Review

Food Allergy: Searching for the Modern Environmental Culprit

Anna S. Eisenstein,†, Brandon Hilliard, Sophia Silwal, and Andrew Wang

†Department of Dermatology, Yale University School of Medicine, New Haven, CT; ‡Department of Immunobiology, Yale University School of Medicine, New Haven, CT; †Yale University, New Haven, CT; ‡Department of Medicine (Rheumatology), Yale University School of Medicine, New Haven, CT

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.

Copyright © 2020

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

*To whom all correspondence should be addressed: Anna Eisenstein, The Anlyan Center, 300 Cedar Street, New Haven, CT, 06519; Tel: 203-500-3918; Fax: 203-785-7053; Email: anna.eisenstein@yale.edu. Andrew Wang, The Anlyan Center, 300 Cedar Street, New Haven, CT, 06519; Tel: 203-785-2454; Fax: 203-785-7053; Email: andrew.wang@yale.edu.

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.

Keywords: food allergy, evolutionary mismatch, type II immunity

Author Contributions: AE, BH, SS, AW generated concept, wrote, and edited manuscript.
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 allergies. 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
The pathogenesis of food allergy is undoubtedly 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 food allergy is a significant risk factor. 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 undoubtedly 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-4Ra) 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 Fcc 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.
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 filagrin 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-
*Staphylococcus* 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 contextually 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 hypothe-
nosis, 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 allergens 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 FceRI receptors [111]. Unbound FceRI is unstable [112], so inhibiting its interactions with IgE downregulates the FceRI 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 IL-4 have also shown great promise in the clinic. Dupilumab is a human IgG4 monoclonal antibody that binds IL-4Ra 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 dupilumab 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 redevelop 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-4Ra 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]. Breast-fed 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 turn 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.

**Funding:** AE is supported by T32 AR007016-43 from NIH/NAAMS and Dermatologist Investigator Research Fellowship from the Dermatology Foundation. AW is supported by an NIH Award (K08 AI128745) and awards from the Pew Scholars, Food Allergy Science Initiative, and Charles H. Hood Foundations.

**REFERENCES**

1. Asero R. Hypersensitivity to lipid transfer protein is frequently associated with chronic urticaria. Eur Ann Allergy Clin Immunol. 2011;43(1):19-21. Epub 2011/03/18.
2. Renz H, Allen KJ, Sicherer SH, Sampson HA, Lack G, Beyer K, et al. Food allergy. Nat Rev Dis Primers. 2018;4:17098. Epub 2018/01/05. doi: 10.1038/s41575-017-0006-6.
3. Loh W, Tang MLK. The Epidemiology of Food Allergy in the Global Context. Int J Environ Res Public Health. 2018;15(9). Epub 2018/09/21. doi: 10.3390/ijerph15092043.
4. Profet M. The function of allergy: immunological defense against toxins. Q Rev Biol. 1991;66(1):23-62. Epub 1991/03/01. doi: 10.1086/417049.
5. Palm NW, Medzhitov R. Pattern recognition receptors and control of adaptive immunity. Immunol Rev. 2009;227(1):221-33. Epub 2009/01/06. doi: 10.1111/j.1600-065X.2008.00731.x.
6. Poussel G, Turner PJ, Worm M, Cardona V, Deschildre A, Beaudouin E, et al. Food-induced fatal anaphylaxis: From epidemiological data to general prevention strategies. Clin Exp Allergy. 2018;48(12):1584-93. Epub 2018/10/06. doi: 10.1111/cea.13287.
7. Breiteneder H, Radauer C. A classification of plant food allergens. J Allergy Clin Immunol. 2004;113(5):821-30; quiz 31. Epub 2004/05/08. doi: 10.1016/j.jaci.2004.01.779.
8. Altmann F. The role of protein glycosylation in allergy. Int Arch Allergy Immunol. 2007;142(2):99-115. Epub
Eisenstein et al.: Food allergy: searching for the modern environmental culprit

37. Siicherer SH, Furlong TJ, Maes HH, Desnick RJ, Sampson HA, Gelb BD. Genetics of peanut allergy: a twin study. J Allergy Clin Immunol. 2000;106(1 Pt 1):53-6. Epub 2000/07/11. doi: 10.1067/mai.2000.108105.

38. Wandstrat A, Wakeland E. The genetics of complex autoimmune diseases: non-MHC susceptibility genes. Nat Immunol. 2001;2(9):802-9. Epub 2001/08/30. doi: 10.1038/ni0901-802.

