

Review

Balancing Tolerance or Allergy to Food Proteins

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Dietary proteins usually induce immune tolerance, but may trigger life-threatening immune responses in the case of food allergy. The associated type 2 immunity, linked with specific IgE production and the activation of mast cells and basophils, is well understood but the mechanisms related to preventing food allergy are still being deciphered. Recent insights into the mechanisms that regulate oral tolerance and dietary antigen sampling have revealed unique regulatory events that occur during early life and into adulthood. Drawing from both recent clinical and experimental discoveries, this article focuses on current evidence for how several key stages of life present mechanistic points that might participate in tipping the balance between food protein tolerance and allergy.

Increasing Prevalence of Food Allergies

Despite of its increasing prevalence and recognition, food allergy is clearly not a new problem. In 1928 Albert Rowe elegantly outlined the clinical history of a patient with food allergy and his successful experience with an elimination diet [1]. In stressing the importance for considering family history of atopy, the inconsistencies of skin testing, the psychological aspects of food aversions being discounted as ‘whims or fancies’ by physicians, and several key foods to be eliminated, Rowe imparts opinions that seem far ahead of their time. The past decade has been an incredibly important window in helping to shine a spotlight on food allergy as a disease. A wealth of studies have helped to highlight the limited treatment options for food allergy, escalating prevalence, continued difficulties in diagnosis, and the sociological impact on health and well-being. By contrast, our mechanistic understanding of the processes that limit most of us from exhibiting immunological reactions to foods has remained largely incomplete. Recent breakthroughs in this area have finally allowed us to glimpse the sophisticated and complex events that allow us to partake in something as simple as eating.

The key immunological mechanisms thought to contribute to the allergic sensitization responses (particularly dominated by allergen-specific IgE) and the processes of reactivity (particularly the most severe forms, including anaphylaxis) have been reviewed previously [2]. Instead, this review examines the evidence for how the immune system exerts a balance over our responses to dietary antigens during several key stages of development, drawing significantly from epidemiological studies of food allergy. The disruption of this balance, through relatively unknown causes, is likely responsible for the sensitization and ultimately the reactivity to food antigens. It is interesting to note that these two events that are seemingly independent because, somewhat surprisingly, food sensitization remains much more common than food allergy.

Neonatal and Early-Life Influences on Food Allergy Development

The proteins in foods represent an important nutrient component that is transmitted from mother to embryo. A recent study of 20 healthy women during two distinct stages of pregnancy described the detection of several major food allergens in amniotic fluid [3], suggesting that

Trends

Food allergy has become an important clinical problem as its prevalence increases across the world.

Successful clinical trials on early introduction of foods have demonstrated the importance of early oral exposure in prevention.

The sampling of dietary proteins by the intestinal immune system imparts specialized and localized tolerance processes that occur independently from microbe-driven responses.

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our first experience of dietary allergens occurs *in utero*. Owing to the need to suppress maternal immunity towards paternal antigens, the fetal microenvironment represents a uniquely specialized site of tolerance, but how this contributes to establishing immune tolerance to foods is unknown. Cord blood has provided an opportunity to interrogate this maternal–offspring interface and has demonstrated intriguing findings. In a recent prospective study that examined the cord blood immune profiles from newborns, it was found that individuals that would ultimately develop food allergies presented a higher ratio of monocytes to CD4⁺ T cells and lowered numbers of regulatory T cells (Tregs) [4]. Functionally, the CD14⁺ monocytes isolated from these cords also displayed a heightened innate inflammatory response (IL-1 β , IL-6, and tumor necrosis factor, TNF) when stimulated by the bacterial ligand lipopolysaccharide (LPS), suggesting an intrinsic alteration in their activation potential. The authors connected this with the disruption of tolerance and priming towards Th2 and allergy by demonstrating that these cytokines modulated IL-2 production, suppressed Treg induction, and instead promoted an IL-4-expressing T cell that bore similarities to Th2 cells. This potential for extremely early life events to influence food allergy has also been supported by circumstantial clinical evidence in adult patients who underwent cord blood transplantation for hematological disorders and developed new-onset food allergy within 1 year of transplant, a condition referred to as ‘transplant-acquired food allergy’ [5,6]. One caveat to these conclusions is that differences in Tregs from cord blood have already been demonstrated between atopic (individuals with evidence for existing IgE responses) and non-atopic mothers, and these were associated with atopic dermatitis [7,8]. These differences might thus relate to atopy and allergy in general, as opposed to dietary tolerance or food allergy specifically.

