

Mechanisms of food allergy

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The prevalence of food allergy continues to rise, particularly in 'westernized' societies; it has been linked to the 'hygiene hypothesis' and the increased diversity of food consumption worldwide. The pathogenic mechanisms and Th1/Th2 paradigm are being closely examined with respect to the occurrence of inflammatory and injury/repair responses at different mucosal sites. Genetically modified plants as potential food sources and allergenicity are current topics of controversy.

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Abbreviations

AD atopic dermatitis

OAS oral allergy syndrome

Introduction

Adverse reactions to foods are a particular problem for infants and young children (reported incidences of 2–8% compared with 1–2% in adults) that can present with a wide spectrum of clinical reactions, including cutaneous, gastrointestinal and respiratory symptoms as well as systemic anaphylactic symptoms. Immunologically, food-protein allergy is defined as an IgE-mediated reaction. Non-immunologically mediated mechanisms fall into the categories of enzymatic or transport deficiencies (e.g. lactase deficiency or glucose/galactose malabsorption, respectively) or other, undefined reactions. No single symptom is pathognomonic nor is a single laboratory test diagnostic for food allergy. Clinical diagnosis is based on a double-blind, placebo-controlled food challenge establishing a causal relation between ingestion and subsequent reactions. In this review, we summarize advances and controversial issues in the field of food allergy; we will address the 'hygiene hypothesis', the pathogenesis of food-hypersensitivity reactions, the allergenicity of food proteins, atopic dermatitis (AD), Th1/Th2 lymphocyte polarization and options for immunotherapy of food allergy. Two excellent reviews on the topic of food allergy are recommended [1*,2*].

The hygiene hypothesis

A key contribution in reducing the incidence of allergic disease can be found in the quote cited by Voelker [3] "We must learn how to safely 'train' our immune system, especially during infancy, in order to prevent allergy".

Numerous scientific reports suggest that the reduction of communicable diseases as a result of vaccinations and hygiene in Western countries may have contributed to the increased incidence of atopic diseases — this is the 'hygiene hypothesis'. Lynch *et al.* [4] suggest that studying the IgE antibody system in a natural state (e.g. during parasitic infections) might give insight into reasons why it apparently malfunctions to cause atopic disease — a revision of the 'IgE immune system hypothesis', which states that, in the absence of environmental exposure to parasites, an atopic state may result that favors a specific IgE responses to innocuous proteins.

In a retrospective case/control study of Italian Air Force cadets evaluated for exposure to airborne viruses (measles, mumps or rubella) and orofecal or foodborne infections (*Toxoplasma gondii*, *Helicobacter pylori* or hepatitis A virus), researchers found that cadets with no exposure to enteric infections were nearly three times more likely to have atopy and allergies than those who were exposed to pathogens [5*]. The authors suggested that a westernized diet — with its antimicrobial additives and low microbial content, consistent with a decline in orofecal infections — may contribute to the allergy/asthma epidemic; however, based on the parameters of their study, virtually none of the atopic participants could be proved to have been protected against atopy by having measles.

These results were confirmed in a large national study in Finland, which showed substantially more atopic disease among children and adolescents with a history of naturally occurring measles infections compared with those without a history of measles infection [6]. This is in contrast to earlier studies and a recent case/control study by Bodner *et al.* [7] in which both the effect of having two or more siblings and of acquiring measles were significantly related to a lower risk of asthma. Family size, the age at which viral and bacterial vaccinations were given, the incidence of naturally occurring orofecal or foodborne infections and the genetic predisposition of the individual may well contribute to the continued conflicting data regarding risk of atopic disease.

In light of the differences in reported incidences of increased atopy and in light of the hygiene hypothesis, there are several factors that may affect measurement of the outcome and that need to be addressed: intrinsic differences in the severity of the disease; lifestyle or environmental factors; cultural attitudes and diet; communication problems; and the doctor–patient interaction [8]. An understanding of the basic mechanisms of allergic disease and its associated diseases, and the education of genetically predisposed parents with this information may help in reducing the incidence of allergic disease in the newborn and early adolescents of future generations.

