edra REVIEW | Eur Ann Allergy Clin Immunol | Vol 57, N.4, 147-153, 2025

Riccardo Asero[1], Valerio Pravettoni[2], Danilo Villalta[3], Enrico Scala[4]

Is gastrointestinal epithelial barrier dysfunction the only responsible for sensitization to food allergens?

[1]Allergology Clinic, Clinica San Carlo, Paderno Dugnano, Milan, Italy
[2]Department of Internal Medicine, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy
[3]Immunology and Allergy Unit, S. Maria degli Angeli Hospital, Pordenone, Italy
[4]Clinical and Laboratory Molecular Allergy Unit, IDI-IRCCS, Rome, Italy

Key words

Epithelial barrier; epithelial damage; food allergy; allergen sensitization; immune tolerance.

Corresponding author
Riccardo Asero
Allergology Clinic
Clinica San Carlo
via Ospedale 21
20037 Paderno Dugnano, Milan, Italy
ORCID: 0000-0002-8277-1700
E-mail: r.asero@libero.it

Doi
10.23822/EurAnnACI.1764-1489.378

Impact statement

Evidence is accumulating that sensitization to food allergens occurs outside the intestinal tract in most instances, as if the first contact is with the intestinal it results in immune tolerance.

Summary

Epithelial barriers are crucial defenses against pathogens and allergens, and recent theories suggest that environmental factors may compromise them, leading to type 2 inflammation and conditions such as asthma, atopic dermatitis, food allergy, and rhinitis. While skin and respiratory barriers show clear dysfunctions in allergies, the role of the gut epithelium is less defined, particularly given its ability to absorb nutrients and maintain immune tolerance under normal conditions.

Research indicates that gastrointestinal barrier integrity typically remains preserved in food allergies, allowing for the development of immune tolerance to ingested food antigens through mechanisms like Treg cells and IgA. Allergies to cow's milk or hen's egg proteins often resolve with age, highlighting the gut's evolving role in allergen sensitization.

Studies like the LEAP (Learning Early About Peanut Allergy) trial demonstrate the preventive benefits of early allergen exposure against peanut allergy, supporting the dual allergen exposure hypothesis. New allergens such as alpha-Gal and gibberellin-regulated proteins (GRP) reveal distinct sensitization pathways beyond traditional ingestion routes, implicating non-dietary sources in allergen introduction.

Introduction

Epithelia constitute the primary defensive barrier against pathogens, pollutants, and allergens. There is an increasing consensus that the dysfunction of epithelial barriers may initiate the development of type 2 inflammation and, consequently, allergic diseases such as asthma, atopic dermatitis, food allergy, and rhinitis. This concept, first proposed in 2017 (1), and subsequently revisited and expanded by Akdis in 2021 (2), posits that, in the presence of a genetic predisposition, mucosal damage induced by environmental factors, including agents associated with industrialization, urbanization, and modern life, may explain the rise in allergic, autoimmune, and other chronic diseases. Indeed, epithelial barrier dysfunctions associated with type 2 inflammatory responses have been extensively documented in asthma, chronic rhinosinusitis with nasal polyposis (CRSwNP), atopic dermatitis (AD), and eosinophilic esophagitis (EoE) in both children (3) and adults (4-6). For these conditions, biologics targeting IgE, IL-5, or IL-4 and IL-13 receptors are widely used with excellent results. Unlike other epithelial barriers (*e.g.*, skin, respiratory tract, and esophagus), the gastrointestinal tract epithelium possesses unique features that may play a protective role against allergies

and should be considered when investigating the processes leading to sensitization to food allergens. First, the intestinal epithelium is naturally structured to absorb nutrients, and it has been known for many years that, under normal conditions, about 2% of food proteins are absorbed and systemically distributed in an immunologically active form (7). Second, there is a lack of consistent evidence that gastrointestinal epithelial barrier function is impaired in food allergy in humans (8). Finally, under normal conditions, the contact between food allergens and the immune system following intestinal absorption leads to specific immune tolerance mediated by antigen-specific Treg cells, IgA, and T clonal anergy (9, 10).

