Food allergy endotypes revisited

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In the last century, food allergy has become recognized as an increasingly prevalent and heterogeneous condition. Advances in biomedical technology have revealed complex genetic, environmental, immune, and metabolic pathways underlying the pathogenesis of food-allergic disorders. These findings permit classification of distinct food allergy endotypes with unique pathophysiologic features. In this review, we suggest that these endotypes of food-allergic disorders should be defined on the basis of (1) whether or not the allergic antibody IgE plays an essential role in disease pathogenesis, (2) the molecular features of the allergen (protein vs carbohydrate), and (3) the molecular markers associated with prognosis, severity, or clinical presentation. Beyond these broad categories, additional subtypes with unique mechanistic characteristics are discussed. (J Allergy Clin Immunol 2025;■■■:■■■-■■■.)

Key words: *Food allergy, pollen-food allergy syndrome, oral allergy syndrome, anaphylaxis, α-gal syndrome, meat allergy, FPIES, food protein–induced enterocolitis syndrome, endotype*

Abbreviations used

AD:	Atopic dermatitis
α-gal:	Galactose-α-1,3-galactose
AGS:	α-gal syndrome
BAT:	Basophil activation test
CCD:	Cross-reactive carbohydrate determinant
CM:	Cow's milk
DC:	Dendritic cell
FA:	Food allergy
FLG:	Filaggrin
FPIES:	Food protein–induced enterocolitis syndrome
GOS:	Galacto-oligosaccharide
LTP:	Lipid transfer protein
NSAID:	Nonsteroidal anti-inflammatory drug
OFC:	Oral food challenge
PA:	Peanut allergy
PFAS:	Pollen-food allergy syndrome
ses-IgE:	Sequential epitope-specific IgE
sIgE:	Specific IgE
SPT:	Skin prick test
Treg:	Regulatory T
TRP:	Transient receptor potential
WDEIA:	Wheat-dependent exercise-induced anaphylaxis

The National Institute of Allergy and Infectious Diseases expert panel defined food allergy (FA) as "an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food."[1] This definition broadly captures the mechanism and manifestation of allergic disorders to food. However, clinicians treating food-allergic patients recognize the tremendous heterogeneity of the ways in which FA develops and presents. Modern technology has yielded significant insights into the complex genetic, environmental, immune, and metabolic pathways underlying the pathogenesis of allergic disorders. As such, a recent position paper by the European Academy of Allergy and Clinical Immunology proposed that the current nomenclature and classification systems are antiquated and thus suggested updates.[2]

In this review, we propose and describe endotypes of FA, focusing on the mechanisms underlying the development and natural course of FA (Fig 1). Classification by endotype involves distinguishing disease states on the basis of their underlying pathophysiologic mechanisms, such as characteristic immune signatures and/or biomarkers. This contrasts with phenotypes, which are identified on the basis of observable features, such as specific signs or symptoms (Box 1). We propose to broadly classify endotypes of food-allergic disorders on the basis of (1) the role of IgE (IgE-mediated, non–IgE-mediated, or mixed); (2) the type of allergen (protein vs carbohydrate) driving sensitization; and (3) the molecular markers associated with prognosis, severity, or clinical presentation, with additional subtypes described.

ENDOTYPE OF IgE-MEDIATED FA

IgE-mediated FA (IgE-FA) is a type I or immediate hypersensitivity reaction and the most common food-allergic disorder.[3] Patients with IgE-FA present with classic allergic symptoms that develop quickly following allergen exposure, with the most severe manifestation being systemic, life-threatening anaphylaxis.[4] The central role of food-specific IgE (sIgE) in immediate allergic reactions was demonstrated in the early 20th century through passive sensitization experiments.[5] Fish-tolerant volunteers were injected intradermally with fish-allergic patient and control sera. Approximately 24 hours later, they were fed fish. A wheal and flare reaction developed at the sensitized site within several minutes to 1 hour in more than 90% of subjects, but no reaction occurred at the control site.

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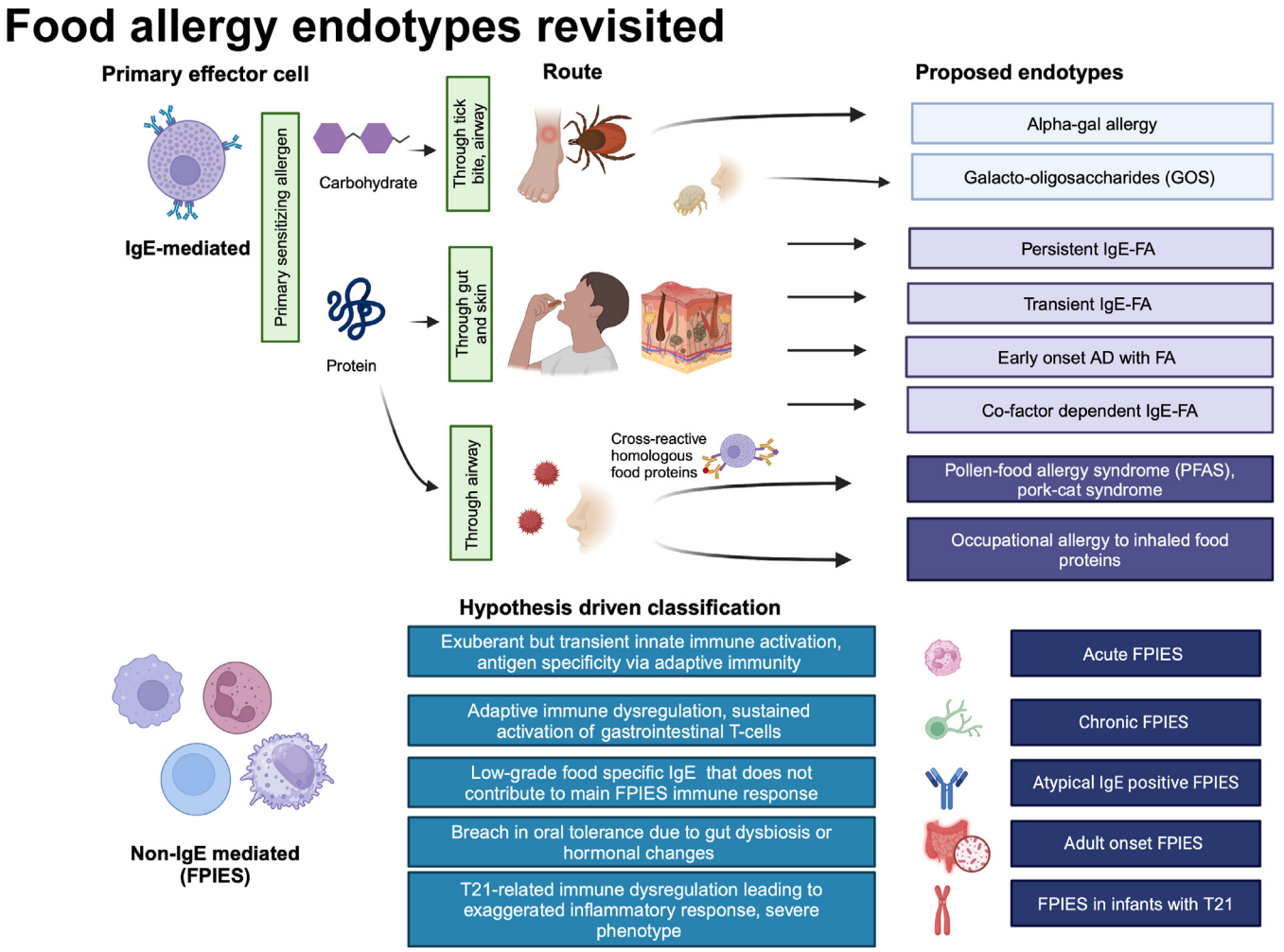