39. Palm NW, Rosensten RK, Medzhitov R. Allergic host defences. Nature. 2012 Apr 25;484(7395):465-72. doi: 10.1038/nature1047.

40. Beizat V, Li J, Lin JX, Ma CS, Li P, Bousfiha A, et al. A recessive form of hyper-IgE syndrome by disruption of ZNF341-dependent STAT3 transcription and activity. Sci Immunol. 2018;3(24). Epub 2018/06/17. doi: 10.1126/sciimmunol.aat4956.

41. Engelhardt KR, McGhee S, Winkler S, Sassi A, Woellner C, Lopez-Herrera G, et al. Large deletions and point mutations involving the dedicator of cytokinesis 8 (DOCK8) in the autosomal-recessive form of hyper-IgE syndrome. J Allergy Clin Immunol. 2009;124(6):1289-302 e4. Epub 2009/12/17. doi: 10.1067/j.jaci.2009.10.038.

42. Holland SM, DeLeo FR, Elloumi HZ, Hsu AP, Uzel G, Brodsky N, et al. STAT3 mutations in the hyper-IgE syndrome. N Engl J Med. 2007;357(16):1608-19. Epub 2007/09/21. doi: 10.1056/NEJMoa073687.

43. Grant AV, Araujo MI, Oliveira RR, Gao P, Cruz AA, et al. Functional polymorphisms in IL13 are protective against high Schistosoma mansoni infection intensity in a Brazilian population. PLoS One. 2012;7(5):e35863. Epub 2012/05/11. doi: 10.1371/journal.pone.0035863.

44. He H, Isnard A, Kouriba B, Cabantous S, Dessein A, Dounmo O, et al. A STAT6 gene polymorphism is associated with high infection levels in urinary schistosomiasis. Genes Immun. 2008;9(3):195-206. Epub 2008/02/15. doi: 10.1038/gene.2008.2.

45. Fumagalli M, Pozzoli U, Cagliani R, Comi GP, Riva S, Clerici M, et al. Parasites represent a major selective force for interleukin genes and shape the genetic predisposition to autoimmune conditions. J Exp Med. 2009;206(6):1395-408. Epub 2009/05/27. doi: 10.1084/jem.20082779.

46. Gyan BA, Goka B, Cveticovic JT, Kurtzhalis JL, Adabayeri V, Perlmann H, et al. Allelic polymorphisms in the repeat and promoter regions of the interleukin-4 gene and malaria severity in Ghanaian children. Clin Exp Immunol. 2004;138(1):145-50. Epub 2004/09/18. doi: 10.1111/j.1365-2249.2004.02590.x.

47. Basehore MJ, Howard TD, Lange LA, Moore WC, Hawkins GA, Marshik PL, et al. A comprehensive evaluation of IL4 variants in ethnically diverse populations: association of total serum IgE levels and asthma in white subjects. J Allergy Clin Immunol. 2004;114(1):80-7. Epub 2004/07/09. doi: 10.1016/j.jaci.2004.05.035.

48. Clough D, Kappeler PM, Walter L. Genetic regulation of parasite infection: empirical evidence of the functional significance of an IL4 gene SNP on nematode infections in wild primates. Front Zool. 2011;8(1):9. Epub 2011/04/20. doi: 10.1186/1742-9994-8-9.

49. Kawashima T, Noguchi E, Arinami T, Yamakawa-Ko-bayashi K, Nakagawa H, Otsuka F, et al. Linkage and association of an interleukin 4 gene polymorphism with atopic dermatitis in Japanese families. J Med Genet. 1998;35(6):502-4. Epub 1998/06/27. doi: 10.1136/jmg.35.6.502.

50. Noguchi E, Shibasaki M, Arinami T, Takeda K, Yokouchi Y, Kawashima T, et al. Association of asthma and the interleukin-4 promoter gene in Japanese. Clin Exp Allergy. 1998;28(4):449-53. Epub 1998/06/26. doi: 10.1046/j.1365-2222.1998.00025.x.

51. Rosenwasser LJ, Klemm DJ, Dresback JK, Inamura H, Mascali JJ, Klimpert M, et al. Promoter polymorphisms in the chromosome 5 gene cluster in asthma and atopy. Clin Exp Allergy. 1995;25 Suppl 2:74-8; discussion 95-6. Epub 1995/11/01. doi: 10.1111/j.1365-2222.1995.tb00428.x.