While human studies did not directly address the role of specific antigens, Gerhold *et al.* utilized a well-established murine model of allergic airway inflammation to ovalbumin (OVA) to examine the effects of antigen exposure throughout pregnancy, and they studied the subsequent capacity of the offspring to become sensitized [9]. While the pups from non-exposed mothers generated robust antigen-specific IgE responses and developed airway inflammation, those from the exposed mothers were significantly protected. This protection was associated with the development of Tregs expressing the master regulator FoxP3 [which can be derived from both the thymus (tTregs) and the periphery (pTregs)]. FoxP3-deficient mice suffer from a variety of spontaneous inflammatory and autoimmune diseases in which both tTregs and pTregs contribute to suppression, including failure of oral tolerance and development of food allergy [10]. Similarly, maternal exposure to peanut during pregnancy and lactation was reported to reduce the development of peanut-specific IgE in the offspring, but only upon low-dose exposure [11]. This effect seems to be dramatically different if the mother is already sensitized or undergoes sensitization during pregnancy, with several studies describing heightened sensitization in the offspring [12–14], and epigenetic alteration of the *IL4* gene locus [12]. Such epigenetic modifications and their associations with food allergy have been extensively studied and were reviewed recently [15].

In the earliest days of life, breastfeeding represents another potential route of exposure to maternal dietary antigens. Extensive literature has described the detection of food allergens in breast milk, including several major peanut allergens [16–18]. In mice, administration of human breast milk that contained peanut allergens before weaning diminished the efficiency of subsequent sensitization attempts, suggesting the induction of an oral tolerance response [18]. Furthermore, the study of a limited panel of immune mediators present in breast milk demonstrated that reduced levels of IL-1 β and IL-6 were associated with subsequent food allergy development in children [19]. These two cytokines are associated with the induction of a Th17 response that might help to counteract Th2 priming and allergy development [20]. High IL-1 β in breast milk has also been shown to reduce the risk of developing atopic dermatitis [21]. However, the contribution of breast milk-associated influences as a protective or sensitizing

influence over food allergy has remained controversial, particularly because several population-based studies have yielded modest or no associations between the choice of formula versus breastmilk feeding and subsequent food allergy development [22–24]. A recent study on peanut exposure during pregnancy and lactation in mice also concluded that there was no effect on the development of oral tolerance versus peanut allergy in the pups [25]. Mechanistically, this might not be surprising if we consider the important contribution of Tregs to the development of oral tolerance, as previously reviewed [26]. It has been shown in mice that FoxP3⁺ thymocytes are delayed in their appearance versus their CD25⁺ FoxP3[−] counterparts, with neonates requiring several weeks for FoxP3⁺ cells to reach full competency of numbers [27,28]. Interestingly, this window coincides with the weaning age of a mouse and the introduction of solid dietary constituents. However, the origin of Tregs during pup development remains unclear. While the thymus remains an important site of their development, the activation of CD4⁺ T cells in the periphery when TGFβ is present promotes FoxP3 expression, dependent on the intronic FoxP3 enhancer conserved non-coding sequence 1 (CNS1), and differentiation into induced or peripheral Tregs (pTregs) [29]. These pTreg cells have been shown to be crucial both for the control of intestinal microbiota composition and the suppression of allergic responses [30]. In particular, pTregs prevented the development of elevated IgE levels as the mice aged.

While it is unclear whether breastfeeding directly initiates protective tolerance in infants, transfer of maternal secretory IgA antibodies through breast milk is thought to be an important source of early protection against infection in newborns before the development of their own intestinal IgA-secreting cells [31]. In mice, maternal secretory IgA was demonstrated to be important in the establishment and composition of the intestinal microbiota, and to limit inflammation in a model of dextran sodium sulfate induced colonic damage [32]. In addition to the role of IgA during infection, it is likely to also be associated with food allergies. Indeed, a clinical study demonstrated that mothers who avoided cow's milk during breastfeeding had lower levels of specific IgA, and that this was associated with the development of cow's milk allergy in their children [33].