In effect, hypersensitivity to cow's milk or hen's egg proteins, which is extremely common in infancy and early childhood and generally attributed to gut immaturity, is outgrown in most instances later in childhood (11, 12), persisting into adolescence or adulthood only in a minority of cases. Furthermore, *de novo* sensitization to cow's milk or hen's egg proteins in adulthood is exceptionally rare, and adult allergic individuals encountered in clinical practice have typically been allergic to these foods since childhood, with the exception of sensitization to hen's egg alpha livetin allergen, present in feathers and excrements of domestic birds (parrots or canaries), which occurs via the respiratory tract. In animal models of food allergy or asthma, mice (most commonly BALB/c) are sensitized to ovalbumin or other allergens by epicutaneous, subcutaneous, or intraperitoneal (rarely respiratory) administration of the allergens. Once sensitized, they are challenged orally or via the respiratory tract (13-17). This is because the initial sensitization via the oral route would be very difficult to achieve in the absence of adjuvants.

The idea that food allergy/sensitization may originate outside the gut, at least in adults, was suggested thirteen years ago in an article reviewing a large series of case reports and case series on sensitization to foods via the skin or respiratory tract (18). Since then, several novel types of food allergies have been described, and we have witnessed enormous progress in understanding the patho-mechanisms of sensitization to foods and other allergens. This article will critically review some of these newly described food allergies, focusing particularly on the routes of sensitization to the corresponding allergens.

Materials and methods

A PubMed search covering the last thirteen years of published scientific papers was conducted to identify novel types of food allergies and to verify whether the most recent findings in this field could support our previous hypotheses (18). The newly described food allergens in the literature were categorized by models and discussed individually, with particular emphasis on the possible modes of sensitization, since in many cases sensitization via the gut appeared highly unlikely.

Food allergy models

The LEAP study

One of the most intriguing models of food allergy development in children has been the LEAP (Learning Early About Peanut Allergy) Study. The authors of this study observed that peanut allergy developed more frequently in Jewish children living in the UK who strictly avoided peanuts compared to Jewish children from Israel who were early introduced to peanuts (19). Building on this observation, the same group conducted randomized studies on peanut consumption in infancy (20), concluding that the early introduction of peanuts significantly decreased the frequency of peanut allergy development among high-risk children and modulated immune responses to peanuts. The same group later demonstrated that the tolerance induced by oral ingestion is allergen-specific, does not prevent the development of other food allergies (21), and is long-lasting (22). Skin protein deficiencies increase the severity of eczema and risk of food allergy to peanuts (23, 24).

These findings fully confirmed the dual allergen exposure hypothesis proposed in 2008 (19), which suggested that primary exposure through the skin and/or airways leads to sensitization, whereas exposure through the gut leads to tolerance. This study has eventually led to a complete paradigm shift in clinical practice regarding food avoidance in high-risk children.

Galactose-alpha-1,3-Galactose (alpha-Gal)

The observation in 2007 of anaphylactic reactions upon the first administration of Cetuximab occurring exclusively on a regional basis (25), and of the development of delayed IgE-mediated anaphylactic reactions following the ingestion of red meat in the same areas, led to the identification of a common allergen: the oligosaccharide galactose-alpha-1,3-galactose (alpha-Gal) (26). Sensitization to this novel allergen was eventually found to follow the bite of different ticks, such as the lone star tick in the US (27), *Ixodes ricinus* in Europe (28), *Amblyomma sculptum* in South America (29), and *Haemaphysalis longicornis* in Japan (30), which inject this non-primate mammalian oligosaccharide into the human host. Alpha-Gal allergy, therefore, represents a typical example of extra-intestinal sensitization to a food allergen.

