

The year in food allergy



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Research into food allergy continues to rapidly evolve, accompanying and driving real changes in the clinical approach to these diseases. The past year has seen the rollout of the first treatment approved for active management of food allergy, more data on alternative methods of treatment, the continued evolution of strategies for prevention of food allergy, a renewed interest in phenotyping food allergy subtypes, and, importantly, key new insights into the pathophysiology of food allergy. We expect that in the coming years, the therapies that are in preclinical or early clinical evaluation now will make their way to the clinic, finally allowing the possibility of safe and effective treatments for food allergy. (*J Allergy Clin Immunol* 2022;149:867-73.)

Key words: Food allergy, oral immunotherapy, epicutaneous immunotherapy

In developed countries, an estimated 5% to 10% of the population of developed countries has food allergy, causing significant burden to quality of life.¹ Food allergy most commonly presents in childhood, although there is a growing recognition that adults may frequently present with new-onset food allergy.^{2,3} Although many questions remain about the pathophysiology of food allergy, including the genetic basis of susceptibility,⁴ the location and mechanisms of sensitization,⁵ the environmental factors that contribute to allergy,^{6,7} and how allergy can resolve, our understanding of the disease has vastly improved in the past decade. Research into food allergy continues to rapidly evolve, accompanying and driving real changes in the clinical approach to these diseases. Over the past year, important advances in the prevention, treatment, epidemiology, and pathophysiology of food allergy have been published in this journal and others. Here, we highlight important recent publications in the field, with the goal of identifying important breakthroughs and trends over that past year.

Abbreviations used

DC: Dendritic cell
EPIT: Epicutaneous immunotherapy
MMC: Mucosal mast cell
OIT: Oral immunotherapy
Tfh: T follicular helper
Treg: Regulatory T

PREVENTION OF FOOD ALLERGY

Now 6 years out from the Learning Early About Peanut Allergy (LEAP) study,⁸ it remains clear that early introduction of peanut and other foods is a powerful tool to prevent food allergy.⁹ Indeed, early introduction may also prevent other diseases; in the Enquiring About Tolerance study, which was primarily designed to understand whether introduction of multiple foods, including wheat, before age 6 months prevented food allergy, researchers also noted a marked reduction in celiac disease among those infants who had been randomized to the early introduction of multiple foods.¹⁰

There are even hints that this approach may be working on a population level to prevent food allergy. In Finland, a whole society approach to reducing allergy had very promising results. The Finnish Allergy Program, which was launched in 2008 and had many elements targeting all citizens in the country, included, among other strategies, support for introduction of solid foods between age 4 and 6 months, discouragement of allergen avoidance unless necessary, increased contact with the natural environment, discouragement of unnecessary antibiotics, and promotion of oral immunotherapy (OIT) for food allergy. Among other encouraging trends, this program appeared to result in a 50% drop in food allergy diets in daycare.¹¹

Despite the evidence for early introduction, strategies for implementation are still being ironed out. In a survey of allergists/immunologists who are members of the American Academy of Allergy, Asthma & Immunology, 97% of those who responded were aware of guidelines developed by the National Institute of Allergy and Infectious Diseases that were published in 2016,¹² but only 65% of those were fully implementing the guidelines.¹³ The most common deviations were considering family history as a risk factor and conducting skin testing in non-high-risk infants. Who to screen, if anyone, before early introduction has continued to be a controversial topic. Consensus recommendations about the approach to primary prevention of food allergy through nutrition from a Canadian-American group endorsed by the American Academy of Allergy, Asthma & Immunology, the American College of Allergy, Asthma and Immunology, and the Canadian Society for Allergy and Clinical Immunology recommend introduction of egg and peanut around 6 age months without screening except by parental preference,¹⁴

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C.A.K. is supported by National Institutes of Health (NIAID) grant number U01AI125290.

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication November 11, 2021; revised December 28, 2021; accepted for publication December 31, 2021.

Available online January 12, 2022.