Controversial approaches that may contribute to protection from allergic sensitization to food include dietary instruction to mothers with an atopic history during the fetal and neonatal period, optimized breast feeding and the regulation of cytokines in the mother and fetus [9,10,11•].

The pathogenesis of food-hypersensitivity reactions

It is abundantly clear that inflammatory disorders of the human intestine — including food allergy, celiac disease and Crohn's disease — are associated with epithelial barrier dysfunction but what is not clear is if the epithelial barrier dysfunction is a consequence of inflammation or a predisposing factor.

In both ulcerative colitis and Crohn's disease, cytokine imbalance has been proposed to play a significant role in the initiation and perpetuation of the disorders. Th1 cytokines (IFN- γ and TNF- α) predominate in Crohn's disease and Th2 cytokines (IL-4 and IL-5) tend to predominate in ulcerative colitis. Bahn *et al.* [12] focused on the characterization of ulcerative colitis using genetically engineered animal models and have evidence that chronic colitis can be observed in TCR α knockout mice, in which the Th2 pathway — driven by IL-4 — plays a crucial role. In clinically and histologically active disease, Th2-like cytokines (IL-4 and IL-13) showed a significant correlation with clinical, endoscopic and histological severity in patients with ulcerative colitis [13]. IL-10 was speculated to play an important role in the pathogenesis of intestinal inflammation rather than the progression or improvement of the disease. Although no disease-specific antigens have been identified in either ulcerative colitis or Crohn's disease, Kakazu *et al.* [14] present a comprehensive report on the *in situ* expression of Th cell cytokines in intestinal bowel disease. The demonstration of IFN- γ with the rare expression of IL-4 and IL-10 in granulomas suggests that a Th1, not a Th2, immune response is involved in granulomas of Crohn's disease. The authors suggest that in actively inflamed mucosa, where the mucosal barrier is disrupted, various agents including bacteria and food antigens can secondarily stimulate macrophages or lymphocytes in various ways that modify the primary condition.

Patients with or without allergic diseases have been shown to have elevated intestinal membrane permeability. Observations on patients in whom the skin or lungs are involved indicate that a circulating factor may be responsible for the alteration in epithelial barrier function. Various candidate substances, all of which are components or contaminants of foods, may induce specific/nonspecific inflammation and alter mucosal membrane permeability. These include, firstly, molecules that trigger the release of IL-4, secondly, various candidate proteases and superantigens, and, thirdly, (as recently described) dietary lectins [15•,16]. IL-4 is produced by T cells, mast cells and basophils in close proximity to intestinal and respiratory epithelium and is ideally situated to modify epithelial

physiology. Circulating IL-4 may be a predisposing factor that contributes to intestinal inflammation, thereby allowing uptake of luminal antigens that gain access to the mucosal immune system [17].

In both animals and humans with food allergy, intestinal biopsies demonstrate an increased number of intraepithelial lymphocytes, mucosal mast cells and eosinophils [18,19,20•,21•]. IgE, mast cells, eosinophils and IL-5 have been identified to be important in the expulsion of parasites from the intestinal tract.

Eosinophil accumulation is considered a hallmark of chronic allergic inflammation and the identification of factors regulating eosinophil migration and homeostasis in the gastrointestinal tract and peritoneal cavity of animal models is an active area of research. IL-5 — the eosinophil-selective hematopoietin, which regulates eosinophil growth, differentiation and survival — has been well documented in the allergic disorders. However, the mechanism of eosinophilic inflammation in different diseases has recently raised some controversy. A major finding — that the interaction of IgE antibody and antigen is insufficient to provoke eosinophil infiltration into peritoneal cavities of allergic mice — contradicts many previous findings; a difference in the response to passive, compared with active, sensitization suggests that IgE antibody by itself was insufficient to provoke eosinophilic inflammation in a mouse model.

