IgE and non-IgE food allergy: A review of immunological mechanisms

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ABSTRACT

Background: *Food allergic (FA) conditions have been classified as immunoglobulin E (IgE) and non-IgE–mediated reactions that affect as many as 8% of young children and 2% of adults in Western countries, and their prevalence seems to be rising. Although the immunologic basis of IgE-mediated FA is well established, the mechanisms that govern non-IgE–mediated FA are not well understood and are marked by a paucity of comprehensive insights.*

Objective: *The purpose of the present report is to examine the current classification and epidemiology of non-IgE–mediated FA, the latest immunologic mechanisms that underlie the three most commonly cited non-IgE FA conditions,* viz., *eosinophilic esophagitis, food protein-induced enterocolitis, and food protein–induced allergic proctocolitis, and explore what allergist/immunologists in practice should be aware of with regard to the condition.*

Methods: *An extensive research was conducted in medical literature data bases by applying terms such as FA, non-IgE allergy, tolerance, unresponsiveness, cytokines, $CD4^+$ T helper cell pathways, and key cytokine pathways involved in FA.*

Results: *Current evidence now supports the view that immune dysregulation and cytokine-induced inflammation are the fundamental bases for both IgE- and non-IgE–mediated FA. The existing non-IgE–related FA literature is mostly characterized by a relative dearth of mechanistic information in contrast to IgE-mediated FA, in which the immunologic underpinnings as a T helper type 2 directed entity are well established. Although the need for future methodologic research and adherence to rigorous scientific protocols is essential, it is also necessary to acknowledge past contributions that have given much to our understanding of the condition. In the present report, a novel signature cytokine-based classification of IgE-mediated and non-IgE–mediated allergy is proposed that may offer a novel template for future research in the field of non-IgE–mediated FA.*

Conclusion: *The present report provides an overview of the current classification and frequency of IgE– and non-IgE–mediated FAs, and offers insights and potential solutions to address lingering questions, particularly when concerning the latest immunologic mechanisms that underlie the pathogenesis of non-IgE-mediated FA. Although some progress has been made in recent years toward making diagnostic and treatment options available for these conditions, there still remain many lingering questions and concerns to be addressed, which can be fully understood by future research.*

(J Food Allergy 6:37–46, 2024; doi: 10.2500/jfa.2024.6.240003)

The exploration of adverse reactions to foods dates back to ancient times during which this intricate subject has faced considerable challenges influenced by a tapestry of experiences, myths, and beliefs, and a limited comprehension of the underlying mechanisms of pathogenesis. Despite ongoing efforts, which have led to some progress, the management of the condition still falls short of achieving optimal outcomes and its pathogenesis remains enigmatic. In a recent thought-provoking article, Smith[1] delves into the complex landscape of food allergy (FA) from both the historical and social-science perspectives, and explores how three pivotal discoveries have influenced the trajectory of the condition. First, the study of the epidemiology has not only shed considerable light on the apparent rise in the prevalence of FA but has also led to the emergence of theories, *e.g.*, the hygiene hypothesis,[2] which posits that increased cleanliness and reduced exposure to infections in early childhood may contribute to the subsequent development of allergic disorders. Second, our understanding of immunologic mechanisms associated with the pathogenesis of FA has experienced a substantial leap forward with the seminal discovery of immunoglobulin E (IgE) in 1966,[3] providing the mechanistic basis for IgE-mediated FA. The first observation relevant to IgE and FA, however, was made before the IgE discovery by the Prausnitz-Kűstner experiment in

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The author has no conflicts of interest to declare pertaining to this article

Funding provided by the Eastern Food Allergy & Comorbidity Conference

Presented at the Eastern Food Allergy & Comorbidity Conference, January 4, 2024, Palm Beach, Florida

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1921.[4] However, the discovery of IgE has paradoxically revealed a substantial gap in our understanding of the mechanisms that underlie non-IgE–mediated FAs, which highlights a deficiency in our knowledge of this condition that the present paper seeks to address and elucidate. Third, the examination of the experiences of those who experience FAs and their caregivers has provided valuable qualitative insights that have shaped our responses to FA and enhanced our understanding of its etiology. Yet, despite these advances, numerous unanswered questions persist, particularly with regard to non-IgE–mediated FA. These include inquiries into the classification and frequency of the condition, the immunologic mechanisms that underlie the three most commonly cited non-IgE-mediated FA conditions, *viz.*, eosinophilic esophagitis (EoE),[5] food protein-induced enterocolitis (FPIES),[6] and food protein–induced allergic proctocolitis (FPIAP),[7] and a need to explore what allergist/immunologists in practice should be aware of with regard to non-IgE–mediated FAs. The purpose of the present report is to offer some insights and possible solutions to address these questions.

