

The immunologic basis for gastrointestinal food allergy

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Purpose of review

Food allergies are common in children, although rare in adults. They can be life threatening via anaphylaxis, especially to peanut, and cause distress to children and parents because of the disease itself, and then through the difficulty of pursuing a strict elimination diet. In parents/carers and adults, this has significant impact on quality of life. The purpose of this review is to determine the therapeutic potential and current treatments for these conditions by understanding and manipulating the immune response.

Recent findings

The single largest change in attitude to food allergies has been the realization that delaying exposure to foods may be harmful in terms of immune sensitization. Instead, strategies aimed at early introduction of foods to induce oral tolerance are now being re-evaluated. At the same time, very encouraging results are being obtained in desensitizing allergic children via oral tolerance. The aim of this strategy is not necessarily to induce complete tolerance to foods in allergic children but to raise the threshold dose at which adverse events occur, to minimize reactions to trace amounts of allergens.

Summary

Food allergies are now recognized as being a treatable component of the atopic march.

Keywords

oral tolerance, regulatory T cell, weaning

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Introduction

The majority of children and adults consume the foods necessary for health without a problem. However, in a minority (around 5% in children), the immune system responds inappropriately and the individual becomes sensitized to food antigen(s). It is critically important, however, to realize that healthy children are not tolerant to foods in the sense that they do not respond immunologically because it is very well established that all bottle-fed babies have high levels of serum antimilk immunoglobulin G (IgG) antibodies [1]. A further implication of this observation is that because IgG antibodies are T-cell dependent, all infants must have T cells responsive to food antigens. Indeed, several years ago, we clearly demonstrated cow's milk responsive T helper cell type 1 (Th1) cells in the Peyer's patches and blood of healthy children [2].

Accordingly, the critical question is not necessarily exposure to food antigens but the nature and type of immune response which an individual generates to these antigens. This is not to say that the type of exposure, dose and timing might not influence the immune response generated, but these are variables that are superimposed

upon the complexity of the immune system in an outbred population and in children, at a time when the immune system is itself evolving and maturing. Unsurprisingly, therefore, given this complexity and heterogeneity, progress in understanding gastrointestinal food allergy remains rather slow. At the same time, food allergy in children, when properly diagnosed, is relatively easily and permanently treated by a period of avoidance, during which time, in the absence of antigen, functional immunological tolerance usually emerges. Although recognizing that animal studies contribute greatly to understanding basic processes, in this update, we have decided to concentrate on clinical studies because of the increasing emphasis on translational studies in immunology.

Immunopathology of food allergy

The great majority of cases of food allergy are IgE mediated with more immediate onset. Delayed onset adverse clinical responses are thought to be mediated by Th2 cells eliciting eosinophil and cytokine-mediated injury. This distinction is not particularly robust, and many delayed onset cases have high IgE, and some immediate onset cases have normal IgE [3]. Overt small intestinal damage is not a feature of immediate onset food

allergy, most biopsies being within histological limits; however, local mast cell-mediated reactions will alter gut permeability and fluid secretion. Allergic reactions are typically associated with eosinophilic infiltrates into tissues and the gut is no exception. The most common eosinophilic disorder of the gut is eosinophilic esophagitis, but this is a part of a series of disorders, including eosinophilic gastritis, enteritis and colitis [4]. It is important to exclude reflux disease, so an allergic cause for eosinophilic esophagitis is encouraged by lack of response to proton pump inhibitors. If the patient is skin prick test positive to a food allergen, dietary elimination leads to improvement in most cases, especially in children [5]. Elemental diets may also be useful but are difficult to tolerate. Food-induced enterocolitis with bloody diarrhea is not very common, but why the colon should be a target organ in some children is not known. It has been also claimed that food allergy is associated with intestinal lymphoid hyperplasia [6]. Apart from this finding, however, the gut disease in food allergy is what might be predicted from a basic knowledge of Th2 and IgE-mediated injury.

A notion that has recently been revisited is that IgA deficiency may be associated with food hypersensitivity [7]. The mechanism is presumably the same as proposed in the 1970s, namely that absence of IgA results in a defect in immune exclusion and increased entry of food allergens into the systemic circulation.