52. Albuhairi S, Rachid R. Novel Therapies for Treatment of Food Allergy. Immunol Allergy Clin North Am. 2020;40(1):175-86. Epub 2019/11/26. doi: 10.1016/j. iac.2019.09.007.

53. Turkie PW. Childhood food allergies: An evolutionary mismatch hypothesis. Evol Med Public Health. 2017;2017(1):154-60. Epub 2018/03/30. doi: 10.1093/ emph/cox14.

54. Cooper PJ, Chico ME, Rodrigues LC, Ordenez M, Strachan D, Griffin GE, et al. Reduced risk of atopy among school-age children infected with geohelminth parasites in a rural area of the tropics. J Allergy Clin Immunol. 2003;111(5):995-1000. Epub 2003/05/14. doi: 10.1067/ mai.2003.1348.

55. Scrivener S, Yemanbeberhan H, Zebenigus M, Tilahun D, Girma S, Ali S, et al. Independent effects of intestinal parasite infection and domestic allergen exposure on risk of wheeze in Ethiopia: a nested case-control study. Lancet. 2001;358(9292):1493-9. Epub 2001/11/14. doi: 10.1016/S0140-6736(01)06579-5.

56. Nyan OA, Walraven GE, Banya WA, Milligan P, Van Der Sande M, Ceesay SM, et al. Atopy, intestinal helminth infection and total serum IgE in rural and urban adult Gambian communities. Clin Exp Allergy. 2001;31(11):1672-8. Epub 2001/11/07. doi: 10.1046/j.1365-2222.2001.00987.x.

57. van den Biggelaar AH, van Ree R, Rodrigues LC, Lell B, Deelder AM, Kremersn PG, et al. Decreased atopy in children infected with Schistosoma haematobium: a role for parasite-induced interleukin-10. Lancet. 2000;356(9243):1723-7. Epub 2000/11/30. doi: 10.1016/S0140-6736(00)03206-2.

58. Fallon PG, Mangan NE. Suppression of TH2-type allergic reactions by helminth infection. Nat Rev Immunol. 2007;7(3):220-30. Epub 2007/02/24. doi: 10.1038/nri2039.

59. Yazdanbakhsh M, Kremersn PG, van Ree R. Allergy, parasites, and the hygiene hypothesis. Science. 2002;296(5567):490-4. Epub 2002/04/02. doi: 10.1126/ science.296.5567.490.

60. Godfrey RC, Gradients CF. Allergic sensitisation of human lung fragments prevented by saturation of IgE binding sites. Nature. 1976;259(5543):484-6. Epub 1976/02/12. doi: 10.1038/259484a0.

61. Larrick JW, Buckley CE, 3rd, Machamer CE, Schlager GD, Yost JA, Blessing-Moore J, et al. Does hyperimmuno-globulinemia-E protect tropical populations from allergic
744 Eisenstein et al.: Food allergy: searching for the modern environmental culprit

disease? J Allergy Clin Immunol. 1983;71(2):184-8. Epub 1983/02/01. doi: 10.1016/0091-6749(83)90097-0.

62. Hagel I, Lynch NR, Perez M, Di Prisco MC, Lopez R, Rojas E. Modulation of the allergic reactivity of slum children by helminthic infection. Parasite Immunol. 1993;15(6):311-5. Epub 1993/06/01. doi: 10.1111/j.1365-3024.1993.tb00615.x.

63. Werfel T, Allam JP, Biedermann T, Eyerich K, Gilles S, Guttman-Yassky E, et al. Cellular and molecular immunologic mechanisms in patients with atopic dermatitis. J Allergy Clin Immunol. 2016;138(2):336-49. Epub 2016/08/09. doi: 10.1016/j.jaci.2016.06.010.

64. Brown SJ, Asai Y, Cordell HJ, Campbell LE, Zhao Y, Liao H, et al. Loss-of-function variants in the filaggrin gene are a significant risk factor for peanut allergy. J Allergy Clin Immunol. 2011;127(3):661-7. Epub 2011/03/08. doi: 10.1016/j.jaci.2011.01.031.

65. Ashley SE, Tan HT, Vuillemot P, Dharmage SC, Tang MLK, Koplin J, et al. The skin barrier function gene SPINK5 is associated with challenge-proven IgE-mediated food allergy in infants. Allergy. 2017;72(9):1356-64. Epub 2017/02/19. doi: 10.1111/all.13143.