Gibberellin-Regulated Proteins (GRP)

In recent years, severe allergic reactions to peach and other plant-derived foods have been observed in specific regions of the world, particularly Japan, Southern France, and Italy, in individuals not sensitized to the well-known allergens PR-10, profilin, or lipid transfer protein. The pan-allergen responsible for these allergic reactions was eventually identified as gibberellin-regulated protein (GRP). Cross-inhibition studies indicated that the primary sensitizer is cypmaclein, a minor allergen in cypress pollen (31-34). Thus, GRP allergy represents a novel type of pollen-food syndrome.

Plant defensins

Defensins are another example of primary sensitization to molecules found in pollens (in this case, Asteraceae, specifically Art v 1 in Artemisia and Amb a 4 in Ambrosia), with cross-reactivity to homologous molecules in plant foods (such as Ara h 12 and Ara h 13 in peanut, or Api g 7 in celery), long recognized as the "Mugwort-Celery-Spice Syndrome" (35, 36). Defensins are small peptides of approximately 5 kDa in weight, rich in cysteine and therefore highly resistant to proteolytic digestion, temperature, and pH. Sensitization to plant defensins is predominantly observed in Northern Europe (0.45%) and accounts for about 6% of food-induced anaphylaxis cases in Europe linked to consumption of celery, coriander seed, fennel, cumin seeds, anise seed, *etc*. (37). The phenomenon of defensins is yet another example of food reaction triggered by sensitization to aeroallergens.

Mint pollinosis and anaphylaxis

Interesting is the case of a man who, after starting to cultivate mint plants in his backyard. developed nasal congestion, cough and wheeze while gardening during the pollen season of mint. He experienced an anaphylactic reaction within five minutes of eating a peppermint candy (38). Other systemic reactions are reported in the literature after the assumption of products containing mint (39-41).

Shrimp allergy

House dust mites (HDM) and crustaceans, as well as mollusks and other invertebrates, share many allergens in a complex interaction (42). Shrimp is the second cause of food allergy in Italy (43). It is not yet fully clear whether shrimp allergy originates as a primary phenomenon or because of airborne house dust mite allergy, as cross-inhibition studies between shrimp and mites have not been conducted thus far. However, in a study on a large group of HDM-allergic subjects, about 20% were sensitized to crustaceans, and 41% of these had never eaten crustaceans before (44). Two studies on shellfish allergies highlight occupational risks and clinical features. In a pilot study of Greenlandic snow crab workers, 40% showed positive skin prick tests for snow crab and 21% had specific IgE antibodies. Asthma symptoms were common (45%), and 11-22% of workers had probable or possible occupational asthma (45). Meanwhile, a study on shellfish hypersensitivity in 48 patients found that shrimp and squid were the most frequent allergens, causing urticaria/angioedema (81%), asthma (38%), and rhinitis (29%). Prick tests yielded better diagnostic results than CAP, with significant associations between clinical history and test results for crustaceans and cephalopods (46).

Edible insects

Edible insects are considered novel food in the European Union, as they were not consumed by humans in the EU before 1997 (47). Recently, our research group conducted a comprehensive survey involving over 2000 participants who had never previously consumed insect proteins, as these were not available in the Italian market until 2023 (48). Surprisingly, just under 10% of the study population showed sensitization to *Tenebrio molitor, Acheta domesticus, or Locusta migratoria,* despite never having consumed these protein sources before. This represents another clear example of sensitization not induced by ingestion of the culprit food, barring inadvertent exposure, which is plausible but objectively unproven.

Fish allergy

Fish allergy is particularly common in areas with a high supply of fish. A recent study demonstrated that fish allergy is often present in early childhood, with 95% of fish-allergic children also having atopic dermatitis (49). This significant proportion was corroborated by another study on fish allergy in children, which importantly observed that the median age at the first reaction was 12 months, with most children reacting upon their first exposure (50). Jellyfish is another marine animal which can sensitize humans through skin contact. Sensitization can then lead to anaphylaxis when the jellyfish is ingested cooked (a typical food of the oriental world) (51) as reported by several case reports (52, 53).

