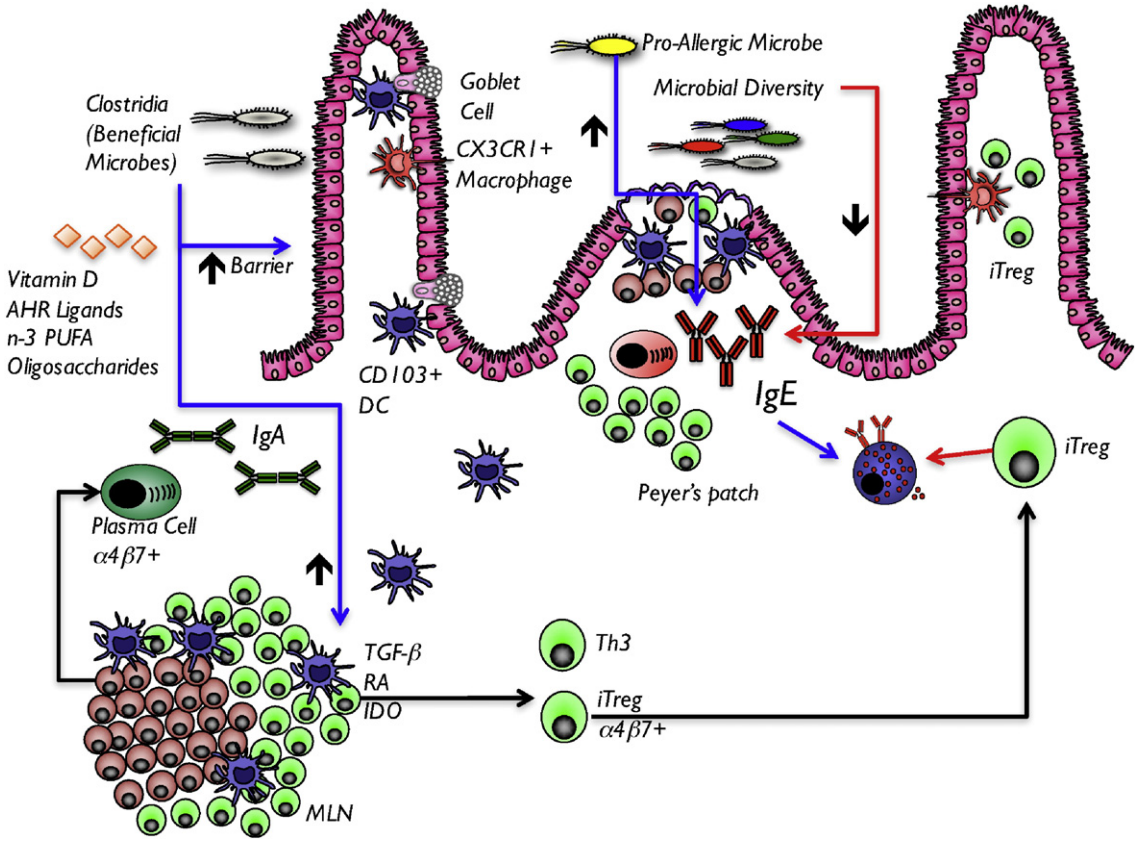

Fig. 2. Microbiota and diet influence the development of allergy and tolerance. Microbial diversity suppresses IgE class-switching, which occurs within the Peyer's patch. Strains of bacteria including Clostridia have been shown to suppress allergy, and to enhance the generation of Tregs and improve epithelial barrier function. There is also evidence that microbial composition can promote food allergy, suggesting the role of pro-allergic bacteria. Nutrients including vitamin D, aryl hydrocarbon receptor (AHR) ligands, polyunsaturated fatty acids (PUFA) and oligosaccharides can also suppress food allergy through enhancement of regulatory responses.

