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Mechanisms and Environmental Determinants of Food Allergies: An Integrative Review

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Abstract
IgE-mediated food allergy is a growing global health concern characterized by a dysregulated immune response to dietary proteins, causing symptoms from urticaria to anaphylaxis. This review critically examines current evidence on the immunopathology, diagnosis, and management of IgE-mediated food allergy, aiming to identify gaps and priorities for future research. A comprehensive search of PubMed, Scopus, and Web of Science was performed up to April 2025 using terms related to food allergy, including pathophysiology, epidemiology, diagnosis, and treatment. English-language original and review articles were selected to provide a broad overview, and data were synthesized narratively to summarize key findings and emerging trends globally. Prevalence has surged over the past two decades, affecting up to 10% of populations in Western nations, with rising cases in non-Western regions linked to urbanization and dietary changes. The pathophysiology involves failure of oral tolerance, TH2 polarization, and IgE-mediated activation of mast cells and basophils, which upon re-exposure, release histamine, leukotrienes, and cytokines, driving acute inflammation. Key allergens include peanuts, milk, eggs, and shellfish, with proteins like Ara h 2 (peanut) and tropomyosin (shellfish) resisting digestion, enhancing immunogenicity. Contributing factors encompass genetic predisposition, epithelial barrier defects (e.g., filaggrin mutations in atopic dermatitis), and altered gut microbiota, which disrupt regulatory T-cell (Treg) function critical for immune tolerance. Current management relies on allergen avoidance and emergency epinephrine, while adjunct therapies like antihistamines and corticosteroids address mild symptoms. Despite advances, diagnostic challenges persist, particularly in resource-limited settings, compounded by misdiagnosis and inadequate access to care. Emerging research highlights microbiota modulation, epicutaneous immunotherapy, and Treg induction as promising strategies to restore tolerance. Future directions emphasize the need for biomarkers, precision therapies, and elucidating interactions between genetic, environmental, and immunological drivers to mitigate the global burden of food allergy.

Keywords: IgE (Immunoglobulin E), Mast cells, Allergen, Basophils, T-helper cells, Oral tolerance.

Introduction
IgE-mediated food hypersensitivity (food allergy) is a rapidly expanding global malady resulting from an oral tolerance failure, where the immune system exhibits an exaggerated response to harmless dietary proteins (Suresh et al., 2021). Such immune hypersensitivity, which is mainly mediated by immunoglobulin E (IgE), can trigger rapid and sometimes severe response after repeated susceptibility to the allergen. For the last twenty years, the incidence of IgE-mediated food allergy has significantly risen, particularly in children together with adolescents within Western cultures. It now affects as much as 10% of the global populace (Nwaru et al., 2014; Sicherer and Sampson, 2018). In non-Western parts like Africa, Asia, and Latin America, experience endemic underdiagnosis. However, Western diets and the application of food additives led to an upsurge of food allergy cases in Nigeria (Ayodele and Arinola, 2016). However, low public awareness and widespread misinterpretation of symptoms as infections or malnutrition, and restricted access to allergy specialists, diagnostic facilities, and emergency care, all delay accurate diagnosis and management (Rutkowski et al., 2019). Urbanization and changes in lifestyle also result in shifts in

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immune tolerance by reduced exposure to microbes and environmental alterations (Fiocchi et al., 2016; Nicolaou et al., 2015). Dietary allergies must be distinct from non-immune-mediated dietary intolerances, including those due to enzyme deficiency or due to toxic reactions. It is often a misdiagnosis, with more than 20% of individuals unnecessarily altering their diet based on suspected allergy (Gupta et al., 2018; Sampson, 2004). Despite progress in understanding the basic immunologic mechanisms, therapy remains mere allergen avoidance and symptomatic treatment of the acute allergic process. The ongoing risk of catastrophic reactions, such as anaphylaxis, highlights the need for more robust prevention and therapy (Bindslev-Jensen et al., 2004; Sicherer and Sampson, 2018). The pathogenesis involves a complex combination of environmental, immunological, and genetic variables. Sensitisation occurs before IgE formation, and exposure activates mast cells and basophils, releasing mediators like histamine, leading to allergic manifestations (Sicherer et al., 2010; Suresh et al., 2021). This review critically examines current evidence on the immunopathology, diagnosis, and management of IgE-mediated food allergy, aiming to identify gaps and priorities for future research.

Search Strategy

A comprehensive search of PubMed, Scopus, and Web of Science was performed up to April 2025 using terms related to food allergy, including pathophysiology, epidemiology, diagnosis, and treatment. English-language original and review articles were selected to provide a broad overview, and data were synthesized narratively to summarize key findings and emerging trends globally.

Overview of Food Allergy

An adverse reaction that ensues when a person eats, comes into contact with, or inhales a food protein, also referred to as an allergen, is called a food allergy. The immune system produces immunoglobulin E (IgE), a kind of antibody, in response to an allergen. IgE is replicated; these copies go through the circulation and bind to the immune system's mast cells and basophils. According to recent cohort studies, the number of food allergy cases in Africa has significantly increased (Sicherer et al., 2010; Obeng et al., 2018). The rise in allergies can be attributed to urbanisation, dietary changes, and increased knowledge and reporting (Botha et al., 2019). Detailed birth group investigations, using precise sampling methods and explicit end measures, show that the increase is not solely due to self-diagnoses or improved awareness of the condition. Asthma, allergic rhinitis, and atopic dermatitis (AD) show similar trends, indicating an increasing prevalence of these disorders. A variety of foods can cause food allergies; however, Health Canada has identified ten common allergens: peanut, eggs, Cow’s milk (CM), shellfish and fish, tree nuts, wheat, sesame, and soy (Health Canada, 2018). The inherent progression of IgE-mediated food sensitivity is determined by the specific allergen. CM along with egg allergies often manifest at early infancy. This is due to the underdeveloped immunological network, which usually targets any food protein (allergen) as a threat. Some children grow out of childhood-onset allergies, while tolerance in others may not emerge till adolescence. An illustration indicating reaction to allergy mediated by IgE is presented in Fig. 1.

