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REVIEW

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Food Allergy: Searching for the Modern Environmental Culprit

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Food allergy is a modern disease. Its exponential increase in prevalence in the last 70 years cannot be explained by genetic factors alone. In this review we discuss the hypotheses that have been suggested previously, and the evidence that supports them, to explain this rise in prevalence as well as the medical treatments that have developed as a result of basic exploration within these paradigms. We argue that one major area of fruitful exploration that would help generate new ideas may be systematic analyses of the unknown factors of the modern environment that may contribute to the formation of food allergy. Through this lens, we review the current understanding of food allergy pathogenesis and propose novel research directions, with implications for the current strategies for managing food allergy.

INTRODUCTION

The prevalence of food allergy has increased exponentially since the 1950s, and particularly over the past decade, presenting a significant public health burden in the developed world. With the rise of allergic rhinitis, asthma, atopic dermatitis, food allergy, and anaphylaxis, the increased prevalence of allergic diseases notably contributes to both morbidity and economic burden with food allergy alone in the United States accounting for $24.8 billion in cost annually [1].

This review focuses on food allergy, or the loss of oral tolerance and the generation of type-II immunity and inflammation to food-derived antigens. Globally, the prevalence of food allergy ranges from 1-5% in developed countries within Europe and in the United States, while Australia reports the highest prevalence of immunoglobulin E (IgE)-mediated food allergy, with 10% of infants demonstrating challenge-confirmed allergies to one or more food allergens [2]. Despite inconsistencies in diagnostic criteria and a lack of high-quality evidence based on the gold standard of oral food challenges, studies using proxy measures of food allergy together with allergen-specific IgE present compelling data that food

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Abbreviations: IgE, immunoglobulin E; AGE, advanced glycation end; LTP, lipid transfer protein; CTx, cholera toxin; PRR, pattern-recognition receptors; TLR, toll-like receptors; DSS, dextran sodium sulphate; LEAP, Learning Early About Peanut Allergy; OIT, oral immunotherapy; SLIT, sublingual immunotherapy; EPIT, epicutaneous immunotherapy.

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allergy prevalence is exponentially rising [3]. This review dissects food allergy pathogenesis from the perspective of attempting to understand why there has been a rise in prevalence in food allergy. First, the issue is framed in terms of the current understanding of food antigens and the immunologic understanding of type-II immunity. Second, we address prevailing hypotheses, the hygiene hypothesis and the dual allergen exposure hypothesis. Finally, we propose an alternative explanation for the rise in food allergy in our modern world.

IMMUNOGENICITY OF FOOD ANTIGENS

To begin our discussion on understanding why food allergies are so much more common in modern times, we start by considering the observation that allergies to certain foods are more prevalent than others, which has led to the hypothesis that certain food antigens possess intrinsic immunogenic characteristics. One dominant idea in the field is that certain food antigens may contain irritant or toxic properties and thus contain intrinsic damaging properties that would stimulate an immune response [4,5]. This idea is supported by epidemiological data, which demonstrate that certain food allergens are more prone to causing anaphylaxis, suggesting that certain food allergens may possess unique properties that confer higher immunogenicity. Peanuts and tree nuts are the most common triggers of fatal anaphylaxis; in one systemic review, these were implicated in 87% of deaths [6]. This has led to the awareness that 50% of all plant food allergens can be categorized into a handful of structural protein families [7], which are all storage or plant defense proteins. Furthermore, both enzymatic (*i.e.* glycosylation) and non-enzymatic (*i.e.* advanced glycation end (AGE) products) modifications have been shown on these antigens to alter their immunogenicity [8,9], and may be a function of how the food is processed. Roasting peanuts, for example, greatly increases AGE formation [10]. These modifications may, for example, affect the ability of food antigens to reach the intestines after gastric and pancreaticobiliary enzymatic digestion where the immune response to food is thought to occur and/or elicit a greater immune response directly as a result of these modifications. It remains unclear what common molecular characteristics of food allergens confer immunogenicity to them and their mechanisms of action, and this is a current area of intense investigation.