Recently, eosinophil levels in the gastrointestinal tract have been shown to be predominately modulated by eotaxin and less significantly by IL-5, GM-CSF and lymphocytes [22]. In their murine model, this group of investigators demonstrated that oral allergen challenge to sensitized mice promoted allergic inflammation characterized by Th2-associated eosinophil accumulation in the peripheral blood and small intestine and further demonstrated that eotaxin was critical in regulating allergen-induced eosinophil trafficking to the lamina propria of the small intestine [23]. With this model, it should be possible to investigate the allergic response in the gastrointestinal tract and hopefully provide therapeutic regimens not only for allergic gastroenteritis but also for other inflammatory bowel diseases where eosinophils are in evidence.

Clinical and pathologic data suggest that a distinct population of patients with Gastro-esophageal reflux disease (GERD) have allergic esophagitis rather than acid reflux disease or allergic gastroenteritis [24]. The subjects presented with an allergic history, failed to respond to GERD treatment, had normal esophageal pH and had large numbers of eosinophils in esophageal biopsy specimens. Compared with allergic gastroenteritis, no eosinophilic lesions were present in stomach or duodenal biopsy specimens, suggesting that patients with allergic esophagitis represent a distinct group of allergic gastroenteritis.

We are just beginning to understand the critical role of epithelial cells and dendritic cells in regulating the immune response to ingested antigens; these cells can determine tolerance or sensitization. Functionally, it has been proposed that gut dendritic cells may be grossly different to dendritic cells elsewhere or that gut dendritic cells might preferentially localize in different regions — beneath M cells of Peyer's patches or beneath epithelial cells — or that they may have different antigen capture and processing capabilities [25]. Although substantial information is available on the cells, chemokines/cytokines and physiology of the intestinal mucosa [26], the mechanism of sensitization and allergic responses directed against innocuous proteins is still unknown.

The allergenicity of food proteins

Food allergens are normally naturally occurring proteins; however, new allergenic epitopes may result from technological processing, digestion or heat treatment. The immunochemical and physicochemical properties that account for a protein's unique allergenicity continue to be poorly understood. [27]. Although not universal to all food-protein allergens, various factors have been correlated with allergenicity [28]: resistance to proteolysis (leading to stability in simulated gastric or intestinal fluids); post-translational glycosylation (this would increase receptor-mediated uptake); and enzymatic activity (this would nonspecifically activate immune cells; see also Update).

IgE cross-reactivity between pollen and food allergens has been suggested to represent a molecular basis for the allergic symptoms in patients with oral allergy syndrome (OAS) [29•]. The authors suggest that it was likely that contact with pollen allergens through the respiratory tract could induce, maintain and boost the cross-reactive IgE antibodies that were responsible for food allergy in OAS. These findings open an area of investigation that could lead to the development of novel forms of diagnosis and treatment of OAS and other food allergies, based on recombinant pollen allergens that bear the relevant cross-reactive food-allergen epitopes.

Recently, considerable debate has concentrated on the possible unforeseen risks associated with the accumulation of new proteins/metabolites in crop plants that may contribute to toxins, allergens and genetic hazards in the human diet [30•]. In order to construct experimental conditions that extrapolate to human dietary use, long-term animal feeding experiments, and quality and safety assessments are being undertaken on transgenic crops of potato [31] and rice [32]. What is not recognized is the role that these structures take in the sensitization phase of the allergic response, as individual proteins or as proteins either in the context of a complex food or in the context of nonspecific inflammatory responses. Moreover, there is no unanimous agreement on firm criteria upon which to base the extent of protein hydrolysis of infant formulas (i.e. should hydrolysis be exhaustive, high or partial?); nor are

there firm criteria for transgenic or recombinant/mutagenized food source material (i.e. should food be classed as having reduced allergenicity, being hypoallergenic or being nonallergenic?). Although there are 'decision trees' that help to guide our determinations of allergenicity, it is unlikely that a universal guideline will clearly identify all potential allergenic molecules.

