Genetics of Food Allergy

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Allergic reactions to foods are an important medical problem throughout the industrialized world. The occurrence of food allergy appears to be strongly influenced by genetics, but the basis of the genetic predisposition to food allergy has not been differentiated from that for atopy in general. In addition, genetic susceptibility alone does not explain the prevalence of food allergy satisfactorily, leaving ample room to consider the importance of environmental influences (external, maternal, and gastrointestinal environment) and interactions between the host and the environment. Several features of food allergy are highlighted in this review: 1) patients with severe food allergies are overwhelmingly atopic, but food allergy occurs only in approximately 10% of patients with other atopic diseases; 2) most patients are clinically reactive to a single food, and although a substantial minority have multiple food allergies, the variety of bone fide food allergies in a given individual is limited; 3) foods contain multiple proteins whereas only a small subset are allergenic; 4) there is likely an important contribution of the environment, becoming manifest in genetically susceptible individuals.

Introduction

Hypersensitivity to foods is now recognized as a problem throughout the industrialized world [1•]. These allergic reactions may be immunoglobulin E (IgE)-mediated, cell-mediated, or both, and are most common in infancy [1•]. In the United States, there are an estimated 4 million people with well-substantiated food allergies [2]. Those with food allergies may be very sensitive to the pertinent substance. In placebo-controlled food challenges, peanut-sensitive patients react to as little as 100 μg of peanut protein [3]. In Montreal, 1.5% of early elementary school students were recently found to be sensitized to peanuts [4].

This review is focused on IgE-mediated food allergy, a condition that affects up to 6% of children and often persists beyond childhood to affect up to 4% of the adult population [1•,5•]. IgE-mediated reactions to foods are thought to be the most common cause of anaphylaxis when it occurs outside of the hospital and are estimated to cause 125 deaths per year in the United States [6]. An analysis of 32 fatalities thought to be due to food-induced anaphylaxis revealed that peanut was the likely responsible food in 62% of the cases [7]. For this reason, allergies to peanuts have been studied in more detail than have allergies to any other specific food.

A relatively small number of foods account for most food allergies, and most patients are allergic to one or a few foods. In the United States, the predominant allergenic foods are milk, egg, and peanut for children and peanut, tree nuts, fish, and shellfish for adults, although sensitization can occur to many other foods as well [1•,5•]. Children who are sensitized to tree nuts and peanuts tend to be highly atopic, with a history of eczema, asthma, and rhinitis [8–10]. In spite of this high incidence of atopy, only a minority (2%–32%) of tree nut–allergic and peanut-allergic patients are allergic to other foods [8–10]. In a random telephone survey, similar findings were reported for seafood allergy. Of those responding, 2% reported a convincing history of allergy to shellfish, 0.4% for finfish, and 0.2% for both [11]. Therefore, although 50% of those sensitive to finfish were also sensitive to shellfish, only 10% of those sensitive to shellfish were sensitive to finfish. Furthermore, of those allergic to finfish, 33% reported that they were allergic to only one type of finfish. Seventy-seven percent of the respondents did not report other food allergies [11].

Peanut allergy frequently becomes manifest early in life and, in more than 74% of cases, following the first oral exposure to peanuts [12,13]. This observation has led to an investigation of other possible routes of first exposure (and thus, sensitization), including in utero, via breast milk, and via exogenous application of peanut-protein containing oils, especially to disrupted skin [14–16]. The prevalence of peanut allergy appears to be increasing, with most evidence pointing to a doubling in industrialized countries within the past decade, which coincides with an increasing prevalence of atopic (allergic) disease in general [1•,10,13]. Thus, anaphylactic and other allergic reactions to foods appear to occur in individuals with other atopic diseases and are significant medical problems of increasing importance [1•,6,17].

A number of factors must come together to result in food allergy. The most obvious are the nature of the allergen, the process whereby the allergen is presented to the immune system, and the immune response to the allergen. However, the environment (broadly defined to include maternal influences and the microbial constituents of the gastrointestinal tract) can affect individuals differently, based on genetic predisposition. Furthermore, the individual can react to an allergen in different ways, depending on the timing, method, and context of its presentation. In many ways, food allergy is thought to be due to a failure of immune tolerance mediated by the mucosal immune system [18•]. An excellent discussion of genetic and environmental influences that may lead to the development of food allergies has recently been published [19•].