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0091-6749/\$36.00

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<https://doi.org/10.1016/j.jaci.2021.12.785>

in contrast to the aforementioned National Institute of Allergy and Infectious Diseases guidelines. In an attempt to provide some data to inform these decisions, our group conducted a prospective study at Johns Hopkins and Massachusetts General Hospital that enrolled infants with various risk factors (moderate to severe eczema, food allergy except peanut allergy, and family history of peanut allergy) who had never ingested peanut and evaluated them for peanut allergy. Among those with at least moderate eczema, we found a very high rate of peanut allergy (nearly 20%), rising with each month of age and with increased severity of the eczema, suggesting that there may be some value in screening infants who are at very high risk of peanut allergy. In contrast, we found a very low risk of peanut allergy (1%) among those with family history as the sole risk factor, supporting guidelines that do not recommend screening this risk category.¹⁵ In addition, we found that Ara h-2 specific IgE performed best as a screening tool, and suggest that screening with Ara h-2 specific IgE only may be best if screening in infancy is needed.¹⁶

Early introduction has not been without some unintended consequences, including a report in 1 center of a trebling in the rate of peanut or tree nut aspiration among infants after recommendations for early introduction of peanut,¹⁷ and an apparent increase in peanut-related food protein-induced enterocolitis syndrome.¹⁸ More research is needed as these public health programs roll out to optimize the approach.

Clearly, early peanut introduction is not going to prevent all food allergy, because it is allergen specific and does not even prevent all cases of peanut allergy. Other approaches are needed, including evaluating the efficacy of early introduction of other foods for preventing food allergy. Sakihara et al¹⁹ randomized 491 newborns in Japan to either ingest at least 10 mL of cow's milk formula daily or avoid cow's milk between age 1 and 2 months, with the outcome assessed by oral food challenge at age 6 months. They found an 88% reduction in cow's milk allergy, which corresponded to a 6% absolute risk reduction, a result similar to what has been found for peanut.

It is ever more apparent that dysfunctional skin barrier is part of the pathogenesis of food allergy.²⁰ Even without clinical atopic dermatitis, patients with peanut allergy have barrier dysfunction evidenced by transepidermal water loss and skin-tape stripping.²¹ Given the central role of skin barrier dysfunction in the pathogenesis of food allergy, approaches that address the skin barrier directly are an intuitive approach to prevention. Unfortunately, after a few early promising results, a Cochrane systematic review of emollient use found that they do not prevent atopic dermatitis (7 trials) or food allergy (1 trial).²² In fact, in the Enquiring About Tolerance cohort, frequency of moisturizer use at 3 months was associated with subsequent development of food allergy,⁷ potentially because of the facilitation of exposure to food allergens at the epidermis. Various different approaches to improve skin barrier function to prevent food allergy are currently being evaluated.

TREATMENT OF FOOD ALLERGY

In 2020, Palforzia became the first treatment for food allergy to be approved by the Food and Drug Administration.²³ Leonard et al²⁴ provided practical recommendations for implementing immunotherapy for food allergy into clinical practice, including suggestions for evaluating whether offering OIT is right for a given practice. As OIT becomes a real clinical option, what to do after the initial period of OIT has been an open question. In

a series of randomized-controlled studies comparing daily to non-daily dosing after the first year of dosing with Palforzia peanut OIT, both treatment groups showed frequent, mostly mild, dose-related allergic reactions, but these appeared to be more common, and accompanied by less desensitization to peanut, among those randomized to less-than-daily dosing regimens.²⁵

A major barrier to OIT is the occurrence of adverse events with dosing. Omalizumab may facilitate OIT, and has typically been administered in the context of OIT in doses based on what is recommended for asthma: total IgE and weight. Azzano et al²⁶ reported on a retrospective analysis of 181 patients treated with omalizumab-facilitated OIT and found that omalizumab dose per weight was more associated with success than traditional dosing, suggesting that basing omalizumab dose on weight alone, in this context, might be more successful.

