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Allergies: Un updated review article of food allergy

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***Abstract*---Background:** Food allergy (FA) is increasingly recognized as a significant global health issue, with ongoing research shedding light on its mechanisms and progression. This updated review emphasizes recent findings, particularly concerning biomarkers related to desensitization and tolerance development. **Aim:** The primary objective of this article is to synthesize current advancements in the understanding of FA, focusing on the role of epithelial barrier function, immune response mechanisms, and potential therapeutic strategies. **Methods:** This review synthesizes findings from recent studies concerning food allergy pathophysiology, specifically examining the interplay between the epithelial barrier, immune responses, and potential interventions, including emollient therapy

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and immunotherapy. **Results:** The integrity of the epithelial barrier is crucial for immune tolerance to allergens. Disruptions due to genetic mutations or environmental factors lead to increased susceptibility to FA. Current interventions, including the use of emollients and dietary modifications, have shown mixed results in preventing allergic manifestations. Additionally, new insights into immunological responses, particularly involving IgE glycosylation and T follicular helper cell dynamics, contribute to our understanding of allergy mechanisms. **Conclusion:** Maintaining a healthy epithelial barrier and understanding the immune system's complex interactions are vital for developing effective prevention and treatment strategies for food allergies. Ongoing research is necessary to elucidate the precise mechanisms underlying allergen sensitization and tolerance.
***Keywords*---**Food allergy, epithelial barrier, immune response, desensitization, tolerance, biomarkers.

Introduction

Food allergy (FA) represents an escalating global health concern. Current research is yielding deeper insights into the etiology and progression of this condition. This update builds on our prior article1 by highlighting recent advancements in the field, particularly regarding biomarkers associated with desensitization and the development of tolerance.

The Influence of Barrier Function on Food Allergy

Epithelial cells serve as the primary physical defense at the intersection of the "exposome" and the human body, playing a vital role in sustaining tissue homeostasis. The exposome encompasses external factors such as allergens, pollutants, detergents, and microbes, alongside internal elements, specifically the microbiota and metabolic products. [2] Preserving optimal barrier function is essential for enabling appropriate immune responses to allergens. Thus, dysfunction of the epithelial barrier and altered permeability, which can result from genetic mutations or single nucleotide polymorphisms in critical genes such as filaggrin, SPINK [5,3] SERPINB7, KLK7, and Claudin-1 [4, 5] are implicated in the development of atopic dermatitis (AD) and FA. [6-10] Barrier irregularities stem from reductions in ceramides, antimicrobial peptides, serine protease, and dysbiosis of the skin/gut microbiome due to external factors, notably detergents. [4, 11, 12] A recent review in *Allergy* delves deeper into these ideas.[13] The association between AD and FA is further elucidated by the dual-allergen exposure hypothesis, which posits that initial allergen exposure through compromised skin, in the absence of prior gastrointestinal tract (GIT) exposure, predisposes individuals to a Th2-type inflammatory immune response. Conversely, initial allergen exposure via the GIT fosters regulatory immune responses and facilitates tolerance induction.[14, 15] Therefore, food allergen sensitization and FA development are likely associated with skin barrier impairment and possibly microbial colonization. [4, 15-17] Commensal bacteria are essential for the protection of skin microbiota, T cell maturation, and the stimulation of antimicrobial peptide synthesis by keratinocytes. Dysbiosis within

the skin microbiome, often assessed by the prevalence of Staphylococcus aureus, is positively linked to the severity of AD, indicating its potential as a biomarker for the condition.[18, 19]

