

Mechanisms that define transient versus persistent food allergy



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Currently, we have a poor understanding of why some food allergies are outgrown and others are not. Deciphering the immune basis of the natural resolution of food allergy will likely provide critical information for developing new therapies for the treatment of persistent food allergies. There are limited cohort studies that have followed children with food allergy over time, but information generated from such cohorts points to features of innate and adaptive immunity, as well as environmental differences (microbiome) that discriminate those with persistent versus transient food allergy. Studies from mouse models highlight the importance of novel subsets of memory B cells rather than plasma cells combined with antigen re-exposure and T-cell help in the maintenance of IgE. In this review we discuss these findings from human cohorts and experimental systems and discuss existing gaps in our knowledge. (*J Allergy Clin Immunol* 2019;143:453-7.)

Key words: *Tolerance, food allergy, anaphylaxis, natural history, IgE, components, epitopes, innate immunity, regulatory T cells, microbiome, memory B cells*

Food allergy has its origins in early life and affects 6% to 8% of the pediatric population. Some food allergies are commonly outgrown, whereas others are more likely to persist into adulthood. Milk and egg allergies, which are the most common allergies of childhood, are 2 allergies that are commonly outgrown in childhood. A multicenter observational Consortium for Food Allergy Research (CoFAR) study of 3- to 15-month-old infants enrolled with milk or egg allergy and/or eczema showed that approximately 50% of infants with egg allergy outgrew their egg allergy at a median age of 6 years.¹ The same cohort showed that 52.6% of children with milk allergy had outgrown their milk allergy at a median age of 63 months.² This is a slower rate of resolution than has been described in population-based (not selected as high-risk) cohorts. The population-based Australian

Abbreviations used

CoFAR: Consortium for Food Allergy Research

DC: Dendritic cell

Foxp3: Forkhead box P3

Treg: Regulatory T

HealthNuts cohort showed that 47% of infants with egg allergy outgrew their egg allergy at 2 years of life³ and that the prevalence of egg allergy decreased from 9.5% at 1 year of life to 1.2% at 4 years of life.⁴ In the EuroPrevall birth cohort of more than 12,000 children from countries throughout Europe, 57% of children with IgE-mediated milk allergy had outgrown their milk allergy by 2 years of life.⁵

Unlike milk and egg allergy, peanut and tree nut allergies are commonly persistent. A 4-year follow-up of peanut allergy in the HealthNuts cohort found that 22% of children given a diagnosis of peanut allergy at 1 year of life had resolved their peanut allergy by 4 years of life.⁶ This is consistent with previous reports on the resolution of peanut allergy.⁷ There is limited information on tree nut allergy, with one report of a resolution rate of 9%.⁸ The occurrence of spontaneous resolution, even with peanut and tree nut allergies, demonstrates that true tolerance can be achieved in food allergy, and there is a need to understand the immune basis of this resolution to develop more rational therapies for the treatment of persistent food allergy.

PREDICTORS OF FOOD ALLERGY RESOLUTION

Food-specific immunoglobulins

In the CoFAR natural history cohort milk-specific IgE level, skin prick test response size to milk, and the severity of atopic dermatitis at baseline were the 3 most important factors predicting resolution of milk allergy.² Similarly, egg-specific IgE level and the severity of atopic dermatitis at baseline were the 2 most important parameters predicting resolution of egg allergy.¹ A calculator incorporating these factors was generated to predict resolution of milk and egg allergy.^{1,2} A limitation of the CoFAR natural history study was the absence of protocol-driven food challenges. The use of IgE levels to categorize subjects introduces bias toward finding a role for IgE in clinical outcomes. However, the CoFAR study also analyzed a subset of the cohort with confirmed food allergy or tolerance (based on patient report of reaction or tolerance after exposure or challenges performed as part of clinical care).

Predictors of persistent peanut allergy (defined as persistent at 4 years of age) in the HealthNuts cohort included skin test response size and peanut-specific IgE measured at 1 year of age.⁶ Eczema in the first year of life was not predictive of peanut allergy

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Terms in boldface and italics are detailed in the glossary on page 454.

persistence. Allergen-specific IgG₄ levels have not been found to be predictive of natural resolution, but IgG₄ levels are increased by allergen exposure.