Epicutaneous immunotherapy (EPIT) may be safer, albeit less effective, than OIT. This year, 2 reports conflicted about whether longer-term therapy with EPIT may improve outcomes. Scurlock et al²⁷ found no statistically significant increase in desensitization after 130 weeks of EPIT for peanut compared with 52 weeks of therapy, while in a larger study, Fleischer et al²⁸ found that after 36 months of therapy, 52% of patients treated with EPIT reacted to a dose of 1000 mg or more of peanut protein, compared with 40% at 12 months. In the later study, and in another reported by Brown-Whitehorn et al,²⁹ up to about 10% of treated patients are able to sustain desensitization after 2 months off therapy. EPIT may be another option in the clinic in the coming years.

For milk and egg allergy, the recognition that most children with milk or egg allergy can tolerate extensively heated, or baked, forms of these foods has changed pediatric allergy practice. However, whether this accelerates desensitization, and how it may compare to OIT with unheated forms of the foods, was previously unknown. In a randomized trial of 50 patients with egg allergy who were able to tolerate baked egg, unbaked egg OIT was generally associated with better outcomes than OIT with baked egg, including more sustained unresponsiveness (44% vs 11%) and less withdrawal (13% vs 30%), with a similar profile of side effects.³⁰

Because the microbiome has been shown to be altered in food allergy, manipulating it to hasten resolution may be a promising approach.³¹ Unfortunately, a strategy of adding synbiotics to an amino acid-based formula did not improve resolution of IgE-mediated cow's milk allergy in a randomized-controlled study of 169 infants conducted in multiple countries.³²

CLASSIFYING FOOD ALLERGY SEVERITY

Understanding the prevalence of severe or protracted anaphylaxis to foods is important for decisions about how best to manage food allergy reactions. Patel et al³³ conducted a systematic review of 86 studies published between 1946 and 2020 that reported 10 or more anaphylaxis events due to food or venom. Of the more than 36,000 events captured, 7.7% were treated with multiple doses of epinephrine, suggesting that this outcome was relatively rare. From the same group, Ruiz-Garcia et al³⁴ studied 57 adults who had objective symptoms to a peanut challenge. Reactions were associated with significant increases in heart rate and peripheral blood volume, and with decreases in cardiac stroke volume. These changes were reversed with intravenous fluids, suggesting that more attention to cardiovascular complications of anaphylaxis may be needed. Limitations of this study included a population that was all adults and a lack of comparison between intravenous

fluids and epinephrine. Interestingly, cardiovascular changes were independent of apparent severity of the anaphylaxis symptoms, suggesting limitations in our ability to classify anaphylaxis severity.

In an attempt to standardize classification of severity of acute allergic reactions, a 21-member multidisciplinary panel of allergy and emergency room experts was convened to create a severity grading system.³⁵ They came to agreement on a grading system, which they published in this journal, but emphasize that it should be validated and refined on the basis of both wider expert opinion and in prospective cohorts. A key use of such a grading system would be to develop biomarkers of severity.³⁶

In addition to the severity of individual reactions, there is a need to define food allergy phenotypes and understand whether management decisions can be tailored to patient disease severity. A systematic review published in the *World Allergy Organization Journal* concluded that no consensus on food allergy severity exists.³⁷ A key question underlying opportunities to define severity phenotypes and differentiate management approaches is how stable individual reaction thresholds are across time. Patel et al³⁸ conducted a systematic analysis of eliciting doses among 3151 participants, of whom 534 underwent repeated challenge, and found low heterogeneity in reaction threshold at the lowest doses; 71% of participants were limited to ½ log change or less variability between repeated food challenges. This suggests that patients with food allergy may be able to be classified according to reaction threshold, with avoidance strategies tailored to their thresholds.³⁹

PATHOPHYSIOLOGY OF FOOD ALLERGY

Novel models

Food-allergic reactions are triggered by cross-linking of allergen-specific IgE by allergens. A novel mouse model of pollen food allergy syndrome was reported in which mice sensitized to birch pollen develop IgE-dependent oral allergy symptoms in response to challenge with cross-reactive apple extract.^{8,40} Heating of the apple extract abolished symptoms. This mouse model could be used to test novel therapeutics, as well as *in vivo* cross-reactivity between pollens and foods.