Tracking down immune response genes that might influence sensitization to foods

IgE responses are strictly T-cell dependent and driven by class switching to the epsilon locus by Th2 cytokines. These cytokines, such as interleukin (IL)-4, IL-5 and IL-13, are clustered on chromosome 5q31–33. Consequently, there have been a number of studies on functional single-nucleotide polymorphisms (SNPs) at these loci, which might confer genetic susceptibility to allergy. A relatively consistent finding has been the association of IL-13 variants with total IgE levels, and a recent study [8] demonstrated that these variants are associated with sensitization to foods, particularly eggs. To the authors' knowledge, there have been no genome-wide association (GWA) studies on food allergy. However, a lesson to be taken from GWAs in other complex diseases is that multiple variants with a small effect contribute to the overall disease phenotype. It is highly unlikely, therefore, that a food allergy gene with a large effect exists.

However, a gene that has a strong association with eczema and asthma is filaggrin, a protein important in skin barrier function [9]. There are no reports of filaggrin mutations and food allergy *per se*; however, a recent study

[10] has shown that a combination of filaggrin mutations and sensitization to foods early in infancy can help predict who will develop asthma. The link between filaggrin and eczema is also intriguing given that transdermal sensitization may be important in the development of peanut allergy [11].

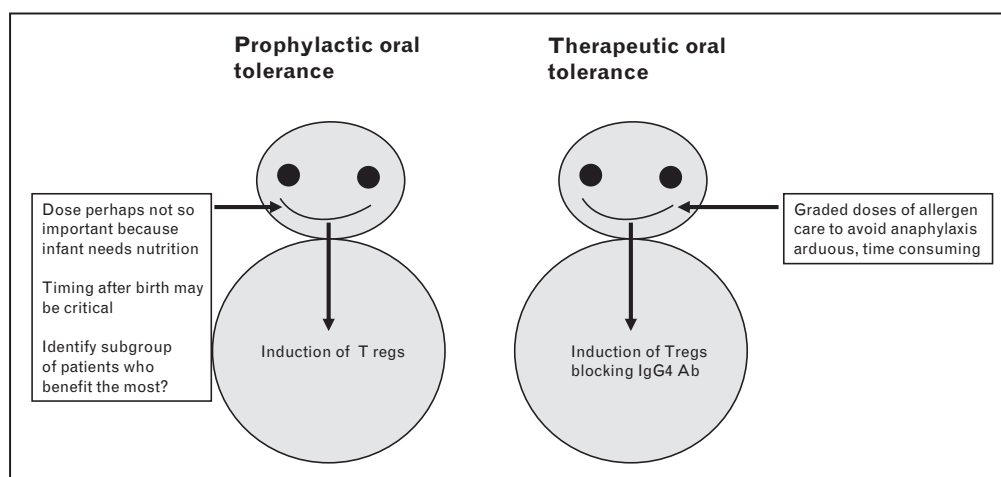
Does the timing of introduction of foods modulate the development of food allergy?

Rarely, maternal dietary proteins in breast milk can sensitize the infant; however, it is still recognized that breast milk is the best source of nutrition in the first few months of life. A controversy, which began in the 1970s and remains unresolved, is whether the introduction of food antigens into the diet either early in life, or later, has any effect on the development of food allergy, atopy or allergic asthma.

Since 2001, the WHO has recommended that exclusive breastfeeding persists up to 6 months of age. This policy has been adopted across much of the industrialized world. An immunological rationale for longer breastfeeding is that delivering large amounts of foreign proteins into the gut of a very young baby by way of cow's milk, perhaps before the postnatal Th2 to Th1 switch has occurred, or in the absence of T regulatory cells (Tregs), might result in Th2 sensitization and allergy. In 2009, however, it is becoming clear that this change has had no significant effect on the incidence of allergy (essentially neutral), and that indeed late introduction of foods might be deleterious [12]. For example, Mihrshahi *et al.* [13] followed a cohort of children with a family history of asthma and found that longer breastfeeding was associated with an increased risk of atopy. Filipiak *et al.* [14] showed no effect of delaying foods until after 6 months on the development of eczema, a finding confirmed by Zutavern *et al.* [15] for food sensitization. Snijders *et al.* [16] showed that delaying introduction of cow's milk until after 6 months increases eczema. Venter *et al.* [17] showed that weaning at greater than 16 weeks increased sensitization to food allergens and, interestingly, showed that maternal avoidance of allergens had no effect. Overall, therefore, the case that delaying introduction of foods till after 6 months might reduce the development of food allergy is difficult to sustain and in fact may be deleterious.