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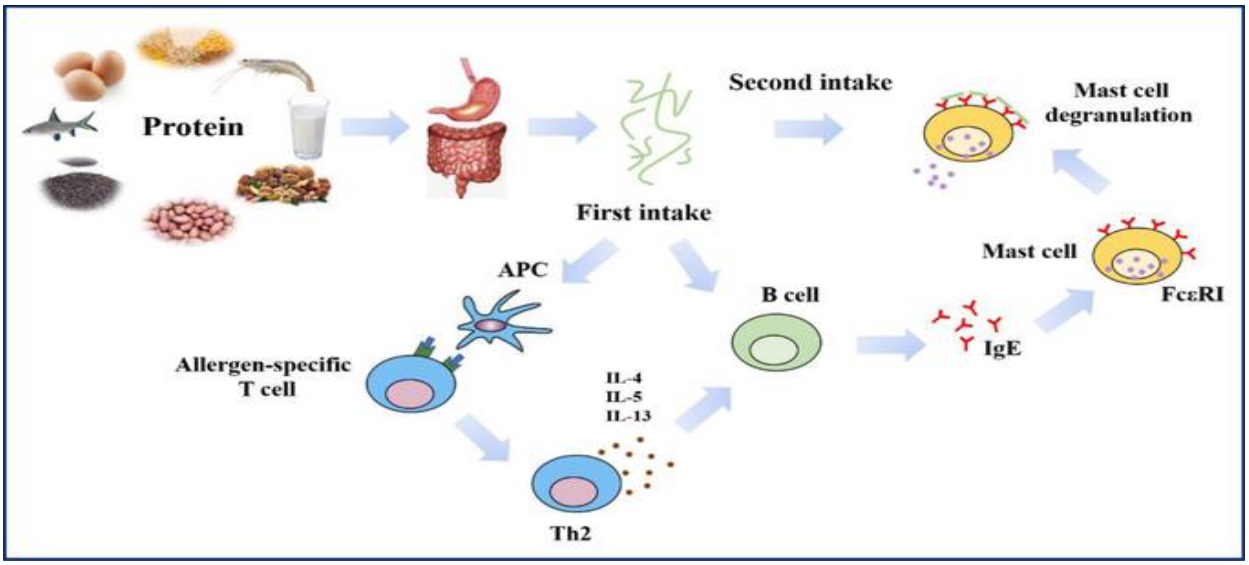

Figure 1: Representation of a reaction to allergy mediated by IgE (Sun et al., 2022)

Allergy Prevalence and Characteristics in Nigeria

Although rigorous food allergy testing remains limited and underutilized in low-resource settings like Nigeria, the following data as shown in Table 1 summarizes the available allergen-specific tests and their characteristics:

Table 1: Allergy Prevalence and Characteristics (Hossny et al., 2019)

Allergen	Prevalence rate	Major Allergenic Protein	Allergenic Characteristics
Egg (White)	2.3% of egg white group: 1019 patients with atopic dermatitis Self report.	Ovalbumin(G d 2)(heat-labile), Ovomucoid(Gd 1) (heat-stable)	Ovalbumin easily denatures at temperatures above 70°C and is quickly broken down by pepsin. It mostly contains conformational IgE epitopes, which makes it more significant in raw or lightly cooked eggs and less so in baked products. Whereas ovomucoid is heat-stable and has resistance to pepsin, potent IgE binding is possible due to linear/stable epitopes: the main trigger is well-heated or baked eggs.
Cereals and legumes (Peanuts, soy, bailey)	Cereals & legumes group: 11.4% sensitivities/self-reported food allergies; **peanut** not separated explicitly.	Ara h1, Ara h2 and Ara h3 (Arachis hypogaea 1,2 & 3 – especially 2 as the dominant component).	Ara h 2/6 maintain IgE-binding capacity even after roasting or boiling due to internal disulfide-rich.structure also, Ara h 2/6–derived peptides retain allergenicity in gastric conditions; intact and digested forms still cause mediator release.
Seafood	14% seafood group: General population (972 children and adults) Self report.	Tropomyosin	Tropomyosin remains structurally intact even after boiling or frying, and it also has strong resistance to digestive enzymes; denaturation does not abolish IgE reactivity.

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Cow's Milk	2.5% 1019 patients with atopic dermatitis Self report.	Casein (heat-stable) and Whey (heat-labile).	Casein which is highly heat-stable, IgE-binding persists even after pasteurisation or baking (e.g. remains intact up to 120 °C) and digestion-resistant peptides survive gastric enzymes, so reactions persist in curdled, baked or solid dairy products where as whey is heat-labile and begins to denature around 65–70 °C, losing conformational epitopes becoming more susceptible to pepsin digestion, thus IgE reactivity often declines with cooking or high-heat processing.

Common Food Allergy Triggers and Their Mechanism

1. Peanut Allergy Mechanism

The proteins in peanuts, particularly Ara h 1, Ara h 2, and Ara h 3, are notable for their stability and resistance to digestion (Shah et al., 2019). These storage proteins, crucial in peanut allergic reactions, maintain their structure even when exposed to heat during cooking methods like roasting. Roasting can even enhance their allergenicity by altering their protein structure, making them more recognizable to the immune system. This resistance to digestive enzymes, like pepsin, is due to their robust three-dimensional structure. As a result, these proteins remain immunologically active as they traverse the digestive tract and reach the gut lining (Sampson, 2001).

The allergic process then unfolds in stages. First, the peanut proteins are absorbed through the intestinal epithelium. Here, antigen-presenting cells (APCs), specifically dendritic cells, recognize and engulf the proteins. These APCs then process the proteins and present fragments (epitopes) via MHC class II molecules to naive CD4+ T-helper cells. In individuals predisposed to allergies, this interaction drives a TH2-dominated immune response, a hallmark of allergic reactions. These triggered TH2 cells release cytokines, comprising Interleukin-13 (IL-13) and Interleukin-4 (IL-4). IL-4 promotes the switch of B cells to produce allergen-specific IgE antibodies. IL-13 enhances IgE production and contributes to allergic inflammation (López-Torrejón et al., 2003; Shah et al., 2019).

B cells specifically produce IgE antibodies that target these peanut proteins (Ara h 1, Ara h 2, Ara h 3). These IgE antibodies then bind to high-affinity FcεRI receptors on mast cells and basophils, a process known as mast cell priming (López-Torrejón et al., 2003). This essentially arms these cells, preparing them to react when exposed to allergen.