Detection and biology of IgE

Food-specific IgE or allergen-specific IgE levels are not highly predictive of clinical reactivity when present at low levels, leading to the question of what factors beyond abundance of IgE might contribute to food allergy. Shade et al⁴¹ identified glycosylation of IgE, specifically sialic acid content on IgE, as a key factor that contributes to effector cell degranulation and anaphylaxis. Understanding the mechanism by which IgE is sialylated may lead to interventions that could reduce clinical reactivity in sensitized individuals. Alternatively, incorporation of glycosylation into measures of IgE could improve prediction of clinical reactivity. Increased resolution of antibody specificity through measurement of IgE to linear epitopes also improves the prediction performance of food allergen-specific IgE. Measurement of epitope-specific IgE in children enrolled in the LEAP study revealed differences between sensitized and allergic children, whereas peanut-specific IgE did not discriminate between these 2 groups.⁴² This suggests that the IgE detectable in sensitized children is targeted to conformational epitopes, whereas IgE in allergic children is targeted to

linear epitopes. This technology is now being offered as a diagnostic test by Allergenis. A role for IgE beyond traditional food allergy was reported by Aguilera-Lizarraga et al,⁴³ who showed that patients with irritable bowel syndrome have local hypersensitivity reactions to gluten, wheat, soy, and milk, which may underlie post-meal abdominal pain. They showed in mice that infection could lead to local mucosal production of food-specific IgE that was undetectable in serum, and antigen reexposure led to visceral hypersensitivity.

T-cell subsets

CD4⁺ T_H cells orchestrate the generation of immune tolerance or allergy through the production of cytokines and interaction with B cells and other cell types. Regulatory T (Treg) cells are essential for the prevention of food allergy, and Turner et al⁴⁴ demonstrated that the level of TGF-β expression on Treg cells determined susceptibility to allergy or tolerance in mice, and latency associated peptide (a component of the surface TGF-β complex) was less abundant in humans with food allergy. Downregulation of TGF-β was mediated by IL-4 signaling through signal transducer and activator of transcription 6, whereas upregulation of TGF-β was mediated by a consortium of Clostridiales species. The finding that Clostridiales species can enhance the regulatory function of Treg cells through this mechanism suggests their potential utility as a microbial therapeutic.

IL-4-producing T cells have traditionally been lumped together as T_H2, despite a great deal of heterogeneity within the type 2 T-cell response. Gowthaman et al⁴⁵ identified a novel CD4⁺ T-cell subset that produced IL-4 as well as IL-13, but importantly was part of the T follicular helper (T_{fh}) subset identified by expression of the B-cell follicle-homing marker CXCR5 and expression of the T_{fh} transcription factor Bcl6. IL-13 derived specifically from this cell type (termed T_{fh}13 cells) was necessary for the generation of high-affinity IgE that could support anaphylaxis, and these cells could be identified in atopic humans. A protocol to identify T_{fh}13 cells in mice and humans was subsequently published.⁴⁶ The importance of type 2 cytokines in maintenance of IgE was demonstrated by Bruton et al,⁴⁷ who used a human *in vitro* restimulation approach to identify factors necessary for IgE production on allergen exposure. Blockade of IL-4Rα, which is shared between IL-4 and IL-13 signaling, suppressed the generation of IgE after peanut stimulation of PBMCs from individuals with peanut allergy. This suggests that the use of dupilumab in peanut allergy could reduce the production of peanut-specific IgE. Ongoing trials will soon answer that question.

IL-4 was additionally shown to contribute to food allergy by promoting the differentiation of mucosal mast cell (MMC)9s, an MMC subset producing IL-9.⁴⁸ Tomar et al⁴⁸ developed an *in vitro* culture method to derive MMC9s in response to stem cell factor, IL-3, IL-4, and IL-33, and showed that IL-4 was essential for MMC9 generation dependent on the transcription factor basic leucine zipper ATF-like transcription factor (BATF). MMC9s are required for the expansion of mature granulated mast cells in the intestinal mucosa that directly drive symptoms after activation via IgE. T-cell-mast cell interactions have also been shown to contribute to the response to OIT. Mast cells desensitized by OIT in mice were uniquely able to promote the generation of Treg cells, which were reproduced by desensitization of mast cells *in vitro* followed by coculture with T cells.⁴⁹