However, regardless of the intrinsic immunogenicity of certain food antigens, it is unclear why, after abundantly being consumed for millennia, there would now be immune responses directed towards these foods. Several observations argue against intrinsic immunogenicity of food antigens as being the sole driver of food allergies. First, there are food allergies reported to virtually every type of food. Thus, while certain food antigens may be intrinsically more or less allergenic, it is likely that any food antigen can become a food allergen in the appropriate immune-stimulating context. Second, it is clear that geographical location is important in the commonality of various food allergens. While allergies to milk and egg, which have been and continue to be widely consumed in most countries, are common irrespective of the geographic region [3], other food allergies show distinct geographic variation, and correlate with the extent to which they are consumed. For example, in Thailand, a country which has historically and continues to consume large quantities of shrimp, shrimp is the most common food allergen [11]. Likewise legumes, commonly consumed in India, are a major food allergen in India [12], while sesame seed, commonly consumed in the Middle East, is a major food allergen in the Middle East [13]. Sesame has been cultivated in the Middle East for over 3000 years and much more widely consumed there than in the US, where allergies to sesame is comparatively less [14]. Lipid transfer protein (LTP) allergen, commonly found in peaches, is the most frequent cause of food allergy in Italy and the Mediterranean Basin, where they have been and continue to be primarily cultivated [1]. In the example above, roasting peanuts is also not a "modern" innovation, and reports of roasting peanuts can be found as early as the First Century in China, where peanut allergy is common [15]. It is therefore possible that one major driver of food allergy may simply be its degree of availability and consumption in addition to any intrinsic properties.

Thus, in light of the fact that it is unlikely that food antigens or our genes have evolved so much in the last 70 years to drive the emergence of food allergy as a modern disease, it is likely that what has changed to confer increased immunogenicity to food is something different in the modern environment. The question then becomes what modern factors are now contextualizing these food antigens to render them immunogenic.

FRAMING THE PROBLEM: APPROACHING THE ASYMPTOTE REVISITED FOR ALLERGIC IMMUNITY

It is now well-established that in order to generate an immune response to an antigen – for it to become an immunogen – there must be an adjuvant present which may be intrinsic or extrinsic to the antigen [5,16]. Food antigens themselves are likely the same as they were 70 years ago. That is, peanuts have unlikely evolved so much in 70 years to have acquired intrinsic antigenic differences that are now suddenly sufficient to possess adjuvant properties and thus confer immunogenicity to the antigen. As with the experimental immunologist's "dirty little secret" of Freund's Adjuvant to elicit type-I immune

responses, the experimental food allergist's "dirty little secret" is cholera toxin (CTx) and other bacterial toxins, which are required to elicit type-II responses. The need for bacterial toxins as adjuvants to break oral tolerance and generate food allergy is inherently problematic since the parts of the world with high prevalence of cholera have low prevalence of allergic disease [2,17].

It is now well-established that antigen responses can be skewed towards so-called type-I immunity, predominated by a characteristic cellular (neutrophil, monocyte, Th1 T-cell) and humoral (complement-fixing and opsonizing antibodies) responses or type-II immunity, predominated by distinct cellular (mast cell, basophil, eosinophils) and humoral (IgE, non-complement-fixing) components depending on the presence of an adjuvant which contextualizes the antigenic response. Exogenous type-I adjuvants have the unifying feature of engaging of pattern-recognition receptors (PRR) such as toll-like receptors (TLR) [16,18,19]. In the case of natural infections with viruses or bacteria, both antigen and adjuvant, which signal through PRRs, are present in the pathogen and sufficient to generate type-I immunity.

In the case of allergic responses (type-II immunity), the molecular mechanisms underlying the characteristics of adjuvants that skew toward type-II immunity are complex and not well understood. Classic exogenous type-II adjuvants used in the experimental settings include CTx and aluminum salts (Alum), which are required to induce allergenicity to antigens introduced by the orogastric route and intraperitoneal routes, respectively. CTx and Alum can generate a type-II response to an array of divergent antigens, which suggests that, while there may be intrinsic properties of allergens that confer allergenicity, any antigen can become an allergen in the presence of allergic adjuvants [20-22], consistent with the epidemiological observations that allergies exist to virtually all substances. The characteristics that make certain adjuvants type-I polarizing and others type-II polarizing has been an area of intense focus. It has been particularly confusing because the dichotomy of TLR agonists as type-I adjuvants and "others" as type-II adjuvants breaks down, particularly in the case of LPS and Alum [23-25]. "Low-dose" LPS appears to produce type-II adjuvant responses while "high-dose" LPS appears to produce type-I adjuvant responses, while Alum, a potent inflammasome activator [26], induces primarily type-I responses in humans. In addition to dosing, the contribution of route of administration and environmental context all appear to contribute to determining the ensuing immunologic response [23]. In this regard, adjuvanticity has been best studied in the case of helminth and parasitic infections, where parasite glycans, biopolymers (like chitin), proteases, bioactive lipids, and host-produced proteins such as thymic stromal lymphopoietin and other "alarmins," have been shown to instruct and shape type-II immune responses [27]. Interestingly, the adjuvant contexts of antigens in a normal infectious framework appear to be fundamentally different than those where the adjuvant is exogenous [28].