66. Suaini NHA, Wang Y, Soriano VX, Martino DJ, Allen KJ, Ellis JA, et al. Genetic determinants of paediatric food allergy: A systematic review. Allergy. 2019;74(9):1631-48. Epub 2019/03/06. doi: 10.1111/all.13767.

67. Chu DK, Llop-Guevara A, Walker TD, Flader K, Goncharova S, Boudreau JE, Moore CL, Seunghyun In T, Ellis JA, et al. Genetic determinants of paediatric food allergy revisited. Allergy. 2014;69(1):17-27. Epub 2013/10/15. doi: 10.1111/all.12268.

68. Lowe AJ, Leung DYM, Tang MLK, Su JC, Allen KJ. The skin as a target for prevention of the atopic march. Ann Allergy Asthma Immunol. 2018;120(2):145-51. Epub 2018/02/08. doi: 10.1016/j.anai.2017.11.023.

69. Hill DA, Spergel JM. The atopic march: Critical evidence and clinical relevance. Ann Allergy Asthma Immunol. 2018;120(2):131-7. Epub 2018/02/08. doi: 10.1016/j.anai.2017.10.037.

70. Hill DJ, Hosking CS, de Benedictis FM, Oranje AP, Diepgen TL, Bauchau V, et al. Confirmation of the association between high levels of immunoglobulin E food sensitization and eczema in infancy: an international study. Clin Exp Allergy. 2008;38(1):161-8. Epub 2007/11/22. doi: 10.1111/j.1365-2222.2007.02861.x.

71. Martin PE, Eckert JK, Koplin JJ, Lowe AJ, Gurrrin LC, Dharmage SC, et al. Which infants with eczema are at risk of food allergy? Results from a population-based cohort. Clin Exp Allergy. 2015;45(1):255-64. Epub 2014/09/12. doi: 10.1111/cea.12406.

72. Miyaji Y, Yang L, Yamamoto-Hanada K, Narita M, Saito H, Ohya Y. Earlier aggressive treatment to shorten the duration of eczema in infants resulted in fewer food allergies at 2 years of age. J Allergy Clin Immunol Pract. 2020;8(5):1721-4 e6. Epub 2019/12/11. doi: 10.1016/j.jaci.2019.11.036.

73. Du Toit G, Roberts G, Sayre PH, Bahnsen HT, Radulovic S, Santos AF, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. N Engl J Med. 2015;372(9):803-13. Epub 2015/02/04. doi: 10.1056/NEJMoa1414850.

74. Diestal MF, Leung DYM, Beck LA, Berin CM, Boguniewicz M, Busse WW, et al. Report from the National Institute of Allergy and Infectious Diseases workshop on “Atopic dermatitis and the atopic march: Mechanisms and interventions”. J Allergy Clin Immunol. 2019;143(3):894-913. Epub 2019/01/15. doi: 10.1016/j.jaci.2019.01.003.

75. Dharmage SC, Lowe AJ, Matheson MC, Burgess JA, Allen KJ, Abramson MJ. Atopic dermatitis and the atopic march revisited. Allergy. 2014;69(1):17-27. Epub 2013/10/15. doi: 10.1111/all.12268.

Epicutaneous sensitization to food allergens in atopic dermatitis: What do we know? Pediatr Allergy Immunol. 2020;31(1):7-18. Epub 2019/09/22. doi: 10.1111/pai.13127.

77. Davidson WF, Leung DYM, Beck LA, Berin CM, Boguniewicz M, Busse WW, et al. Report from the National Institute of Allergy and Infectious Diseases workshop on “Atopic dermatitis and the atopic march: Mechanisms and interventions”. J Allergy Clin Immunol. 2019;143(3):894-913. Epub 2019/01/15. doi: 10.1016/j.jaci.2019.01.003.

78. Dharmage SC, Lowe AJ, Matheson MC, Burgess JA, Allen KJ, Abramson MJ. Atopic dermatitis and the atopic march revisited. Allergy. 2014;69(1):17-27. Epub 2013/10/15. doi: 10.1111/all.12268.

79. Martin PE, Eckert JK, Koplin JJ, Lowe AJ, Gurrrin LC, Dharmage SC, et al. Which infants with eczema are at risk of food allergy? Results from a population-based cohort. Clin Exp Allergy. 2015;45(1):255-64. Epub 2014/09/12. doi: 10.1111/cea.12406.