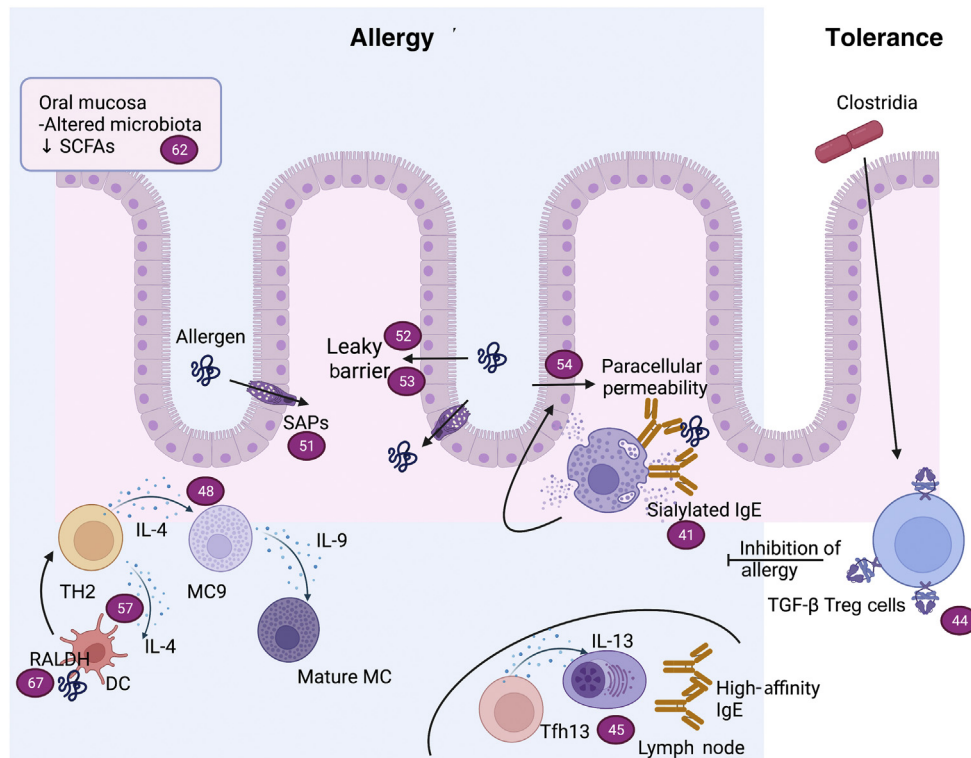


FIG 1. Selected advances in pathophysiology of food allergy. Schematic showing factors contributing to food allergy (blue shaded) or tolerance. Circled numbers indicate references associated with each mechanism. Recent advances include a greater understanding of factors contributing to IgE pathogenicity such as sialylation of IgE, the role of antigen uptake and barrier function in food allergy, and a greater understanding of the source and impact of type 2 cytokines on innate cells, antigen presentation, and B-cell class-switching. MC, Mast cell; RALDH, retinaldehyde dehydrogenase; SAP, secretory cell-associated passage; SCFA, short-chain fatty acid.

Epithelial barrier function

The intestinal epithelial barrier is a key area of regulation in food allergy, as recently reviewed by Newberry and Hogan.⁵⁰ The cytokine IL-13 was identified as a factor contributing to antigen uptake across the epithelium via secretory cell-associated passages, which are channels that can rapidly transport intact food allergens across epithelial barriers.⁵¹ Previously described across goblet cells, this article shows that all secretory epithelial cells including goblet cells, Paneth cells, and enteroendocrine cells can form channels in response to IL-13. The delivery of intact antigen across these secretory cell-associated passages delivers antigens to mast cells below the level of the epithelium. Permeability of antigens across the gastrointestinal epithelium was described as a susceptibility factor to anaphylaxis when comparing C57BL/6 (resistant) and C3H/HeJ (susceptible) mice.⁵² This association of susceptibility with gastrointestinal permeability was also found with another genetically susceptible mouse strain, the CC027/GeniUnc strain generated by the Collaborative Cross initiative.⁵³ After allergen exposure in a sensitized mouse, further epithelial dysfunction was noted. Epithelial chloride secretion through cystic fibrosis transmembrane conductance regulator, and increased paracellular leak of macromolecules, underlies the fluid secretion and diarrhea that can occur after allergen exposure.⁵⁴ There have not yet been therapies developed that specifically promote gastrointestinal barrier function, but the use of dupilumab to target IL-4/IL-13 or microbial therapeutics