CLASSIFICATION AND FREQUENCY OF ADVERSE REACTION TO FOODS

Adverse food reactions are defined as an abnormal response related to the ingestion of a food.[8] For ease of discussion, they can be classified into two main categories: (1) food intolerance, based on the characteristics of the food or the host, and (2) immunologically mediated or FA reactions, which have been classified as IgE-mediated, non-IgE–mediated, or mixed reactions (Fig. 1). Food intolerance adverse food reactions can be further subdivided into those that are due to the inherent properties of the food (*e.g.*, a toxic contaminant, a pharmacologically active component such as caffeine or alcohol or those due to abnormal response(s) of the host [*e.g.*, lack of an enzyme such as lactase in lactose intolerance or a metabolic disorder, or a food aversion due to psychological issues]).[8] In contrast to the immunologically mediated adverse food reactions, which are consistently reproducible and dose-dependent, the food intolerance reactions are also dose-dependent but are not consistently reproducible.[8]

There is evidence that suggests that both IgE-mediated and non-IgE–mediated FAs have been increasing globally.[9,10] The reasons for this increase are complex and seem to involve a combination of genetic, epigenetic environmental, and lifestyle factors, which have become a topic of concern and a focus of ongoing research in several centers throughout the world. Although the vast majority of adverse food reactions reported by the general population are food intolerances,[8] the most common adverse food reactions in the Western world are the IgE-mediated FA reactions, which have the highest prevalence of 8% in children and 4% in adults.[7]

The incidence of non-IgE–mediated FA conditions, including EoE, FPIES, and FPIAP, although not known with certainty, can be variable but not less common

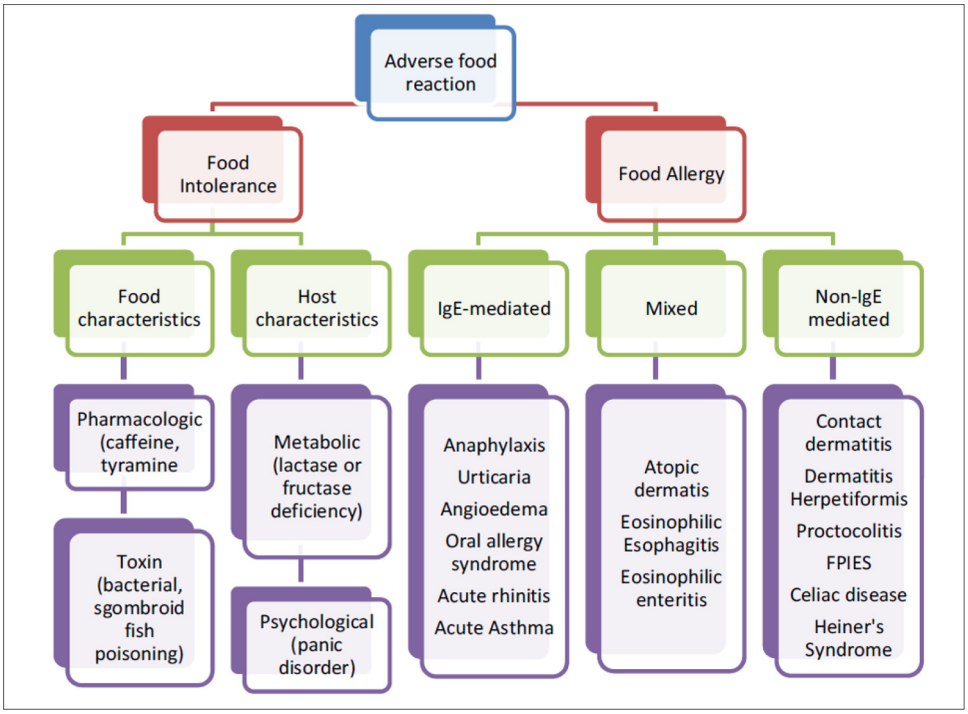


Figure 1. *Schematic representation of the classification of adverse reaction to foods (reproduced with permission from Ref. 8).*

than IgE-mediated FA in which estimates suggest that 10.8% of U.S. adults and 7.6% of children have at least one current FA.[9,10] A schematic representation of the evolution of non-IgE–mediated FA research, as indicated by the number of publications cited in PubMed, which spans the period from 1980 to 2023, providing an overview of the increasing research trends on the topic of non-IgE–mediated FA in recent years is illustrated in Fig. 2.

HOST IMMUNE RESPONSES TO FOOD ALLERGENS

Immunologic Mechanisms of IgE-Mediated FA

The development of FA involves the integrated involvement of several components of both the innate and the adaptive immune systems. The immunologic underpinnings of IgE-mediated FA hypersensitivity are well established, with a comprehensive understanding of the molecular and cellular mechanisms involved. In the case of IgE-mediated FA, the adaptive immune response takes center stage, characterized by a sophisticated interplay of IgE antibodies orchestrating allergic reactions to specific food antigens.[11] Although components of the innate immune system are initially activated as part of the host's inflammatory response, it is the subsequent involvement of the T helper type 2 (Th2) driven IgE-mediated responses of the adaptive immune system that are responsible for most of the clinical and laboratory findings seen in IgE-mediated FA (*e.g.,* hives, pruritus, eczema, angioedema, and wheezing).