80. Miyaji Y, Yang L, Yamamoto-Hanada K, Narita M, Saito H, Ohya Y. Earlier aggressive treatment to shorten the duration of eczema in infants resulted in fewer food allergies at 2 years of age. J Allergy Clin Immunol Pract. 2020;8(5):1721-4 e6. Epub 2019/12/11. doi: 10.1016/j.jaci.2019.11.036.

81. Du Toit G, Roberts G, Sayre PH, Bahnsen HT, Radulovic S, Santos AF, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. N Engl J Med. 2015;372(9):803-13. Epub 2015/02/04. doi: 10.1056/NEJMoa1414850.

82. Du Toit G, Sayre PH, Roberts G, Sever ML, Lawson K, Bahnsen HT, et al. Effect of Avoidance on Peanut Allergy after Early Peanut Consumption. N Engl J Med. 2016;374(15):1435-43. Epub 2016/03/05. doi: 10.1056/NEJMoai514209.

83. Perkins MR, Logan K, Bahnsen HT, Marrs T, Radulovic S, Craven J, et al. Efficacy of the Enquiring About Tolerance (EAT) study among infants at high risk of developing food allergy. J Allergy Clin Immunol. 2019;144(6):1606-14 e2. Epub 2019/12/10. doi: 10.1016/j.jaci.2019.06.045.

84. Lack G, Fox D, Northstone K, Golding J, Avon Longitudinal Study of P, Children Study T. Factors associated with the development of peanut allergy in childhood. N Engl J Med. 2003;348(11):977-85. Epub 2003/03/15. doi: 10.1056/NEJMoa013536.

85. Williams MR, Gallo RL. The role of the skin micro-
biome in atopic dermatitis. Curr Allergy Asthma Rep. 2015;15(11):65. Epub 2015/09/26. doi: 10.1007/s11882-015-0567-4.

86. Cogen AL, Yamasaki K, Sanchez KM, Dorschner RA, Lai Y, MacLeod DT, et al. Selective antimicrobial action is provided by phenol-soluble modulins derived from Staphylococcus epidermidis, a normal resident of the skin. J Invest Dermatol. 2010;130(1):192-200. Epub 2009/08/28. doi: 10.1038/jid.2009.243.

87. Tsilochostrictou O, du Toit G, Sayre PH, Roberts G, Lawson K, Sever ML, et al. Association of Staphylococcus aureus colonization with food allergy occurs independently of eczema severity. J Allergy Clin Immunol. 2019;144(2):494-503. Epub 2019/06/05. doi: 10.1016/j.jaci.2019.04.025.

88. Leung DYM, Calatroni A, Zaramela LS, LeBeau PK, Dyjack N, Brar K, et al. The nonlesional skin surface distinguishes atopic dermatitis with food allergy as a unique endotype. Sci Transl Med. 2019;11(480). Epub 2019/02/23. doi: 10.1126/scitranslmed.aav2685.

89. du Toit G, Sayre PH, Roberts G, Lawson K, Sever ML, Bahnson HT, et al. Allergen specificity of early peanut consumption and effect on development of allergic disease in the Learning Early About Peanut Allergy study cohort. J Allergy Clin Immunol. 2018;141(4):1343-53. Epub 2017/11/04. doi: 10.1016/j.jaci.2017.09.034.

90. Natsume O, Kabashima S, Nakazato J, Yamamoto-Hanada K, Narita M, Kondo M, et al. Two-step egg introduction for prevention of egg allergy in high-risk infants with eczema (PETITT): a randomised, double-blind, placebo-controlled trial. Lancet. 2017;389(10066):276-86. Epub 2016/12/13. doi: 10.1016/S0140-6736(16)31418-0.

91. de Silva D, Halken S, Singh C, Muraro A, Angier E, Arasi M, et al. Primary Prevention of Cow’s Milk Sen-

92. Odelram H, Vanto T, Jacobsen L, Kjellman NI. Whey antigen-induced regulatory T-cell function and hypomethy-

93. Odelram H, Vanto T, Jacobsen L, Kjellman NI. Whey hydrolysatc compared with cow’s milk-based formula for weaning at about 6 months of age in high allergy-risk infants: effects on atopic disease and sensitization. Allergy. 1996;51(3):192-5. Epub 1996/03/01.