The effector phase occurs upon subsequent ingestion of peanuts. When proteins in peanut (Ara h 1, Ara h 2, or Ara h 3) cross-link the IgE antibodies already bound to mast cells and basophils, it triggers degranulation (Bublin et al., 2013). This results in the release of a cocktail of stored inflammatory mediators. Histamine causes increased vascular permeability, vasodilation, edema, increased vascular permeability, and smooth muscle contraction, with resultant symptoms like wheezing and diarrhea. Leukotrienes and prostaglandins amplify inflammation and bronchoconstriction (Bublin et al., 2013). Cytokines further boost the immune response and attract more immune cells to the affected area. Ara h 1, a vicilin protein, is a major sensitizer due to its stability and high immunogenicity. Ara h 2, a conglutin protein, is a potent elicitor of allergic reactions. Ara h 3, a glycinin protein, contributes to cross-reactivity and overall immune activation (López-Torrejón et al., 2003; Bublin et al., 2013).

2. Milk Allergy Mechanism

Similar to peanut allergies, milk allergies are often triggered by the stability and resistance to digestion of key milk proteins, particularly casein and whey. Casein, a phosphoprotein constituting approximately 80% of milk proteins, forms micelles that enhance its stability and resistance to enzymatic breakdown in the gastrointestinal tract (Kiewiet et al., 2015). Whey proteins, including beta-lactoglobulin and alpha-lactalbumin, also possess a compact structure that confers resistance to digestion. Beta-lactoglobulin, in particular, is known for its high allergenicity (Fiocchi et al., 2019).

The sensitization phase mirrors that of peanut allergies. The resistance of casein and whey proteins allows intact allergenic fragments to reach the intestinal epithelium, enhancing their immunogenicity (Pali-Schöll et al., 2018).

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Antigen-presenting cells (APCs), such as dendritic cells in the gut lining, capture these proteins. These APCs then present allergenic peptides to naive CD4+ T-helper cells via MHC class II molecules, activating a TH2-dominated immune response (Kiewiet et al., 2015).. Like peanut allergies, milk allergies are characterized by this TH2 response, driven by the release of cytokines such as Interleukin-4 (IL-4) and Interleukin-13 (IL-13). Interleukin-4 (IL-4) causes B lymphocytes to flip classes and produce IgE antibodies against casein and whey proteins (Kiewiet et al., 2015). IL-13 increases IgE production and modulates allergic inflammation. B cells then produce allergen-specific IgE that targets casein and whey proteins, which then bind to FcεRI receptors on mast cells and basophils, priming these cells for a future allergic reaction (Fiocchi et al., 2019).

The effector phase is elicited by re-exposure to the allergen. The consumption of milk containing intact casein or whey proteins can cross-link the IgE antibodies bound to mast cells. This leads to mast cell degranulation, causing the release of inflammatory mediators. Leukotrienes and prostaglandins sustain inflammation and contribute to respiratory and gastrointestinal symptoms. Cytokines recruit additional immune cells, further amplifying the allergic response (Nicolaou et al., 2022; Shingankar et al., 2023).

3. Ovalbumin and Ovomucoid Allergy Mechanism

Egg and shellfish allergies are triggered by specific proteins within these foods that elicit an immune response. In egg allergies, ovalbumin and ovomucoid are key players. Ovalbumin, constituting approximately 54% of egg white protein, is heat-labile, but retains some allergenic potential even after cooking, according to Giuseppe and Manti (2024). Ovomucoid, while only about 11% of egg white protein, is regarded as a major allergen due to its remarkable resistance to heat and enzymatic digestion (Giuseppe and Manti, 2024). This stability allows these proteins to remain intact during food preparation and digestion, increasing the likelihood that they will trigger an immune response.

The allergic reaction unfolds in two phases: sensitization and effector. During sensitization, intact ovalbumin and ovomucoid are absorbed in the gut and presented to the immune system by antigen-presenting cells (APCs). In individuals predisposed to allergies, APCs present these proteins to naive CD4+ T-helper cells, causing them to differentiate into TH2 cells (Benedé et al., 2015). Activated TH2 cells then release cytokines, notably IL-4 and IL-13, which promote IgE class switching in B cells, leading to the production of allergen-specific IgE antibodies (Giuseppe and Manti, 2024). These IgE antibodies bind to FcεRI receptors on mast cells and basophils, effectively priming these cells to react to egg proteins.

The effector phase occurs upon re-exposure to egg proteins. When ovalbumin or ovomucoid cross-links with the IgE antibodies on sensitized mast cells, it triggers degranulation, releasing a cascade of inflammatory mediators. Histamine causes itching, swelling, and vasodilation. Leukotrienes and prostaglandins contribute to prolonged inflammation, smooth muscle contraction, and respiratory symptoms while cytokines amplify the allergic response by recruiting other immune cells (Giuseppe and Manti, 2024).

4. Tropomyosin Allergy Mechanism

Shellfish allergies are frequently caused by tropomyosin, a heat-resistant protein abundant in shellfish like shrimp, crab, and lobster. Faber et al. (2017) highlighted that tropomyosin's resilience to heat and enzymatic digestion makes it a primary shellfish allergen, as it retains its allergenic structure throughout food processing and digestion.
Similar to egg allergies, the shellfish allergy mechanism involves sensitization and effector phases. Tropomyosin's structural stability allows it to reach the gut mucosa, where APCs, such as dendritic cells, process it. These APCs then activate TH2 cells by presenting tropomyosin peptides via MHC class II molecules to naive CD4+ T-helper cells, leading to their differentiation. The TH2 cells release IL-4 and IL-13, which drive B cells to produce tropomyosin-specific IgE antibodies (Faber et al., 2017). These IgE antibodies bind to mast cells and basophils, sensitizing them to tropomyosin.

Upon subsequent consumption of shellfish, tropomyosin cross-links with the IgE on sensitized mast cells, triggering degranulation. This releases inflammatory mediators such as histamine, causing itching, swelling, and gastrointestinal discomfort. Leukotrienes and prostaglandins lead to smooth muscle contraction and respiratory

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symptoms, while cytokines intensify the inflammatory response by attracting other immune cells (Alsailawi et al., 2021).