In addition to the magnitude of the specific IgE response, the epitope specificity of the IgE response appears to be an important factor determining transience versus persistence. Studies examining persistent milk and egg allergy highlighted the importance of binding to **linear epitopes** in predicting allergy persistence.⁹⁻¹² In the HealthNuts cohort the magnitude of egg white-specific IgE was predictive of egg allergy persistence.¹³ Measurement of IgE binding to egg components (ovomucoid, ovalbumin, and ovotransferrin from egg white and α -livetins from egg yolk) did not improve prediction of egg allergy persistence compared with egg white-specific IgE, but binding to all 4 allergens increased the risk of persistent egg allergy by a factor of 4. Thus the diversity or breadth of the IgE response appears to contribute to persistence.

Using a **microarray**-based approach to profile linear epitope binding, Caubet et al¹⁴ found that children with persistent milk allergy had stronger and more diverse binding to α -S and β caseins in the context of milk allergy. Furthermore, those who outgrew their milk allergy were more likely to have IgE and IgG₄ antibodies recognizing the same epitopes. The magnitude and quality (diversity) of the IgE response to foods appears to be critical to allergy persistence.

Food-specific T-cell responses

There is a lack of information on T-cell phenotypes associated with the natural history of food allergy. In the CoFAR natural

history cohort, food-specific T-cell responses were examined by culturing **PBMCs** with food extracts and purifying **CD25⁺** T cells after 48 hours of stimulation. Gene expression on the CD25⁺ fraction, including activated T cells and regulatory T (Treg) cells, was examined by using semiquantitative **RT-PCR**. At baseline, milk- and peanut-induced IL-4 expression was associated with milk and peanut allergy, respectively.¹⁵ Baseline or serial measures of milk-induced IL-4, **IFN- γ** , IL-10, or forkhead box P3 (Foxp3) were not associated with milk allergy persistence versus resolution.² Egg-induced IL-4 expression had a small (hazard ratio, 1.04) but significant ($P < .05$) association with egg allergy persistence, but this was a minor contribution compared with IgE levels.¹

Peanut-specific T-cell responses were examined in a small cohort ($n = 4$) of children who had outgrown their peanut allergy.¹⁶ Intracellular cytokines produced by proliferating cells were described as more T_H1 skewed in those who outgrew allergy, although this was presented as a ratio between IFN- γ or **TNF- α** and T_H2 cytokines, and therefore it is not clear whether this was due to a decrease in levels of T_H2 cytokines, an increase in levels of T_H1 cytokines, or both.

Qamar et al¹⁷ studied 11 children in whom tolerance to egg or peanut had recently developed in comparison with 22 children with egg or peanut allergy. Tolerance was associated with an increase in frequencies of Foxp3⁺CD25⁺**CD127^{low}** Treg cells and IL-10-expressing CD4⁺ T cells and Treg cells. IL-10 production from Treg cells was elicited by the tolerated antigen on stimulation *in vitro*, as had previously been reported by using detection of IL-10 in culture supernatants.¹⁸

GLOSSARY

CD25: Also known as IL-2 receptor α (IL2RA), a cell marker that is constitutively expressed by regulatory T cells that respond to IL-2, which is generated by T cells during an immune response for their immunoregulatory function.

CD73: 5'-Nucleotidase is an ectoenzyme that catalyzes the conversion of AMP to adenosine. CD73 has many physiologic roles, such as regulation of barrier function, adaptation to hypoxia, ischemic preconditioning, anti-inflammation, and leukocyte extravasation.

CD80: A costimulatory molecule found on antigen-presenting cells, such as dendritic cells, activated B cells, and monocytes, that binds to CD28 or cytotoxic T lymphocyte-associated protein 4 on T cells.

CD127 (IL-7 receptor α): A protein that is one subunit of the heterodimer IL-7 receptor found on the surfaces of various cell types. Signaling of CD127 is essential for T-cell development and regulation of naive and memory T-cell homeostasis.

GERMINAL CENTER MEMORY CELLS: A subtype of B cells formed within germinal centers after a primary immune response and critical for generating a robust antibody-mediated immune response on re-exposure.