FIG 1. Classification of FA endotypes. For IgE-FAs, endotypes are defined on the type of sensitizing allergen and route of sensitization. For FPIES, endotypes are proposed on the basis of our understanding of putative pathophysiologic mechanisms. *T21*, Trisomy 21.

Box 1. Definitions of terms used in the review

Endotype: A subtype of a disease defined by distinct functional or pathophysiologic mechanisms.
Phenotype: Observable characteristics of an organism resulting from the interaction of its genotype and environment.
Epitope: The region of an allergen recognized by specific IgE or T cells.
Sequential/linear epitope: Epitope consisting of a continuous sequence of amino acid residues.
Conformational epitope: Epitope is formed by the 3-dimensional conformation adopted by the interaction of contiguous or discontiguous amino acid residues.
Molecular spreading: The expansion of an immune response from a singular primary sensitizing protein to other partially homologous or cross-reactive proteins across different allergenic families within a food.
Epitope spreading: The immune system's diversification from targeting an initial epitope to additional epitopes, either within the same allergen or across different allergens. This term is used more broadly in the scientific community, in various immunologic conditions (eg, autoimmunity and cancer).

Genetics plays a critical role in IgE-FA susceptibility, influencing both epithelial barrier integrity and immune responses.[6] Immune-antigen interactions at the epithelial barrier play a central role in sensitization.[6-8] Mutations in the filaggrin (FLG) gene impair epithelial barrier function, increasing allergen penetration and sensitization.[9,10] Polymorphisms in immune signaling genes such as IL-4RA, IL-13, and STAT6 drive T_H2-skewed immunity by enhancing IL-4 and IL-13 signaling and promoting allergen-sIgE production.[11,12] Genome-wide association studies have identified loci associated with peanut allergy (PA), such as 11q13.5, implicating genes such as *LRRC32* involved in T-cell regulation.[13,14] Epigenetic modifications, including DNA methylation of immune-related genes, further modulate allergic phenotypes.[6] Gene-environment interactions, such as allergen exposure during critical windows, amplify these genetic effects.[9]

Fig 2 presents a schematic of endotypes of IgE-FA. Under the umbrella of IgE-FA, distinct endotypes are identified on the basis of the nature of the sensitizing allergen. Within the endotype of IgE-FA to carbohydrates, the major antigens of clinical relevance are galactose-α-1,3-galactose (α-gal), short-chain galacto-oligosaccharides (GOSs), and cross-reactive carbohydrate determinants

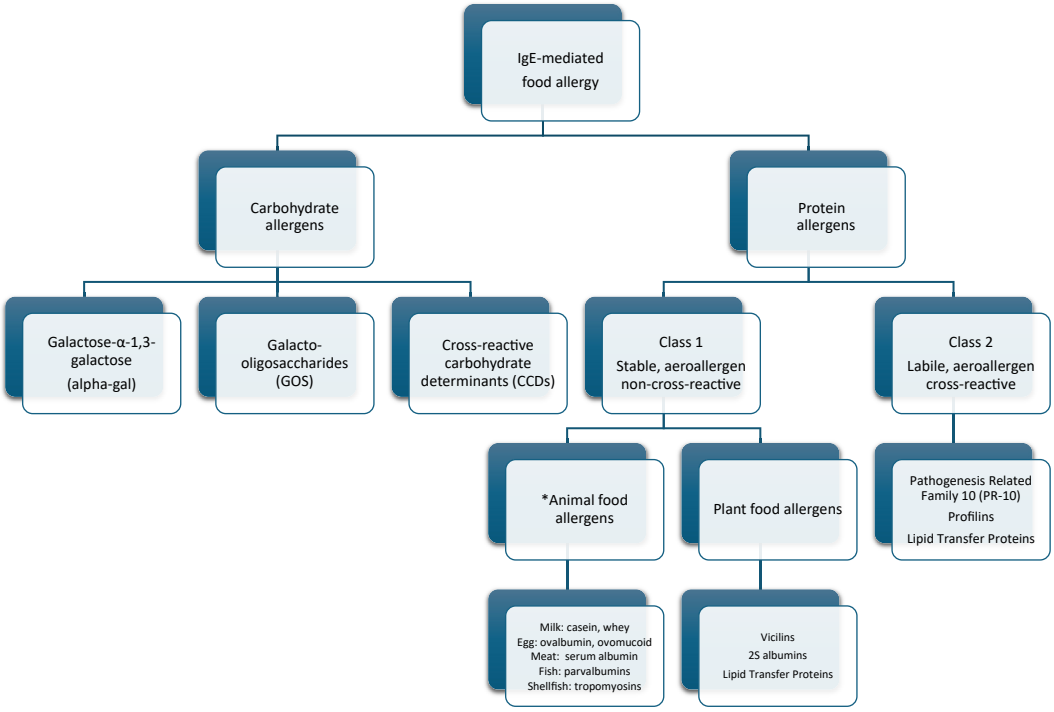

FIG 2. Classification of FA endotypes based on IgE involvement and the type of sensitizing allergen. *Sensitization to serum albumins in mammalian meat, milk, and egg yolk might occur via ingestion or secondary to inhalation of the cross-reactive serum albumins in animal dander (cat or dog), leading to pork-cat syndrome. Sensitization to crustacean tropomyosin might occur via ingestion or secondary to inhalation of the cross-reactive tropomyosin in arthropod aeroallergens from dust mites and cockroach.