Immunological Mechanism

The gastrointestinal tract (GIT), oral cavity, skin, and rarely the respiratory system is among the places where food sensitisation can occur (Ando and Kawakami, 2019). Most dietary proteins are broken down in the stomach and intestines by digestive enzymes and gastric acid after consumption. Nevertheless, some complete proteins and peptides survive and are transferred to the mucosal layer from the intestinal lumen. Specialised gut epithelial cells called M cells, which are found above Peyer's patches are responsible for this transport (Keating et al., 2018). An Illustration showing microbiota interacting with the mucosal immune system to induce tolerance is presented in Fig. 2 below:

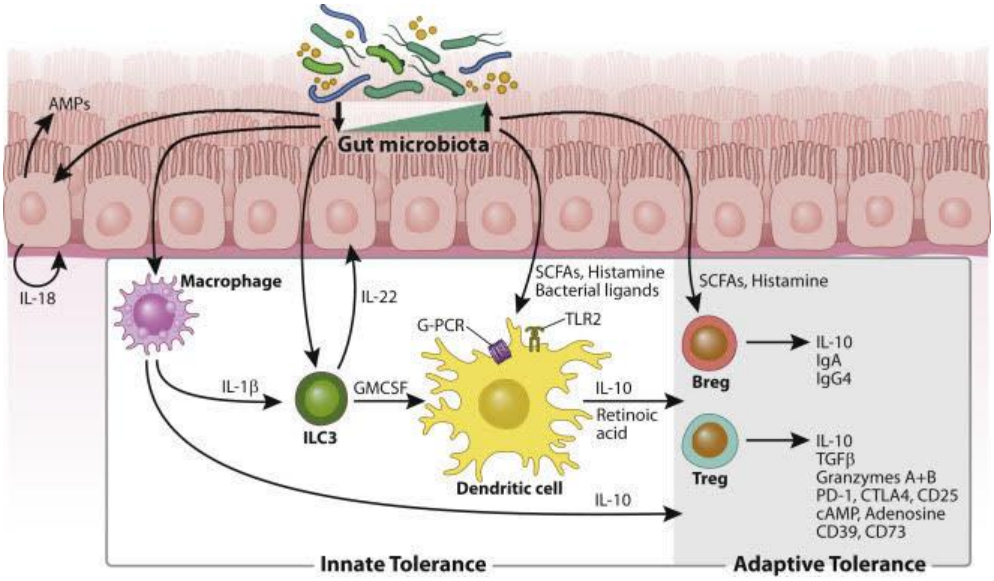

Figure 2: Illustration showing Microbiota interacting with the mucosal immune system to induce tolerance (O'Mahony et al., 2021)

Mucosal dendritic cells (DCs) can sample ingested antigens and allergens via extending their dendrites into the gastrointestinal lumen, following their capture of these proteins or peptides, DCs digest them before moving to the draining lymph nodes' T-cell areas. They display antigens on MHC class II molecules and engage with naive T lymphocytes there (Hourihane et al., 1998). The immune system's reaction is determined by the expression of costimulatory molecules and the activation of various DC subsets. For instance, T cells are activated when CD28 on T cells binds with CD80/CD86 on DCs. On the other hand, CD80/CD86 inhibits T-cell activation and averts an overreactive immunological response when it interacts with T cells' cytotoxic T lymphocyte-associated protein 4.

The development of TH2 polarisation is influenced by several variables. Innate lymphoid cells (ILCs), basophils, and natural killer T cells release IL-4, which is crucial for fostering type 2 immune responses (Savage et al., 2016). IgE class-switching and the proliferation of allergy effector cells are mediated by a distinct fraction of antigen-specific TH2 cells (TH2A cells) in allergic patients (Wambre et al., 2012). Furthermore, the induction of allergic sensitisation to food allergens depends on the activation of DCs via the OX40 ligand (OX40L). Food sensitisation and food allergies might result from the unintentional activation of DCs and lymphocytes by advanced glycation end products, which are created during high heat treatment or in the presence of high sugar concentrations. One of the main antibody classes in atopic individuals, IgE, is a sign of allergic sensitivity. The development of B-cells, the transition of immunoglobulin classes to IgE, and the differentiation of B-cells into plasma cells, which manufacture antibodies, are all facilitated by TH2 lymphocytes and the cytokines they produce. IgE causes instantaneous reactions because it activates mast cells and basophils, causing their granules to be released. The availability of dietary proteins is altered by histamine, prostaglandin, and mast cell proteases during sensitisation and subsequent exposure to the allergen. The TH2-stimulating factors TSLP, IL25, and IL-33 are also produced in greater amounts

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by epithelial cells at the same time. These cytokines also upregulate the OX40L on dendritic cells (DCs) and sustain the development of a variety of immune cells that help in the generation of IL-4 and IL-13. This, in turn, revs up the IDs and lessens the allergen-related Tregs and activates mast cells. While only been demonstrated in animal models of asthma but not food allergy, IL-33 influences Treg cells and immune tolerance. On the other hand, in mice sensitized through the skin, IL-33 enhances FIAN by acting on mast cells. Another essential component of IA is the migration and activation of intraepithelial lymphocytes in response to allergic sensitisation, which is predicted by γδ T cells in mice. Recent studies have demonstrated that mAb against TSLP, the IL-33 receptor, or IL-25 dramatically inhibited the formation of food allergies in mice.

Nevertheless, none of the mAbs that targeted one of these cytokines were able to manage the known food allergies. Hence, all three anti-TH2 mAbs were required for effective food allergy control.

Skin Barrier Dysfunction as a Pathway for Food Allergen Sensitization

Difficulties with the skin barrier are associated with food sensitivities and contribute to the understanding of the skin penetration of allergens in patients diagnosed with Atopic Dermatitis (AD) (Werfel et al., 2016). Some of the facts and findings of the latest research works done in this field can support this as follows: For instance, the skin on the parts of the body that is aired but not covered becomes worse when there is an allergen instance in cases of AD depicts complications with the outer skin layer (epidermis) (Werfel et al., 2015). Decreased Filaggrin action leads to increased water loss through the skin, enhanced allergen penetration, and skin infections caused by Staphylococcus aureus. This accounts for why those people who have mutations in the Filaggrin gene have shown elevated total IgE levels, greater sensitivity to multiple allergens, severe AD, and allergic asthma.

Skin problems are caused by the malfunction of the tight junction barrier in the granular layer of the skin, as well as the outer layer (Benedetto et al., 2011), and immune diseases that occur in AD patients. Research indicates that a poor skin barrier in neonates and at the age of 2 months can predict the establishment of clinical AD; therefore, skin defects increase the level of allergen sensitivity (Wang et al., 2022).

Immunological Mechanisms Underlying Natural and Therapeutic Tolerance

Treg cells in the gut mucosa must be sufficiently activated for oral tolerance to dietary antigens. This environment also supports the growth of Treg cells, which happens via a variety of pathways, such as those mediated by retinoic acid and short-chain fatty acids (Barcik et al., 2015), which are produced when the gut microbiota ferments dietary fibre.