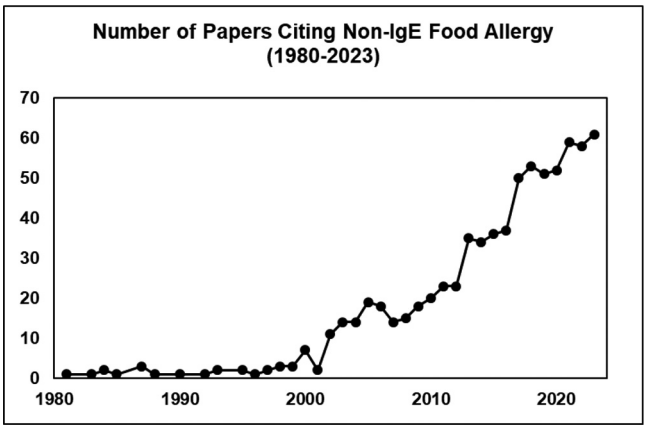


Figure 2. *Evolution of non-IgE–mediated food allergy research as suggested by the number of publications cited in PubMed that spanned the period from1980 to 2023. The following "search parameters" were used when articles were searched for in PubMed: keywords: non-IgE-mediated food allergies (e.g., "non-IgE-mediated food allergy," "cell-mediated food allergy," "delayed-type food hypersensitivity"), and the publication date range from 1980 to 2023. IgE = Immunoglobulin E.*

For ease of discussion, the immunologic events involved in the pathogenesis of IgE-mediated FA can be divided into three phases: sensitization, challenge, and elicitation of clinical findings.[11] The first phase of sensitization begins when a genetically predisposed individual is exposed to allergen *via* ingestion or, less frequently, by skin contact or inhalation, during which a Th2 cytokine-rich environment eventually leads to allergen-specific IgE production. Subsequently, when the allergen-specific IgE binds to high-affinity IgE receptors on the surface of basophils and mast cells, these cells now become ''primed.'' Although the mechanisms that underlie allergic sensitization are not completely known, a breakdown in tolerance mechanisms with deficiencies of immunoregulatory T regulatory (Treg) function are thought to be responsible for this phase of the IgE-mediated FA response.

After sensitization, exposure to the same or a closely related allergen during the second phase of challenge, cross-linking of two adjacent FceRIs on the surface of basophils and mast cells leads to the degranulation of these cells with the release of potent mediators that initiate allergic symptom during the elicitation phase. The clinical manifestations seen during this phase present as a rapid-onset acute allergic reaction mediated by IgE antibodies in response to specific food proteins, such as milk, eggs, wheat, peanuts, tree nuts, fish, shellfish, soy, and sesame.

Immunologic Mechanisms of non-IgE–Mediated FA

The clinical manifestations, epidemiology, pathophysiology, and management of non-IgE–mediated FAs were reviewed in a report by Zhang *et al.*[12] In contrast to IgE-mediated FA, in which the adaptive immune response takes center stage, non-IgE–mediated FA predominantly involves mechanisms associated with the innate immune system, most of which have not yet been fully elucidated. Unlike IgE-mediated FAs that may result in multiorgan system involvement, *e.g.,* anaphylaxis, non-IgE–mediated FAs are a group of disorders characterized by subacute or chronic inflammatory that primarily affect the gastrointestinal tract that include FPIES,[6,13] FPE, FPIAP,[7] and eosinophilic gastrointestinal disorders, *e.g.,* EoE.[5,12] Although extensive advances have been made in understanding these disorders, more information is needed on the pathophysiology of these FAs.[12] In addition to the predominant involvement of innate immunity, similarities among the non-IgE–mediated FAs include T-lymphocyte processes, alteration of the intestinal lumen at the cellular level, with the appearance of inflammatory cells and associated histologic changes, and specific cytokine profiles that suggest food-specific, T-cell, and immune-mediated responses. Although FPIES and FPIAP typically resolve in early childhood, eosinophilic gastrointestinal disorders

typically do not. Emerging new biologic therapies for EoE offer promise of additional treatment options. Further studies that identify the immunopathogenesis, associated biomarkers, and mechanisms of tolerance are needed to inform prevention, diagnosis, and management. As will be elaborated on in the following section, an emerging body of literature is defining the key cytokines associated with $CD4^+$ Th cell subpopulations and cytokine pathways. These studies are beginning to distinguish differences between IgE-mediated and non-IgE–mediated FAs.