(CCDs). Protein antigens are typically classified as class 1, that is, stable, food-derived proteins, or class 2, that is, labile proteins that cause reactions because of cross-reactivity after sensitization to aeroallergens. Table I provides the phenotypic features of the endotypes of IgE-FA discussed in this review.[15-45]

Mechanisms of IgE-FA development

Allergic sensitization and elicitation. IgE-FA develops when there is a breakdown of oral tolerance leading to T_H2-allergic sensitization and secretion of allergen-sIgE. After eating, food antigens cross mucosal barriers in the gastrointestinal tract. In a state of tolerance, these antigens are processed by dendritic cells (DCs) without immune activation. Tolerogenic cytokines such as IL-10 are released, leading to differentiation of naive T cells into regulatory T (Treg) cells and a humoral response characterized by robust IgA and IgG4 and low IgE production. Allergic sensitization to food might occur through the skin, oral mucosa, gastrointestinal tract, or respiratory tract.[27] During sensitization, epithelium that is damaged or inflamed triggers release of proinflammatory cytokines including IL-25, IL-33, and thymic stromal lymphopoietin.[3,4] These cytokines promote T_H2 polarization by stimulating innate lymphoid cell secretion of IL-4 to suppress Treg cells and upregulation of OX40 ligand by activated DCs, which primes T cells for a T_H2 immune response. T_H2 lymphocytes and their associated cytokines drive B cells to proliferate and class-switch to IgE. Following sensitization, a pool of allergen-sIgE–secreting plasmocytes and memory B cells is established in tissues and circulation and contributes to the long-lasting immunologic memory characteristic of persistent IgE-FA.[28,29] On subsequent allergen exposures, sIgE binds to high-affinity FcεRI receptors on mast cells and basophils. Cross-linking of these receptors triggers the release of preformed mediators such as histamine and newly synthesized cytokines, leukotrienes, and prostaglandins.[4] Food-sIgE can be quantified in serum and monitored over time to assess tolerance. Functional IgE-cross-linking may be assessed via *in vitro* basophil activation test (BAT), which has potential as a biomarker reflecting the likelihood of allergic reaction on ingestion.[30]

Epitope recognition and spreading. The nature of the epitope recognized by sIgE has implications for prognosis and the strength of the immune response. sIgE may be specific for a continuous sequence of amino acids, termed a linear epitope, or amino acids in their 3-dimensional structure, termed a conformational epitope.[31-33] Detection of sIgE directed against sequential epitopes is associated with persistent IgE-FA, whereas immune responses targeting 3-dimensional conformational epitopes, such as those in cow's milk (CM) and hen's egg white that change shape when heated, are associated with tolerance of baked milk/egg and a milder allergic phenotype (Fig 3). This is discussed in detail in later sections on persistent and transient IgE-FA.

Epitope spreading. Epitope spreading describes the diversification of immune responses from an initial dominant protein epitope to additional epitopes either within the *same molecule* or among *structurally related proteins of the same allergen*. This has been best described in autoimmunity,[34] but given that allergens are proteins, epitope spreading is expected to similarly

TABLE I. Endotypes of FA and their phenotypic and mechanistic features

IgE-FA	Phenotypic (clinical) features	Endotypic features
Classic IgE-FA: Protein epitopes		
Persistent IgE-FA	• More common for peanut, tree nuts, sesame, shellfish, and fish • Less common for milk or egg, although associated with inability to tolerate baked forms • Associated with early-onset or severe AD, severe anaphylaxis, multiple FA, and high initial or rising food-sIgE levels[15]	• Increased B-cell and T-cell epitope diversity[16,17] • Predominant ses-IgE and ses-IgE expansion[18] • High affinity IgE binding[16]
Transient IgE-FA	• More common for milk, egg, soy, and wheat allergy • Associated with low initial IgE levels, tolerance of baked forms of milk/egg, and high threshold of reactivity[19]	• Predominant sensitization to conformational epitopes • Changes associated with tolerance development: declining sIgE levels, increased IgG4 and IgA, and lower IgE-binding affinity[20]
FA and AD	• Early-onset AD[21]	• Skin tape stripping profile: reduced FLG, distinct lipid and protein expression profiles, higher *S aureus*, and increased T_H2 immune response[22,23]
Severe FA	• Difficult to predict patients at higher risk of severe reactions from phenotypic features[24]	• Sensitization to Pru p 3 (peach) and 2S albumins (tree nuts)[25,26] • Monosensitization to Ana o 3 (cashew)[27] • Monosensitization to single LTP[28] • Sensitization to higher number of sequential epitopes on CM casein[29]
Sensitization through inhaled food proteins	• Adults with occupational exposure—baker's asthma (wheat), seafood-processing facilities (shellfish) • Predominantly respiratory presentation, may tolerate ingestion	• Baker's asthma: predominant sensitization to α-amylase inhibitor[30]
Sensitization to food proteins homologous with aeroallergens (PFAS, pork-cat syndrome, tropomyosin syndrome, and bird-egg syndrome)	• PFAS symptoms are generally limited to the oropharynx (pruritus, tingling, angioedema, and perioral urticaria) with rare progression to systemic symptoms[31,32] • Patients with PFAS often tolerate cooked or processed foods as they are sensitized to heat-labile proteins; CRD is helpful for diagnosis • Allergic rhinoconjunctivitis typically precedes PFAS; rarely aeroallergen sensitization may be asymptomatic • Pork-cat syndrome involves reactions to pork after sensitization to cat aeroallergen[35] • Tropomyosin syndrome describes reactions to shellfish after sensitization to dust mite[36,37] • Bird-egg syndrome begins with sensitization to bird, with later reactions to egg yolk[38,39]	• Sensitization to class 2 allergens such as PR-10 proteins or profilins[33] • Sensitization to LTP, in particular Pru p 3, or monosensitization to LTP without cosensitization to PR-10 or profilins is associated with increased severity or systemic reactions[34] • In pork-cat syndrome, sensitization to cat serum albumin (Fel d 2) results in reactivity to porcine albumin and allergic reactions on ingestion of pork[35] • In tropomyosin syndrome, sensitization to tropomyosin in house dust mite is thought to cause cross-reactivity with tropomyosin in shellfish[36,37] • In bird-egg syndrome, people sensitized to bird aeroallergens react to egg yolk; this appears to be due to cross-reactivity between avian and egg α-livetin (Gal d 5)[38,39]
Cofactor-dependent IgE-FA (eg, FDEIA and WDEIA)	• Presence of cofactor (exercise, NSAIDs, or alcohol) is necessary for clinical reaction; food ingestion without the cofactor is tolerated[15]	• ω-5-Gliadin sensitization highly associated with wheat FDEIA[40]
Carbohydrate epitopes		
AGS	• Delayed urticaria or anaphylaxis 2-6 h after mammalian meat consumption[41]	• α-Gal sensitization through tick bites[42] • Antigen is thought to enter the circulation 2-3 h after ingestion with lipid metabolism
GOS	• Immediate allergy on first consumption of formula enriched with short-chain GOSs[43]	• Sensitization is thought to be related to local dust mites[44]
CCDs	• Generally asymptomatic[45]	• Sensitization to glycan moieties on plant and insect glycoproteins[45] • Absence of clinical reactivity is attributed to sIgE lacking the spatial configuration or valency to activate effector cells[45]; IgG4 blocking antibodies may also contribute