Through the production of cytokines such as IL-10, TGF-β, and IL-35, cytolytic activity facilitated by granzymes A and B, and interaction with DCs through inhibitory molecules, Treg cells exert their immunosuppressive effect.

FoxP3 expression was induced (Palomares et al., 2014). While natural Treg cells do not directly contribute to oral tolerance, Treg cells are essential for it. Furthermore, it has been documented that induced Treg cells play a key role in regulating mucosal TH2 responses and the development of oral tolerance. Compared to healthy, age-matched children, atopic children with food allergies typically exhibit lower percentages of CD25+CD127loFoxP3+ Treg cells, which may indicate a potential deficiency in the maintenance of immunological tolerance.

A major factor in TH2-driven inflammatory and allergy reactions in the skin, lungs, and gut is the activation of innate lymphoid cells by local epithelial cytokines.

It has been demonstrated that intestinal regulatory ILCs adversely regulate inflammation, a phenomenon that can also happen in other inflammatory tissues. By producing IL-10, a subset of B cells known as regulatory B (Breg) cells contributes to the regulation of immunological responses. According to animal models, mesenteric lymph node-resident CD5+ Breg cells that produce IL-10 might prevent IgE-mediated responses to cow's milk allergens (Kim et al., 2017).

Epicutaneous immunotherapy prevented anaphylaxis in an adjuvant-free model of food allergy that included oral allergen challenges and epicutaneous sensitisation (Tordesillas et al., 2017). Although allergic animals have reduced intestinal Treg cell production, epicutaneous antigen administration results in the induction of a distinct fraction of LAP+FoxP3-Treg cells that are found in the gastrointestinal system. These cells represent an anaphylaxis preventive

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population suppressing mast cell activation through a TGF-β-dependent pathway without dampening T- or B-cell responses.

Regulatory T and B Cells in the Regulation of Immune Tolerance

Oral tolerance to food antigens requires adequate activation of Treg cells within the gut mucosa. This environment is also permissive to the expansion of Treg cells, which occurs through different mechanisms, including that mediated by retinoic acid and short-chain fatty acids (Barcik et al., 2015) arising from the gut microbiota's anabolic cellular respiration of dietary fibre. Through the production of cytokines such as IL-10, TGF-β, and IL-35, cytolytic activity facilitated by granzymes A and B, and interaction with DCs through inhibitory molecules, tregs exert their immunosuppressive effect.

Induced FoxP3-expressing (Palomares et al., 2014) Treg cells play a critical role in oral tolerance, whereas natural Treg cells do not contribute directly. It has been further reported that induced Treg cells are central cell players in controlling mucosal TH2 responses. In children who outgrow their milk allergy, there is an increased frequency of CD4+CD25+ Treg cells, suggesting their participation in the development of oral tolerance. Atopic children with food allergy generally have lower percentages of CD25+CD127loFoxP3+ Treg cells than healthy, age-matched children, suggesting a possible insufficiency in the maintenance of immune tolerance.

A major factor in TH2-driven inflammatory and allergic reactions in the skin, lungs, and gut is the activation of innate lymphoid cells by local epithelial cytokines. As seen in other inflammatory tissues, regulatory ILCs in the colon have been shown to negatively regulate inflammation. By producing IL-10, a subpopulation of B cells known as regulatory B (Breg) cells contributes to the regulation of immunological responses. According to animal models, mesenteric lymph node-resident CD5+ Breg cells that produce IL10 may prevent IgE-mediated responses to cow's milk allergens (Kim et al., 2017).

In an adjuvant-free model of food allergy using epicutaneous sensitization and oral allergen challenges, epicutaneous immunotherapy provided protection against anaphylaxis (Tordesillas et al., 2017). Intestinal generation of Treg cells was impaired in allergic mice; however, epicutaneous antigen application induces a unique subset of LAP+FoxP3-Treg cells that home to the gastrointestinal tract. These cells represent an anaphylaxis preventive population that suppresses mast cell activation through a TGF-β-dependent pathway without dampening T- or B-cell responses as indicated in Fig. 3.

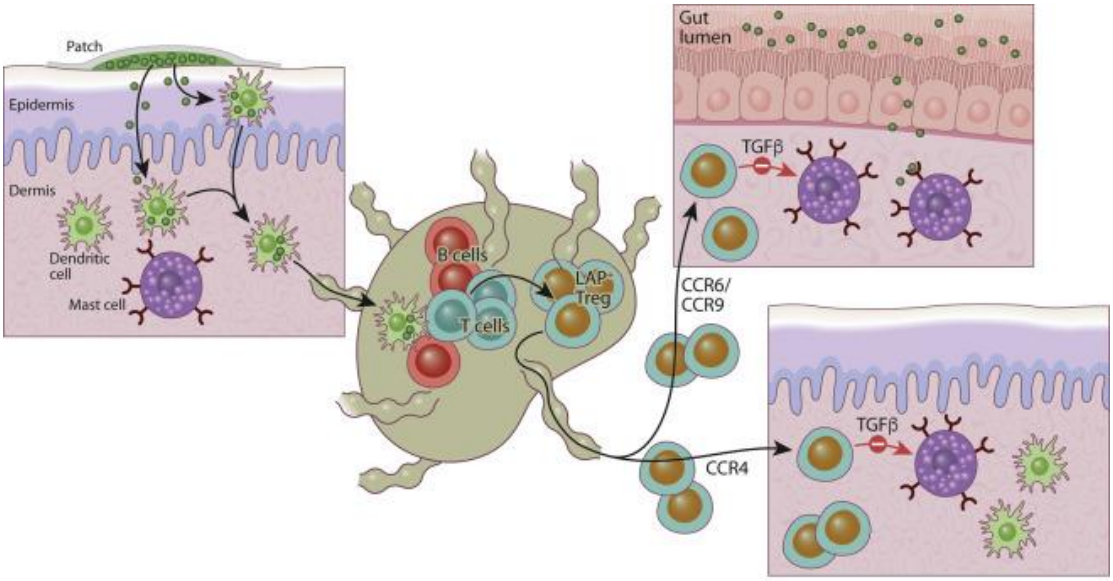

Figure 3: Epicutaneous immunotherapy and its role in mitigating anaphylactic responses in mice (O'Mahony et al., 2018)

Functions of Microbiota

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The interactions among innate and adaptive immune cells and gut microbiota significantly influence the balance between immunological tolerance and inflammation. Recent research emphasizes the vital importance of bacterial microbiota composition and metabolic activities in either fostering allergic diseases or establishing protective immune tolerance pathways (Butto et al., 2017).