94. Usarkova S, Mezawa H, Okuyama M, Usarkov T, Hirono D, Gocho N, et al. Primary Prevention of Cow’s Milk Sen-

95. Falth-Magnusson K, Kjellman NI. Allergy prevention by maternal elimination diet during late pregnancy--a 5-year follow-up of a randomized study. J Allergy Clin Immunol. 1992;89(3):709-13. Epub 1992/03/01. doi: 10.1016/0091-6749(92)90378-f.

96. Chu DK, Wood RA, French S, Fiocchi A, Jordana M, Waserman S, et al. Oral immunotherapy for peanut allergy (PACE): a systematic review and meta-analysis of efficacy and safety. Lancet. 2019;393(10187):2222-32. Epub 2019/04/30. doi: 10.1016/S0140-6736(19)30420-9.

97. Nurmatau U, Dhami S, Arasi S, Pajno GB, Fernandez-Rivas M, Muraro A, et al. Allergen immunotherapy for IgE-mediated food allergy: a systematic review and meta-analysis. Allergy. 2017;72(8):1133-47. Epub 2017/01/07. doi: 10.1111/all.13124.

98. Caminiti L, Pajno GB, Crisafulli G, Chiera F, Collura M, Panasci G, et al. Oral Immunotherapy for Egg Al-

99. PALISADE Group of Clinical Investigators, Vickery BP, Vereda A, Casale TB, et al. AR101 Oral Immunomo-

100. Vickers BP, Berglund JP, Burk CM, Fine JP, Kim EH, Kim Ji, et al. Early oral immunotherapy in peanut-allergic preschool children is safe and highly effective. J Allergy Clin Immunol. 2017;139(1):173-81 e8. Epub 2016/08/16. doi: 10.1016/j.jaci.2016.05.027.

101. Chihraraj RS, Purington N, Andorf S, Long A, O’Laughlin KL, Lyu SC, et al. Sustained outcomes in oral immunotherapy for peanut allergy (POISED study): a large, randomised, double-blind, placebo-controlled, phase 2 study. Lancet. 2019;394(10207):1437-49. Epub 2019/09/17. doi: 10.1016/S0140-6736(19)31793-3.

102. Syed A, Garcia MA, Lyu SC, Bucayu R, Kohli A, Ishida S, et al. Peanut oral immunotherapy results in increased antigen-induced regulatory T-cell function and hypomethy-

103. Kostadinova AI, Willemse LE, Knippels LM, Garssen J. Immuno-therapy - risk/benefit in food allergy. Pediatr Allergy Immunol. 2013;24(7):633-44. Epub 2013/10/12. doi: 10.1111/pai.12122.

104. Wood RA, Kim JS, Lindblad R, Nadeau K, Henning AK, Dawson P, et al. A randomized, double-blind, placebo-

105. Chu DK, Wood RA, French S. Oral immunotherapy for peanut allergy (PACE): a systematic review and meta-analysis of efficacy and safety (2019). Lancet. 2019;393(10184):745.
108. Chalmers JR, Haines RH, Bradshaw LE, Montgomery AA, Thomas KS, Brown SJ, et al. Daily emollient during infancy for prevention of eczema: the BEEP randomised controlled trial. Lancet. 2020;395(10228):962-72. Epub 2020/02/23. doi: 10.1016/S0140-6736(19)32984-8.

109. Skjerven HO, Rehbinde EM, Vettukattil R, LeBlanc M, Granum B, Haugen G, et al. Skin emollient and early complementary feeding to prevent infant atopic dermatitis (PreventADALL): a factorial, multicentre, cluster-randomised trial. Lancet. 2020;395(10228):951-61. Epub 2020/02/23. doi: 10.1016/S0140-6736(19)32983-6.

110. Lowe A, Su J, Tang M, Lodge CJ, Matheson M, Allen KJ, et al. PEBBLE Study protocol: a randomised controlled trial to prevent atopic dermatitis, food allergy and sensitisation in infants with a family history of allergic disease using a skin barrier improvement strategy. BMJ Open. 2019;9(3):e024594. Epub 2019/03/15. doi: 10.1136/bmjopen-2018-024594.

111. Presta L, Shields R, O’Connell L, Lahr S, Porter J, Gorman C, et al. The binding site on human immunoglobulin E for its high affinity receptor. J Biol Chem. 1994;269(4):26368-73. Epub 1994/10/21.