Anisakis allergy

Anisakiasis is a fish-borne parasitic disease caused by consuming raw or undercooked fish or cephalopods contaminated by third-stage larvae of Anisakis simplex or other members of this nematode family. The live larvae can elicit a parasitic infection of the digestive tract or, occasionally, other organs, causing erosive and/or hemorrhagic lesions, ascites, perforations, and allergic reactions such as anaphylaxis, acute/chronic urticaria, and angioedema (54). There is a consensus that an active infection is required to initiate allergic sensitivity to Anisakis. In other words, the immune system comes into direct contact with the Anisakis allergen only after the parasite causes mucosal damage. In effect, already in 2000 Purello D'ambrosio and co-workers noted that in a population of fishermen/fishmongers, Anisakis hypersensitivity had caused urticaria/angioedema episodes in 72% of cases and respiratory symptoms in 28% of cases (55).

The prevalence of sensitization to Anisakis was found to be higher than that to fish, with rates of 8% and 6%, respectively. Reactivity to Anisakis-specific IgE was linked to bronchial hyperreactivity and dermatitis and showed a significant increase in correlation with fish consumption. Sensitization to Anisakis is associated with cutaneous symptoms (OR 1.9), whereas sensitization to fish is correlated with rhinoconjunctivitis (OR 2.7) (56).

Cereals

There have been reports, particularly from Japan, indicating that the use of wheat-germ cosmetics, such as soaps and face scrubs, has frequently led to sensitization to wheat (57, 58). This serves

as a clear example of percutaneous sensitization to food allergens in adults. Furthermore, severe allergic reactions, including anaphylaxis, have been documented in individuals allergic to house dust mites who suffer from rhinitis and/or asthma after ingesting cereals contaminated by mites (59).

Lipid transfer protein

Lipid transfer protein and its possible ways of sensitization have been extensively reviewed in our previous paper (18). In recent years an unusual way of sensitization to this allergen has been reported via Cannabis smoke (Can s 3 is the primary sensitizing LTP in these cases) (60, 61). Albeit not always clinically expressed, this is one further example of sensitization to a food allergen through the skin and/or the respiratory tract.

α-Livetin and the Bird-egg syndrome

Gal d 5 (α-Livetin), an allergen present in egg yolk, plays a crucial role in the phenomenon known as Bird-egg syndrome. This allergen is also prevalent in the serum, feathers, meat, and excrement of birds, making it a common environmental allergen in places where birds such as parrots, pigeons, or canaries are found or bred. In adults, sensitization generally occurs initially through inhalation, leading to conditions such as asthma or rhinoconjunctivitis, and is subsequently followed by the development of an egg allergy (62).