A study involving children with milk allergies (Huang et al., 2017) found that those who developed tolerance to milk by age 8 had an enriched presence of Firmicutes, particularly Clostridium species, in their early gut microbiome. Likewise, children with allergies to peanuts or tree nuts exhibited lower microbial diversity and higher levels of Bacteroides species compared to non-allergic controls. Research with germ-free mice indicated that lacking gut microbiota intensified allergic reactions, and transferring microbiota from allergy-prone mice could induce allergic susceptibility in germ-free subjects. The authors (Burton et al., 2014) found that intestinal macrophages sense microbial signals, triggering the secretion of IL-1β. This cytokine, in turn, prompts type 3 innate lymphoid cells to produce GM-CSF. This same GM-CSF stimulates dendritic cells and macrophages to generate retinoic acid and IL-10, which are crucial for inducing and expanding mucosal Tregs necessary for oral tolerance to dietary antigens. A disruption in the microbiota–immune interaction leads to weakened immune regulatory functions and diminished oral tolerance.

Moreover, histamine, produced by gut microbiota, influences mucosal inflammation via histamine receptor 2. A recent study (Mortha et al, 2014) showed that asthma patients had a higher abundance of histamine-producing microbes in their gut compared to healthy individuals, yet the precise link to allergic reactions to food allergens remains unclear.

Experimental studies in mouse models with specific bacterial strains like Bifidobacterium or Clostridium demonstrated protection against food allergen sensitization by promoting mucosal Treg cells. Clostridia also stimulated ILC3s to produce IL-22, which helped maintain the epithelial barrier, resulting in reduced gut permeability to dietary proteins. In humans, Bifidobacterium longum 35624 increased FoxP3+ Tregs in the peripheral blood. Moreover, combining Lactobacillus rhamnosus GG with peanut oral immunotherapy has shown encouraging results in promoting desensitization.

However, the effectiveness of probiotics alone remains unclear due to inadequate controls used in some of these experiments. Many questions about the role of the microbiota in food sensitization, tolerance induction, and long-term immune regulation remain open. Second, the contribution of local microbiota at locations like the tonsils, upper gastrointestinal tract, and skin to immune responses remains to be explored in greater detail, particularly for their possible contributions to immunotherapy and the acquisition of long-term tolerance.

Recent findings also separate Treg cells induced by dietary antigens in the small intestine from those induced by microbiota in the colon, stressing the complexity of immune regulation induced by the gut microbiota. Further studies are required to understand these mechanisms for the optimization of strategies regarding the manipulation of the microbiota for immune tolerance.

Mechanisms of Desensitization and Sustained Responsiveness

The reasons why some people maintain a reduced allergic response or remission after immunotherapy, where their allergy symptoms lessen and may not return even after they encounter the allergen again, are still unclear. It's not known if this lasting improvement and temporary reduction in allergic reactions happen through different processes, or if they are steps toward fully tolerating the allergen (see Fig. 4).
One main idea is that oral immunotherapy (OIT) works by encouraging regulatory T cells (Treg cells) to increase their production of calming chemicals like IL-10 and TGF-β. However, we don't know which specific types of Treg cells are most important for successful immunotherapy. A recent study found that people who achieved lasting improvement had certain changes in their Treg cells that suggest a role for epigenetics—how genes are influenced by factors other than DNA sequence. This might be important for making allergies less severe and for long-term tolerance to develop (Mortha et al., 2014).

More research is needed to understand exactly how lasting improvement happens and whether it's different from

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what makes desensitization work. Figuring this out will help us improve immunotherapy methods to better help people become less allergic to things they react to. A typical cellular mechanisms underlying desensitization, remission, and tolerance is presented in Fig. 4 below:

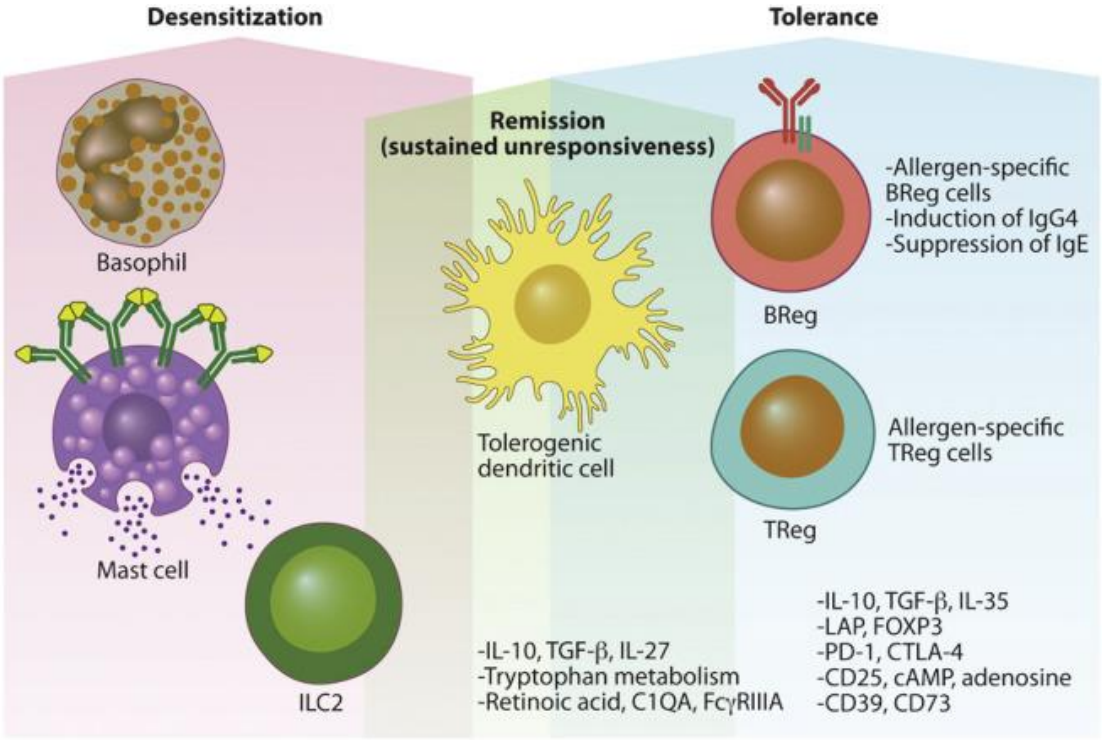

Figure 4: Cellular mechanisms underlying desensitization, remission, and tolerance (Sampson et al., 2018)