112. Borkowski TA, Jouvin MH, Lin SY, Kinet JP. Minimal requirements for IgE-mediated regulation of surface Fc epsilon RI. J Immunol. 2001;167(3):1290-6. Epub 2001/07/24. doi: 10.4049/jimmunol.167.3.1290.

113. Sampson HA, Leung DY, Burks AW, Lack G, Bahna SL, Jones SM, et al. A phase II, randomized, doubleblind, parallelgroup, placebocontrolled oral food challenge trial of Xolair (omalizumab) in peanut allergy. J Allergy Clin Immunol. 2011;127(5):1309-10 e1. Epub 2011/03/15. doi: 10.1016/j.jaci.2011.01.051.

114. Savage JH, Courneya JP, Sterba PM, Macglashan DW, Saini SS, Wood RA. Kinetics of mast cell, basophil, and oral food challenge responses in omalizumab-treated adults with peanut allergy. J Allergy Clin Immunol. 2012;130(5):1123-9 e2. Epub 2012/07/18. doi: 10.1016/j.jaci.2012.05.039.

115. Beck LA, Thaci D, Hamilton JD, Graham NM, Biber T, Rocklin R, et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. N Engl J Med. 2014;371(2):130-9. Epub 2014/07/10. doi: 10.1056/NEJMoai1314768.

116. Burton OT, Logsdon SL, Zhou JS, Medina-Tamayo J, Abdel-Gadir A, Noval Rivas M, et al. Oral immunotherapy induces IgG antibodies that act through FcgammaRIIb to suppress IgE-mediated hypersensitivity. J Allergy Clin Immunol. 2014;134(6):1310-7 e6. Epub 2014/07/22. doi: 10.1016/j.jaci.2014.05.042.

117. MacGinnitie AJ, Rachid R, Gragg H, Little SV, Larkin P, Cianferoni A, et al. Omalizumab facilitates rapid oral desensitization for peanut allergy. J Allergy Clin Immunol. 2017;139(3):873-81 e8. Epub 2016/10/19. doi: 10.1016/j.jaci.2016.08.010.

118. Abdel-Gadir A, Schneider L, Casini A, Charbonnier LM, Little SV, Harrington T, et al. Oral immunotherapy with omalizumab reverses the Th2 cell-like programme of regulatory T cells and restores their function. Clin Exp Allergy. 2018;48(7):825-36. Epub 2018/04/28. doi: 10.1111/cea.13161.

119. Geuring MB, Cazenzi J, Lawson MA, Ng DC, Slack E, Hopfelmeyer S, et al. Intestinal bacterial colonization induces mutualistic regulatory T cell responses. Immunity. 2011;34(5):794-806. Epub 2011/05/21. doi: 10.1016/j.immuni.2011.03.021.

120. Lathrop SK, Bloom SM, Rao SM, Nutsch K, Lio CW, Santacruz N, et al. Peripheral education of the immune system by colonic commensal microbiota. Nature. 2011;478(7368):250-4. Epub 2011/09/23. doi: 10.1038/nature10434.

121. Chistiakov DA, Bobrıyev YV, Kozaroy E, Sobennia IA, Orekhov AN. Intestinal mucosal tolerance and impact of gut microbiota to mucosal tolerance. Front Microbiol. 2014;5:781. Epub 2015/01/30. doi: 10.3389/fmicb.2014.00781.

122. Pandiyyan P, Bhaskaran N, Zou M, Schneider E, Jayaraman S, Huehn J. Microbiome Dependent Regulation of Tregs and Th17 Cells in Murcosa. Front Immunol. 2019;10:426. Epub 2019/03/25. doi: 10.3389/fimmu.2019.00426.

123. Palm NW, de Zoete MR, Flavell RA. Immune-microbiota interactions in health and disease. Clin Immunol. 2015;159(2):122-7. Epub 2015/07/05. doi: 10.1016/j.clim.2015.05.014.

124. Zheng D, Liwinski T, Elinav E. Interaction between microbiota and immunity in health and disease. Cell Res. 2020;30(6):492-506. Epub 2020/05/21. doi: 10.1038/s41422-020-0332-7.

125. Bunyavanich S. Food allergy: could the gut microbiota hold the key? Nat Rev Gastroenterol Hepatol. 2019;16(4):201-2. Epub 2019/03/03. doi: 10.1038/s41575-2019-0123-0.