CRD, Component-resolved diagnostics.

occur in allergic responses. This phenomenon encompasses both *intra-allergen* and *inter-allergen* mechanisms, leading the immune system to recognize and react to multiple epitopes within a single allergen or its homologs.[35,36] In CM allergy, initial sensitization to an epitope on αS1-casein may expand to additional epitopes on the same protein or to other milk proteins (eg, β-casein).[35] This process reflects enhanced antigen processing and presentation, with T-cell help, driving B-cell

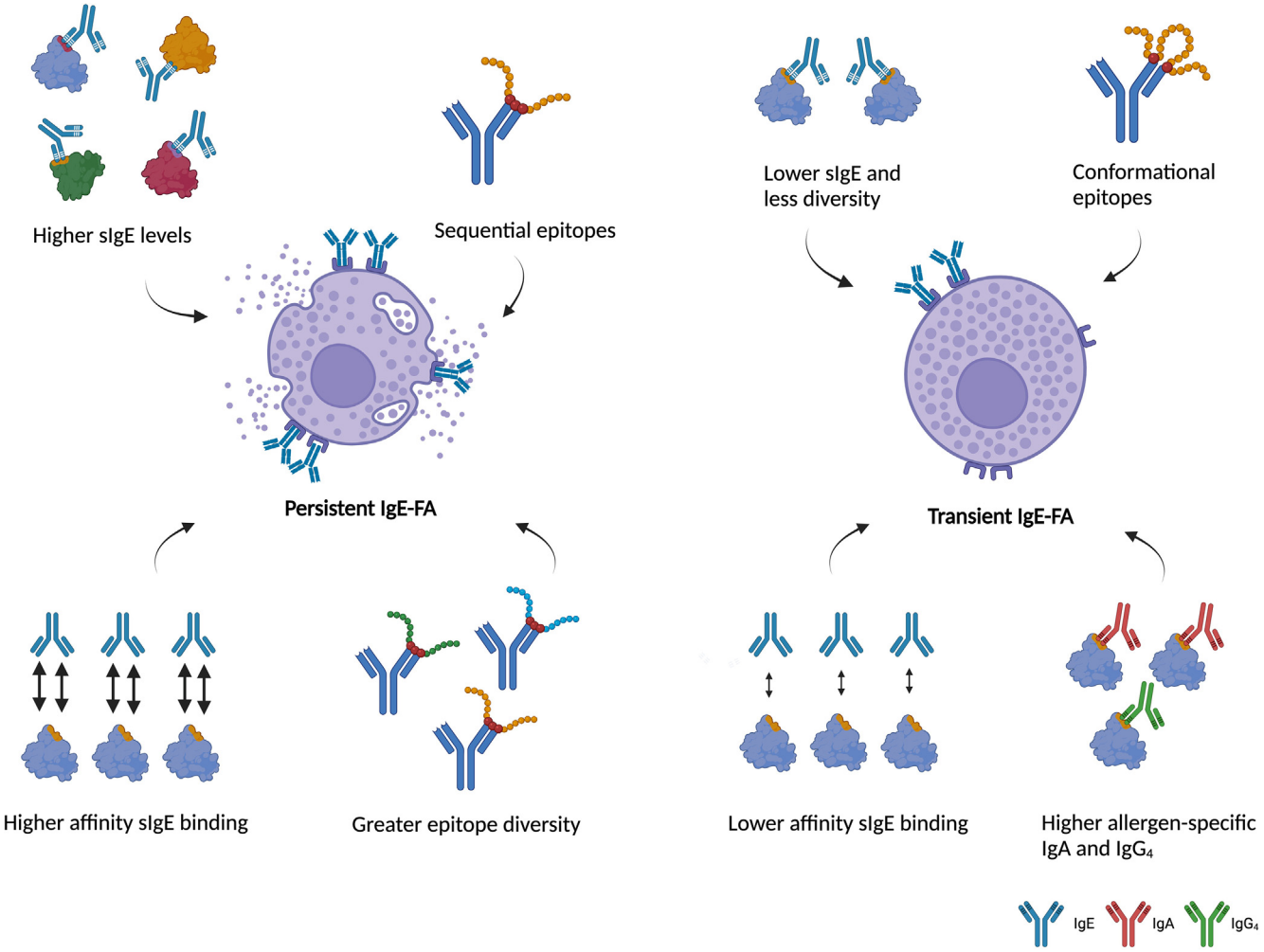

FIG 3. Humoral immune changes associated with endotypes of persistent and transient IgE-FA. Persistent IgE-FA is associated with increasing levels of food-sIgE, increasing IgE diversity with expanding repertoire of recognized proteins, high-affinity IgE binding, and the expansion of ses-IgE. In contrast, transient IgE-FA is associated with decreasing sIgE levels, increased food-specific IgG4 and IgA, and shift to lower-affinity epitopes, correlating with reduced clinical reactivity. Adapted from Hemmings et al.[43]

IgE diversification.[34] Intra-allergen epitope spreading can intensify the allergic response by broadening IgE reactivity, perpetuating T_H2-driven inflammation, and reducing the likelihood of natural tolerance development (Fig 3).

Molecular spreading. In contrast, molecular spreading refers to the broadening of the immune response from recognizing a singular primary sensitizing protein to other partially homologous or cross-reactive proteins across different allergenic families within a food.[37] This phenomenon represents a *cross-reactive* mechanism, because it involves the recognition of conserved epitopes shared among *unrelated proteins*. For example, although direct evidence is limited, in PA, sensitization is thought to begin with Ara h 2 (a 2S albumin) but then extends to vicilin and legumin proteins Ara h 1 and Ara h 3 through molecular spreading.[16] Molecular spreading may also drive cross-reactivity to seemingly unrelated allergens because of structural similarities between shared protein families. For instance, sensitization to house dust mite tropomyosin can lead to IgE reactivity against tropomyosins in shrimp, crab, and lobster.[17] Similarly, in birch pollen allergy, sensitization to Bet v 1 frequently results in cross-reactivity to food PR-10 proteins, such as Mal d 1 (apple) or Ara h 8 (peanut).[37] This cross-reactive spreading amplifies sIgE responses, increases basophil reactivity, and enhances the severity and persistence of allergic disease.[17] Advanced diagnostics, such as peptide microarrays, have further elucidated the patterns of molecular spreading and their clinical implications.[38]