Breg cells might play a role in the success of immunotherapy, indicated by increasing specific IgG4 levels following oral immunotherapy (OIT) for food allergens. This increase, alongside a drop in IgE levels, could be due to the down-regulation of IL-4 (which promotes IgE) and the up-regulation of IL-10 (which aids in IgG4 production). OIT has been demonstrated to elevate peanut allergen-binding B cells in the bloodstream, potentially leading to alterations in allergen-specific IgG4 through somatic mutation. However, improvements in clinical outcomes do not always correspond with blood IgG4 levels.
During immunotherapy, IgA can also be generated, possibly inhibiting allergen binding and transport in epithelial cells (ECs). Its role in mitigating allergic reactions necessitates further investigation, especially since IgA deficiency is linked to an increased risk of food allergies.
Immunotherapy triggers rapid desensitization of mast cells and basophils, significantly reducing the risk of systemic anaphylaxis to other allergens. Although the exact mechanisms of food allergies remain uncertain, it is believed that allergen immunotherapy may involve processes similar to rapid drug desensitization. The duration of this desensitization is variable; it occurs swiftly with venom immunotherapy but generally unfolds over several months during OIT. The extent of allergen interaction with immune cells and the regulatory influence of the immune environment—varying by organ and tissue—can affect the bodily response. Various strategies, including targeting histamine receptor 2 and IgG antibodies against FcγRIIb on mast cells, have been suggested for achieving desensitization. Individual thresholds and other factors impact these interactions (Mortha et al, 2014).
Overall, whether one develops an allergy or tolerance to food antigens results from a complex interplay among immune cells, microbiota, nutrition, and allergens. Nonetheless, blood IgG levels do not always reflect clinical improvements.

In the course of immunotherapy, IgA may also be produced, potentially aiding in the prevention of allergen binding and transport within epithelial cells (ECs). However, considering the association between IgA deficiency and a

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heightened risk of food allergies, more research is required to understand its role in allergy prevention. During the early stages of the immunotherapy process, mast cells and basophils experience rapid desensitization, which decreases the risk of systemic anaphylaxis to other allergens. While the precise mechanisms underpinning food allergies remain unclear, allergen immunotherapy may operate akin to swift medication desensitization. The duration of this desensitization process can vary; it happens almost instantly with venom immunotherapy, while OIT often necessitates several months.

The immune environment's regulation of the quantity of allergens interacting with immune cells varies depending on the organ and tissue, and can determine how the body responds. Several methods, including histamine receptor 2 and IgG antibodies targeting FcγRIIb on mast cells, have been hypothesized to induce desensitization. Individual thresholds, as well as other factors, influence these interactions (Mortha et al., 2014). In essence, the emergence of dietary allergies or tolerances is a complicated interaction between immune cells, microbiota, nutrition, and allergens. However, limitations in our understanding of how natural tolerance develops have hindered the growth of immunotherapy medicines that accurately imitate this process. Enhancing OIT protocols with tolerance-inducing drugs such as specific probiotics or prebiotics may help more patients attain long-term unresponsiveness, but additional study is required to fully understand the complexities of food antigen tolerance. The possible pathway for food allergy reaction is as shown in Fig. 5.

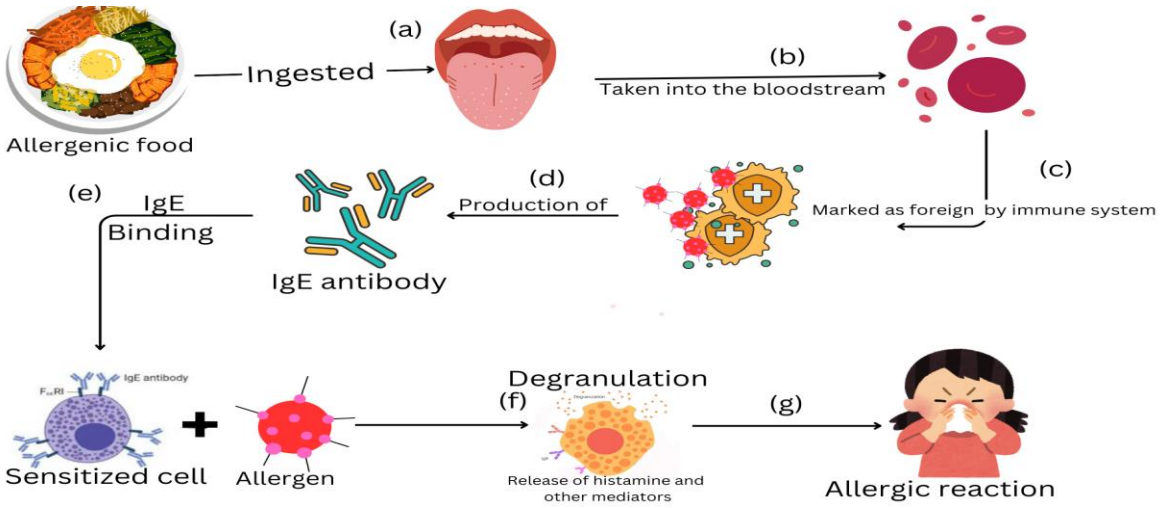

Figure 5: Pathway for food allergy reaction (Sicherer et al., 2023)

Allergen Exposure: The process starts with ingesting an allergenic food that contains specific proteins recognized as antigens by the immune system.
Absorption and Sensitization: After digestion, these proteins are absorbed through the intestinal mucosa into the bloodstream. In sensitized individuals, the immune system mistakenly recognizes these proteins as harmful agents.
Production of IgE: B cells, which are a subset of white blood cells, are activated in response to the first exposure and develop into plasma cells that produce allergen-specific immunoglobulin E (IgE) antibodies. Sensitisation refers to this process.
Mast Cell Binding: The produced IgE antibodies bind to the high-affinity IgE receptors (FcεRI) on basophils and mast cells, thereby priming these cells for later exposures to the allergen.
Subsequent Allergen Exposure: When the allergen is encountered again, it crosslinks the IgE antibodies on the mast cell surface. This cross-linking triggers a signaling cascade within the mast cells.
Degranulation: The signaling cascade triggers mast cell degranulation, releasing pre-formed mediators like histamine, leukotrienes, and prostaglandins. This process occurs via exocytosis, leading to an immediate hypersensitivity reaction.