The Critical Role of Cytokines and $CD4^+$ Th Pathways Involved in the Pathogenesis of Both IgE– and non-IgE–Mediated FA

Within the adaptive immune system are found the key cytokines and subpopulations of both the $CD8^+$ Th and $CD4^+$ Th subpopulations that underlie key pathways of inflammation that may offer a more complete understanding of pathogenetic mechanisms responsible for both IgE-mediated and non-IgE–mediated FAs. These subpopulations consist of the Th $CD4^+$ Th1, Th2, Th17, and Treg cells, important in Th function and the T cytotoxic $CD8^+$ T cells important in the killing of viral-infected and malignant cells.

During the initial phase of FA disease, the food allergen is taken up by antigen-presenting cells, primarily the dendritic cells, which process the allergen into peptides, which are then presented to naive Th cell populations. A critical event that occurs during this initial phase is the release of cytokines from many of the innate immune cells, which prime the immune system for an encounter with the with T and B cells of the adaptive immune encounter. There is recent evidence that this release of cytokines and stimulation of key the Th cell pathways are critically important and hold the key to an understanding of the mechanisms involved in IgE– and non-IgE–mediated FA.

Table 1 **Key cytokines of $CD4^+$ Th cell subpopulations cytokine pathways that underlie mechanisms of inflammation for IgE– and non-IgE–mediated FA**

Pathway	Description	Function	Cytokines Produced
Th1	Th1 cells that are involved in promoting cell-mediated immune responses	Drive the pro-inflammatory responses; they help activate macrophages and cytotoxic T cells to combat intracellular pathogens such as viruses	IFN-γ, TNF-α, IL-2
Th17	Th17 cells are known for their role in pro-inflammatory responses; they produce cytokines that recruit immune cells to sites of infection and inflammation	Drive the pro-inflammatory responses associated with Th17 cells; these responses are important for defense against certain pathogens but can also contribute to autoimmune diseases	IL-17, IL-22, IL-23, IL-6 TN F-α
Treg: subtypes Tr1 and Tr3	Treg cells, often referred to as Tregs, are a subset of CD4 T-cells that play a critical role in maintaining immune system balance; they produce anti-inflammatory cytokines and help suppress excessive immune responses to prevent autoimmune reactions and maintain tolerance; Tr3 cells are not as well-known as the Tr1 subtypes	Diminished numbers of Treg cells in allergies and autoimmune diseases; thought to play a role in pathogenesis; believed to play a role in regulating immune responses, particularly at mucosal tissues	TGF-β, IL-10; FOXP3 T cells
Th2	Th2 cells are involved in promoting humoral immune responses, particularly against extracellular pathogens	They play a role in allergies and autoimmune diseases.	IL4, IL-5, IL-6, IL-10, IL-13

Th = T helper; IgE = immunoglobulin E; FA = food allergy; Th1 = T helper type 1; IFN-γ = interferon-γ; TNF-α = tumor necrosis factor-α; IL = interleukin; Treg = regulatory T cell; TGF-β = transforming growth factor β; FOXP3 = forkhead box protein P3.

Table 2 **Comparison of clinical and pathogenetic features of IgE-mediated FA with EoE, FPIES, and FPIAP***

Feature	IgE-Mediated FA	Non-IgE–Mediated FA		
		EoE	FPIES	FPIAP
Clinical features	A rapid-onset acute allergic reaction mediated by IgE proteins, such as milk, eggs, wheat, peanuts, tree nuts, fish, shellfish, soy	A chronic delayed non-IgE inflammatory FA disease of the esophagus with eosinophilia and symptoms of dysphagia, esophageal food impaction and fibrosis that affect primarily adults	Predominantly seen in infants in acute and chronic forms symptoms of vomiting, diarrhea, and sometimes dehydration	Primarily affecting infants with a delayed onset of symptoms of blood and mucus in stools, fussiness, irritability, and GI discomfort
Epidemiology	According to a cross-sectional population-based survey in the United States, reported, the prevalence of IgE-mediated FA in children was 7.6%# and 10.8% in adults §	Estimated prevalence at 56.7/100,000	Estimated prevalence between 0.34 and 0.7% in infancy	FPIAP prevalence estimates range widely from 0.16% in healthy children and 64% in patients with blood in stools¶
Pathogenesis	A predominantly Th2 pathway–mediated disease	EoE involves a continuum of inflammatory responses, leading to tissue damage, initially accumulation of eosinophils contributes to tissue damage by release inflammatory mediators. eotaxin-3, IL-3 in tissue; later release of TGF-β contributes to fibrosis responsible for scarring and impaction	T cells play a central role with pan-activation of food-specific lymphocytes, innate immune compartment (monocytes, neutrophils), elevated ESR and CRP	The pathogenesis of FPIAP involves an abnormal inflammation in the lower intestine and rectum; although the exact mechanisms are not fully understood, it is believed to be driven by a T-cell–mediated response
Cellular changes	Eosinophils; mast cells; Th2 cells; iNKT; ILC2	Eosinophils; mast cells; Th2 cells; iNKT; ILC2	Eosinophils in tissue and blood; lymphocytes, plasma cells; polymorphonuclear leukocytes in those with rectal bleeding	CD3+ cells; eosinophils; regulatory T cells; CD4 cells shifted toward Th2
Cytokine changes	IL-4; IL-5 Th2; IL-13	IL-4; IL-5 Th2; IL-13; CCL26 (eotaxin-3)	TNF-α; TGF-β; IL-10; IP-10 (CXCL-10); ↑Th17	CXCL13; CCL11 (eotaxin-1); IL-6