Atopic dermatitis

The development of allergy and the 'atopic march' from AD to allergic asthma has been linked to a variety of factors, including a genetic predisposition, the environment, the rate of infections and increased vaccination schedules in modernized societies. A meta-analysis on the age of onset of the atopic march revealed that in the first year of life, there is an incidence of AD in 79.8% (60.2–100%) of all infants, of cow's milk allergy in 72.2%, egg allergy in 71% and fish allergy in 51.3% [33]. Despite significant progress in immunodermatology, a unifying pathogenic concept of AD has still not been established. Wollenberg and Bieber [34•], and Leung [35••] focus on the current clinical, therapeutic, genetic and immunopathogenetic features of AD. This disease is characterized by infiltration of inflammatory cells, particularly eosinophils and CD4⁺ lymphocytes, and commonly exists with other allergic conditions that have elevated serum IgE. Nearly 80% of children with AD will eventually have allergic rhinitis or asthma, suggesting that respiratory allergy and AD have a common systemic link [35••]. In a subset of patients with AD, Sicherer and Sampson [36•] clearly established a laboratory and clinical relationship of the allergic pathogenesis to specific food allergens.

In skin-patch testing for AD, eczematous reactions may occur within 24 to 48 hours, with dermal infiltration of lymphocytes and eosinophils. Investigations in animal models clearly show a direct connection between the Th1 and Th2 responses in the skin [37•,38]. T cells in biopsy specimens secrete IL-4, IL-5 and GM-CSF — typical of a Th2-mediated event — early, followed 48 hours later by a shift toward a more inflammatory, Th1-type response. Differences in T cell cytokine secretion, immunohistology and the immunophenotype of epidermal dendritic cells between 'extrinsic' AD (IgE-associated dermatitis) and 'intrinsic' AD (dermatitis without increased serum IgE) have been documented [39,40]. Taha *et al.* [41] demonstrated an increased expression of eotaxin and MCP-4 in acute and chronic AD lesions, suggesting that these factors play a major role in the pathophysiological mechanisms of AD.

Valenta *et al.* [42] raised some intriguing hypotheses regarding the role that IgE-mediated autoreactivity may play in severe and chronic forms of atopy; the authors suggested that the elucidation and 3-D structure of several environmental allergens has revealed structural and immunologic similarities with human proteins and suggested a mechanism in which autoallergy could lead to tissue damage by release of mediators in gastrointestinal,

respiratory, oropharyngeal and optic tissues. Whether these pathogenetic mechanisms contribute to food allergy is a new area of investigation; however, the similarity of environmental allergens with human proteins may be responsible for cross-reactivities, establishing a cytokine environment that could contribute to Th2-cell activation and cascading events.

An intriguing concept in the care and treatment of all atopic skin is the recommended interface between two specialties: the dermatologists, who are definitely more formally trained to provide care of the atopic skin, and the allergists, who have an in-depth appreciation of the immune response [43•]. In treatment of AD, Tacrolimus ointment suppressed the delayed allergic response; however, it did not inhibit the immediate allergic reaction in rats [44]. Investigations into the contribution of both Th1 and Th2 cells and cytokines in AD may benefit from the combined treatment recommended by representatives of the two specialties in defining the various causative mechanisms of the disease (see also Update).

Th1/Th2 polarization

Romagnani [45•] addresses the 'Th2 hypothesis in allergy' in a review of the role of lymphocytes in allergic disease (see also Update). Allergy has been traditionally described primarily as a polarized Th2 CD4⁺ response; however, a cooperative setting of Th1 and Th2 cells has been suggested to promote eosinophilic airway inflammation. Although the clinical symptoms and reactions of food allergy are similar to those of inhalant allergy, the mechanisms of food allergy are less evident.