In addition to these antigen-specific immune processes, there also exists substantial evidence for a contribution of dietary factors on immune skewing, and this is particularly evident for vitamin D and food allergy. It has been shown that high vitamin D levels in either maternal or cord blood are associated with an increased risk of developing food allergy [34]. Suggesting the importance of a balance, vitamin D deficiency is also associated with increased risk of sensitivity to food allergens [35]. The links between vitamin D biology and Tregs have been extensively dissected and recently reviewed [36].

Early Dietary Allergen Exposures Can Promote Tolerance

While the role of prenatal exposure to specific antigens has not been extensively studied in humans, recent findings from early introduction of peanuts into the diet of children have shed light on the role of early-life exposure. Building from previous studies that had correlated protection from peanut allergy with early consumption [37], the Learning Early about Peanut Allergy (LEAP) study was designed to assess whether regular consumption of peanut could influence the progression towards peanut allergy in a group of high-risk children [38]. In this study, the risk factors were defined as severe eczema, preexisting food allergy to egg, or both. This highlights the important phenomenon of the 'atopic march', in which preexisting allergic disease in an individual significantly increases their risk of developing further allergies [39]. The LEAP study achieved remarkable outcomes from early introduction of peanut, with an incidence of 17.2% in the avoidance group but only 3.2% in the consumption group. While primarily designed to test the efficacy of early introduction, the study did also provide insights into some immunological differences between the patient groups. Interestingly, both did show some development of peanut-specific IgE over the 60 months of the study, but high levels of IgE

were more common in the avoidance group, whereas peanut-specific IgG4 levels were higher in the consumption group.

The potential for IgG4 as a protective antibody relates in part to its inability to bind to complement or to form immune complexes [40]. The ratio of IgG4 to IgE has indeed been used as a mechanistic determinant associated with allergy protection in the LEAP study, as well as in several studies on successful immunotherapy trials [41–43]. A recent follow-up study of the LEAP trial participants 12 months later demonstrated continued protection and maintained IgG4/IgE ratio against peanut allergens [44]. While these findings are exciting from the position of therapy and control of peanut allergy in the setting of high-risk individuals, it is important to note that the majority of healthy people do not carry food allergen-specific IgG4 or IgE antibodies, and this therefore represents a protective mechanism in sensitized individuals rather than a general mechanism of oral tolerance. In addition, an expansion of this early introduction approach to six allergens (peanut, cooked egg, cow's milk, sesame, white fish, and wheat) in the Enquiring about Tolerance (EAT) trial yielded mixed results, with significant benefit seen for peanut and egg allergy in patients who adhered to the treatment protocol, but no benefits were seen for the other allergens [45]. In light of these facts, it seems more likely that early consumption acts to limit a pre-existing aberrant immune response, rather than resetting the immune system to the tolerance response observed in healthy individuals. It also remains to be determined if the protective effects of early introduction are possible to all potential allergens, and whether IgG4 is the underlying key mechanism of protection or whether further mechanisms are at play.

Despite the potential for these early-life events that might contribute to tolerance to dietary proteins, some individuals progress from sensitization to food allergy. The recent interest in food allergy is driven in part by the significant increases in prevalence in recent years. Current estimates suggest that food allergy has nearly doubled in prevalence, and now affects up to 8% of school-aged children and 5% of adults in the USA [46]. The underlying cause of this increase remains unknown. Furthermore, treatment consists mainly of careful avoidance of the trigger foods, with tremendous impact on quality of life [47].