The major histocompatibility (MHC) class II molecules form the interface whereby exogenous peptides (from food allergens) are presented to the adaptive immune system. Therefore, it is important to begin this discussion with a brief review of food allergens and then a brief review of the MHC system. Because food-allergic subjects are almost all atopic, our current understanding of the genetics of atopic disease is discussed before discussing the genetics of food allergy.

Food Allergens

Food allergens, recognized by their ability to bind IgE, represent a small subset of known food proteins, and, for the most part, they are members of a restricted number of protein families and superfamilies [20,21,22•]. The most prominent families of food allergens are the cupin superfamily, the prolamin superfamily, and the pathogenesis-related proteins (PR), which consists of 14 separate plant-protein families (see Table 1 in Breiteneder and Radauer [22•]). On a structural and functional level, food allergens are characterized by one of several independent features. These are the ability to bind a variety of ligands; the ability to interact with membranes and other lipid structures; stability to denaturation; glycosylation; and the presence of repetitive structures such as multiple linear IgE-binding epitopes [23•,24•]. Jenkins et al. [25••] have recently examined conserved surface features within plant-food allergen families to generate a simpler classification of four structural families. Although great effort has been spent to reach an understanding as to why only a small subset of food proteins are allergenic and progress has been made, this has not yet been achieved [23•,24•,25••,26].

The HLA System

The major histocompatiblility complex (MHC) is a complex group of genes on chromosome 6p21.31 that includes the genes that code for the human leukocyte antigens (HLA) [27,28]. MHC class I molecules (HLA-A, HLA-B, and HLA-C) are highly variant heterodimers composed of a variant α chain and an invariant molecule, β2-microglobulin. MHC class II molecules (HLA-DR, HLA-DQ, and HLA-DP) are highly variant heterodimers composed of a 34 kD α chain that is noncovalently associated with a 29 kD β chain [27]. Together there are more than 1300 HLA class II alleles, although these can vary in frequency in any given population and are often inherited in groups (haplotypes) [29]. Soluble exogenous antigens are internalized by antigen-presenting cells (APCs) and, following unfolding, disulphide reduction, and proteolytic cleavage, peptides bind to MHC class II proteins within a well-defined binding groove. Antigenic exogenous peptides from proteins such as food allergens are thus specifically bound in the binding groove of a restricted repertoire of MHC class II molecules and are then recognized by specific T-cell receptors on CD4 T cells leading to T-cell activation [29,30].

Class II molecules have four primary pockets (P1, P4, P6, and P9) and three minor pockets (P3, P7, and P10) within their binding groove. Recently, there is an appreciation of significant homologies within the peptide-binding groove that are shared among immunogenically disparate HLA alleles. These homologies within the peptide-binding groove have been called "shared epitopes" [31] and "restrictive supertype patterns" or "functional groups" [32•].

Distinct functional groups (A, De, Dr, E, Q, R, and a) have been defined within pockets of HLA-DRB by Ou et al. [32•]. Within these pockets, polymorphic residues of the β chain (at residues 70, 71, and 74) play a particularly important role in immune recognition. As summarized by Ou et al. [32•], functional group "A" has been associated with rheumatoid arthritis, functional group "De" with pemphigus vulgaris, "Dr" with allergic aspergillosis, "E" with Hashimoto's thyroiditis, "Q" with psoriasis, "R" with SLE, and "a" with multiple sclerosis. In addition, functional group "Dr" has been associated with atopy to dust mite [33] and functional group "E" with the latex-fruit syndrome in latex-sensitive patients [34•]. Homology within the peptide-binding groove may allow disparate HLA alleles to present the same peptide. Likewise, peptides with different sequences may have conserved amino acids and bind the same HLA allele. In this view, it is felt that distinct MHC alleles that have homologous binding grooves will bind peptides in a similar manner and hence initiate a similar T-cell response. This approach to simplifying HLA association studies has been successfully applied to show unexpected homology within the peptide-binding groove domains of otherwise disparate HLA-DPB1 alleles in chronic beryllium disease [35,36] and has underscored the genetic associations between specific HLA-DRB1 alleles and susceptibility to rheumatoid arthritis (RA) in smokers [37,38].