In inhalant allergy, Th2 cells induce airway eosinophilia, mucus hypersecretion and airway hyper-responsiveness whereas Th1 cells cause a neutrophil-predominant inflammatory response without any characteristic features of asthma [46]. Using IL-4^{-/-} mice, Th2 responses to inhaled (intranasal) ovalbumin were diminished whereas Th2 responses after epicutaneous exposure remained intact [47••]. Epicutaneously induced Th2 responses were not seen in Stat6^{-/-} mice that were exposed to ovalbumin; however, a Th1-type response was in evidence. When IL-13-depleted, IL-4^{-/-} mice were epicutaneously sensitized to ovalbumin, a loss of Th2 responses was evident, suggesting that the skin, compared with the airways, of atopic individuals may be a more important site of initial Th2 sensitization to environmental allergens. Quiros *et al.* [48•] found that IL-12 and soluble CD40 (sCD40) levels in pollen-allergic subjects agreed with the classical Th1/Th2 paradigm (i.e. they had normal IL-12, and elevated sCD40); however, serum IL-12 levels were increased in food-sensitized children, suggesting that different immunopathogenetic mechanisms may be evident. Investigations into the role of sensitization in one mucosal area contributing to the pathology and symptoms in related mucosal areas and the singular and/or cooperative effects of Th1/Th2 cells and secreted cytokines will undoubtedly be areas of interest in the near future.

Options for immunotherapy

In human trials and animal models, substantial progress has been made with insect-sting and inhalant immunotherapy; however, clinical trials have not yet provided definite immunologic mechanisms and responses to the various immunotherapy regimens in food allergy as compared with insect-sting or inhalant immunotherapy regimens. Contradictory results about the efficacy of immunotherapy in these diseases can be explained by a number of differences, such as types of allergy (seasonal or perennial inhalant allergy, food allergy or allergic contact dermatitis), length of immunotherapy, target organs (skin, lung or gastrointestinal tract) and the experimental protocols (dose, frequency and duration of treatment). The dysregulation of the immunoregulatory mechanisms operative at local sites (e.g. skin, respiratory tract or gastrointestinal tract) and the genetic variations in humans or animal models under investigation may be salient features of the disease process.

Selected peptides (T cell epitopes lacking IgE-binding activity) and peptides with non-IgE-binding activity or mutagenized epitopes are being actively screened as rational strategies for safe, specific immunotherapy regimens in food-allergy models [49•]. However — based on the investigations of a major Der p2 T cell epitope expressing immunogenic properties (cryptic B cell epitopes were suggested to be present) — careful consideration of the immunogenic/allergenic potential (e.g. provoking IgG compared with IgE) of peptides that are used to induce T cell anergy should be performed [50•].

In animal studies, treatment with cDNA encoding IFN- γ or IL-4, or vaccinations using DNA expressing CpG motifs, have been shown to be effective approaches for treatment of allergen-induced asthma [51–53]. Although a number of candidate genes and their polymorphisms have been identified that appear to be relevant to inflammatory cell action and linked to atopy [54–57], it is important that we understand the genetic factors that might also be involved in tissue repair and remodeling at mucosal surfaces.

Animal models of food allergy

Although there is no completely satisfactory food-allergy animal model for studying the clinical features and the mechanisms of immunopathogenesis of IgE-mediated food allergy, several recent animal models are under investigation. As with inhalant allergy, the regulation of the balance between Th1 and Th2 activities has been suggested to be important for food allergy. In addition, the binding of CD80 on antigen-presenting cells to its counter-receptor on T cells has been shown to induce a Th1 immune response whereas the binding of CD86 to its counter-receptor on T cells enhances the Th2 response. IL-12 has also been shown to be important for induction of Th1-dominant responses. Investigations are aimed at establishing food-induced anaphylactic animal models, ameliorating ongoing IgE-mediated allergy and preventing food allergy.