Monosensitization versus polysensitization

Within the same allergen. Monosensitization involves IgE targeting a single epitope, whereas polysensitization targets multiple epitopes within the same allergen. In PA, polysensitization to multiple Ara h 2 epitopes correlates with increased basophil activation and more severe clinical outcomes.[17]

Within the same allergenic food source. Polysensitization can occur within the same allergenic source, as exemplified by the peanut storage proteins Ara h 1, Ara h 2, and Ara h 3. Among these, Ara h 2 is the most clinically significant, with strong predictive value for systemic allergic reactions.[39] Ara h 1 and Ara h 3, although less potent individually, contribute to the

overall immunogenic profile of PA when sensitization occurs to multiple peanut proteins. This phenomenon is attributed to the structural conservation and shared IgE-binding epitopes among these storage proteins, which amplify allergic responses.[17,39]

Across different foods. Some proteins, such as vicilins and 2S albumins, are conserved across various food groups such as fruits, vegetables, nuts, and seeds.[40] Although this does not always result in clinical reactivity, it may in some cases. For example, patients exquisitely sensitive to cashew/pistachio may experience allergic reactions to citrus seeds, with sIgE apparently directed against citrin.[41] Citrin and Ana o 2 are both 11S globulins belonging to the cupin superfamily, and so the significant homology between these proteins is thought to underlie the coreactivity.

Subclinical sensitization. Sensitization does not always lead to clinical reactivity, and clinical evaluation is critical to assess the actual risk of reaction.[42] Subclinical sensitization refers to the production of sIgE without corresponding allergic symptoms. Various mechanisms have been proposed to explain this observation, including low sIgE affinity, targeting of nonclinically relevant epitopes, and poor effector activation, perhaps because the sIgE targets conformational regions that fail to cross-link FcεRI on mast cells and basophils.[43] This phenomenon is supported by findings that low-affinity IgE often arises in the absence of key signals, such as IL-13 from Tf_H13 cells, which are required for the production of high-affinity IgE capable of driving severe allergic responses and anaphylaxis.[44]

FA and atopic dermatitis

Atopic dermatitis (AD) is an important risk factor for IgE-FA.[45] The dual allergen hypothesis posits that early contact with food through a disrupted, inflamed cutaneous epithelial barrier in the absence of ingestion promotes a T_H2-skewed immunologic response and IgE-FA.[46] However, only one-third of children with AD develop IgE-FA, and children with early-onset AD and IgE-FA may represent a unique endotype.[21] Studies of children with AD and IgE-FA using noninvasive skin-stripping techniques have revealed distinct features including increased transepidermal water loss related to lower levels of FLG and sphingosine ceramide, increased gene expression related to DCs and T_H2 immune pathways, and higher levels of *Staphylococcus aureus*.[22,23] These characteristics set them apart from food-allergic children without AD as well as from nonallergic children.

FLG is a stratum corneum protein that plays a crucial role in skin barrier integrity by aggregating keratin filaments.[47] When hydrolyzed, FLG breakdown products contribute to the production of essential components that maintain pH balance, retain moisture, and influence the skin microbiome.[48,49] FLG loss-of-function mutations are associated with increased FA.[50] Many individuals with PA but no AD also demonstrate decreased FLG breakdown products despite having normal transepidermal water loss, suggesting an important role of FLG in the development of IgE-FA, even in the absence of AD.[51] In Japanese and European birth cohorts, FLG loss-of-function mutations were associated with persistent egg sensitization in both cohorts, with this association independent of AD in the Japanese cohort. Further studies are necessary to clarify the pathophysiology and characterize patients with IgE-FA and impaired FLG function in the absence of AD.

Endotypes of severe FA

Food-allergic reactions range from mild to severe.[52] Mild symptoms include transient oral pruritus or a few urticarial lesions, whereas severe reactions can affect the respiratory, cardiovascular, or neurologic system, requiring epinephrine or hospitalization. Various grading scales classify severity, an example of which is the updated Consortium for Food Allergy Research anaphylaxis scale (grades 1-5).[53] Grade 1 reactions involve mild mucocutaneous, respiratory, or gastrointestinal symptoms. The grade increases with increasing reaction severity, with grade 3 symptoms sufficient to limit activity. Grade 4 includes life-threatening cardiovascular, neurologic, or lower respiratory tract symptoms, and grade 5 denotes fatal reactions.

Identifying patients at higher risk of severe reactions is an important unmet clinical need.[24] Young children are most likely to be evaluated in the emergency department/hospital.[54] However, infants and toddlers usually develop cutaneous and/or gastrointestinal symptoms and are generally thought to have lower risk for severe reaction.[24,55] The risk of severe reaction, including fatal and near-fatal anaphylaxis, appears to be the highest in adolescence and young adulthood.[24,56-59] This might be in part attributable to the age-related transition to allergy self-care as well as risk-taking behavior with regard to food choices, cross-contact precautions, and carrying epinephrine. However, these behavioral considerations are most applicable in the teenage years, and data from the United Kingdom suggest that the increased risk of fatal anaphylaxis may persist into the fourth decade of life.[24] As such, biologic factors may be at play, although because of rarity of food-allergic reactions of this severity, mechanisms are yet to be elucidated.[59] A recent meta-analysis found that a higher sIgE level, larger skin prick test (SPT) wheal size, BAT, previous history of anaphylaxis, and concomitant asthma were not predictors of reaction severity.[24] However, cofactors may play a role in reaction severity, as discussed later.

Certain molecular features may correlate with reaction severity. Sensitization to specific major allergens is associated with a higher risk of anaphylaxis.[25,60,61] Notable examples of this include 2S albumins (eg, Ara h 2 in peanut and Ana o 3 in cashew) and lipid transfer proteins (LTPs) such as Pru p 3 in peach.[62] In addition, the molecular nature of the epitope appears to affect the potency of the allergic response; in PA, IgE specific to linear/sequential epitopes and higher epitope diversity have been associated with increased reaction severity.[18,63,64]

Transient FA: Development of tolerance in childhood

Most children with milk, egg, soy, and wheat allergy have a transient IgE-FA phenotype and develop tolerance naturally.[65-69] Clinical predictors include tolerance of baked milk/egg, lower sIgE levels and smaller SPT wheal sizes at presentation, decreasing sIgE levels and SPT wheal size over time, and absence of AD, allergic rhinitis, or asthma.[19,70] Lower levels of sIgE to the heat-stable proteins casein and ovomucoid in milk and egg, respectively, are associated with tolerance of baked milk/egg.[71,72] Most milk- and egg-allergic children who tolerate baked milk/egg are primarily sensitized to conformational epitopes, as previously described.[73]