126. Kalliomaki M, Kirjavainen P, Eerola E, Kero P, Salminen S, Isolauri E. Distinct patterns of neonatal gut microflora in infants in whom atopy was and was not developing. J Allergy Clin Immunol. 2001;107(1):129-34. Epub 2001/01/10. doi: 10.1067/mai.2001.111237.

127. Bisgaard H, Li N, Bonnelykke K, Chawes BL, Skov T, Paludan-Müller G, Stokholm J, Smith B, Krogfelt KA. Reduced diversity of the intestinal microbiota during infancy is associated with increased risk of allergic disease at school age. J Allergy Clin Immunol. 2011 Sep;128(3):646-52.e1-5. doi: 10.1016/j.jaci.2011.04.060.

128. Sjogren YM, Jen StyleSheet MC, Bottcher MF, Bjorksten B, Sverremark-Ekstrom E. Altered early infant gut microbiota in children developing allergy up to 5 years of age. Clin Exp Allergy. 2009;39(4):518-26. Epub 2009/02/18. doi: 10.1111/j.1365-2222.2008.03156.x.

129. Roger LG, Costabile A, Holland DT, Hoyles L, McCartney AL. Examination of faecal Bifidobacterium populations in breast- and formula-fed infants during the first 18 months of life. Microbiology. 2010;156(Pt 11):3329-41. Epub 2010/09/25. doi: 10.1099/mic.0.04322-0.

130. Martin VM, Virkud YV, Seay H, Hickey A, Ndahayo R, Rosow R, et al. Prospective Assessment of Pediatrician-Diagnosed Food Protein-Induced Allergic Proctocolitis by Gross or Occult Blood. J Allergy Clin Immunol Pract. 2020;8(5):1692-9 e1. Epub 2020/01/10. doi: 10.1016/j.jaip.2019.12.029.

131. Vuillermin PJ, O’Hely M, Collier F, Allen KJ, Tang...
132. Hayen SM, den Hartog Jager CF, Knulst AC, Knol EF, Garssen J, Willemsen LEM, et al. Non-Digestible Oligosaccharides Can Suppress Basophil Degranulation in Whole Blood of Peanut-Allergic Patients. Front Immunol. 2018;9:1265. Epub 2018/06/27. doi: 10.3389/fimmu.2018.01265.

133. Cuello-Garcia CA, Brozek JL, Fiocchi A, Pawankar R, Yepes-Nunez JJ, Terracciano L, et al. Probiotics for the prevention of allergy: A systematic review and meta-analysis of randomized controlled trials. J Allergy Clin Immunol. 2015;136(4):952-61. Epub 2015/06/06. doi: 10.1016/j.jaci.2015.04.031.

134. Fiocchi A, Pawankar R, Cuello-Garcia C, Ahn K, Al-Hammadi S, Agarwal A, et al. World Allergy Organization-McMaster University Guidelines for Allergic Disease Prevention (GLAD-P): Probiotics. World Allergy Organ J. 2015;8(1):4. Epub 2015/01/30. doi: 10.1186/s40413-015-0055-2.

135. Hsiao KC, Ponsonby AL, Axelrad C, Pitkin S, Tang MLK, Team PS. Long-term clinical and immunological effects of probiotic and peanut oral immunotherapy after treatment cessation: 4-year follow-up of a randomised, double-blind, placebo-controlled trial. Lancet Child Adolesc Health. 2017;1(2):97-105. Epub 2018/09/01. doi: 10.1016/S2352-4642(17)30041-X.

136. Tang ML, Ponsonby AL, Orsini F, Tey D, Robinson M, Su EL, et al. Administration of a probiotic with peanut oral immunotherapy: A randomized trial. J Allergy Clin Immunol. 2015;135(3):737-44 e8. Epub 2015/01/17. doi: 10.1016/j.jaci.2014.11.034.

137. Pollier J, Moses T, Goossens A. Combinatorial biosynthesis in plants: a (p)review on its potential and future exploitation. Nat Prod Rep. 2011;28(12):1897-916. Epub 2011/09/29. doi: 10.1039/c1np00049g.

138. Nagata K, Yamazoe Y. Genetic polymorphism of human cytochrome P450 involved in drug metabolism. Drug Metab Pharmacokinet. 2002;17(3):167-89. Epub 2004/12/25. doi: 10.2133/dmpk.17.167.