In animal studies, vaccination strategies with cDNA containing CpG motifs plus IFN γ or IL-4 have been shown to be effective approaches for treatment of allergen-induced asthma [51–53]; however, investigation into the mechanisms of food allergy using animal models continues to be a front-running topic. The oral delivery of the gene for the peanut allergen, Ara h 2, in chitosan particles was shown to modulate murine anaphylactic responses [58*]. This mode of therapy delivery took into consideration two important features for the induction of mucosal tolerance: the DNA was protected from digestion by being complexed with chitosan and the adhesive property of chitosan for the intestinal wall enhanced endocytosis by cells of the gastrointestinal tract. The results showed an increase in serum IgG_{2a} and a decrease in IgE, suggesting a Th1-type protective response. Investigations by Li *et al.* [59] indicated that the type of immune response in mice to plasmid DNA encoding Ara h 2 is strain-dependent; this suggests interindividual variations in response similar to those seen in the human.

Although this murine animal model provided a clinical spectrum of food-induced allergy, the anaphylactic antibody was shown to be IgG₁ and disease was not due to antigen-specific IgE.

The generation of a murine model of anaphylaxis was subsequently induced using oral sensitization and challenge that clearly mimicked the clinical features of anaphylaxis in human subjects [60]. Two significant observations from these investigations merit consideration: firstly, the allergenicity of peanut proteins was increased compared with cow's-milk proteins, as both an adult and weanling murine model of peanut allergy could be established in the peanut model; and, secondly, both mouse IgE and human IgE bound to similar Ara h 2 epitopes.

In an ovalbumin-induced diarrhea model of food allergy, Kweon *et al.* [61] showed that the route of administration (systemic, followed by oral, routes of sensitization) and the mouse strain (BALB/c and SJL/J compared with C57Bl/6 and C3H/HeJ) were essential factors. Moreover, the authors showed that the large-intestine CD4⁺ $\alpha\beta$ T cell fraction possessed higher levels of IL-4 and IL-13 in contrast either to splenic or small-intestine cells from test animals or to control animals. Using Stat-6-deficient mice, direct evidence was presented that ovalbumin-induced diarrhea was completely dependent on Stat-6-regulated Th2-type responses. The authors concluded that there may be a tightly regulated cross-network system between systemic and selected mucosal compartments (spleen compared with the large intestine).

Evidence for the mechanisms of how peptide analogues induce T cell modulatory effects is lacking; however the use of peptide therapy continues to be a well-sought-after immunotherapeutic strategy. Active sensitization by the intraperitoneal route followed by peptide immunotherapy

was used to show that a Th1-skewing ovalbumin peptide analogue inhibited allergen-specific responses and airway inflammation whereas a Th2-skewing peptide analogue, as well as the wild-type peptide, aggravated the ongoing allergic response [62]. Similar convincing findings by von Garnier *et al.* [63], who used therapy that involved a peptide allergen derived from phospholipase, support the concept that peptide immunotherapy is able to induce T cell anergy, a decrease in allergen-specific IgE and a shift in allergen-specific T cell cytokine secretion from a Th2 to a Th1 pattern. Treatments such as these, applied to food allergy, are encouraging but efficacy in human trials remains to be determined.

Conclusions

In the context of allergic disease, interest has focused on IgE, mast cells, basophils, eosinophils, interleukins and receptor-transduction pathways associated with different allergic responses. Critical correlations between cell numbers and cytokines may not be in evidence in the different allergic responses; nor do they provide confirmative evidence of causation. As investigations continue, there is a need to consider if cells are being recruited in response to inflammation or injury at the site rather than being part of the causative mechanism. Progress will ultimately link the mechanisms causing allergic inflammation and those leading to fibrotic changes in the environment of tissue injury and repair.

Update

Since the original submission of this review, three particularly interesting papers have been published. The first [64] reviews some of the molecular and biochemical data concerning structural information on plant-derived allergenic molecules. The second [65] presents the first comparison of FK506 with steroids and disodium cromoglycate; it focuses on the mechanisms and effects of FK506 on mast cells and basophils. The third [66] is a comprehensive review of relevant articles dealing with the properties, the mechanisms, the transcription-regulatory factors and the pathophysiological consequences of Th1 or Th2 polarization. Conceptual and experimental data in both humans and animal models of atopic allergy are highlighted with therapeutic options for immunopathologic reactions involving the Th1/Th2 paradigm. A summation of the hygiene hypothesis is also made.

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