Atopy: Genetic and Environmental Influences

Genetics

A detailed discussion of the genetic basis of atopy is beyond the scope of this article and has been recently reviewed

[39]. In summary, atopy is a complex phenotype with a strong heritable component and with many candidates for susceptibility genes that overlap with susceptibility for asthma (which has an important atopic component in many patients) [39–41,42••]. Genes that have been associated with atopy fall into several broad categories, including those related to Th2-type cytokines (interleukin [IL]-4, IL-5, IL-9, and IL-13) and can modulate IgE levels, the major histocompatibility complex alleles (HLA-DRB1*01, DRB1*0701, and DQB1*02), which are related to immune responsiveness, the beta chain of the high-affinity receptor for IgE (FcεRI) affecting activation of mast cells by IgE/allergen, other genes (eg, PHF11) that can influence IgE levels by unknown mechanisms, and genes of the innate immune system (eg, CD14, a co-receptor for lipopolysaccharide [LPS]) and CARD15 (part of the intracellular LPS receptor) that respond to commensal bacteria and affect gut homeostasis [39].

Environment

A substantive body of basic and clinical research supports the theory that naturally occurring infections and exposure to microbes can prevent the development of atopic disease [43]. The main pathway by which microbes are believed to have this allergy-protective effect is via stimulation of toll-like receptors (TLRs) by microbial TLR ligands. The "hygiene hypothesis" may be most apropos if such exposures occur in early childhood [44]. Thus, factors that may influence the end result of exposure to endotoxin include timing of exposure, the amount of exposure, and the host response to that exposure.

Although asthmatics are reported to be hypersensitive to inhalation of endotoxin, there is evidence that exposure to higher levels of endotoxin in house dust early in life are protective of the development of atopic dermatitis, allergic rhinitis, and atopy-associated asthma in children [45]. This is due, at least in part, to induction of Treg/Th1 T cells [45–48]. Furthermore, differential bacterial colonization observed between atopic and less-atopic populations [49] and positive effects of probiotics [50] on reduced expression of atopic disease also support the hygiene hypothesis and the importance of TLR signaling. In regard to food allergy, there is limited circumstantial evidence of a relationship between endotoxin exposure and development of food allergy. In one recent study, dog ownership (which is linked to increased exposure to endotoxin) was associated with a lower likelihood (7%) of developing food allergy in infancy compared with lack of dog ownership (15%; $P = 0.05$) [51].

Genetics and environment

The effect of host response to endotoxin on the development of allergic disease has also been studied. Functional polymorphism in the receptor for endotoxin (TLR4) or gene products important to endotoxin-mediated stimulation of TLRs (CD14) appears to alter the likelihood and/or severity of atopy and allergic disease [52•,53•,54]. TLR polymorphisms with functional consequences in humans were first identified in a subgroup of people with reduced airways and immune responses to inhaled endotoxin [55]. The substitution mutation Asp299Gly blunts cellular and airway responses to endotoxin. This polymorphism has since been studied in greater detail and found to exist in 3% to 6% of different populations. Subsequent studies have revealed conflicting findings, some supportive [56] and some not supportive [57,58]. Zambelli-Weiner et al. [54] looked at an interaction between the CD14 genotype and the environment, but in the context of asthma and atopy. They looked at an association between this CD14/-260 polymorphism and levels of environmental (house dust) endotoxin (HDE) in a population of African descent in Barbados. They found that the TT genotype was associated with more severe asthma but not with atopy and that the CC genotype was a risk factor for asthma if the HDE levels were low.

Food Allergy: Genetic and Environmental Influences (Fig. 1)

Genetics

A twin study by Sicherer et al. [42••] has clearly demonstrated that the expression of peanut allergy has a substantial genetic basis (mean, 81.6%; 95% confidence interval, 41.6%–99.7%). An assumption in these calculations is that there was no interaction of genetic and environmental influences [42••]. Given more recent evidence that some genetic components associated with atopy and food allergy (eg, polymorphisms in CD14) may influence the response of an individual to the environment, this assumption may have led to an overestimation of the genetic basis for peanut allergy. As further evidence of a genetic basis, there is a demonstrable increase in the concordance of peanut allergy among genetically nonidentical siblings (6.9%) and dizygotic twins (6.8%) than among the general population (1.3%) [42••,59]. Donovan et al. [60] described a family with peanut allergy and found that peanut allergy was segregated with the paternal HLA-DR4 haplotype and not with the TCR-α or TCR-β alleles. Thus, although genetics clearly plays a role in the expression of the food allergy phenotype, the remaining contributions must come from environment influences and from chance.