The events following contextualized antigen exposure are now well understood and have been described in detail in several reviews [29-32]. Briefly, following contextualized antigen encounter by dendritic cells, they then transport the allergen to draining lymph nodes where it is presented to naïve CD4+ T cells, which differentiate into allergen-specific CD4+ T cells in the presence of IL-4 and other type-II cytokines. In turn these CD4+ T cells produce high levels of IL-4 and IL-13, which lead to B cell isotype class switching to IgE and the production of memory B cells and plasma cells [33]. The allergen-specific IgE antibodies produced by plasma cells bind to high-affinity FcεRI receptors on mast cells and basophils and await allergen exposure. The effector phase occurs when an allergen is encountered in a previously sensitized host. Allergen binding to allergen-specific IgE causes cross-linking of FcεRI receptors on sensitized mast cells and basophils and ultimately leads to the release of preformed and newly formed inflammatory mediators like histamine and platelet activating factor. Memory allergen-specific Th2 cells produce IL-4, IL-5, and IL-13 among other cytokines, which maintain allergen-specific IgE levels, eosinophilia, mucus production, and recruitment of inflammatory cells to inflamed tissues. Altogether this results in tissue damage and the signs and symptoms observed clinically as allergic disease.

However, basic understanding of what in our modern environment are type-II adjuvants, their mechanism of action, and whether there are unifying molecular features that impart type-II adjuvanticity generally are unknown. We propose that the search for the modern culprits with adjuvant properties converge on two categories of environmental factors which are likely highly interrelated: 1) the addition of modern allergic adjuvants introduced after the 1950s, and/or 2) the modern addition or removal of factors that would weaken mechanisms of maintaining immunological tolerance. It is from this lens that we now discuss the current paradigms of food allergy pathogenesis.

RIGHT GENES AT THE WRONG TIME: HYGIENE HYPOTHESIS AND EVOLUTIONARY MISMATCH

The Genetics of Food Allergy

The pathogenesis of food allergy is undoubtably complex. Decades of work suggest that heritable factors likely set the threshold for developing food allergies. A family history of two or more family members with a

history of allergies is a strong predictor of food allergy in the child [34]. GWAS studies focused on food allergy to peanuts, for example, mapped genetic susceptibility into the HLA locus [35], which is also the most highly associated locus in GWAS studies in autoimmune diseases. What will likely emerge as more genetic studies are performed in phenotypically well-characterized patients with food allergy is that genetic susceptibility to food allergy will be very similar to autoimmune diseases, where susceptibility is polygenic and confers a polymorphism "load" that sets the threshold for the likelihood of developing disease [36]. This idea is exemplified in monozygotic twin studies, where concordance of peanut allergy is estimated at 60%, as compared to a concordance rate of 6% in dizygotic twins [37], a rate, again, similar to the concordance rates observed in autoimmune diseases [38].

Evolutionary Mismatch

Why would we have evolved genes that lead to allergic diseases? As with autoimmune diseases, which are generally type-I immune responses, diversification of the genes implicated in the pathogenesis of food allergy were likely driven by evolutionary pressures to defend against infections. In the case of allergy, these would include parasitic infections and/or the ingestion of toxins/irritants which are common in many foods and produced by pathogens [5,39], and the genes and pathways that are involved are postulated to have undergone selection for maintaining host defense against these environmental insults. At the extremes, as in autoimmune conditions, there are examples of highly penetrant rare mutations that either lead to hyperallergenic states, such as mutations in *Dock8*, *Stat3*, and *Znf341* [40-42], or states associated with high susceptibility to parasitic infections, such as mutations in genes like *IL-13* and *STAT6* [43,44] that are within the same pathway of allergic defense.

Studies using population genetics suggest that we have adapted to parasitic infections with alteration in our genes such that we have a reduced risk for infectious disease but a subsequently higher risk for autoimmune and allergic conditions [45]. Their analysis of diversity of interleukin (*IL*) genes within the Human Genomes Diversity Project of 52 populations and the pathogen burden in these geographic locations found that the genetic diversity of five *IL* genes had been subjected to selective pressure from pathogens [45]. Moreover, polymorphisms in *IL-4*, which plays a central role in defense against parasitic infections, have been identified that affect total serum IgE levels, likelihood of severe malaria in Ghanaian children, and rate of nematode infection in lemurs [46-48]. Furthermore, the *IL-4* polymorphism, C590T, has been shown in two studies to be associated with atopy, including increased total IgE production, skin test positivity, asthma, and atopic dermatitis [49-51]. Furthermore, individuals with mutations in IL-4 receptor α (IL-4Rα) were found to be at an increased risk of developing food allergies [52].