The principal management strategy for AD involves the application of emollients aimed at bolstering barrier function. The notion of preventing barrier dysfunction in vivo through the application of moisturizers remains an area of active exploration. Various emollient formulations, including the prevalent paraffin/petroleum base and a trilipid base (3:1:1—ceramides, cholesterol, and free fatty acids), are commonly employed. [20, 21] Emollients may mitigate severity and extend intervals between AD exacerbations [22] by decreasing trans-epidermal water loss [21] and enhancing overall hydration. [23] This is particularly critical for neonatal skin, which is characterized by a fragile stratum corneum with diminished lipid content and moisturizing factors. Emollients, especially those with a trilipid formulation, could foster tolerance through an elevated IgG4/IgE ratio, increased IL-10 and LAP+ T cells, and a reduction in IL-4 producing CD4+ T cells.20 Additionally, the free fatty acids in the trilipid formulation may activate peroxisome proliferator-activated receptors (PPARs), which are typically downregulated in AD, thus potentially alleviating inflammation. [24] Initial pilot studies suggested that regular use of emollients could avert AD.20, [25] However, larger randomized controlled trials, such as BEEP,26 a multicenter study involving newborns at high risk for allergies, found that daily application of paraffin/petroleum-based emollients did not prevent eczema by the age of 2 years nor decrease the incidence of FA, despite high adherence to treatment. [26] The PreventADALL27 trial, which included newborns, confirmed that neither intensive emollient use (both paraffin/petroleum-based and emollient bath oil) nor early introduction of complementary feeding diminished the development of AD. [27] Allergic sensitization at 6 months was associated with eczema, dry skin, and compromised skin barrier function at 3 months of age. [28] Nevertheless, the formulations of emollients may still hold relevance, and further large-scale population studies assessing the efficacy of different emollients in treating AD are currently in progress. [25, 29-31]

Elucidating Humoral Mechanisms of Allergen Recognition

The recognition of allergens by IgE and the subsequent cross-linking of receptors are fundamental to the initiation of acute allergic responses. The glycosylation present in the constant region of the antibody is critical for IgE to activate its effector functions. Specifically, the existence of an oligomannose glycan at the N394 position in human IgE is essential for proper structural integrity and binding to the FcεRI receptor, which is necessary for triggering anaphylaxis. [32] Individuals with peanut allergies (PA) produce IgE antibodies that exhibit a higher content of sialylation compared to those without allergies, and this sialylation enhances the effectiveness of IgE-induced degranulation in vivo. [33, 34] Consequently, the sialylation of IgE may serve as an additional diagnostic marker for allergies. Glycosylation in other immunoglobulin isotypes, such as IgG, may also play a role in establishing atopic predispositions during early life. During a healthy pregnancy, antibodies featuring di-galactosylated glycans in the Fc domain are selectively transferred across the placenta, contributing to early innate immune responses by stimulating natural killer cell activity. [35] In

asthma contexts, pregnant mice experiencing exacerbations exhibited elevated levels of a pro-inflammatory glycosylation pattern, indicated by the lack of galactose and sialic acid end branches on the Fc region of IgG1. Maternal glycosylation profiles were correlated with patterns observed in offspring who later developed allergic asthma. [36] The significance of glycosylation in IgG functionality is underscored by distinct IgG Fc glycosylation patterns identified between healthy children and those with recurrent respiratory infections. [37]