Howell et al. [61•] studied HLA class II loci by polymerase chain reaction in 50 peanut-allergic subjects, 34 non–peanut-allergic relatives, and 293 unrelated controls. They found significant differences between the peanut-allergic subjects and the controls for the presence of DRB1*08, DRB1*08 /12tyr16, and DQB1*04, but no significant differences between the peanut-allergic patients and their non–peanut-allergic relatives [61•]. Therefore, it appears likely that Howell et al. were identifying HLA associations that may be important for atopy within their population but not necessarily for peanut allergy.

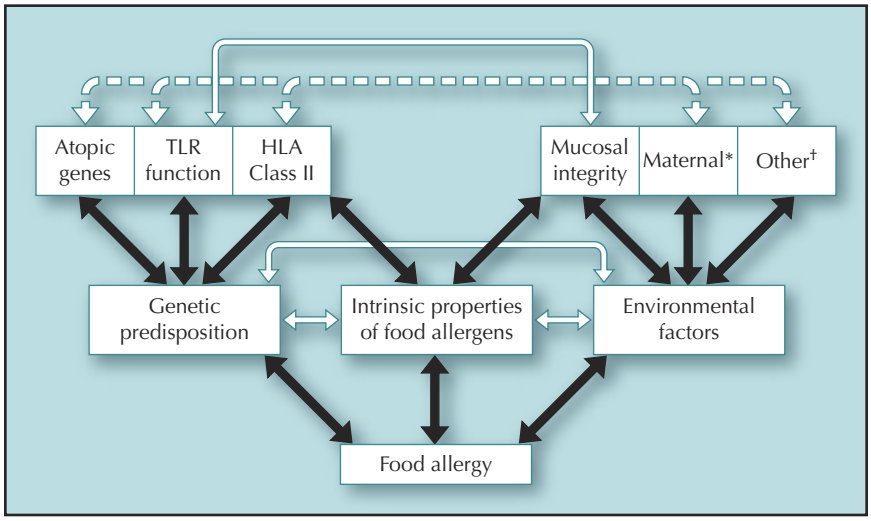

Figure 1. Schematic representation of possible interactions among genetic predisposition, intrinsic properties of food allergens, and environmental factors. *Black lines* denote clear associations, *white lines* denote associations for which there is some but not extensive evidence, *dotted lines* denote conjecture. *Maternal influences include the age of the mother, the mode of delivery, maternal ingestion of potential allergens, and breast-feeding. †Other environmental factors include exposure to endotoxin and bacterial DNA in house dust, and timing and route of exposure to allergenic foods.

More recently, Hand et al. [62] studied HLA polymorphisms in nut-allergic (tree nut and not peanut) patients in South Wales. They studied HLA-A, HLA-B, DRB1, and DQB1 at "2-digit resolution" in 84 patients with symptoms of nut allergy and compared these with 82 atopic non–nut-allergic subjects and 1798 random blood donors. Although increased frequencies of HLA-B*07 and DRB1*1 were found, neither of these were statistically significant when corrected for the number of alleles studied [62].

Blanco et al. [34•] investigated the HLA class II linkage for the latex-fruit syndrome in a Spanish population using high-resolution DNA typing. They studied 78 latex-allergic patients without spina bifida and 68 controls. They compared expression of HLA alleles, and markers for the IL4-RI and FcεRI-β chain between latex-sensitive subjects and the controls and between the 33% of the latex-sensitive subjects who were also allergic to fruits and the 67% who were not. Unlike previous investigators who had studied larger populations of latex-allergic patients, they found no statistically significant differences between the total latex-sensitive population and the controls [34•,63]. However, the comparison of the fruit-allergic, latex-sensitive patients to the fruit-tolerant, latex-sensitive patients revealed important findings. Within the HLA DQ alleles, they found that the presence of allele DQB1*0201 was associated with high susceptibility to fruit reactivity. The initial evaluation of the DRB1 alleles did not reveal any statistical association, but when these data were reanalyzed by grouping the known alleles into seven functional groups based on peptide binding groove motifs in pocket 4 as described by Ou et al. [32•], they found that the presence of HLA-DRB1 alleles belonging to functional group "E" confirmed susceptibility to fruit allergy. These findings were further enhanced when the presence or absence of a specific allele was assessed. In this focused analysis, DRB1*0301 and DRB1*0901 were identified as susceptibility alleles (increased likelihood of fruit allergy), and DQB1*0202, DRB1*0701, and DRB1*1101 were identified as resistance alleles (no fruit allergy) [34•]. The authors go further to suggest that these groups of alleles form two different haplotypes that are in linkage disequilibrium and may confer reactivity or lack of reactivity (respectively) to specific peptides within the hevein-like domain of plant class I chitinases [34•]. Thus, because HLA determinants recognize specific peptides, analysis of HLA alleles as genetic determinants of food allergy may depend on recognition of the important peptides driving T-cell activation.