While there are likely genetic factors that contribute to an individual's place on the spectrum between susceptibility to parasitic infection and propensity for allergic disease, one could imagine that environmental factors could shift this balance in one direction or another [53]. From this perspective, aspects of the modern environment could have the potential to shift this curve on a population wide scale and consequently lead to a substantial increase in allergic disease (Figure 1). There are epidemiologic and population-based studies that support this concept of evolutionary mismatch. Perhaps the best studied example in support of this idea is the observation that the decrease in parasitic infections correlates with increased susceptibility to developing allergies. It is now well-established that the prevalence of allergic diseases is greater in industrialized countries as compared to non-industrialized countries, where the prevalence of parasitic infection is greater. Helminth infections (such as *Ascaris lumbricoides*) in Ecuadorian children have been shown to be protective against allergen skin test reactivity [54]. There is an inverse relationship between risk of wheezing and hookworm infection in Ethiopian individuals [55], and between atopy and intestinal helminth infection in Gambian adults [56]. A 2000 Lancet study found that children in Gabon with previous schistosomiasis infection were less likely to have a positive skin reaction to house-dust mite [57]. Furthermore, the authors found an inverse relationship between IL-10 levels and skin reactivity and positive correlation with IL-10 levels and helminth infection, suggesting that high levels of IL-10 during helminth infection is protective for the development of allergy [57]. Other mechanisms have been proposed for the inverse relationship between parasitic infections and allergic disease and have been reviewed previously [58,59]. For one, the large increase in IgE synthesis during parasitic infections has been hypothesized to either saturate mast cell Fcε receptors and inhibit allergic response [60] or impairs the production of allergen-specific IgE [61,62]. Another theory posits that helminth infection results in a modified type-II immune response including T cell hypo-responsiveness, increased Tregs and elevated levels of IL-10, and transforming growth factor-β [58], all factors that reduce the allergic response. However, whether decreased parasite load causes, as opposed to correlates with, allergy has yet to be definitively established. Nonetheless, the concept of evolutionary mismatch between the genes involved in allergic defense and the modern environment—the causative aspects which are as yet unclear—is a useful framework to generate testable hypotheses that explain why allergies are more prevalent in modern times.

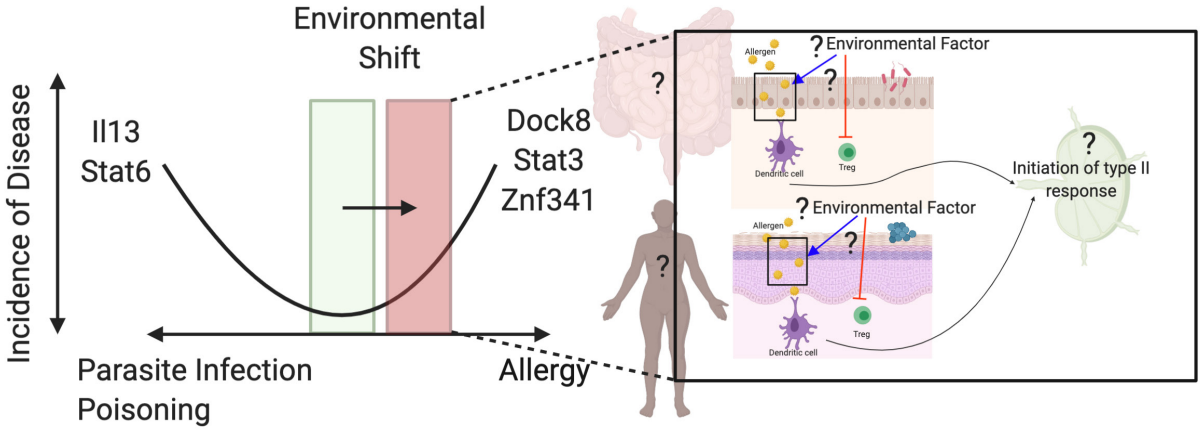

Figure 1. **An illustrative depiction of how an environmental factor may cause an increase in the prevalence of food allergy**. The incidence of food allergy and parasitic infection or poisoning from toxins lies on a u-shaped curve, where certain genetic or environmental factors can shift the likelihood of developing food allergy. Genetic factors that may alter IL-13 or Stat6 functionality may make an individual more prone to parasitic infections, while altered function of *Dock8*, *Stat3*, and *Znf341* can promote an allergenic phenotype. Given the exponential rise in food allergy, an environmental factor is likely at play. While the events following antigen exposure are well-understood (reviewed in [29-32]), it is not clear how (promote allergen recognition by dendritic cells or inhibit T regulatory cells) and where (intestinal epithelium and/or the skin) an environmental factor may act.