The other side of the coin, however, is to ask whether early introduction of foods might play a role. Mihrshahi *et al.* [13] also examined the effect of infant feeding practices in high-risk children on the development of atopy at 5 years of age. Introduction of solid food before 3 months was significantly protective; however, food allergy was not specifically examined. Peanut allergy can be particularly dangerous because allergic attacks can occur on the first known exposure to trace amounts

Figure 1 Oral tolerance is a very well documented phenomenon whereby oral administration of a specific antigen induces unresponsiveness to the same antigen when it is given parenterally in immunogenic form (e.g. with an adjuvant)



Its use in preventing food allergy may be prophylactic by finding the optimal timing, dose and patients to be treated; alternatively, graded oral doses of allergen given to already sensitized individuals also appear to have beneficial effects. Mechanisms may involve blocking antibodies or Treg cells.

of peanut due to inadvertent sensitization from the environment. There is some slight evidence that oral administration of peanuts can be protective in infants receiving high environmental exposure [18]. In a very interesting study [19^{••}] comparing peanut allergy between UK and Israeli Jews, the low incidence of peanut allergy in the latter may have been due to early consumption of peanuts in very young children in Israel.

The phenomenon in which oral administration of antigen dampens subsequent immune responses to the same antigen given by another route is very well described and is known as 'oral tolerance' (Fig. 1). But whether oral tolerance can be used therapeutically in humans to prevent inappropriate immune responses is highly contentious. Despite compelling work in animals, feeding of collagen had no effect on rheumatoid arthritis and feeding myelin had no effect on multiple sclerosis. These disappointing results, however, are somewhat different from the situation in children, as the antigens were given to patients with preexisting disease, whereas in infants, the antigens would be used prophylactically. In a very interesting recent paper, Prescott *et al.* [20^{••}] argue not only that delayed introduction of solids may be deleterious and promotes sensitization to allergens, but also that there may be a critical window at 4–6 months of age at which oral tolerance may be effective. Studies are ongoing to test this hypothesis.

Regulatory T cells and food allergy

It is now clear that there exists a population of CD4⁺, CD25⁺ T cells in blood whose primary function is to regulate immune responses. These cells are derived from

the thymus and express the transcription factor forkhead box P3 (FoxP3). Children with mutations in FoxP3 develop the immunodysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome with very high Th2 responses, high IgE levels and allergies [21]. Six years ago, Karlsson *et al.* [22] reported that children who had outgrown cow's milk allergy had higher numbers of Tregs with more potent function than children who had remained allergic. In a very interesting study, Smith *et al.* [23] looked at Treg function in cord blood from infants who later developed egg allergy by 12 months of age. Infants who developed allergies had lower Treg function than infants who were tolerant to foods, suggesting that a defect in Tregs may predispose to food allergy. Similarly, infants with higher numbers of allergen-specific Tregs had milder disease and a more favorable outcome than those who had lower frequencies of Tregs [24[•]]. Taken together, the evidence is accumulating that differences in Treg activity may be a factor in the development and resolution of food allergies (Fig. 1), but many further studies are needed.

Desensitization in food allergy

Desensitization by repeated systemic treatment with allergen is a recognized therapy for atopic disease. It is still not entirely clear how it works, but it probably involves induction of Tregs or blocking antibodies, or both (Fig. 1). Two main strategies have been used for oral desensitization. Sublingual immunotherapy (SLIT) involves placing a small amount of the allergen under the tongue. Oral immunotherapy (OIT) involves feeding small amounts of the allergen. A more recent addition is the use of extensively heated food allergens based on the

idea that IgE antibodies are directed against conformational epitopes (three-dimensional shapes of the molecule), which are destroyed and denatured when the protein is heated or baked. Theoretically, therefore, these should be well tolerated, and this was confirmed in a recent study [25], in which 75% of milk allergic children tolerated extensively heated milk.

In 2004, Meglio *et al.* [26] reported an open-label study, in which children with proven IgE-mediated cow's milk allergy underwent a rigorous and extremely long desensitization protocol using increasing doses of cow's milk. After desensitization, 15 of the children could tolerate 200 ml of milk per day. These same children were studied almost 5 years later and tolerance had persisted [27]. Although these results are interesting, the transient nature of cow's milk allergy makes firm conclusions difficult, and as the authors point out, the desensitization protocol is arduous and must be done by trained staff to avoid potentially dangerous anaphylactic reactions.