A key factor influencing the capacity of IgE to provoke clinical reactions is its affinity. The process of affinity maturation in germinal centers is regulated by T-follicular helper (Tfh) cells, which facilitate the selection and proliferation of B cells. [38] The affinity of IgE may be particularly influenced by Tfh cells. A recently discovered IL-13-producing Tfh13 cell is necessary for the production of elevated IgE levels and subsequent allergen-induced anaphylaxis in murine models. Tfh13 cells exhibit a distinct cytokine profile (IL-13hiIL4hiIL-5hiIL-21lo), co-express transcription factors BCL6 and GATA3, and are found in greater abundance among PA individuals. [39] The characteristics of epitope recognition impact the severity of allergic reactions through the diversity and abundance of epitopes,40 their proximity, and their overlap with other isotypes (e.g., IgG4). [41, 42] Recent comparisons of linear epitopes from peanut allergens Ara h 1–11 between PA individuals and sensitized, nonallergic individuals revealed that seven peptides derived from the seed storage proteins Ara h 1, 2, and 3 were preferentially recognized by IgE from PA patients. Furthermore, the IgG4 ratio was elevated in peanut-sensitized nonallergics compared to PA individuals, indirectly indicating a functional role for IgG4 in the development of tolerance. [43] Notably, Ara h 2 sIgE is recognized for enhancing diagnostic accuracy, outperforming extract-based methods. [44-47] Machine-learning techniques applied during early life (ages 3–15 months) indicated that the IgE peanut epitope repertoire could predict the onset of PA by age 4.48 Bead-based assays employed in the context of egg allergy demonstrated that egg-allergic children had elevated levels of epitope-specific IgE and IgD, coupled with reduced IgA and IgG to Gal d 1 when compared to atopic controls.49, 50 Therefore, ongoing research focusing on both linear and conformational IgE epitopes across various isotypes could broaden the resources available for predicting the progression of atopic diseases and responses to therapeutic treatments. The production of local antibodies through reservoirs of IgE+ B cell lineages in the gastrointestinal tract (GIT) that undergo local class switching may play a significant role. Sequential biopsies from the upper GIT of patients with peanut allergy (PA) exhibited an increase in IgE+ B lineage cells within the mucosa, which correlated positively with systemic peanut-specific IgE levels. The B-cell clonal lineages identified in the biopsies included both IgE+ and non-IgE+ isotypes, indicating that class switch recombination may occur at a local level (51). Consequently, the GIT could serve as a critical reservoir for allergen-specific plasma cells that may later migrate to other tissues (51).

Unraveling the Complexity of the Cellular Network in Food Allergy

The innate immune system provides a rapid, nonspecific defense mechanism that acts as a precursor to the adaptive inflammatory allergic responses. Key effector cells in this context include basophils and mast cells, which release histamine and various preformed inflammatory mediators following exposure to allergens.

Basophils play a pivotal role in food allergy pathophysiology, as they produce substantial amounts of IL-4, which aids in recruiting and activating mast cells, as well as in the proliferation and isotype switching of B cells towards IgE antibody production (52). Basophils from allergic individuals demonstrated heightened sensitivity to IL-1β and IL-33 compared to those from healthy individuals (54). The alarmin IL-33, which triggers inflammation at mucosal and epithelial surfaces upon exposure to environmental stimuli, is a significant component of type 2 immune responses and serves as a potent activator of mast cells. A recent study identified the first human mutation in the IL-33 gene, revealing a complex phenotype characterized by immune dysregulation dominated by type 2 inflammation (55). Additionally, IL-33 and IgE-mediated activation of mast cells inhibited the conversion of naïve T cells into regulatory T cells (Tregs) in a murine coculture model (56). Similarly, a murine knockout of CD300f, an inhibitory receptor on mast cells, led to reduced Treg numbers and intensified allergic responses (57). These findings suggest that inhibiting IL-33 and IgE during oral immunotherapy (OIT) could be advantageous for diminishing allergic responses by downregulating mast cell activation (MAT) and fostering Treg generation (56). Correspondingly, a small clinical study indicated that a single dose of the anti-IL-33 biologic Etokimab increased the threshold for peanut reactions in allergic patients, as well as reduced allergen-specific type 2 cell frequencies and cytokine production (IL-4, -5, -9, and -13), along with peanut-specific IgE levels (58).