Hygiene Hypotheses

Closely related to the evolutionary mismatch idea is the hygiene hypothesis. In this paradigm, the modern environment lacks both microorganism exposure and infectious burden—and particularly helminth and parasite burden—which subsequently increase susceptibility to allergic sensitization due to a disruption in the equilibrium between type-I and type-II immune responses. The hypothesis is derived from the observation that allergic disease increased dramatically after the advent of sewage, water treatment, vaccination, and antibiosis, and that rural regions exhibit the lowest rate of allergic disease when compared to similar urban regions. As discussed above, many studies have also shown that parasitic infections have been associated with decreased risk of allergic disease [54-56]. Migration studies show that offspring of migrants from countries with low incidence, which were generally less developed and less "hygienic," acquire the same incidence as their "more" hygienic host countries, suggesting a central role for hygiene in developing allergies [34]. However, to date, it is unclear if the lack of infectious burden is the driving—as opposed to correlative—factor. In both the evolutionary and hygiene hypotheses paradigms, identifying the specific environmental factors, which are currently poorly understood, that are mismatched with the specific genetic burdens, which also currently lack more detailed analyses, for developing food allergy, are important continued areas of active research.

OUTSIDE IN OR INSIDE OUT: THE EPITHELIUM IN THE DEVELOPMENT OF ALLERGY

Events at the Epithelial Barrier

The genetic studies of allergy susceptibility support the current understanding of the cells and pathways involved in food allergy. Food allergy at the simplest level represents a loss of tolerance to food-derived antigens and the development of type-II immunity to them [32,63]. Food allergy is thought to occur in a stepwise process, first requiring a sensitization phase and then an effector phase.

During sensitization, dendritic cells that reside in the host intestinal epithelium are exposed to a food antigen in a currently unclear mechanism of action. Presumably, the antigen must cross through the epithelium and be acquired by a dendritic cell in an immune-stimulating context; however, this process has not been clearly elucidated. Indeed, the initiating events in which the antigen is contextualized by the immune system to be allergenic are currently unknown. What has been proposed is that disruption of the epithelial barrier is likely a required component. This is supported by hypomorphic mutations in *filaggrin* and *SPINK5* genes, which encode important proteins in maintaining epidermal barriers, for example, and which are associated with increased susceptibility to atopic dermatitis and food allergy [64-66]. In animal models, this is supported by the requirement for the co-introduction of bacterial toxins (CTx and *Staphylo-*

coccus toxin) despite the fact that parts of the world with high prevalence of cholera have low prevalence of allergic disease [2,17]. These agents are thought to primarily disrupt the epithelial barrier in order to break tolerance to co-introduced food antigens. Damage to epithelial cells and the release of "alarmins" such as IL-33 have also been shown to be required for developing food allergy in animal models [67]. However, not all agents that damage gut epithelium or induce IL-33 appear to break oral tolerance. For example, IL-33 plays an important role in dextran sodium sulphate (DSS)-induced colitis and is a commonly used detergent that leads to epithelial damage, but application of DSS is insufficient to break oral tolerance [68].

One obvious explanation for why, for example, DSS would not be sufficient to break oral tolerance could be attributed to the fact that it induces damage primarily to the large intestine, whereas the initiating events of food allergy are thought to occur in the small intestine, where food absorption primarily occurs. CTx, for example, causes damage to the entire gastrointestinal tract. Indeed, where precisely in the gastrointestinal tract the initial sensitization event occurs, are currently poorly understood. The development of oral tolerance has previously been demonstrated to require the Peyer's Patch and certain mesenteric lymph nodes that drain the small intestine [69,70]. Recent resolution of the specialized characteristics of different draining lymph nodes associated with different segments of the gastrointestinal tract may lead to novel insights into the early events precipitating the loss of oral tolerance [71].

Thus, both the relevant human equivalents in the modern world of adjuvants like CTx and the mechanistic characteristics of the types of harmful environmental exposures that lead to allergic sensitization are unknown. Moreover, even the precise anatomic location where the loss of tolerance occurs, which may not be the same for every antigen, is poorly understood. Indeed, emerging evidence suggest that distal barrier disruption in the skin could provide the inflammatory context that would break oral tolerance (Figure 1).

Dual Allergen Exposure Hypothesis

There is increasing evidence that cutaneous allergen exposure in infancy leads to food allergy and conversely, that early oral allergen exposure through early feeding of allergenic foods leads to oral tolerance [72,73]. Atopic dermatitis is often associated with development of other allergic diseases including food allergies, asthma, and allergic rhinitis. This is characterized by the concept of the "atopic march" [74-76]. Severe atopic dermatitis arising in infancy increases the risk of food allergy [77-79]. For example, the HealthNuts study found that 50% of children with early onset severe atopic dermatitis have egg, peanut, or sesame seed allergy by 12 months of age [79]. Furthermore, in children with atopic dermatitis, lack of effective topical treatment is associated with an increased risk of food allergy [80]. Non-oral exposure to peanut through the skin or respiratory tract can result in allergic sensitization and food allergy [72,73,81-83]. The ALSPAC birth cohort found that topical creams containing peanut oil to the skin of children with atopic dermatitis was an independent risk factor for the development of peanut allergy [84].