In a randomized, placebo-controlled trial of 97 children using increasing doses of cow's milk given in hospital for 10 days and then over a longer period at home until 150 ml in a day could be tolerated, Longo *et al.* [28^{••}] found that after 1 year, 36% of the treated group were completely milk tolerant compared with 0% of the placebo group. In a smaller study of 20 cow's milk allergic children with very rigorous endpoints, Skripak *et al.* [29^{••}] showed that in double-blind, placebo-controlled food challenge, children given placebo remained intolerant of milk (only tolerant of 40 mg), whereas of those undergoing an oral desensitization protocol, the dose increased to 5140 mg. IgE levels did not change, but the treatment group showed markedly increased serum IgG4 antibodies.

Densitization also occurs in other food allergies. SLIT for peach allergy allowed adults to tolerate higher doses of peach than patients given placebo, but the effect was not as dramatic as seen in children [30]. Likewise, studies on desensitization to egg are underway [31,32].

It is important to remember, however, that the goal of OIT is not just allowing a previously allergic child to tolerate foods. A secondary and arguably more important goal is to increase the dose at which anaphylactic responses are elicited to prevent life-threatening responses to trace amounts of allergens.

A role for prebiotics and probiotics

A potential link between the beneficial effect on eczema incidence in children of giving the mother probiotics before birth, and then probiotics to the infant, was highlighted by Kalliomäki *et al.* [33] around 10 years ago and

has led to much interest. The area, however, has been confounded by the fact that in succeeding studies, different probiotics and protocols have been used. Although probiotics involve the delivery of 'good' bacteria into the gut, prebiotics use oligosaccharides to encourage the growth of endogenous 'good' bacteria (lactobacilli and bifidobacteria) in the colon. A recent Cochrane review [34[•]] suggested that there was no good evidence that probiotics affected the development of eczema nor any subgroup of patients who might be helped. The authors, however, did comment that the problem of different studies using different probiotics was a major confounder, and that studies with new probiotics might be worthwhile. However, probiotics were considered well tolerated. It is often claimed that individual probiotics need to be assessed for their health benefits because different strains have different effects. So, when designing studies, it is human nature to make them novel and not repeat what has gone before; so it will take a while before sufficient studies are available with individual probiotics, given using the same protocols, to achieve adequate data for evaluation. For prebiotics, a meta-analysis [35] suggested that there are insufficient data to make any conclusion as to whether they help in allergic disease or food hypersensitivity. However, a more recent study [36[•]] suggested that prebiotics could decrease the incidence of allergies and infections in children.

Other topics of interest

In one study [37], six of 28 children who had received orthotopic liver transplant developed food allergy. Others have suggested that it is the immune suppression (tacrolimus), which leads to food allergy [38,39]; however, it may also be the absence of a functioning liver. At the same time, there are animal data to suggest that after feeding antigens, the Th2 cells, which generate inappropriate responses to food, are made in the liver and their function may be modulated by liver transplantation [40].

Across the world, interventions are being considered to prevent and stop the atopic march [41,42[•]]. The Finnish Allergy Programme 2008–2018 is a highly ambitious project to reduce the burden of allergies [43[•]]. The scientific background of this proposal is essentially immunology, focussing around continuous exposure to antigens and strengthening and restoring immune tolerance. The International Pediatric and Asthma Consortium is another ambitious project with the final aim of treating food allergies [44], and EuroPrevail is a survey of allergy across Europe [45]. For reasons that are still unclear, a successful treatment for allergic rhinitis, the anti-IgE antibody omalizumab, has not been formally tested in food allergy, although it showed some success in a single case report [46] (for a summary see Table 1).

Table 1 Summary of strategies to prevent or treat food allergies

Prevention of food allergies	
Breastfeeding >6 months	No effect or deleterious
Maternal avoidance of allergens	No effect
Hypoallergenic cows milk formulae	Beneficial effect in the predisposed infant
Earlier introduction of allergens	Studies underway
Probiotics and prebiotics	Inconclusive
Treatment of food allergies	
Oral tolerance	Showing promise, optimal time needs to be established, subgroups who benefit need to be identified
Drugs (e.g. anti-IgE)	Needs to be systematically evaluated

IgE, immunoglobulin E.

One area in which progress has been slow is in the understanding of the delayed onset food allergies, in which direct damage by T cells and their products is likely to be involved. This is probably because biomarkers in these children are not available, they are less common and double-blind, placebo-controlled food challenges are the way to demonstrate tolerance and these are expensive and arduous. Nonetheless, because IgE responses are T-cell dependent, it is highly likely that strategies to tolerate immediate-type food allergies are working through T cells, so there may be translational crossover.

Conclusion

Food allergy is now being addressed as a major health issue in developed countries with new interventional strategies, all of which focus around immunological tolerance.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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