The role of mast cells in the development of allergic diseases can be traced back to early life. In rodent models, fetal mast cells can become sensitized by maternal allergen-specific IgE, displaying allergen sensitivity upon postnatal exposure (59). A human ex vivo placental perfusion model demonstrated that functional peanut allergen could be transferred across the placenta, although evidence of IgE transfer remained unsubstantiated even with omalizumab treatment, which suggests the possibility of IgG-mediated transport (60). These findings raise questions regarding their relevance to human physiology, as they challenge the notion that IgE is not transferred to the fetus (59, 60). Rare subsets of immune cells, such as innate lymphoid cells (ILCs), are concentrated at mucosal sites and play crucial roles in initiating and regulating allergic responses. ILC2s are capable of producing pro-allergenic cytokines, including IL-5, IL-4, IL-13, and IL-9 upon activation by alarmins (IL-33, IL-25, and TSLP). IL-13 produced by ILC2s contributes to the development of T follicular helper (Tfh) cells and the generation of allergen-specific IgE (61, 62). Recent research has acknowledged the regulatory function of ILC2 cells in controlling inflammation, though it remains unclear whether there exists a distinct group of regulatory ILCs (ILCregs) or merely a subset of ILC2s that secrete tolerogenic IL-10. ILCreg cells have been identified in human intestines and kidneys, where they suppress inflammation and inhibit ILC1/3 cell activation via IL-10 and TGF-β1 production (63, 64). Following allergen immunotherapy (AIT), the upregulation of IL-10+ ILC2 cells in allergic individuals suggests a role in promoting tolerance (65).

T and B cells serve as key components of the adaptive immune system, responsible for generating allergen-specific memory. The Generation R cohort study indicated that children with atopic diseases exhibited a higher proportion of Th2, Th17, Treg, memory Treg, and CD27+IgA+ memory B cells in comparison to nonatopic children, highlighting essential regulatory processes that may be

initiated during allergic disease (66). PA patients with decreased tolerance and heightened clinical sensitivity possess a larger, more diverse repertoire of allergen-specific CD4+ T cells compared to hyporeactive patients, which is enriched with Th2-skewed effector T cells that respond more robustly to allergen exposure (67). Moreover, highly reactive patients show an increased frequency of peanut-specific Th2a cells, characterized by the expression of CRTH2, CD161, and CD49d, alongside the co-secretion of type-2 cytokines (68). Th2a cells are implicated in the pathogenesis of atopic diseases and are significantly reduced in allergic patients undergoing AIT (68). The suppression of Th2a-like cells correlates with improved treatment outcomes following OIT (69). In a Phase 2 clinical trial (NCT02626611) of multi-food OIT protected by omalizumab, participants aged over ten demonstrated a significant decrease in both Th2a and Th17 cells, with alterations in DCreg markers STAB1 and FcγRIIIa (70). Therefore, monitoring the frequencies of Th2a and Th17 cells, along with DCreg markers, could provide additional biomarkers for assessing the success of OIT. Regulatory T cells (Tregs) are thought to be essential mediators of tolerance induction (71, 72). A lower proportion of naïve Tregs at birth and in cord blood has been identified as a predictor of food allergy (FA) development during infancy (73, 74). Various Treg subtypes are involved in tolerance, including FoxP3+ Tregs, TGF-β-secreting Th3 cells, and IL-10-secreting type 1 regulatory T (Tr1) cells. Notably, Tr1 cell populations were found to be significantly more abundant in younger (<6 years old), nonallergic children compared to food-allergic children, with these Tr1 cells exhibiting elevated levels of CCR6, a marker indicative of gut homing, suggesting a role in fostering local tolerance (75). Thus, adaptive immune cells not only play a vital role in the development of FA but also in the processes of desensitization and tolerance induction.

Lessons from Rodent Data on Food Allergy

Recent studies in murine models have uncovered novel mechanisms by which the microbiome can promote immune tolerance to food antigens or provoke allergic responses leading to anaphylaxis. Several investigators have conducted fecal microbiota transplants (FMT) from healthy or food-allergic children into germ-free mice. These studies revealed that germ-free mice colonized with bacteria from healthy infants, as opposed to those with cow's milk allergies, exhibited protection against anaphylactic reactions to milk allergens, which was correlated with distinct transcriptomic signatures in the ileal epithelium. Specifically, one clostridial species, Anaerostipes caccae, has been associated with protective effects against allergic responses to food (76). An independent study replicated these FMT findings and demonstrated that the transfer of an infant microbiota characterized by a low ratio of bifidobacteria to Lachnospiraceae directed the murine immune system toward a Th2 atopic profile, resulting in enhanced allergy symptoms in the recipient mice (77).