producing barrier-promoting metabolites could potentially treat food allergy through an impact on gastrointestinal barrier.

Innate immunity and food allergy

The contribution of the innate immune system to development of food allergy is starting to become appreciated.⁵⁵ Cells such as type 2 innate lymphoid cells produce type 2 cytokines that participate in the sensitization process and drive allergic inflammation at mucosal sites, as recently reviewed by Bartemes and Kita.⁵⁶ Dendritic cells (DCs) play a key role in differentiation of naive T cells and generation of a type 2 phenotype. Zhou et al⁵⁷ used an *in vitro* human PBMC culture to show that IL-4 from peanut-specific T cells altered the phenotype of DCs (enhanced CD23 expression on CD11c⁺ DCs and promoted the differentiation of monocyte-derived DCs), such that they would further promote the generation of a type 2 T-cell response. This positive feedback loop was interrupted by OIT for peanut allergy. Yoneyama et al⁵⁸ used a mouse model of food allergy and OIT to demonstrate a novel role for myeloid-derived suppressor cells in addition to Treg cells in the generation of sustained unresponsiveness to antigen after OIT. Depletion of these cells with an antibody against Gr1 (a surface marker on these cells, but not specific to these cells), and inhibition of Notch signaling, led to both a reduction in the myeloid-derived suppressor cell population and suppression of sustained unresponsiveness in mice after OIT.

This intriguing role of myeloid-derived suppressor cells needs to be verified in human cohorts.

Routes of allergen exposure

The dual allergen exposure hypothesis proposes that exposure to food allergens via the gastrointestinal tract in early life results in oral tolerance, whereas exposure through inflamed skin leads to sensitization. Patrick et al⁵⁹ reveal a mechanism for sensitization by the epicutaneous route. Exposure to *Staphylococcus aureus*, which is associated with atopic dermatitis, induced the production of IL-36 from keratinocytes. IL-36 together with IL-4 promoted IgE class-switch by B cells. Smeekens et al⁶⁰ broaden the dual allergen exposure hypothesis to show that exposure through the respiratory tract may also contribute to sensitization to foods. Respiratory exposure to peanut plus indoor dust samples led to sensitization of mice to peanut. LPS was able to enhance sensitization to peanut when administered with peanut, but suppressed sensitization when administered before peanut exposure. This demonstrates that a single factor, such as LPS, can promote or prevent food allergy on the basis of timing of exposure relative to food allergen exposure.

Microbiota

It is now well established that the intestinal microbiota plays a key role in susceptibility to food allergy. Additional studies continue to find differences in the fecal microbial composition of food allergy compared with non-food allergy.⁶¹ Ho et al⁶² expanded that finding to the oral mucosa to demonstrate changes in the oral microbiome associated with peanut allergy. Reductions in Lactobacillales, Bacteroidales, and Bacillales were accompanied by reductions in short-chain fatty acids, and an increase in Neisseria in peanut-allergic individuals was positively associated with type 2 cytokines secreted into the saliva. This indicates a panmucosal dysbiosis that affects sites beyond the large intestine, including sites likely to be involved in sensitization. Marrs et al⁶³ examined the impact of diet on microbial development in early life in the Enquiring About Tolerance study. Inclusion of several allergenic solids into the diet was associated with an increase in microbial diversity, and an increase in species associated with maturation. Therefore, early dietary introduction of solids may contribute to oral tolerance not only through providing antigens but also by altering the microbial milieu that could potentially impact the immune tone of the intestine.