Association studies have helped to provide clues to some factors that are likely to have underlying mechanistic importance in tipping the balance from tolerance to allergy. In particular, strong associations between food allergy and preexisting or coincident atopic dermatitis have been seen over and over again, with food allergy affecting around 15% of atopic dermatitis patients [48]. Patients with mutations in the skin matrix protein filaggrin have an intrinsic defect in their epidermal barrier and a strong predisposition not only to atopic dermatitis [49] but also to peanut allergy [50,51]. Interestingly, this sensitization associated with levels of peanut dust in the homes of the children [51]. This finding supports the idea of priming of the immune system to food allergens occurring through cutaneous exposures derived from within our environment. For asthma in particular, the hygiene hypothesis, whereby early-life exposures to lipopolysaccharide might protect from allergy-associated immune priming, has been supported from several avenues [52]. However, in the case of food allergy there is little evidence for protection via such mechanisms. Instead, an alternative hypothesis has been proposed in which early ingestion of dietary allergens promotes tolerance while cutaneous exposures drive sensitization [53]. Food allergy would then occur after early avoidance of food and exposure through a disrupted skin barrier (e.g., in the presence of filaggrin mutations mentioned above). In experimental models also, the skin has been demonstrated to be a significant site of sensitization [54–56].

Mechanistically, this sensitization requires the Th2-priming effects of thymic stromal lymphopoietin (TSLP) and its effects on basophils [55]. This epicutaneous priming route seems to be sufficient to exert intestinal influences, as shown by a significant expansion of mast cells within the jejunum and the fact that the allergen-specific IgE induced during skin exposure was

necessary for anaphylaxis to occur on oral challenge [56]. Conversely, oral exposure to allergen has also been shown to protect mice from skin allergic immune responses in a similar atopic dermatitis model [57]. Taken together, the evidence seems to implicate the skin as a route through which food allergic reactivity can be initiated, while oral exposure is generally associated with tolerance.

Evolution of Food Allergies: From Childhood to Adulthood

Development of Natural Tolerance

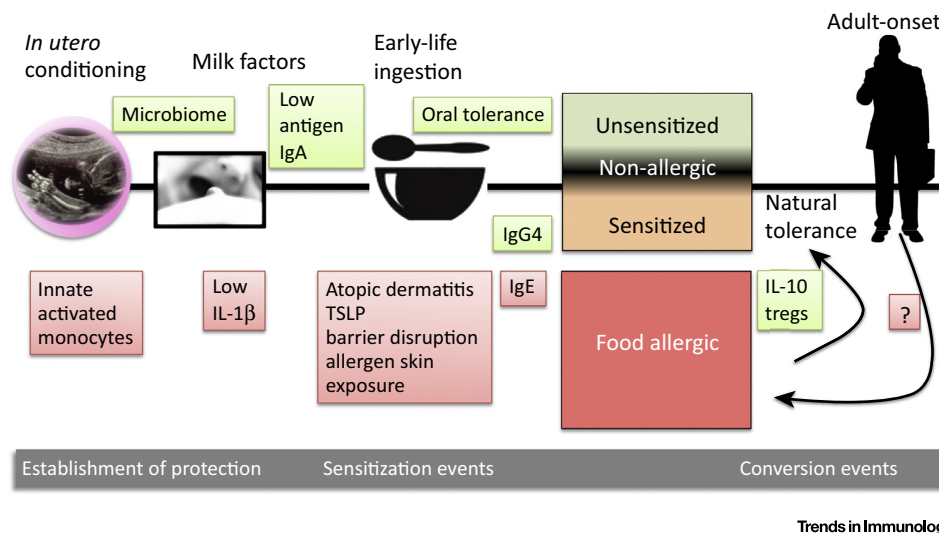
Clinically, it is well established that food allergy can be transient, and that many children eventually 'outgrow' their food allergies, a phenomenon termed 'natural tolerance'. This occurs at different rates for different food allergens: studies have shown that 60–75% of those with cow's milk allergy outgrow by the age of 5 years [58], while this number is only around 50% for egg [59] and 22% for peanut [60]. For cow's milk, natural tolerance was shown to be associated with increased IgG4/IgE ratios [61]. Recent data from our group demonstrated a significant increase in Tregs in the blood of children who had acquired natural tolerance to egg or peanut, compared to either healthy control or food-allergic children [62]. Crucially, IL-10-expressing Tregs, including the Tr1 subset of pTregs that are generally FoxP3-negative [63], were increased upon relevant allergen stimulation in natural tolerance patients but not in allergic individuals. Importantly, this type of outgrowth seems to reflect a true conversion from reactivity to life-long tolerance, while many attempts to induce tolerance by immunotherapy approaches have predominantly resulted in desensitization and return of reactivity on cessation of treatment [64].

