Review

Food allergy: an enigmatic epidemic

M. Cecilia Berin and Hugh A. Sampson

Jaffe Food Allergy Institute, Immunology Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Food allergy is a common disease that is rapidly increasing in prevalence for reasons that remain unknown. Current research efforts are focused on understanding the immune basis of food allergy, identifying environmental factors that may contribute to its rising prevalence, and developing immunotherapeutic approaches to establish immune tolerance to foods. Technological advances such as peptide microarray and MHC class II tetramers have begun to provide a comprehensive profile of the immune response to foods. The burgeoning field of mucosal immunology has provided intriguing clues to the role of the diet and the microbiota as risk factors in the development of food allergy. The purpose of this review is to highlight significant gaps in our knowledge that need answers to stem the progression of this disorder that is reaching epidemic proportions.

Food allergies: a growing clinical problem

Food allergies encompass a broad spectrum of disorders secondary to abnormal immunologic responses to food antigens. IgE-mediated reactions are most common and induce a variety of symptoms that are rapid in onset and may manifest as itchy flushing of the skin and/or urticaria, nausea, abdominal pain and/or vomiting, mild to severe bronchospasm and respiratory distress, hypotension, cardiovascular collapse, and/or death, with cutaneous and abdominal symptoms by far the most common [1]. Although there are a number of non-IgE-mediated food allergic reactions such as eosinophilic esophagitis and food-protein-induced enterocolitis syndrome, we will focus on IgE-mediated reactions in this review.

The exact prevalence of food allergy is difficult to ascertain due to the imprecision of laboratory tests, but recent reviews of the literature estimate that food allergy affects greater than 2% and less than 10% of the US population [2]. The prevalence of food allergy peaks at 6–8% during the first few years of life and is most often due to milk, egg, peanut, fish, and shellfish, although all foods may induce allergic reactions. Most children 'outgrow' their allergy to milk, egg, wheat, or soy during their first decade, but allergies to peanut, tree nuts, fish, and shellfish are often retained for life [1]. Limited data suggest that the prevalence of food allergy has increased in industrialized countries worldwide [3–5], for example estimates of peanut and tree nut allergy tripled in American children between 1997 and 2008 [6], but the reason for this increase remains unknown [7]. Similar increases have been seen in the UK and Australia [4,8]. The 'standard of care' for managing food allergies involves proper diagnosis, including a detailed clinical history, laboratory studies (skin prick tests and/or quantification of food-specific IgE, and often oral food challenge), education about strict dietary avoidance, provision of an emergency plan, and medications (e.g., self-injectable epinephrine) for the treatment of accidental ingestions [9].

In recent years, the field of food allergy has gone through considerable growth and technical advances have allowed for a growing understanding of the immune basis of clinical reactivity to food allergens. The field has begun to focus on the role of environmental risk factors, including diet and the microbiota which will be reviewed here. A number of immunotherapeutic approaches are currently under investigation, including different routes of immunotherapy (oral, sublingual, and epicutaneous), immunotherapy with modified recombinant proteins, and use of anti-IgE monoclonal antibodies combined with immunotherapy [10]. By taking advantage of recent advances at the intersection of immunology, nutrition, and microbiome, the field is poised to make significant inroads to the prevention and treatment of food allergy.

Immune profile of food allergy

Humoral responses to food proteins

By definition, IgE-mediated food allergy is characterized by the presence of IgE specific for antigens within the triggering foods. IgE antibodies are commonly found in healthy controls, but for several foods the level of IgE is predictive of clinical reactivity and probability curves have been established relating the likelihood of tolerating a food based on levels of allergen-specific IgE [11,12]. The lack of clinical reactivity in those with IgE antibodies to foods may relate to the ratio of allergen-specific to total IgE, the ratio of specific IgE to antibodies of blocking isotypes such as IgG4 or IgA, or may relate to the affinity or clonality of IgE antibodies. The ratio of specific to total IgE has been called the specific activity of IgE, and higher specific activity has been shown to be associated with higher levels of basophil activation [13]. The relevance of specific activity of IgE to clinical reactivity and efficacy of anti-IgE therapy for other allergic diseases has been reviewed by Hamilton *et al.* [14]. However, food allergen specific to total IgE ratios have not been found to be more predictive measures of clinical reactivity than food-allergen-specific IgE levels alone [15]. Clinical reactivity may reflect the presence or absence of IgE to relevant components of the food. For example, testing of IgE against components of peanut has shown that IgE against the allergen Ara h 2 is predictive of clinical

Corresponding author: Sampson, H.A. (hugh.sampson@mssm.edu)
Keywords: IgE; anaphylaxis; mucosal immunology; microbiota; Th2; Treg; immunotherapy

1471-4906/$ – see front matter
 http://dx.doi.org/10.1016/j.it.2013.04.003

reactivity, whereas IgE against the allergen Ara h 8 (cross-reactive with the birch pollen allergen Bet v 1) in the absence of IgE to other peanut allergens is predictive of clinical tolerance [16,17]. These differences in reactivity to components of peanut would not be detected by measurement of specific IgE against the whole peanut extract. The clonality of the IgE response to foods can be measured using peptide microarrays [18,19]. Clinical reactivity is associated with recognition of a greater number of epitopes and, for peanut, four informative epitopes were found to be effective in prediction of clinical reactivity [19].