Table 2 **Continued**

Feature	IgE-Mediated FA	Non-IgE–Mediated FA		
		EoE	FPIES	FPIAP
Most common food trigger	Milk, eggs, wheat, soy, fish, shellfish, peanut, tree nuts, sesame	In both adult and pediatric populations, milk, wheat, egg, and soy are the most common food triggers	Oat, egg. peanut, milk, rice	Cow's milk, rice
Natural history	Rare to outgrow	Rare to outgrow	With acute disease, most outgrown by 2–3 years of age	Resolved by 9–12 months

IgE = Immunoglobulin E; FA = food allergy; EoE= eosinophilic esophagitis; FPIES = food protein–induced enterocolitis; FPIAP = food protein–induced allergic proctocolitis; GI = gastrointestinal; Th2 = T helper type 2; IL = interleukin; TGF-β = transforming growth factor β; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; iNKT = invariant natural killer T (cells); ILC2 = group 2 innate lymphoid cells; CCL = chemokine (C-C motif) ligand; TNF-α = tumor necrosis factor-alpha; IP = interferon gamma-induced protein; CXCL = chemokine (C-X-C motif) ligand.
**Reproduced and modified from with permission from Refs. 13 and 30.*
#Adapted from Ref. 29.
§Adapted from Ref. 6.
¶Adapted from Refs. 21–23.

Key Cytokines and Cytokine Pathways Involved in FA

Shown in Table 1 are the important cytokines of the $CD4^+$ Th cell subpopulations and their respective cytokine pathways that underlie mechanisms of inflammation for IgE– and non-IgE–mediated FA. The Th1 cells are composed of pro-inflammatory cells that produce cytokines involved in promoting cell-mediated immune responses and help activate macrophages and cytotoxic T cells to combat intracellular pathogens such as viruses. Once activated, Th1 cells produce interferon (IFN) γ, interleukin (IL) 2, and tumor necrosis factor (TNF) α. A second important T-cell population involved in promoting inflammation is the Th17 group, which produces IL-17, IL-22, IL-23, IL-6, and TNF-α cytokines that recruit immune cells to sites of infection and inflammation.[22] Counterbalancing the pro-inflammatory effects of Th1 and Th17 cells are the Treg cells.[14] Several studies have reported that the numbers of Treg cells[15–17] and CD4 IL-10–secreting type 1 Treg (Tr1) cells are substantially reduced[18,19] and express a less-stable phenotype in patients with allergy. The Treg cells are composed of at least two subtypes. One of the better-studied subtypes is Tr1 cells. These are often referred to as Tregs. Tregs are those that play a critical role in maintaining immune system balance by helping to suppress excessive immune responses to prevent autoimmune reactions and maintain tolerance The less well studied Tr3 Treg cell populations are believed to play a role in regulating immune responses, particularly at mucosal tissues. Collectively, the Treg cells conduct regulatory activities that maintain immune tolerance and suppress excessive immune responses primarily by the release of anti-inflammatory cytokines transforming growth factor β and IL-10. The Th2 cells are the Th cell populations involved in promoting humoral immune responses, particularly against extracellular pathogens that also play a major role in the pathogenesis of the allergic diseases and the autoimmune disorders by the production of IL4, IL-5, IL-6, IL-10, and IL-13.

CLINICAL AND PATHOGENETIC FEATURES OF IgE-MEDIATED FA WITH EOE, FPIES, FPIAP

Unlike IgE-mediated FA in which IgE plays a major pathogenetic role, non-IgE–mediated FA encapsulates a number of disease states caused by different mechanisms.[20,21] With having described the general features of IgE- and non-IgE–mediated FAs, it may now be possible to briefly summarize and compare the clinical and pathogenetic features of the traditional IgE-mediated FA conditions with three of the better studied examples of non-IgE–mediated FA, EOE, FPIES, and FPIAP (Table 2).