7.1. Allergen Immunotherapy

Allergen immunotherapy is an approach to desensitization in which increasing amounts of allergen are administered to reduce reactivity of allergic effector cells. Oral immunotherapy (OIT) provides effective desensitization allowing the majority of subjects to pass a full food challenge after 2–4 years of treatment. Persistent adverse reactions leading to immunotherapy termination occur in approximately 10–20% of subjects (Burks et al., 2012; Narisety et al., 2015). A high proportion of individuals who achieve desensitization develop clinical reactivity if treatment is stopped {Vickery, 2014 #30}. The use of anti-IgE (omalizumab) together with OIT was recently reported to improve the safety of OIT without having significant effects on long term efficacy (Wood et al.). Other routes of immunotherapy, including the sublingual and epicutaneous routes, demonstrate increased safety in comparison to OIT, but at a cost of lower efficacy (Keet and Wood, 2014). Other approaches to improve safety include the use of allergens with mutated IgE binding sites (Wood et al., 2013), peptides lacking the ability to cross-link IgE (Kulis et al., 2012), and allergens chemically modified to destroy conformational epitopes (van Hoffen et al., 2014).

The mechanisms by which allergen immunotherapy leads to clinical protection involves the production of blocking antibodies such as IgA and IgG4 (Vickery et al., 2014), reduction in basophil and mast cell reactivity, generation of regulatory T cells (Syed et al., 2014) and an altered DC phenotype facilitating increased Treg generation and reduced Th2 skewing (Syed et al., 2014; Gorelik et al., 2015). The mechanism of this altered DC phenotype is poorly understood, but human DCs have the capacity to respond to allergens via surface expression of a form of the high affinity IgE receptor FcεRI.

7.2. Adjuvants and Immunomodulation

To date, immunotherapy has primarily been administered as allergen in the absence of other immunomodulation. Bacterial vectors carrying peanut allergens failed in human trials due to reactions to the therapy (Wood et al., 2013), despite many strategies to improve safety including allergen modification, bacterial encapsulation, and intrarectal delivery. The immune consequence of administration was not studied in detail. Other approaches include the use of CpG, either as a soluble adjuvant (Kulis et al., 2013) or encapsulated with allergen within nanoparticles (Pali-Scholl et al., 2013). Inhibition of the mTOR signaling pathway with rapamycin has been shown to suppress food allergy in mice (Yamaki and Yoshino, 2012), and recently it was shown that selective delivery of antigen plus rapamycin within nanoparticles could effectively prevent, and partially treat, food-induced anaphylaxis through induction of regulatory mechanisms (Maldonado et al., 2015). The use of autologous cells as regulatory adjuvants has been demonstrated using allergen-coated splenocytes in mice, which effectively prevents, and partially treats, peanut-induced anaphylaxis (Smarr et al., 2011).

7.3. Microbial therapies

The finding that *Clostridia* strains can suppress allergy in mice (Stefka et al., 2014; Atarashi et al., 2013) suggests the potential use of microbial therapeutics to enhance the development of tolerance when given with allergen immunotherapy. The probiotic *Lactobacillus rhamnosus* GG was recently used together with peanut OIT to effectively induce desensitization compared to placebo, but no OIT group was included as control so it is unclear if there was added efficacy due to the probiotic (Tang et al., 2015). There is currently a great interest in the potential of microbial therapeutics to prevent or treat allergic diseases.

7.4. Future directions

Prevalence of food allergy, particularly peanut allergy, has risen remarkably in the last decades, leading to investigation of contributing environmental factors. Diet and composition of the microbiota are two major inter-related factors that can modify susceptibility to food allergy. Future studies focusing on the intestinal microbiota are needed in human subjects and mouse models to develop rational microbial therapeutics (next-generation probiotics) for the prevention of food allergy. In addition to the intestinal microbiota, the commensal microbiota of the skin needs to be addressed since there is growing evidence that the skin is a site of sensitization to foods. Allergen immunotherapy by the oral, sublingual, or epicutaneous routes show differing levels of efficacy and safety. Studies are needed to test the feasibility of adjuvants (or microbial therapeutics) to optimize the tolerogenic potential of allergen immunotherapy, as well as novel delivery vehicles or allergen modifications to improve safety.

8. Search strategy and selection criteria

Data for this review were identified by searches in PubMed. The references were selected based on the most impactful journals and, when possible, published in the last 5 years. Only articles published in English were included.

Conflict of interest

The authors have no relevant disclosures to report.

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