The metabolites secreted by the microbiome mediate numerous functional effects on intestinal immune cells. Recent investigations have highlighted the role of short-chain fatty acids (SCFAs) such as butyrate, propionate, and acetate, which have been shown to support the polarization and expansion of Tregs (78). Recent findings indicate that SCFAs activating G-protein-coupled receptors (GPCRs) work synergistically with cytokine receptor signaling to provide critical signals for

expanding tissue populations of ILC1, ILC2, and ILC3 (79). Notably, while propionate and butyrate inhibited IgE- and non-IgE-mediated mast cell degranulation, these effects were independent of SCFA receptor stimulation but were associated with the inhibition of histone deacetylases (80, 81). Furthermore, pretreatment of mice with butyrate significantly mitigated allergic responses in three different animal models of FA, which was associated with the induction of tolerogenic cytokines, suppression of Th2 cytokine production, and modulation of oxidative stress (82). GPR109A, a receptor for butyrate and niacin, has also been implicated in the maintenance of epithelial function and as a negative regulator of type 2 immune responses (83). Additionally, a variety of immunomodulatory metabolites derived from bacteria that activate GPCRs, the aryl hydrocarbon receptor, and nuclear receptors have been described and are currently under investigation in murine models of FA (84).

Murine studies have provided insights into the contribution of novel immune cell subsets to FA. Within the small intestine, ILC3s, which are the dominant source of IL-2, are crucial for maintaining Tregs and producing protective IgA responses in the gut (85). ILC3s facilitate immunoglobulin production by recruiting Tfh cells and supporting the differentiation of IgA-producing B cells, particularly in the context of oral tolerance. Their dysregulation can result in impaired Treg development and increased susceptibility to FA (86). Interestingly, the abundance of ILC3s has been linked to variations in microbial diversity and specific taxa within the gut microbiome (87). Understanding the multifaceted immune responses to food allergens is essential for developing targeted therapeutic strategies for managing food allergies. While innate immune mechanisms act as the first line of defense, the interplay between innate and adaptive immune cells is crucial for regulating allergic responses and tolerance. Elucidating the roles of specific immune cell types, cytokines, and the gut microbiome in food allergies provides valuable insights into potential therapeutic interventions, including oral immunotherapy and microbiome modulation. As our knowledge of these complex interactions continues to grow, innovative approaches to prevent and treat food allergies may emerge, offering hope for those affected by these increasingly prevalent conditions.

Mechanisms and Potential Biomarkers of Food Allergy Immunotherapy

Allergen immunotherapy (AIT) is the leading treatment for food allergies (FA), but challenges persist regarding safety, efficacy, and the induction of tolerance. Various administration methods, such as oral immunotherapy (OIT), sublingual immunotherapy (SLIT), and epicutaneous immunotherapy (EPIT), are being investigated. OIT is the most common, typically starting with subthreshold doses of allergens to promote desensitization. Initial immunological changes include reductions in allergen-induced basophil activity and increased production of specific IgE and TGF-β-producing CD4+ T cells. Successful desensitization is often accompanied by a decrease in Th2 cell activity and an increase in regulatory cells, although surrogates like sIgA may not reliably predict outcomes. SLIT uses significantly lower allergen doses to exploit local oral tolerance, with biomarkers such as salivary sIgA correlating with treatment success. EPIT involves allergen application through skin patches to stimulate immune responses, leading to regulatory T cell differentiation. Despite its tolerability, EPIT's efficacy remains

unclear. Ongoing research aims to clarify the tissue-specific effects of AIT and identify reliable biomarkers to assess treatment success across these diverse immunotherapy methods.