IgE-mediated food allergies (FA) commonly affect both children and adults. In contrast, eosinophilic esophagitis (EOE) is primarily seen in adults, while food protein-induced enterocolitis syndrome (FPIES) and food protein-induced allergic proctocolitis (FPIAP) are primarily seen in infants.[22–24] FPIAP prevalence estimates

range widely, from 0.16% in healthy children and 64% in patients with blood in stools.[7,25,26] Whereas the pathogenesis of IgE–mediated FA has been characterized as a Th2-driven condition,[27] the involvement of precise cytokine pathways of the three non-IgE conditions has not been identified. The presence of eosinophils in tissues in all four conditions, however, suggests some involvement of a Th2-mediated component in each. EoE is a recently recognized esophageal inflammatory disease with clinical manifestations arising from esophageal dysfunction. The etiology of EoE is currently being clarified and FA is evolving as the central cornerstone of EoE disease pathogenesis. Given the large number of eosinophils in the esophagus of people with EoE verified by data from murine models EoE is widely considered as the hallmark Th2 disease of the esophagus.[28] It is also known that some eosinophilic inflammation is controlled by other subsets of T cells, such as Th9 or Th17, and control is also exerted by type 2 innate lymphoid cells acting together with basophils. The most common food triggers in IgE-mediated FA include milk, eggs, wheat, soy, fish, shellfish, peanut, and tree nuts, similar to those seen in EOE but differing from those seen in FPIES or FPIAP, in which milk may be a more prominent trigger.[29–31]