Adult-Onset Food Allergy

In the timeline of food allergy development, most of the focus has been on early-life events and the initiation or prevention of food allergy in infants. The LEAP study has helped to emphasize how failure to support early dietary exposure to food allergens might have facilitated a rise in food allergy as a consequence of insufficient engagement of oral tolerance mechanisms. However, food allergy is also seen in adults, despite an extensive history of dietary intake of foods they subsequently become reactive to. On this point, we reported on 171 cases of physician-diagnosed food allergy that developed in adulthood, with the average age of diagnosis being 31 years [65]. The foods represented in these adult-onset food allergy patients were similar to those observed in childhood food allergy, including fish, nuts, soy, milk, eggs, and peanuts. This raises an intriguing immunological question regarding the sustainability of oral tolerance and the factors that might overcome its effects and drive sensitization and reactivity. It is well known that IgE-associated sensitization to foods is significantly more common than the frequency of people who exhibit food reactivity [66–68], a significant problem in the diagnosis of food allergy. It remains to be determined if adult-onset food allergy reflects acquisition of both sensitization and reactivity or acquisition of just reactivity in the face of prior sensitization. Adult-onset food allergy also emphasizes the point that food allergy is not only due to failures to initiate tolerance but that oral tolerance to dietary antigens is a process that seemingly requires maintenance and can be reverted. Factors influencing dietary antigen tolerance and allergy across development are summarized in Figure 1.

Interactions between Responses to Dietary Antigens and the Microbiota

The evidence from food allergy outlined above has begun to provide new avenues of investigation into the processes that balance our responses to dietary antigens. The immune system in the gastrointestinal tract in particular is capable not only of profound inflammatory responses (e.g., towards pathogenic microbes) but also of tolerance. This tolerance has been recently brought to the forefront in the context of the recognition and responses to the microbiota that coexists within our intestinal tract, but several studies have also connected this to dietary tolerance. Much of the immune mediators implicated in early-life aspects of food allergy discussed above have also been implicated in shaping interactions with the intestinal microflora.



Trends in Immunology

Figure 1. Factors Influencing Tolerance and Allergy to Dietary Antigens Across Development. Throughout life, a progression of positive and negative factors might contribute to the fate of immune responsiveness to dietary antigens. In childhood, early events related to establishment of oral tolerance and control of antigen priming processes protect against becoming sensitized. Later in life, natural tolerance might develop in some food-allergic individuals while some adults develop *de novo* food allergy. Tolerogenic factors are shown in green, while factors involved in allergy development are shown in red. Abbreviations: Treg, regulatory T cell; TSLP, thymic stromal lymphopoietin.

For example, IgA in breast milk was demonstrated to alter the microbiome composition and to dramatically shift the flora that persisted into adulthood in mice [32]. This might be important in the context of generating efficient tolerance responses within the intestine because it has been clearly demonstrated that some species of bacteria, particularly a specific collection of toxin and virulence factor lacking strains in the Clostridia class, are crucial for the generation of FoxP3⁺ Tregs within the colon [69,70]. Importantly, germ-free mice or neonates undergoing antibiotic depletion of their commensal flora have been shown to have a heightened susceptibility to food allergy, attributed to alterations in IL-22 induced by Clostridia [10]. In mice with an engineered gain-of-function mutation in the IL-4 receptor α chain, and which exhibit a heightened susceptibility to oral sensitization versus tolerance, a profoundly altered microbiome signature was observed, and this was sufficient to impart susceptibility when transferred into germ-free wild-type mice [71]. This has important implications because it supports the conclusion that the personalized genetic landscape of an individual might be a contributing factor in shaping the balance of their own commensal microbiota, and that both the genetic landscape and the microbiota may contribute to allergic susceptibility. The mechanism for this susceptibility in IL-4R α mutant mice was attributed to deficiencies in Treg numbers and functions. Subsequent studies using this mutant mouse have described reprogramming towards Th2-like cells that fail in their ability to maintain oral tolerance [72], perhaps through crosstalk with type 2 innate lymphoid cells (ILC2) [73].