On a molecular level, natural resolution of FA is characterized by declining sIgE levels, less epitope diversity, lower IgE-binding affinity, increased allergen-specific IgG4, increased Treg cells,

higher levels of inhibitory cytokines, and possibly elevated allergen-specific serum IgA.[20,74-76] This has been best studied in CM allergy, in which patients who tolerated baked milk and/or outgrew their allergy demonstrated lower IgE affinity and less epitope diversity. IgG4 is thought to compete with IgE for allergen binding, blocking effector cell activation, whereas IgA reinforces epithelial barrier integrity and prevents allergen absorption.[77-79]

Persistent IgE-FA

Peanut, tree nut, sesame, and seafood allergies typically persist.[15] Natural history data are most robust for peanut and tree nuts, with an estimated resolution rate of 20% to 30% for PA[69,80] and just 10% to 15% for tree nut allergy.[81,82] Resolution typically occurs within the first 6 years of life, with the likelihood of naturally outgrowing these allergies decreasing after early childhood. Phenotypic features associated with persistent IgE-FA include early-onset, severe AD, severe anaphylactic reactions, multiple FAs, and high initial, peak, or rising sIgE levels.[15]

Increased diversity of sequential epitope-specific IgE (ses-IgE) is associated with more severe reactions and appears to be a biomarker of persistent allergy.[18,63,64] This is best studied in PA, in which epitope-binding maturation and epitope-spreading patterns have shed light on the development of persistent PA. Data from the Learning Early About Peanut study suggest that children in both the avoidance and consumer groups initially developed sIgE to conformational epitopes.[83] Subsequent development of ses-IgE represented a key event in the evolution of persistent PA, which occurred primarily after age 2.5 years and appeared to be mitigated by early oral introduction of peanut. Children in the avoidance arm who developed PA had higher levels of peanut ses-IgE, and peanut ses-IgE repertoire expansion was found exclusively in children who developed PA. In contrast, ses-IgG4 expansion was seen in all children but was delayed and reduced in children who avoided peanut, suggesting that early oral introduction induces ses-IgG4 expansion. Although egg allergy generally has a favorable prognosis, studies have similarly noted ses-IgE development and epitope diversity to predict persistent egg allergy.[84,85]

The replenishment of allergen-sIgE plays a crucial role in sustaining reservoirs of short-lived IgE-expressing cells, contributing to persistent allergy. Populations of T_H2-polarized memory B cells expressing IgG_1 or IgG_4, CD23, and germline immunoglobulin heavy epsilon with highly mutated B-cell receptors have been found to be increased in children and adults with persistent PA.[86,87] These cells serve as precursors to high-affinity, pathogenic IgE-producing cells, which likely drive the long-term persistence of IgE-FA.[88]

IgE-FA with primary sensitization to proteins

Food antigens that can trigger IgE sensitization are mainly proteins.[89] The allergenic potential of food proteins may be influenced by factors such as their stability during food processing and digestion, glycosylation, their ability to bind lipids that protect them from degradation and aid in absorption in the gastrointestinal tract, or their capacity to activate innate immune responses and cause primary sensitization.[90] In contrast, secondary sensitization begins with respiratory exposure to a homologous protein, followed by cross-reactivity with food proteins.[91,92]

Class 1 allergens are the major food allergens implicated in IgE-FA, including anaphylaxis.[89] They are typically water-soluble glycoproteins with molecular masses between 10 and 70 kDa and a high degree of stability during digestion with resistance to heat, acid, and proteases. Class 1 allergens are found in CM (caseins and whey proteins), egg white (ovalbumin and ovomucoid), meat (bovine serum albumin), seafood (tropomyosin in crustaceans and parvalbumin in finned fish), as well as plants, including peanut, legumes, tree nuts, seeds, grains, and fruits/vegetables.

Endotype of IgE-FA to inhaled food proteins as primary sensitizers

Beyond the typical sensitization via skin contact or ingestion, primary sensitization to aerosolized food antigens has been described in adults with occupational exposure. The classic example is baker's asthma, with work-related wheat exposure causing asthma and rhinitis.[93] Unlike classic wheat allergy, patients with baker's asthma are primarily sensitized to α-amylase inhibitor.[94] Despite positive bronchial challenge and IgE sensitization, many patients with baker's asthma continue to tolerate ingestion of wheat, perhaps because of lack of sensitization to gliadin/glutenin proteins or continued regular ingestion of bread inducing persistent tolerogenic mechanisms. In others, a breach in oral tolerance occurs and symptoms develop on wheat ingestion.[95] Occupational asthma and allergy due to aerosolized shellfish and fish allergens have also been documented in 4% to 36% of workers in seafood-processing facilities.[96]

Endotype of IgE-FA secondary to sensitization to homologous airborne allergens

Pollen-food allergy syndrome (PFAS) represents a distinct IgE-FA endotype in which primary sensitization occurs to aeroallergens with subsequent reaction to homologous or cross-reactive food proteins, referred to as class 2 food allergens.[91,92] PFAS is also known as oral allergy syndrome because symptoms are largely limited to the oropharynx, including pruritus, tingling, angioedema, and perioral urticaria elicited by contact with food; systemic symptoms are rare (up to 3%).[97] Patients report previously tolerating raw plant foods only to suddenly experience symptoms later in childhood or as an adult. They frequently report seasonal allergic rhinoconjunctivitis preceding PFAS onset, although there is no clear correlation between severity of rhinoconjunctivitis and PFAS. Rarely, patients report no seasonal symptoms, yet they have evidence of pollen sensitization. Despite pollen sensitization being the primary event, pollen-specific immunotherapy does not consistently ameliorate PFAS symptoms, is currently not recommended for the sole indication of PFAS, and has rarely been reported to induce PFAS.[92,98,99]

The pattern of PFAS foods varies with local aeroallergens. Classic associations include birch pollen allergy with reactions to apple, almond, hazelnut, and peanut; grass allergy with celery, melon, and tomato; mugwort allergy with celery, carrot, parsley, fennel, and peach; and ragweed allergy with melons and banana.[92] Many patients with PFAS tolerate cooked or processed forms of their PFAS triggers because the culprit proteins are labile and readily degraded by heat or digestion.[92] Because of their lability, commercial SPTs have decreased sensitivity, and

prick-prick tests to the fresh foods and/or component-resolved diagnostics are important tools in PFAS diagnosis.