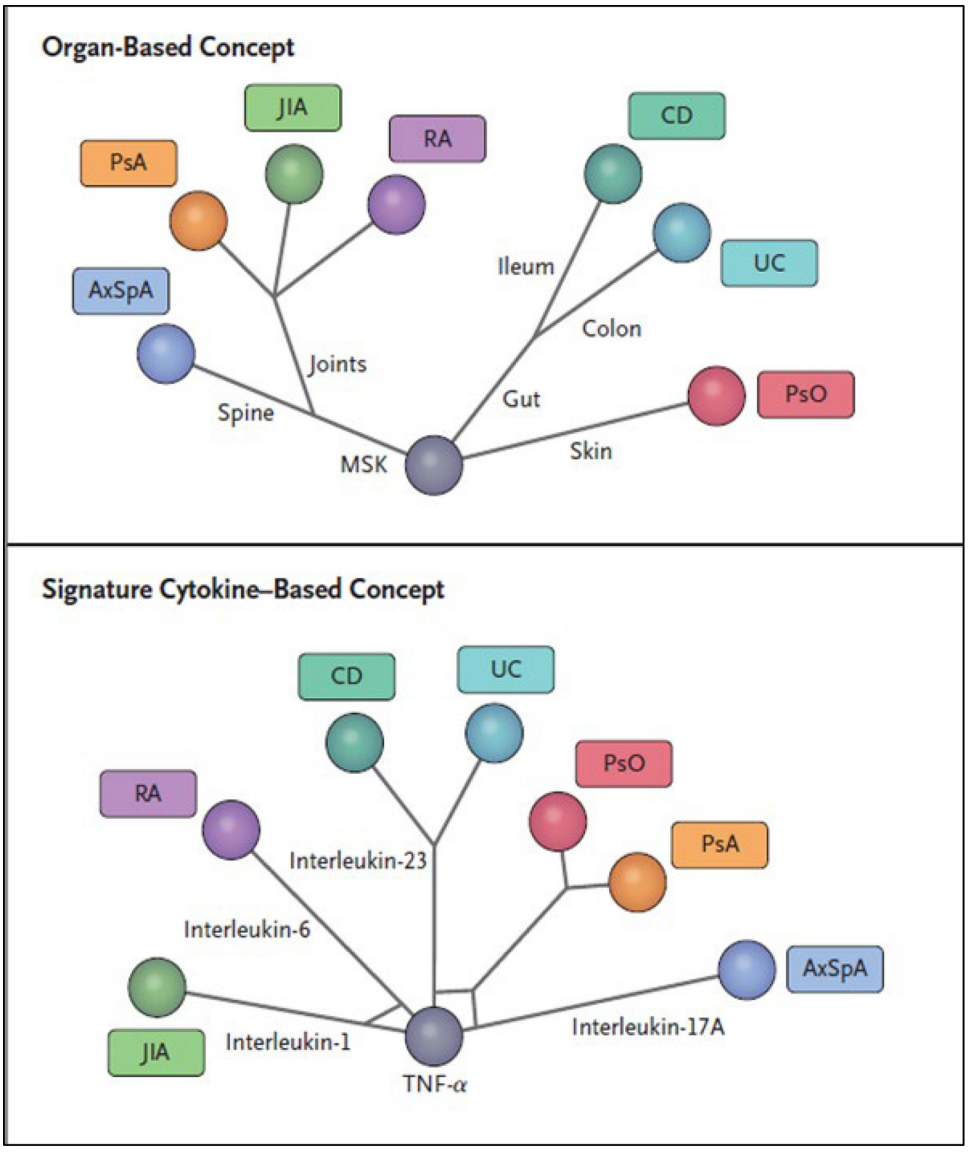


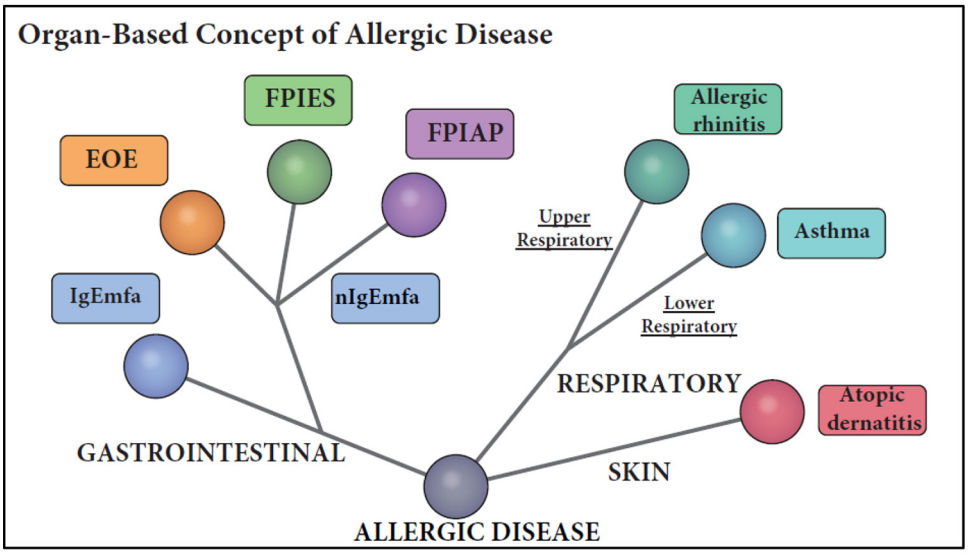
Figure 3. *Organ-based and signature cytokine–based concepts of immune-mediated inflammatory diseases (IMID) of the joints and gut. Top panel, IMIDs of the joints and gut based on the affected organs. Bottom panel, IMIDs of the joints and gut based on the signature cytokine. AxSpA = Axial spondyloarthritis; CD = Crohn disease; JIA = juvenile idiopathic arthritis; MSK = musculoskeletal disease; PsA = psoriatic arthritis; PsO = psoriasis; RA = rheumatoid arthritis; TNF-α = tumor necrosis factor α; UC = ulcerative colitis. (Reproduced with permission from Ref. 32.)*

Although IgE-mediated FA is usually outgrown by school age, symptoms of EOE are rarelyoutgrown and usually persist with the clinical manifestations of FPIES or FPIAP are usually resolved in infancy or early childhood.[30] In addition to common food triggers in FPIES, such as oat, egg, peanut, milk, and rice, there is evidence to suggest that early introduction of nuts may be added to the list. This is highlighted in a recent case report by Zhu and Perkins.[31]

Reframing IgE-Mediated and Non-IgE–Mediated Food Allergies through Signature Cytokine Hubs

In addressing the evolving landscape of IgE– and non-IgE–mediated food allergies (FAs), a critical examination of current immunologic paradigms, as described in this paper, reveals a compelling need for a new perspective. Recognizing this gap in our current understanding, a novel proposal to reevaluate these conditions through the lens of signature cytokine hubs

Panel A.



Panel B.