In line with the idea that distal immunologic events may contextualize antigen exposure at the gut, commensal cutaneous bacteria have been shown to modify and influence the innate immune system and keratinocytes in the epidermis secrete antimicrobial peptides (reviewed in [85]). Commensal bacteria like *Staphylococcus epidermidis* make bacteriocidins that eliminate other bacteria like *Staphylococcus aureus*, in effect maintaining a healthy equilibrium to maintain skin barrier [86]. In one study, *S. aureus* colonization of the skin was found to be related to severity of atopic dermatitis and to increased levels of IgE to hen's egg white and peanut, even independent of severity of atopic dermatitis [87]. Another study found that non-lesional skin of individuals with atopic dermatitis and food allergy had increased number of *S. aureus* as compared to skin from nonatopic individuals [88].

These human studies suggest that atopic dermatitis (epithelial barrier dysfunction) increases the risk for subsequent food allergy potentially through epicutaneous allergen exposure and sensitization. However, we need a better understanding about the interplay between cutaneous exposure to allergens, the innate and adaptive immune system and communication with the gut epithelium to elicit an allergic response to food allergens. Furthermore, the dual allergen exposure hypothesis does not explain the exponential rise in food allergy unless there are identified modern environmental factors that cause an increase in cutaneous barrier dysfunction now, but not prior to the 1950s (Figure 1).

WHERE THESE IDEAS HAVE LED US: CLINICAL TRANSLATION

Currently, the only effective approach to managing food allergies is avoidance and intervention with emergency antihistamine or epinephrine shots in the case of accidental exposure. There are no long-lasting treatments that reverse food allergies. Several therapeutic approaches have been developed built on the scientific frameworks we have discussed.

Leveraging Oral Tolerance

As supported by the dual antigen exposure hypoth-

esis, early introduction to a range of foods, including allergenic items, is now commonly felt to reduce the likelihood of food allergy. In the Learning Early About Peanut Allergy (LEAP) trial, infants who were introduced to peanut allergen at 4-6 months of age had reduced incidence of peanut allergy [81,82,89]. Feeding infants cooked hen's egg starting from age 6 months reduced egg allergy prevalence at 1 year [90]. There is mixed evidence on whether avoiding standard cow's milk formula affects the development of food allergy [91,92]. However, one randomized controlled trial showed a 6% decrease in milk allergy by avoiding supplementation of cow's milk formula in the first week of life [93]. There is low evidence to support maternal dietary avoidance of food allergens in pregnancy or during breastfeeding [94,95].

Another promising method of treating food allergy based on leveraging oral tolerance is known as food immunotherapy. This protocol consists of low dose exposure to the allergenic antigen followed by an escalation period of variable length and eventual maintenance exposure to re-establish oral tolerance via mechanisms which are as yet not entirely clear. The three most common routes of exposure are oral immunotherapy (OIT), sublingual immunotherapy (SLIT), and epicutaneous immunotherapy (EPIT). However, recent meta-analyses have called into question the efficacy of immunotherapy [96,97]. Various clinical trials have reported initial desensitization upon completion of therapy and maintained desensitization with strict maintenance dosing [98-100]; however, similar trials have been unable to achieve sustained unresponsiveness [101,102], defined as continued tolerance to food antigens in the absence of regular antigen exposure. Furthermore, a majority of patients encounter adverse effects during desensitization with 10-20% of patients experiencing severe reactions requiring epinephrine injection [103,104]. A recent meta-analysis of studies with patients that had successfully completed immunotherapy found increased anaphylaxis risk, anaphylaxis frequency, and epinephrine use in individuals following immunotherapy as compared to individuals practicing traditional protective methods of avoidance and emergency epinephrine [105].