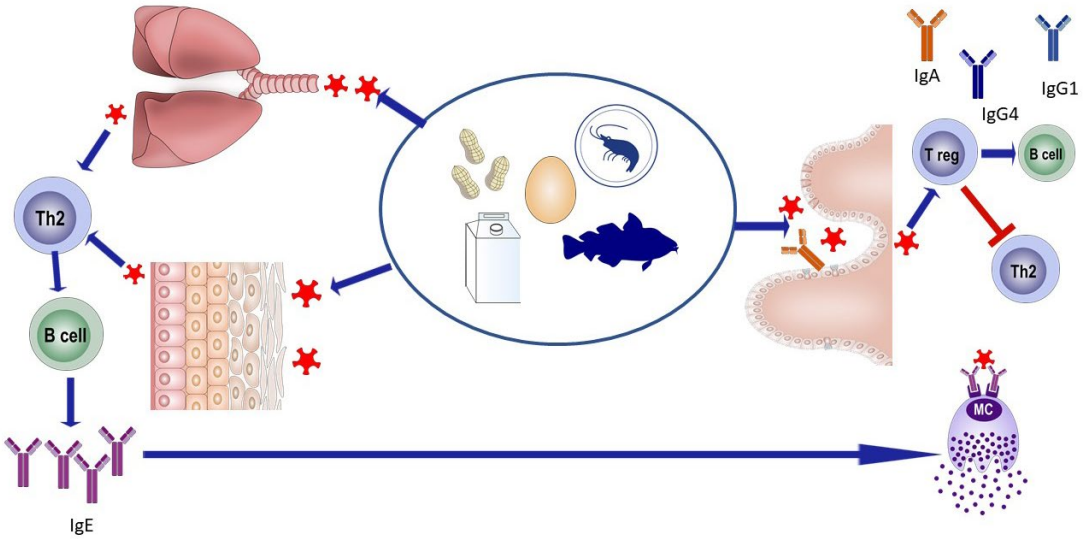
Donkey milk lysozyme allergy

Lysozyme in donkey's and horse's milk, which is suggested as a theoretically safe alternative food in cow's milk allergic children, has been identified as a potentially relevant food allergen. Interestingly, in a recent report the two patients described and thoroughly investigated got most probably sensitized through the skin by using donkey milk-based cosmetics (63).

Conclusions

Significant advancements have been achieved in understanding the development and maintenance of oral tolerance (64, 65), elucidating key mechanisms by which the immune system can discriminate between harmless food antigens and harmful pathogens. However, while the defective epithelial barrier theory is robustly supported for the skin and respiratory tract, its applicability to the gut epithelium remains less conclusive. The gut epithelium's role in food allergy pathogenesis is nuanced, with evidence suggesting that under normal conditions, allergen exposure through the oral route predominantly induces tolerance rather than sensitization (64, 65). Albeit the postulate of gastrointestinal sensitization to food allergens remains, an increasing number of studies consistently highlight that primary sensitization to food allergens often occurs via routes other than the intestinal tract, such as the skin or respiratory mucosa (**figure 1**). This phenomenon challenges traditional paradigms and underscores the complexity of allergen sensitiza-

Figure 1 *- The primary exposure of food allergens via the digestive tract leads to anergy or to the production of specific IgG1, IgG4 and/or IgA. Exposure of the immune system to food allergens via the airways or via damaged skin (in atopic dermatitis patients) leads to Th2-mediated inflammation and eventually to the production of specific IgE antibodies that spread throughout the body. The subsequent ingestion of the same food allergens causes potentially severe allergic reactions.*



tion pathways. The LEAP study exemplifies how early and controlled exposure to allergens can prevent the development of allergies, supporting the dual allergen exposure hypothesis. Conversely, novel allergens like alpha-Gal and gibberellin-regulated proteins (GRP) illustrate instances where sensitization occurs via unconventional routes, such as tick bites or exposure to plant-derived allergens, further expanding our understanding of allergic sensitization mechanisms. A recent systematic review and meta-analysis comparing the prevalence estimates of the eight big food allergies in Europe during the last decade and the previous period concluded that, with some exceptions, the prevalence of allergy/sensitization to cow's milk, egg, wheat, soy, peanut, tree nuts, fish and shellfish had not substantially changed. However, it also noted that more foods beyond the "big eight" have been studied recently, and thus that the balance between the "big eight" and emerging food allergies is probably changing in Europe (66). In clinical practice, these insights require tailored approaches to diagnose and manage food allergies effectively. Better care of atopic dermatitis may contribute to prevent sensitization to food allergens. Future researches should continue to explore the interplay between epithelial barrier function, immune tolerance, and environmental factors to refine strategies for allergy prevention and treatment, aiming to improve outcomes for individuals affected by food allergies globally.

Fundings

None.

Contributions

RA: conceptualization. RA, VP, DV, ES: methodology, supervision, writing – original draft, writing – review & editing.

Conflict of interests

The authors declare that they have no conflict of interests.

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