While the microbiota appears to play a crucial role in the balance between intestinal tolerance and sensitization, recent discoveries have helped to shine a spotlight onto the important role that dietary proteins also play. A study of intestinal biology during development showed that the introduction of solid foods led to massive changes in bacterial composition, with a transition not only to a more stable community but also to increased levels of short-chain fatty acids, vitamin biosynthesis, and carbohydrate utilization [74]. More specifically, a recent study focused on the direct influences of dietary antigens in intestinal homeostasis and revealed a previously under-appreciated biology [75]. By utilizing germ-free mice that were maintained on an elemental diet – an amino-acid based diet devoid of proteins that is utilized clinically in some food allergy patients

[76] – they were able to effectively eliminate exposure to dietary antigens and to dissect the alterations seen in the intestinal homeostasis. Their findings elegantly demonstrate a bifurcation of the intestinal pTreg communities and the mechanisms needed for their initiation, with colonic pTregs being driven by microbiota and those in the small intestine being driven by dietary antigen exposure. The cells at these two distinct locations could also be discriminated from each other based on the expression of the transcription factor retinoid-related orphan receptor γ t (ROR γ t), potentially suggesting differences in developmental cues or functional properties. While ROR γ t is crucial for proinflammatory Th17 responses, the importance of ROR γ t-expressing cells in intestinal tolerance, via both innate and adaptive cell types, has increasingly become evident and was recently reviewed [77]. The study also demonstrates an alteration in the frequencies of specialized tolerogenic dendritic cells (CD103⁺CD11b⁺), which have been shown to interact with macrophages at intestinal gap junctions to establish oral tolerance [78].

Mechanistically, these findings align with recent reports these cells are regulated by high-fiber diet and short-chain fatty acids produced by some microbial species, and are required to protect against food allergy in mice [79]. While dietary proteins were necessary for small intestinal pTreg development, and the introduction of solid food was sufficient to induce their development, questions remain, particularly in how this relates to clinical tolerance in humans. Somewhat surprisingly, mice that did not develop these pTregs still did not exhibit sensitization or reactivity upon introduction of standard chow. Instead, the adoptive transfer of antigen-specific T cells was utilized to elicit allergen-specific inflammatory responses, and these were enhanced in the absence of pTregs. One conclusion from this is that diet-induced pTregs in the small intestine are crucial for suppressing food allergy in sensitized individuals, a state of control that is observed in many people who possess evidence of sensitization to food allergens but no apparent reactivity [68]. However, the underlying mechanisms of oral tolerance that prevent the initiation of sensitization in the majority of individuals remain unclear.

Concluding Remarks and Future Directions

Our understanding of the mechanisms that balance tolerance versus food allergy are beginning to provide insights into how the intestinal immune system is influenced by a complex process of life exposures. Three key recent studies spotlight this. (i) Differences in monocyte responses from the cord blood of children destined to become food allergic implicates *in utero* and maternal influences [4]. (ii) Successful treatment of susceptible children with early introduction of peanut consumption implicates early-life and diet-driven protective processes [38]. (iii) Dietary protein-induced pTreg induction within the small intestine defines a previously unappreciated direct mechanism through which diet alters immune balance [75]. These findings implicate both innate balances but also the importance of acquired protection.

Several issues remain concerning the mechanisms working towards or away from food allergy (see Outstanding Questions). In particular, the differences between those who undergo conversion and those who do not seem to be particularly important. A better understanding of the events driving the acquisition of natural tolerance are likely to guide therapeutic studies and the development of novel treatments, while the events leading to loss of tolerance in some adults is perplexing. Do these adults fail to maintain diet-associated pTregs or is sensitization due to some non-specific failure in barriers? How do dietary processes interact with microbiota-driven signals over the course of food allergy development or protection?

Certainly, these recent developments represent the beginning of a new age in our clinical and mechanistic understanding of food allergies; one that Albert Rowe most likely would not have foreseen.

Outstanding Questions

What are the mechanisms driving natural tolerance acquisition?

What overcomes tolerance in some adults and promotes food allergy?

Diet-associated pTregs are important for controlling inflammation post-sensitization, but most individuals do not become sensitized at all. What are the mechanisms that prevent sensitization?

How do dietary processes interact with microbiota-driven signals over the course of food allergy development or protection?

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