Most PFAS allergens belong to the pathogenesis-related (PR-10), profilin, and LTP families. PR-10 proteins include Bet v 1 (birch), the best-studied PFAS protein. Bet v 1 homologs, which include Mal d 1 (apple), Pru av 1 (cherry), Pru ar 1 (apricot), Pyr c 1 (pear), Cor a 1 (hazelnut), and Ara h 8 (peanut), are labile and easily denatured with cooking, processing, and digestion; thus, systemic reactions are rare. Profilins are similarly sensitive to gastric digestion, and so profilin sensitization carries low risk of systemic symptoms. Profilins share significant homology, with sensitization to profilins associated with multiple pollen-associated FAs.[100,101] LTPs are pan-allergens with better heat and digestion stability and significant ability to bind lipids, which may protect them from degradation. Among the LTPs, Pru p 3 (peach) has been associated with most (68%) cases of LTP-associated anaphylaxis in an Italian study.[102] It has been suggested that Pru p 3 is a primary sensitizer leading to subsequent polysensitization to other LTPs.[103] Sensitization to LTPs without cosensitization to PR-10 or profilin proteins is associated with greater reaction severity.[102]

PFAS to peanut and tree nuts can develop in older children and adults. In contrast to other plant foods, it is more challenging clinically because monosensitization to PR-10 (eg, Ara h 8 and Cor a 1) is uncommon.[104] Patients are usually sensitized to both pollen cross-reactive and non–cross-reactive allergens (eg, vicilins and 2S albumins).[105] Component-resolved testing is helpful in evaluating sensitization patterns, but an oral food challenge (OFC) may be necessary to assess the risk of systemic reaction.[106] Monosensitization to nut PR-10 or profilins is not a risk factor for systemic reactions, unless large doses of nuts are ingested on empty stomach and/or cofactors are present.[92,104]

Tropomyosin syndrome has been suggested as a subtype of oral allergy syndrome.[107,108] Tropomyosin is a heat-stable, highly conserved arthropod pan-allergen, and it is hypothesized that one endotype of shellfish allergy involves primary aeroallergen sensitization to house dust mite tropomyosin leading to cross-reactivity with shellfish. This appears to be characterized by a high threshold and limited oral symptoms. However, this has not been definitively established.

Pork-cat syndrome is a phenomenon in which patients experience allergic reactions to pork after sensitization to cat, usually in adolescence or adulthood.[109] Unlike α-gal syndrome (AGS), these patients experience fairly immediate symptoms, including oral pruritus at the time of ingestion. Well-cooked preparations of pork appear less likely to elicit a reaction. Cat serum albumin (Fel d 2) appears to be the index antigen, which later causes reactions to porcine albumin (82% homologous). It is thought that sensitization occurs slowly over time, explaining why reactions develop later in life. A study of 76 cat-allergic people found that the frequency of sensitization to cat serum albumin was 14% to 23%, whereas 3% to 10% were sensitized to porcine albumin.[110] It is thought that about one-third of these patients may be at risk for symptoms. Similarly, cosensitization to bovine albumin has been reported, mostly associated with exposure through medical tissue adhesives.[111,112]

Endotype of IgE-FA to carbohydrate allergens

Although protein epitopes dominate any discussion about mechanisms of FA, there is precedent to recognize oligosaccharides as immunogenic. The ABO blood type incompatibility serves as one of the most clinically significant examples, but carbohydrate antigens have increasing relevance in FA.[113] Herein, we describe the endotype of FA characterized by food-sIgE to carbohydrate epitopes. Within this endotype, the major antigens of clinical relevance are α-gal, short-chain GOSs, and CCDs.

α-Gal syndrome. At the turn of the 21st century, a series of seemingly unrelated observations led to a discovery of AGS, which serves as perhaps the most elegant example of why FA may best be classified by endotype rather than phenotype.[114,115] Patients with AGS are sensitized to α-gal, an oligosaccharide found in the tissues of nonprimate mammals that is similar to the B antigen in the ABO blood-typing system.[116] The quintessential AGS presentation is urticaria or anaphylaxis 2 to 6 hours after consuming mammalian meat; select patients may react to foods with lesser α-gal content, such as dairy and gelatin.[117] Unlike typical IgE-FA, symptoms are inconsistent, occurring after some ingestions but not others. It is thought that fattier preparations of dairy and meat may be more allergenic, and alcohol appears to be a significant cofactor.[116,118] The most distinctive clinical feature that distinguishes AGS from classic IgE-FA is that symptoms are typically delayed, occurring hours rather than minutes after eating.[117] The "glycolipid hypothesis" has been proposed as a possible explanation. This hypothesis harmonizes the time course of symptoms with what is known about lipid digestion; lipids are packaged into chylomicrons in the intestine, transported into the circulation via the thoracic duct starting about 2 to 3 hours after eating, and then broken down into smaller lipoprotein particles capable of passing through endothelial walls and entering tissues, where they may encounter sIgE-bound mast cells and cause symptoms. Successful desensitization to red meat has been reported for a small series of adult patients[119] and a single child,[120] with related decreases in α-gal–sIgE.

AGS is also distinct from classic IgE-FA with regard to the mechanism of sensitization, which follows lone star tick bite.[121,122] Samples collected pre– and post–tick bite revealed a 20-fold increase in α-gal IgE after tick bites and a correlation between sIgE to α-gal and lone star ticks.[122] Other species of ticks have been associated with mammalian meat allergy abroad, including *Ixodes ricinus* in Europe and *Ixodes holocyclus* in Australia. The surge in AGS cases in the United States has been attributed to increased movement of tick-carrying deer populations into suburban areas after a decrease in hunters and enactment of leash laws for dogs. The mechanism for how allergic sensitization to α-gal develops after tick bites remains elusive, but 3 theories have been proposed, attributing the immune response to (1) α-gal intrinsic to the tick saliva, (2) mammalian glycoproteins or glycolipids from the tick's previous blood meal, or (3) a commensal organism in the tick (similar to how tick-borne illnesses are spread).[121] Recent studies have confirmed the presence of α-gal in the saliva and salivary gland extracts of the lone star tick.[123,124] In addition, α-gal knockout mice demonstrated an increase in sIgE to α-gal and apparent symptoms of AGS after repeated exposure to tick salivary gland extract[125] or tick bites.[126]

AGS has implications beyond FA. The chemotherapeutic cetuximab has an α-gal moiety on the heavy chain of the Fab portion and was noted to cause a disproportionate rate of anaphylaxis in clinical trials conducted in the southeastern United States.[114] AGS has also been associated with increased incidence

of myocardial infarction,[117] and studies showed a higher risk of atherosclerotic plaques, including those with unstable features.[127,128] In addition, there is a risk of exposure to α-gal in the perioperative setting.[129] Heparin is porcine-derived, and although it does not typically contain significant quantities of α-gal, there may be impurities, and high-dose intravenous administration used in cardiopulmonary bypass may be sufficient to elicit a reaction.[130] In addition, porcine or bovine valves have caused perioperative hypersensitivity reactions in patients with AGS,[131] and AGS has been hypothesized as a cause of premature valve degeneration.[132]