Conclusion

Food allergy (FA) represents a growing health concern, particularly as its prevalence continues to rise globally. This updated review illustrates that the interplay between the epithelial barrier and the immune system is pivotal in understanding the etiology of FA. The epithelial cells act as the frontline defense, and their dysfunction—exacerbated by genetic predispositions and environmental exposures—significantly contributes to the risk of developing FA. Disruptions in the barrier function lead to increased allergen exposure, which can initiate inappropriate immune responses. Recent studies highlight the potential of various therapeutic strategies, such as emollient application, to reinforce the skin barrier and reduce the severity of atopic dermatitis (AD), which is often linked with FA. Despite promising initial findings, large-scale randomized controlled trials, like the BEEP and PreventADALL trials, reveal that current strategies may not effectively prevent the onset of AD or FA in high-risk populations. Moreover, advances in immunology reveal complex mechanisms involving IgE glycosylation and T follicular helper (Tfh) cell function that modulate the immune response. The role of basophils and mast cells in the acute allergic response underscores the need for targeted therapies that can address these pathways. Recent insights into the contribution of innate lymphoid cells (ILCs) in promoting allergic inflammation further complicate the understanding of FA pathophysiology, presenting new avenues for research and therapeutic development. In conclusion, the dynamic relationship between the epithelial barrier, immune system, and environmental factors necessitates a multi-faceted approach to both understanding and managing food allergies. Continued investigation into novel biomarkers and therapeutic strategies will be crucial for improving outcomes for individuals affected by FA, thereby enhancing the quality of life for those at risk. The complexities of FA and its associated conditions demand further interdisciplinary collaboration to unravel the underlying mechanisms and develop effective interventions.

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الحساسية: مقالة مراجعة محدثة عن حساسية الطعام

الملخص:

الخلفية :تُعَدُّ حساسية الطعام (FA) قضية صحية عالمية مهمة، حيث يزداد الاعتراف بها كمسألة صحية رئيسية، مع استمرار الأبحاث التي تسلط الضوء على آلياتها وتطورها. تُبرز هذه المراجعة المحدثة النتائج الأخيرة، وخاصةً فيما يتعلق بالعلامات الحيوية المرتبطة بتطوير التسامح والتحسس.

الهدف :الهدف الرئيسي من هذه المقالة هو تجميع التقدم الحالي في فهم حساسية الطعام، مع التركيز على دور وظيفة الحاجز الظهاري وآليات الاستجابة المناعية والاستراتيجيات العلاجية المحتملة.

الطرق :تقوم هذه المراجعة بتلخيص النتائج من الدراسات الحديثة المتعلقة بفيزيولوجيا مرض حساسية الطعام، مع فحص التفاعل بين الحاجز الظهاري والاستجابات المناعية والتدخلات المحتملة، بما في ذلك العلاج المرطب والعلاج المناعي.

النتائج :تُعَدُّ سلامة الحاجز الظهاري ضرورية للتسامح المناعي تجاه المواد المسببة للحساسية. تؤدي الانقطاعات الناتجة عن الطفرات الجينية أو العوامل البيئية إلى زيادة القابلية لحساسية الطعام. أظهرت التدخلات الحالية، بما في ذلك استخدام المرطبات والتعديلات الغذائية، نتائج متباينة في منع مظاهر الحساسية. بالإضافة إلى ذلك، تساهم الرؤى الجديدة حول الاستجابات المناعية، خاصةً المتعلقة بجلايكوزيلاسيون IgE وديناميات خلايا المساعدة الجريبيةT ، في فهمنا لآليات الحساسية.

الخلاصة :يُعَدُّ الحفاظ على حاجز ظهاري صحي وفهم التفاعلات المعقدة للجهاز المناعي أمرًا حيويًا لتطوير استراتيجيات فعالة للوقاية والعلاج من حساسية الطعام. من الضروري إجراء أبحاث مستمرة لتوضيح الآليات الدقيقة التي تكمن وراء تحسس المواد المسببة للحساسية وتطوير التسامح.

الكلمات المفتاحية :حساسية الطعام، الحاجز الظهاري، الاستجابة المناعية، التحسس، التسامح، العلامات الحيوية.