Environment

Environmental elements that may contribute to the presence of food allergy include the timing and route of exposure to potentially allergenic foods, the age of the mother, the mode of delivery, the permeability of the gut epithelium, and the nature of the commensal microorganisms in the gut [5•,18•,19•]. There is general agreement that food allergy is a result of failure of the normal function of the mucosal immune system, a failure of the normal mucosal barrier, or both [5•,18•,19•,64]. The specifics of how this may occur are the subject of intense investigation and point to important interactions between the genetics of the individual and the gastrointestinal environment.

Genetics and environment

TLR ligands, such as bacterial endotoxin and microbial DNA that is hypomethylated, are well-known to promote memory/effector TH1 immune responses [45,48]. In a murine model, peanut allergy could be induced when signaling though TLR4 was reduced either by genetic impairment or by reduction of gut flora due to antibiotic treatment of wild-type mice [53•]. Co-administration of CpG DNA (a ligand for TLR9) could overcome the defect in TLR4 signaling, allowing the induction of peanut allergy [53•]. Another mechanism whereby innate immunity may play a role in the induction of food allergy is by maintaining epithelial homeostasis and integrity [65••]. Wild-type control mice tolerate an orally administered

intestinal epithelial toxicant (dextran sulfate), whereas MYD88-deficient mice (deficient in signaling by all TLRs) experience morbidity and mortality [65••]. As in the work by Bashir et al. [53•], elimination of commensal bacteria by treatment with antibiotics caused the wild-type mice to succumb to dextran sulfate and a protective effect in these antibiotic-treated mice could be restored by oral administration of either endotoxin or lipotechoic acid (TLR4 and TLR2 ligands, respectively.

In humans, a functional polymorphism in the -260 position (in some studies said to be at the -159 position) of the promoter region of CD14 leads to the "TT" genotype that is thought to increase expression of CD14 by decreasing the binding affinity of the transcriptional regulator Sp [66]. This polymorphism has been associated with more soluble CD14 and less serum IgE in those with allergen sensitization [67]. Since then, this finding has been replicated by some [68,69] but not by others [70,71]. Woo et al. [52•] examined the prevalence of the CD14 TT polymorphism in 175 asthmatics and 77 patients with IgE-mediated food allergy. The TT polymorphism (associated with less IgE in some studies but not measured in this study) was associated with a greater risk for nonatopic asthma, and, contrary to prediction, a greater risk for food allergy.

These recent reports (particularly the murine studies) strongly suggest that TLR-mediated signaling may play a major role in maintenance of the intestinal epithelium and in modulating the TH1/TH2 balance in the immune response to food allergens.

Conclusions

Atopy is a complex genetic trait that appears to be strongly influenced by environment. Food allergy (and peanut allergy in particular) most often appears in patients who have other manifestations of atopy (and often rather extensive atopic disease), but there are large numbers of atopic individuals who do not have food allergy. What is it that leads to food allergy in some but not all atopic individuals? Why do a few individuals develop allergies to multiple foods whereas the majority remains monosensitive? Is it the ability to respond to specific T-cell epitopes found in the proteins of specific foods? This is a testable hypothesis. Are the HLA class II molecules of T cells in food-allergic individuals different (in their antigen-binding site) from those in food-tolerant atopics? Is it exposure to specific food proteins at a particular time in development? Are there yet-to-be discovered genetic variations that lead to abnormal gut permeability and aberrant exposure and/or response to food proteins? Do endotoxin and/or bacterial DNA acting via Toll-like receptors play a role in humans, and can this be related to changes in gut permeability? These are all important questions that must be addressed to understand the genetic basis of food allergy.

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