IFN- γ : A cytokine that plays a critical role in inducing and modulating an array of innate and adaptive immune responses. Cellular responses to IFN- γ are mediated by its heterodimeric cell-surface receptor (IFN- γ R), leading to regulation of gene expression. Aberrant IFN- γ expression is associated with various inflammatory and autoimmune diseases.

IL-8: A chemokine known as neutrophil chemotactic factor is produced by a variety of cell types and known to induce chemotaxis and phagocytosis in neutrophils and other granulocytes, causing them to migrate toward the site of infection.

LINEAR EPITOPE: A protein epitope that is recognized by specific antibodies by its linear sequence of amino acids (primary structure). Antibodies can recognize 3-dimensional shapes formed by amino acids brought together by means of protein folding (called a conformational epitope) or by amino acids adjacent to each other in the protein sequence (linear epitope).

MICROARRAY: A multiplexing technology that allows high-throughput analysis of DNA, RNA, or proteins from biological materials. Microarrays can be used to measure gene expression, gene methylation, or, as referred to here, antibody binding to peptides from allergens.

MYELOID COMPARTMENT: A heterogeneous population of cells, including granulocytes, monocytes, and dendritic cells, that originate from the bone marrow. Bone marrow cells can differentiate into myeloid or lymphoid lineages.

PBMC: Any peripheral blood cell with a round nucleus that consists of lymphocytes (T, B, and natural killer cells) and monocytes, whereas erythrocytes and platelets have no nuclei and granulocytes (neutrophils, basophils, and eosinophils) have lobed nuclei.

RT-PCR: A technology that uses a fluorescent reporter molecule to monitor the PCR as it progresses. The fluorescence emitted by the reporter molecule quantifies the product as it accumulates with each cycle of PCR amplification because it makes thousands to millions of copies of specific gene sequences.

TNF- α : A cytokine produced primarily by macrophages that is involved in systemic inflammation and acute-phase reactions. TNF- α is a chief regulator of cell proliferation, survival, differentiation, and apoptosis, whereas its aberrant production and receptor signaling have been implicated in the pathogenesis of several inflammatory diseases.

Innate immunity

The innate immune system functions to integrate cues from environmental triggers (infection, stress, and damage) and relay that information to the adaptive immune system. For example, dendritic cells (DCs) in tissues respond to microbial patterns, damage-associated patterns, or alarmins, with a change in phenotype that determines the function of the T-cell response generated by antigen presentation. Tissue macrophages also respond to environmental cues and release cytokines that can shape the immune response to antigens derived from those tissues. Peripheral blood DCs from patients with food allergy have an altered phenotype compared with those from healthy control subjects, with increased production of proinflammatory cytokine production in response to allergen stimulation.¹⁹ Such responses are likely linked to signaling through FcεRI on DCs. However, alternations in innate immunity have also been shown to precede development of food allergy. Increased frequency of monocytes in cord blood and increased proinflammatory cytokine production in response to LPS was associated with development of food allergy at 1 year of life.²⁰ This increased responsiveness of the **myeloid compartment** to LPS was also identified by Neeland et al²¹ in children with egg allergy compared with nonallergic control subjects. Furthermore, levels of TNF-α and **IL-8** production in response to LPS (measured at 1 year of age) were significantly greater in children with persistent versus transient egg allergy, as determined at follow-up. Therefore factors that have modulatory effects on the innate immune system might promote allergy resolution in a non-allergen-specific manner.

Microbiome

There is growing evidence that the microbiome plays a key role in food allergy. Factors that alter the composition of the microbiome (cesarean section birth and early-life pet exposure) alter the risk of development of food allergy. Dysbiosis precedes the development of food allergy.^{22,23} Work in mouse models has identified protective mechanisms induced by the intestinal microbiota (improved barrier, IgA production, and Treg cells) that prevent food allergy.²⁴⁻²⁶