Genetics and genomics

Susceptibility to food allergy is in part mediated by genetics, and variants in a range of genes including barrier and immune-related genes have been associated with food allergy.⁴ An HLA allele (DPB1*02:01:02) was significantly associated with wheat-dependent exercise-induced anaphylaxis.⁶⁴ The involvement of HLA genes in manifestations of food allergy is consistent with the literature on genetics of food allergy. Gabryszewski et al⁶⁵ studied demographic and genetic features associated with the atopic march. They found that the progression from atopic dermatitis to IgE-mediated food allergy was significantly associated with Asian and Pacific-Islander race, but specific risk alleles were not identified for this progression to food allergy.

Epigenetic modification, such as DNA methylation, is one mechanism by which genes can be modified by environmental exposures. Zhou et al⁶⁶ demonstrated that DNA methylation patterns differ between peanut-allergic and nonallergic individuals. Using a targeted approach analyzing 125 genomic regions, they identified 12 genes that were significantly different in methylation levels, including IL-4 (decreased methylation), IL-12 (increased methylation), IL-17F (decreased methylation), and a range of other immune markers.⁶⁶ Methylation was associated with altered protein production in response to peanut stimulation. This suggests that environmental exposures resulting in epigenetic alterations contribute to food allergy susceptibility.

Allergenicity

In addition to understanding why some individuals are susceptible to food allergy, the question of why some food antigens are potent allergens remains an active area of interest. It has become apparent that food antigens are potent allergens in part due to their ability to interact with the innate immune system. Ruiter et al⁶⁷ found that peanut protein acts via TLR1/2 heterodimers to induce retinaldehyde dehydrogenase 2, an enzyme involved in the generation of retinoic acid. Retinoic acid from DCs in turn generated gut-homing IL-5-producing T cells from naive T cells. Krause et al⁶⁸ also identified innate signaling of monocyte-derived macrophages in response to the peanut protein Ara h 1. Thouvenot et al⁶⁹ published data supporting a novel hypothesis for mechanisms of allergenicity. They found that transcriptional frameshifts, or single-base omissions, occurred at high prevalence in highly allergenic legumes (peanut, soy, sesame), and furthermore show that in mice these variants can induce sensitization without adjuvant. The variants have a more cationic carboxy terminal than the canonical allergens, which is believed to increase affinity of binding to MHC II. Sensitization to the variant also results in reactivity to the canonical allergen.

Preclinical models of immunotherapy

In addition to mouse models of OIT, several studies focused on novel approaches to desensitization or tolerance induction. Khodoun et al⁷⁰ used a monovalent antibody against the human high-affinity IgE receptor FcεRI. This reagent did not generate mast cell activation, but did result in rapid desensitization. Similar to omalizumab, this approach would result in desensitization across allergens, but unlike omalizumab, the onset of desensitization is rapid because there is no need to displace IgE from the FcεRI. Low-dose IL-2 or IL-2-anti-IL-2 complexes have been of interest due to the ability to expand Treg cells. Prophylactic treatment with IL-2 effectively suppressed the generation of food allergy in mice, but therapeutic administration generated significant worsening of anaphylaxis through an IFN-γ-dependent pathway.⁷¹ Because various forms of IL-2 are being used in human trials for autoimmune diseases, it would be of interest to leverage those clinical trials to determine whether any allergic participants had a change in their skin test or basophil activation test reactivity to foods.

CONCLUSIONS

This past year has seen parallel advances in clinical practice and mechanistic understanding of food allergy (Fig 1). We expect that in the coming years, the therapies that are in preclinical or

early clinical evaluation now will make their way to the clinic, finally allowing the possibility of safe and effective treatments for food allergy. In particular, we anticipate that ongoing trials testing immunomodulatory biologics will provide options beyond or in addition to immunotherapy for treatment, while microbial therapies may eventually make it to the clinic for treatment or prevention of the disease, despite early failures. As options for treatment expand, the development of biomarkers and standardized approaches for phenotyping food allergy may lead to individualized approaches to management of this disease.

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