Protecting the Barrier

Given the data that suggest that sensitization occurs across a damaged cutaneous barrier, studies have attempted to show that prevention of skin barrier disruption may reduce risk of food allergy. Two randomized controlled pilot studies supported the idea that prevention of atopic dermatitis and food allergy through use of prophylactic emollients may be effective. In the first study, 124 infants at risk of atopic dermatitis in the United Kingdom and the United States were either advised to use daily emollients or not. Only 22% of infants that used topical emollients developed atopic dermatitis by 6 months of age compared to 43% of infants who were not advised to use topical emollients [106]. The second study was based in Japan and included 118 high risk infants that were randomized to use of emollients or no use. At 32 weeks, 32% of infants in the emollient group had atopic dermatitis, while 47% in the control group developed atopic dermatitis [107]. The Barrier Enhancement for Eczema Prevention (BEEP) study was the first large randomized controlled trial designed to test whether emollients could prevent atopic dermatitis [108]. The study included 1394 infants at risk of developing atopic dermatitis (family history of atopy) who were randomly assigned to receive either emollient and best practice skin care advice or best practice skin care advice alone [108]. Surprisingly, the trial found no difference in development of atopic dermatitis after 2 years between the two groups and also no difference in development of food allergies to milk, egg, or peanut [108]. These findings were unexpected given the promising results of the earlier pilot studies. Another recent randomized controlled trial, the Preventing Atopic Dermatitis and ALLergies in childhood (PreventADALL) study, sought to determine whether skin emollients applied during infancy could prevent atopic dermatitis and whether early food introduction could reduce food allergy. A total of 2387 infants were randomized to a no intervention group, a skin emollients group, an early feeding of allergenic food group, and a combined skin and food intervention group [109]. Neither intervention was effective at reducing the incidence of atopic dermatitis by 1 year [109]. The results for the development of food allergies with these interventions has not yet been reported but will be informative. Finally the Preventing Eczema and Food Allergy in High Risk Infants (PEBBLES) study is ongoing and will also seek to determine whether the use of an emollient (in this case a ceramide-containing emollient) reduces the incidence of atopic dermatitis and/or food allergy [110].

Targeting the Culprit Genes and Pathways

Biologics targeting specific aspects of the immune system involved in allergic responses have a lot of potential in the treatment of food allergy and related morbidities. Omalizumab is one of the best-described antibody therapies for allergic diseases. Targeting the Cε3 domain of circulating IgE, Omalizumab prevents the binding of IgE antibodies to FcεRI receptors [111]. Unbound FcεRI is unstable [112], so inhibiting its interactions with IgE downregulates the FcεRI receptor on the surface of mast cells, basophils, and other antigen presenting cells. Currently, omalizumab is licensed for allergic asthma and chronic urticaria; however, several trials have demonstrated that omalizumab increases the threshold of sen-

sitivity to oral challenge [88,113]. Interestingly, the rapid effect of omalizumab on desensitization implies its effect is primarily mediated by downregulation of FcεRI on basophils rather than mast cells [114].

Like IgE, biologics targeting IL4 have also shown great promise in the clinic. Dupilumab is a human IgG4 monoclonal antibody that binds IL-4Rα thereby inhibiting IL-4 and IL-13 signaling which was recently shown to be successful in atopic dermatitis [115]. There is currently a clinical trial investigating the use of dupliumab as a monotherapy to increase tolerance to peanut antigen (NCT03793608). As previously noted, while immunotherapy alone or immunotherapy supplemented with omalizumab can successfully desensitize patients to food antigens, they fail to infer sustained unresponsiveness in the absence of maintenance exposure [101,102,104,116,117]. Recent research has aimed to elucidate physiologic differences between patients that develop sustained unresponsiveness in the absence of antigen maintenance as compared to those that redeveloped extreme sensitivity. One such study found a significant increase in regulatory T cell function compared to desensitized patients that did not maintain antigen tolerance [102]. Interestingly, this same study found no significant difference in mast cell antibody titer or basophil activation between the two groups. The role of IL-4 in the differentiation of naïve helper cells to Th2 helper cells raises the possibility of IL-4 blockade in skewing T cell development away from a Th2-like profile. Indeed, a recent study found that in mice treated with anti-IL-4Rα reversed Th2 cell skewing and improved their suppressive function [118]. The effectiveness of this treatment in clinical setting has yet to be explored thoroughly; however, a clinical trial investigating dupilumab as an adjunct to immunotherapy is currently underway (NCT03682770). With the use of anti-allergic disease medications, one must consider how this might swing the curve in the other direction, promoting parasitic infections, though randomized controlled trials on dupilumab treatment have not shown increased risk of parasitic infection.

The limitations of the therapies resultant from current paradigms reinforce the need for additional research and investment in novel lines of investigation that could lead to new therapeutic strategies for the treatment of severe food allergy. We argue that a common theme in each of the paradigms is a lack of clear insight into the possible novel factors within the modern industrialized environment that are necessary for food allergy pathogenesis.

UNPACKING THE PATHOGENIC MODERN ENVIRONMENT: EMERGING MODERN CULPRITS

Modern Diet, Antibiosis, and the Impact on Microbiota

There has been increasing evidence that the microbiome plays an important role in food allergy. Microbiota differences are found in children with and without food allergy. Intestinal bacteria alter intestinal barrier integrity and affect immune system development [119,120]. The role of the microbiota in shaping tolerance by T-reg-dependent and independent mechanisms have been previously reviewed [121-124].