There is a great deal of interest in harnessing this information for microbial-based therapies, but it is not known whether the microbiome can be used to facilitate the resolution of food allergy once it has been established. Bunyavanich and colleagues used the CoFAR natural history cohort to examine the relationship between fecal microbial composition and milk²⁷ or egg²⁸ allergy resolution. They found that the microbial composition at 3 to 6 months of age differed significantly in infants with milk allergy that resolved compared with those with persistent milk allergy. They found enrichment of *Clostridium* species and Firmicutes in fecal samples of those in whom milk allergy resolved. Interestingly, *Clostridium* species have been identified as particularly potent inducers of regulatory cell pathways in the gastrointestinal tract.^{24,29,30} Stool samples collected at later time points (6-15 months) did not show any difference between persistent and transient milk allergy, highlighting a critical window in early life in which the microbiota influences disease outcome. In the context of egg allergy, no significant microbial predictors were identified for resolution of egg allergy, although a unique microbial composition was observed in those with egg allergy compared with those with no food allergy.²⁸ However,

the study of egg allergy included stool samples collected from 3 to 15 months, reducing the likelihood to observe a signal that was unique to the 3- to 6-month collection time in patients with milk allergy.

It is not known whether modulation of the intestinal microbiota after the window of early infancy will be useful for enhancing resolution of food allergy. It is also not known whether altering the microbiome by itself could facilitate natural resolution of food allergy or whether administration together with allergen, as has been done with probiotics and oral immunotherapy (OIT),³¹ would be required for microbial-facilitated resolution of food allergy.

RESOLUTION OF FOOD ALLERGY: LESSONS FROM ANIMAL MODELS

Animal models have been used to study mechanisms of sensitization and tolerance to foods, but there are few studies on the mechanisms of allergy persistence. Jimenez-Saiz et al³² focused on maintenance of IgE responses over time in a mouse model of peanut-induced anaphylaxis. Mice were orally sensitized with peanut and the mucosal adjuvant cholera toxin and followed over time. Susceptibility to anaphylaxis was maintained for 6 months but was lost by 12 months after sensitization, which coincided with a loss of detectable peanut-specific IgE. They observed that loss of peanut-specific IgE was preceded by loss of peanut-specific **germinal center memory cells**. Allergen re-exposure and T-cell help were required to maintain germinal center memory cells, which, on activation, replenish the IgE plasma cell compartment and facilitate susceptibility to peanut-induced anaphylaxis.

It has been shown that IgE can be generated through sequential class-switching from IgG₁ memory B cells and that sequential IgG to IgE class-switching results in pathogenic (higher affinity) IgE compared with low-affinity IgE generated by means of direct class-switching.³³ Recent work by He et al³⁴ demonstrated that a unique subset of IgG₁⁺ memory B cells housed allergen-specific IgE memory. Using a B-cell transfer model, they showed that IgG₁⁺ memory B cells that expressed the markers **CD80** and **CD73** were able to transfer production of high-affinity IgE to a naive mouse with T-cell help. In contrast, IgG₁⁺ memory B cells not expressing these 2 markers were unable to support high-affinity IgE and supported production of low-affinity IgE. At high ratios of low-affinity to high-affinity IgE, the low-affinity IgE could inhibit pathogenicity of the high-affinity IgE. This work identifies unique IgG₁ B-cell subsets that house IgE memory and also emphasizes the importance of measuring the affinity of IgE to determine its pathogenicity.

These few studies on IgE memory in animal models highlights the importance of allergen exposure and T-cell help to maintain IgE plasma cells from a pool of memory IgG₁⁺ B cells. It is not clear whether these requirements also exist in human subjects. Allergy can persist for years in the absence of any known exposures, and strict avoidance does not appear to facilitate food allergy resolution. It is not clear whether there is non-oral exposure (perhaps through ubiquitous antigens in household dust) or antigenic mimicry or whether the mechanisms of IgE maintenance are different in mice or human subjects. Studies are needed to understand the cellular basis of elimination of high-affinity IgE in human subjects during resolution of their food allergy.