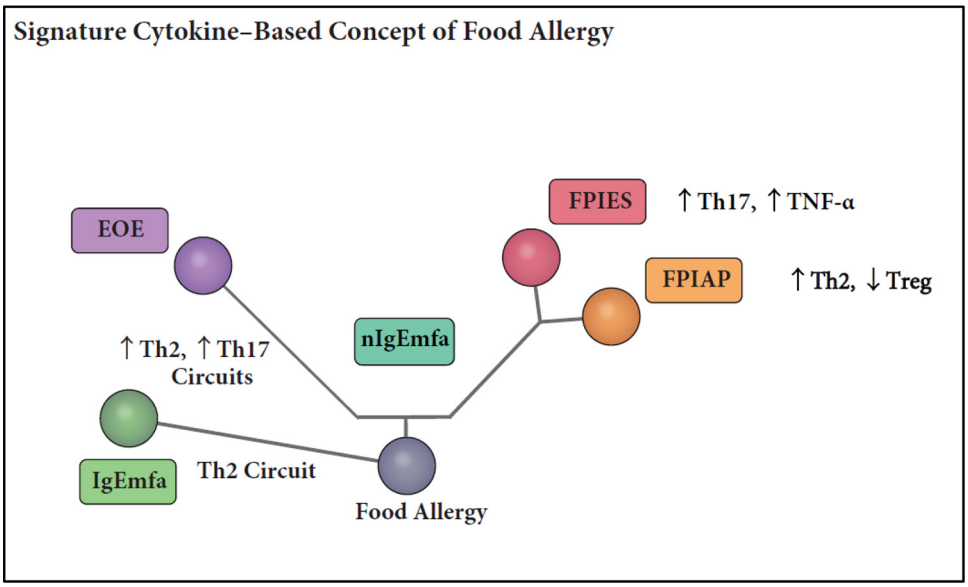


Figure 4. *Proposed organ-based and signature cytokine–based classification of IgE-mediated and non-IgE–mediated FA. Top panel (Figure 4a), an organ-based concept of allergic disease based on the affected organs of the gastrointestinal system, respiratory system, and skin. Bottom panel (Figure 4b), a signature cytokine-based concept of food allergy of IgE-mediated FA (IgEmfa) and non-IgE–mediated FA (nIgEmfa) based on the signature cytokines. IgE = Immunoglobulin E; FA = food allergy; EOE = eosinophilic esophagitis; FPIES = food protein–induced enterocolitis; FPIAP = food protein–induced allergic proctocolitis (adapted from and reproduced with permission from Ref. 32). References that support involvement of cytokines for IgEmfa, EoE, FPIES, and FPIAP can be found in Refs. 20, 26, 29–35, 39–41.*

is presented in this section, which was inspired by a recent publication of Schett *et al.*[32] in which a refined mechanistic classification of immune-mediated inflammatory diseases (IMID) of the joints and gut was proposed to transition from a predominant traditional organ involvement to a modern molecular-based classification derived from the involvement of pro-inflammatory cytokines (Fig. 3). The rationale for adopting this novel proposal to a discussion of IgE- and non-IgE mediated FA is aimed at reframing our understanding of these conditions, offering not only a comprehensive approach to the diagnosis and treatment for the practicing allergist/immunologist but also a catalyst for much needed advancements in research in this area.

Shown in Fig. 4*A* are the major organs involved in allergic disease, *i.e.*, the gastrointestinal, respiratory, and skin organ based allergic diseases. In gastrointestinal disease, these diseases include classic IgE-mediated allergic disease as well as EOE, FPIES, and FPIAP as examples of non-IgE–mediated FA. Also included in Fig. 4 are examples of IgE-mediated respiratory allergic diseases, both upper, *e.g.*, allergic rhinitis, and lower, *e.g.*, asthma, as well as IgE-mediated dermatologic allergy, *e.g.*, atopic dermatitis.[33]

The proposed signature cytokine-based classification of IgE-mediated and non-IgE–mediated allergy is shown in Fig. 4*B*. Of the T-cell pathways described previously, the Th2 pathway is well known to been involved in the pathogenesis of IgE-mediated FA. In reviewing the literature, there is a relative paucity of specific mechanistic data available that describes the pro-inflammatory cytokines and T-cell pathway with non-IgE–mediated FA. By using the data currently available from published studies that contain T-cell pathways described previously,[9,11,27] the proposed signature cytokine-based concept shown in Fig. 4*B* uses cytokine pathways that may drive these conditions that may have potential diagnostic and therapeutic application management of non-IgE–mediated allergic disorders.

The transition from an organ- to a molecular-based classification was initiated by insights derived from disease-associated genetic mutations and polymorphisms of key immune pathways and the development of monoclonal antibodies that target signature cytokine hubs in IMIDs, which have revolutionized the treatment of these disorders. Compared with an organ-based classification, molecular classification more clearly addresses pathophysiologic commonalities across IMIDs that affect different organs but also account for substantial mechanistic differences among IMIDs that affect the same organ.

CONCLUSION

The present report provides an overview of the current classification and frequency of IgE– and non-IgE–mediated FAs. In addition, it offers insights and potential solutions to address lingering questions, particularly concerning the latest immunologic mechanisms that underlie the pathogenesis of non-IgE-mediated FA and focuses on three frequently cited disease conditions: EoE, FPIES, and FPIAP. A congeries of evidence now supports the view that immune dysregulation and cytokine-induced inflammation are the fundamental bases for both IgE– and non-IgE–mediated FA and that an understanding of the cytokine pathways involved in the pathogenesis of these conditions holds the key toward translating this knowledge into practical diagnostic and treatment options available for allergist/immunologists and patients with FAs entrusted to their care. In the past, a predominant focus of the existing literature has been directed to descriptive studies, often characterized by a relative dearth of methodologic rigor compared with established scientific standards that characterize the more comprehensive investigations conducted in IgE-mediated FA. Although the need for future methodologic research and adherence to rigorous scientific protocols is essential, it is also necessary to acknowledge past contributions that have given much to our understanding of the condition. In the present report, a novel signature cytokine-based classification of IgE-mediated and non-IgE–mediated FA allergy is proposed that may offer a novel template for future research in the field of non-IgE–mediated FA. Although this paradigm shift toward a cytokine-induced mechanism in non-IgE–mediated FA represents a departure from the conventional organ-based classification, the concept not only opens new avenues for precise diagnosis but also holds great promise for tailored therapeutic interventions, ushering in a transformative era in clinical practice for more effective management of non-IgE–mediated FAs by more accurate choices of biologics.[34]

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