Modern diets and the use of antibiotics may well influence the threshold of breaking oral tolerance. For example, food allergy within the first year of life is predicted by an increased prevalence of gut *Clostridium* species as compared to *Bifidobacterium* species [125,126]. Other studies have shown that decreased *Bifidobacterium* and *Lactobacillus* at 1-2 months of age increases the risk of developing allergies by 5 years of age [127,128]. Breastfed infants have less overall gut diversity in the first few weeks of life but are mostly colonized by *Bifidobacterium* species [126], while formula-fed babies lack *Bifidobacterium* [129], suggesting that breastfeeding may be protective for development of food allergy. Infants who were breastfed in addition to being fed formula were also demonstrated to have less incidence of allergy than those who were formula-fed alone [130], suggesting tolerance-promoting properties in breast milk which may be absent in formula-fed babies as opposed to allergy-promoting properties that may be present in formula, may be causative, although both possibilities remain plausible.

Maternal diet has been associated with infant microbiota and development of food allergy. *Prevotella* species in maternal stool is associated with a decreased risk of the infant developing food allergy [131]. Women who did not receive antibiotics during pregnancy or came from larger households have increased prevalence of *Prevotella* species in the stool [131]. One explanation for this effect is that *Prevotella* and *Bifidobacterium* species release short chain fatty acids (butyrate and propionate), which, in addition to promoting T-reg development, decrease IgE-mediated basophil degranulation and reduce the development of food allergies [132].

Clinically, evidence is inconclusive on the benefits of probiotics in food allergy and so probiotic supplementation is not currently recommended [133,134]. However, promising results were shown in a double-blind, placebo-controlled randomized trial of probiotic (*Lactobacillus rhamnosus*) and peanut oral immunotherapy (PPOIT) in inducing sustained unresponsiveness to peanut in children previously sensitized to the allergen [135,136].

Furthermore, fecal microbiota transfers have not yet produced reliable results in food allergy but are undergoing phase 1 clinical trials. Studies have not yet been initiated for modulating the skin microbiota to treat food allergy.

Modern Manmade Xenobiotics

Given the rise in food allergy in "modern" times and in developed countries, it would make sense to search for modern xenobiotics that are now widely prevalent (and not previously at high usage) as a source of the increasing allergy prevalence. This xenobiotic would likely be manmade, first introduced in the time of industrialization or during the rise of allergy prevalence and have high usage or exposure rates in the general public. To narrow the search, it may also be helpful to look for xenobiotics that have been shown to be associated with allergic reactions. Some possible examples would include industrial pollutants, food preservatives, allopathic drugs (which are generally derived from plant extracts [137]), especially those widely consumed by the general public. The ability for these environmental factors, and particularly for allopathic drugs, to induce food allergy likely also depends on the dose, timing of administration in relationship to the allergen, delivery form (oral, intravenous, aerosolized) in relation to the allergen, and even location of absorption or toxicity (small versus large intestine, lungs, skin). Moreover, genetic factors of the host would likely also play a role here; for example, polymorphisms in P450 metabolizing enzymes could alter the dose and form of the drug experienced by different individuals [138]. Moreover, large-scale screening and identification of such modern compounds could lead to the identification of common unifying features of type-II adjuvants, or, factors that decrease tolerance mechanisms which in term would inform the current black box of pathogenic events that occur at the epithelial barrier (Figure 1).

CONCLUSION

While the prevalence of food allergy is rising, many of the current paradigms of pathogenesis incompletely explain the phenomenon, we argue largely because of a lack of insight into the precise factors present in modernity that are pathogenic. For one, it is unlikely that over the past 70 years, the food allergen has changed significantly enough to induce more food allergy in susceptible individuals compared to previously. Second, the prevailing paradigms incompletely explain the rise in prevalence of food allergy in our recent history. We propose that the presence of as yet unidentified modern allergic adjuvants could significantly contribute to the rise in food allergy in modern, industrialized nations. From this perspective, while preventative strategies, like early feeding of allergens, have been successful in reducing the risk of food allergy development, the precise reason for this is not well understood and may in fact be due to a reduced chance of coincident exposure to modern adjuvants, which might be more likely to be consumed in childhood rather than infancy. We argue that it may be fruitful to direct scientific inquiry into discovering novel modern allergic adjuvants, should they exist, and that this would lead to novel insights into the basic biology of food allergy and in particular help clarify the initiating events of type-II immunity at the epithelial barrier. Understanding their mechanisms of action would lead to new strategies to combating the rising prevalence of food allergy that potentially would not carry the undesirable biological consequences of targeting the type-II immune response generally. With the exponential advances in technologies, it may be a ripe time to dive more deeply into the "dirty little secret" of experimental allergists and closely explore and deconvolute the "dark matter" of the modern environment to further advance our understanding of oral allergic immunity.

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