It has been shown in mice that low and high affinity IgE are generated through distinct immune pathways and only high affinity IgE can generate anaphylactic responses [20]. Measurement of IgE levels by standard techniques does not reflect affinity and it needs to be determined whether incorporating a measure of affinity [21] would increase the predictive value of IgE measurements. IgG and IgA antibodies to foods are commonly found in food-allergic and healthy subjects [22] but do not relate to clinical reactivity. IgG4 and IgA are thought to be protective by functioning as blocking antibodies, and are increased in response to immunotherapy, for example oral immunotherapy for peanut [23,24], but these antibody levels are generally not predictive of tolerance in the absence of intervention.

Anaphylaxis in mice has been shown to be inducible in the absence of IgE, although generally only at high doses of antigen given systemically. These reactions are mediated by IgG1 and involve activation of macrophages, basophils, or mast cells. Although IgG-mediated anaphylaxis has not been demonstrated in man, biomarkers of IgG-mediated anaphylaxis have been proposed [25] that may help to determine if IgG-mediated anaphylaxis contributes to human food allergy. Other candidates for alternative pathways of effector cell activation include immunoglobulin-free light chains that are elevated in children with cow's milk allergy [26]. Mechanisms of allergen specificity and effector cell activation have not yet been established for this pathway.

T cell responses to food proteins

Class switching to IgE is dependent on T cell help, and therefore the T cell response to food antigens in food allergic subjects compared to healthy controls is of particular interest. Early studies used T cell lines grown from peripheral blood of food-allergic subjects and found a predominant Th2 phenotype. 5-(and 6)-Carboxyfluorescein diacetate succinimidyl ester (CFSE)-based detection of cells proliferating in response to culture with antigen confirmed a Th2 profile in allergen-responsive T cells from food-allergic subjects, and a Th1 profile in healthy controls [27]. More recently, CD154-based detection of antigen-specific T cells after short-term stimulation was used to compare the T cell phenotype of patients with IgE-mediated food allergy, non-IgE-mediated food allergy, and healthy controls [28]. Healthy controls had few allergen-specific T cells that expressed low levels of interferon (IFN)-γ and tumor necrosis factor (TNF)α Food-allergic subjects had significantly greater frequencies of allergen-specific T cells. Interleukin (IL)-4 and IL-13 that drive IgE class switching were elevated in IgE-mediated and non-IgE-mediated food allergy, therefore other factors beyond production of Th2 cytokines must be present to allow IgE sensitization to occur. This may relate to homing properties of the T cells. Human T follicular helper (Tfh) cells provide better help for IgE class switching than non-Tfh cells that express IL-4 [29]. Tfh cells can traffic to B cell follicles through their expression of the chemokine receptor CXCR5, where they are optimally located to provide help for B cell isotype switching. Therefore, this subset of Th cells may be most critical in regulating inappropriate IgE responses to foods, but the contribution of Tfh cells remains to be addressed in the context of IgE-mediated food allergy.

MHC class II tetramers have also been used to identify food-allergen-specific T cells in healthy controls versus allergic subjects without the need for re-stimulation of cells [30]. An epitope from the peanut allergen Ara h 1 was used, and again the frequency of allergen-specific T cells was substantially higher in food-allergic subjects compared with healthy controls, with the number in healthy controls being too low to phenotype reliably. In comparison to the CD4+ population as a whole, these tetramer-positive cells were enriched for the memory marker CD45RA, CD25, and the skin-homing chemokine receptor CCR4, but not the skin-homing receptor cutaneous lymphocyte antigen (CLA). The antigen-specific T cells expressed lower levels of the gut-homing addressin β7 than the general pool of CD4+ T cells, indicating that they are not likely to have originated from the gut. This may relate to sensitization by routes other than the gastrointestinal tract, as will be discussed in more detail later. In peanut-allergic subjects the range of antigen-specific CD4+ T cells detectable with this method was in the range of ten cells per million CD4+ T cells. This low frequency underscores the difficulty of obtaining sufficient allergen-specific T cells for study, particularly when studying pediatric populations. The even lower frequency of antigen-specific T cells in healthy controls makes them difficult to phenotype, so the question has not yet been answered as to whether an active regulatory phenotype consistent with experimentally induced mucosal immune tolerance is the normal immune response to antigens in the diet. A subset of patients with a deletion in a noncoding region of Foxp3 that results in low Foxp3 protein expression develops a severe allergic phenotype associated with hyper IgE, eosinophilia, villous atrophy, and elevated Th2 cytokines in the intestinal mucosa [31]. Mice lacking Tregs induced in the periphery (but having normal level of thymus-derived natural Tregs) develop a spontaneous Th2-biased inflammation at mucosal sites, and develop antibodies to components of the mouse chow (the isotype of these antibodies was not reported) [32]. These data show that Tregs have a role in the suppression of inappropriate immune responses to food antigens. More data are required to determine if food allergy is really a consequence of an impaired regulatory response to foods, which, if true, would suggest that immune tolerance by oral allergen immunotherapy may be unlikely to develop in the absence of additional therapeutic targeting.

Immune mechanisms of food-induced anaphylaxis

In a sensitized individual re-exposure to the food allergen by the oral route can lead to clinical manifestations at local