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Pathophysiological Effects: Released mediators induce a range of pathophysiological effects, including vasodilation, heightened vascular permeability, bronchoconstriction, and sensory nerve stimulation. These lead to symptoms like urticaria, angioedema, gastrointestinal discomfort, and respiratory issues.

Anaphylaxis: In extreme situations, the systemic release of mediators may cause anaphylaxis, which is marked by a swift onset of symptoms including hypotension, airway constriction, and possible loss of consciousness, thus necessitating urgent medical attention.

In conclusion, a food allergy reaction entails a complex immunological process comprising sensitization, re-exposure, and the release of inflammatory mediators, resulting in a range of clinical manifestations.

Management and Treatment Strategies for Food Allergies

Food allergy management relies on a multi-pronged approach, primarily focusing on epinephrine for anaphylaxis, with antihistamines and corticosteroids playing supplementary roles.

Epinephrine: This is the first-line treatment for anaphylaxis. Food allergens trigger the release of inflammatory mediators, leading to vasodilation, airway obstruction, and bronchospasm (Simons et al., 2011). Epinephrine reverses these effects by acting on adrenergic receptors.

- Alpha-1 receptors: Cause vasoconstriction, reversing hypotension and reducing vascular permeability to alleviate swelling, especially in the airway (Sampson et al., 2006).
- Beta-1 receptors: Increase heart rate and contractility, stabilizing blood pressure and ensuring blood flow to vital organs (Brown et al., 2006).
- Beta-2 receptors: Cause bronchodilation, stabilize mast cells to inhibit the release of inflammatory mediators, and relax gastrointestinal smooth muscle (Simons et al., 2011).

The overall physiological effects restore blood pressure, reduce airway swelling and bronchospasm, inhibit further mediator release, improve cardiac output, and relieve gastrointestinal symptoms (Simons et al., 2011; Brown et al., 2006).

Antihistamines: These are used as supplementary treatments for mild to moderate allergic reactions. They function by competitively blocking histamine at H1 and H2 receptors (Simons et al., 2011).

- H1 receptor antagonists: Inhibit histamine attachment, decreasing redness, swelling, hives, sneezing, nasal congestion, and itching.
- H2 receptor antagonists: Reduce histamine-mediated gastric acid secretion, potentially aiding in nausea and abdominal pain.

Physiologically, antihistamines reduce cutaneous, gastrointestinal, nasal, and ocular symptoms. However, they have a limited role in treating the systemic symptoms of severe anaphylaxis (Simons et al., 2011).

Corticosteroids: These are prescribed as secondary or adjunct treatments, particularly for delayed or prolonged allergic responses and to prevent symptom recurrence (biphasic anaphylaxis). They act on glucocorticoid receptors to regulate the immune response and reduce inflammation (Zhou et al., 2021). This is achieved through several mechanisms:

- Suppression of pro-inflammatory cytokines
- Inhibition of mast cell degranulation
- Reduction of vascular permeability
- Downregulation of adhesion molecules
- Inhibition of eicosanoid pathways

Physiologically, corticosteroids prevent biphasic reactions, reduce airway inflammation, and alleviate persistent symptoms (Zhou et al., 2021).

Implications for Low-Research Settings

Access to Epinephrine, particularly auto-injectors, is drastically limited across developing countries of the world. As of 2005, auto-injectors were reportedly unavailable in the majority of low-income countries, and a global survey in 2023 revealed that they were only registered in 32% of nations, with the most absences in LMICs (Low- and Middle-Income countries) like Nigeria (Hossny et al., 2019; Tanno et al., 2023). Even with the presence of epinephrine ampoules, precise dosing during stressful situations is susceptible to errors, and training on their application is infrequent. Given that delays or inappropriate use of epinephrine are closely associated with anaphylactic mortality, this gap has potentially fatal effects (Hossny et al., 2019; Prince et al., 2018).

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A significant amount of healthcare in Nigeria is provided with very limited resources. Chronic medicine shortages, fragmented insurance systems, and underfunded PHCs (Public Healthcare Centres) restrict the ability to regularly stock or prescribe epinephrine (Ephraim-Emmanuel et al., 2018). This results in inadequate readiness, which is exacerbated by a lack of knowledge about food allergies and anaphylaxis among the general public and professionals. Although scaling commercial auto-injectors may not be immediately possible, the discussion should focus on strategies like training community health workers, bolstering cold-chain systems, and promoting accessible formats of epinephrine (e.g., ampoules with visual dosing guides) to better align recommendations with context.

Research Gaps: Microbiota, Epidemiology and Genomics

Although the prevalence of food allergies is increasing worldwide, there is still a dearth of trustworthy data from Africa. It was thought to be uncommon throughout the continent until recently, but according to ISAAC (International Study of Asthma and Allergies in Childhood**)** and new challenge-based research in South Africa, rates are already getting close to those in the West. However, only 11 out of 54 African nations have any data, and the majority rely more on sensitisation or self-reports than oral food challenges (Kung et al., 2014; Hossny et al., 2019). Although they are still poorly understood, genomic, environmental, and lifestyle factors such as helminth co-infection and traditional diets likely cause significant differences in the mean prevalence and allergen profiles among African communities. The gap also exists in microbiome research: a 2021 systematic review discovered that only 168 human microbiota studies from 33 out of 54 African countries focused on diseases that were identified as major public health burdens, with less than 27% of these studies addressing these diseases. The majority of lead authors and funders were located outside of the continent, highlighting a lack of local leadership or capacity (Allali et al., 2021). The lack of data in Nigerian and West African cohorts is a knowledge gap that delays the development of suitable preventive strategies and biomarkers, as early-life gut colonization is increasingly acknowledged as a modulator of allergy risk.

Conclusion

IgE-mediated food hypersensitivities are a specific type of adverse food reaction, marked by swift immune responses to particular dietary proteins. These responses entail complex immunological mechanisms, such as sensitization, and the activation of mast cells and basophils, leading to the release of histamine and other inflammatory substances. Although clinical expressions can range from skin and digestive symptoms to life-threatening anaphylaxis, recent advancements in immunology have clarified the underlying processes. Nonetheless, inconsistencies in diagnosis, especially in low-resource environments, highlight the pressing need for standardized diagnostic tools and improved epidemiological monitoring.

Recommendations

Future studies should focus on creating accurate biomarkers, innovative immunotherapy methods, and approaches to encourage immune tolerance, particularly during early development. It is essential to comprehend how genetic vulnerability, environmental factors, and immune regulation interact in order to mitigate the global effects of IgE-mediated food allergies.

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