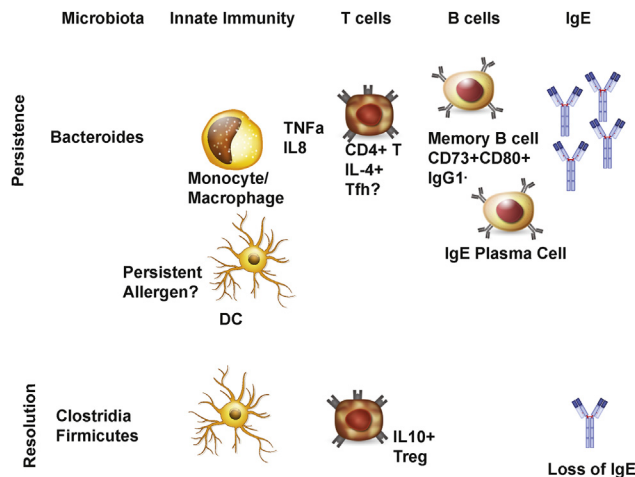


FIG 1. Immune mechanisms of persistence and resolution of food allergy. Low allergen-specific IgE levels are associated with and predictive of food allergy resolution. IgE memory has been shown to be derived not from IgE plasma cells but from IgG⁺ memory cells bearing the markers CD73 and CD80. Allergen-specific T-cell responses associated with food allergy are T_H2 biased, with IL-10-producing Treg cells associated with natural resolution of food allergy. It is not known how or whether follicular helper T cells contribute to maintenance of IgE memory. Persistent food allergy is associated with increased inflammatory responsiveness to Toll-like receptor stimuli by the myeloid compartment, pointing to a role for innate immunity in persistence. The innate immune system responds to cues from the microbiota, which also differs in composition between patients with persistent and resolved food allergy.

FUTURE DIRECTIONS

Our current understanding of the immune mechanisms of food allergy persistence and resolution is shown in Fig 1. Central to the forward progress of our field is a better understanding of the heterogeneity of food allergy, including how immune and clinical parameters relate to one another. If we understand the immune basis of the natural resolution of food allergy, we are much more likely to understand how to interfere with persistent food allergy. It is not clear whether persistent food allergy is a phenotype that can encompass different foods. For example, is persistent milk allergy more similar to peanut allergy than it is to milk allergy that is outgrown in early childhood? Are there common features that unite these persistent food allergies, such as characteristics of the IgE epitopes or antigenic mimicry, that maintain the IgE response despite careful food avoidance? Does persistent food allergy, whether to peanut, milk, or egg, share a common site of sensitization? Do microbial adjuvants (eg, staphylococcal enterotoxin B) play a role in sensitization in persistent food allergy?

Local factors in the gastrointestinal tract have remained mostly inaccessible in our study of human food allergy. There might be local factors that maintain persistent food allergy. For example, we know that highly differentiated (pathogenic-effector) T_H2 cells acquire responsiveness to innate cytokines, such as thymic stromal lymphopoietin, IL-33, and IL-25,³⁵ similar to group 2 innate lymphoid cells. Persistence of food-specific IgE can be maintained by lymphocytes with innate responsiveness that respond to local increased cytokine production. Can interventions that target the gastrointestinal tract, such as modern probiotics³⁰ or dietary fiber,²⁶ alter the intestinal immune milieu and interrupt the maintenance of long-lived IgE? Questions about the

contribution of the gastrointestinal mucosa in patients with food allergy require a method to noninvasively monitor the status of the gut.

There might be other clinical parameters that are predictive of resolution or persistence. For example, we do not know whether another phenotype of food allergy, threshold of reactivity, is associated with resolution or persistence. Are subjects with a high threshold of reactivity more likely to naturally outgrow their food allergy or caught in a state between allergy and tolerance? Are the types of allergy manifestations (site or severity) predictive of persistence or resolution? Lastly, how do we define tolerance, both clinically and immunologically? Under what conditions is an absence of symptoms synonymous with tolerance? For example, someone with food-dependent exercise-induced anaphylaxis would not be considered tolerant, despite the fact that they can eat the food without symptoms in the absence of cofactors, such as exercise or alcohol. Is there an immune signature of a healthy response to foods in someone who was never allergic, and how does that compare to someone with resolved food allergy?

The barrier to answering all of these open questions is the establishment of large cohorts in which food allergy and tolerance are carefully defined and assessed and from which longitudinal biospecimens are available for application of rigorous immune monitoring and biomarker discovery. HealthNuts and CoFAR represent 2 cohorts that have made significant contributions to our understanding of food allergy resolution, but fundamental questions remain to be addressed.

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