GOS allergy. In 2012, 2 case series were published describing CM-tolerant patients from southeast Asia who experienced allergic reactions after ingesting CM-based formula.[133,134] One case was confirmed by OFC, which resulted in anaphylaxis. Other patients were evaluated with SPTs and BATs, which revealed positive results to CM formula preparations containing short-chain GOSs. GOSs are carbohydrate molecules consisting of 1 to 7 galactose units bonded to glucose, and they are added to CM-based formulas as prebiotics.[135]

Reactions occurred on first formula consumption, indicating previous sensitization.[136] Given the geographic restriction, it was hypothesized that the sensitizing antigen must be isolated to that region. All GOS-allergic patients were found to be sensitized to dust mites, including *Blomia tropicalis*, compared with 79% to 83% atopic controls not allergic to GOS. The addition of *B tropicalis* extract strongly inhibited GOS-sIgE *in vitro*; deglycosylated extract reduced its inhibitory effect. On the basis of these studies, the localization of *B tropicalis* to tropical climates explaining why this phenomenon is not observed in other regions, and knowledge that dust mite allergens may be glycosylated, *B tropicalis* was identified as the likely primary sensitizer in GOS allergy.

Cross-reactive carbohydrate determinants. CCDs are glycan moieties on plant and insect glycoproteins that cause allergen-sIgE responses but rarely cause clinical symptoms.[137] These glycans, typically containing α-1,3-fucose and β-1,2-xylose residues, bind IgE but are generally incapable of effectively cross-linking FcεRI-bound IgE on mast cells and basophils to induce degranulation. This is thought to be because CCD-sIgE often lacks the spatial configuration or valency needed for robust effector cell activation.[137] High-affinity IgG4 antibodies specific to CCDs may act as blocking antibodies, further inhibiting IgE-mediated responses. Advances in diagnostic assays that incorporate CCD inhibitors (eg, bromelain glycopeptides) have reduced false-positive results in sensitized but nonreactive individuals, enhancing the accuracy of IgE testing for true allergens.[138]

Special considerations in IgE-FA—Potential new endotypes?

Cofactor-dependent IgE-FA. Cofactor-dependent IgE-FA is a distinct endotype whereby a cofactor is necessary to elicit a reaction.[15] Beyond this endotype, cofactors are also known as augmentation or eliciting factors because they generally lower one's reaction threshold, making someone more likely to react to smaller allergen exposures, even if they are not required to elicit a reaction. Common cofactors include exercise, alcohol, illness, nonsteroidal anti-inflammatory drugs (NSAIDs), heat, menstruation, and sleep deprivation.[139] The prototypic example is food-dependent exercise-induced anaphylaxis, which occurs when people experience anaphylaxis only when certain foods are eaten around the time of exercise; in the absence of physical exertion, these foods are tolerated.[140] Wheat is the classic exercise-induced food trigger, but shellfish, dairy, tomato, celery, and others have been reported.[141] Cofactors are thought to modulate the pathophysiology of allergic reactions by altering immune activation thresholds, barrier function, allergen absorption, and mediator release. Exercise increases intestinal permeability through shear stress and ischemia-induced tight junction disruption, allowing undigested allergens to enter circulation.[142-144] This process is exacerbated by the redistribution of blood flow from the gut to skeletal muscles, promoting systemic allergen dissemination and interaction with sensitized mast cells and basophils. Hyperosmolality and dehydration during physical activity further potentiate basophil histamine release, creating a proinflammatory microenvironment.[145,146] Alcohol and NSAIDs synergistically enhance these effects by inhibiting prostaglandin E_2, a critical modulator of mast cell stabilization, and impairing epithelial integrity.[143,147-149] NSAIDs, in particular, inhibit cyclooxygenase pathways, tipping the balance toward leukotriene production, which amplifies inflammation and histamine release.[150] Environmental factors, such as high humidity or extreme temperatures, and hormonal fluctuations, including those during the menstrual cycle, exacerbate allergic responses by modulating immune cell activity and barrier integrity. Sleep deprivation has been proposed to decrease the threshold for allergic reaction by triggering a stress response affecting the immune and gastrointestinal systems, possibly increasing gastrointestinal permeability and enhancing allergen absorption, similar to other mechanisms.[139]

In wheat-dependent exercise-induced anaphylaxis (WDEIA), tissue transglutaminase activation during exercise, driven by IL-6 elevation, enhances gliadin cross-linking, leading to mast cell activation and mediator release.[151,152] ω-5-Gliadin (Tri a 19) sensitization is present in 80% of patients with WDEIA, whereas sensitization to other wheat proteins, such as globulin (Tri a 20) and glutenin (Tri a 26), is linked to wheat anaphylaxis unrelated to exercise.[153] Epitope-specific profiling has revealed distinct patterns, with ω-5-gliadin and high-molecular-weight glutenin epitopes recognized by 97% of patients with WDEIA but not wheat-sensitized individuals with AD.[154] Soy-dependent exercise-induced anaphylaxis has been linked to sensitization to storage proteins (Gly m 5 and Gly m 6) or aeroallergen cross-reactivity, highlighting the complexity of the food-dependent exercise-induced anaphylaxis endotype.[155,156]

ENDOTYPE OF NON–IgE-FA

The mechanisms of non–IgE-FA remain poorly delineated in comparison with IgE-FA.[157] This stems from the lack of systemic biomarkers and localization of symptoms to the gastrointestinal tract, where tissue is not easily accessible for analysis. Non–IgE-FAs are thought to involve T-cell–mediated immune responses without direct involvement of IgE. Distinct clinical phenotypes have been identified, including food protein–induced enterocolitis syndrome (FPIES), food protein–induced allergic proctocolitis, and food protein–induced enteropathy. In this review, we focus on FPIES, which has been more extensively examined in the recent years, with new insights into the mechanisms of acute reactions.

TABLE II. Hypothesis-driven classification of selected FPIES endotypes and corresponding phenotypes

Hypothesis	Endotype evidence and gaps	Phenotype clinical manifestations
Acute FPIES		
Acute FPIES is associated with exuberant but transient innate immune activation and local intestinal inflammation with adaptive cellular immunity providing antigen specificity via intestinal tissue-resident memory T cells; serotonin released from the intestinal enterochromaffin cells activates the vagus nerve	Sampling of peripheral blood 4-6 h from the onset of acute FPIES symptoms during OFC: ● Innate immune activation, with rapid recruitment and activation of neutrophils, monocytes, eosinophils, and NK cells ● Peripheral neutrophilia often observed on complete blood cell count with differential, peaking at 4-6 h after onset ● Cytokine profiling during acute reactions: elevated levels of IL-6, IL-10, IL-22, and oncostatin M ● Increased expression of CD69 (γδ T cells) and strong T_H17 responses with elevated levels of IL-17A, IL-22, and TARC in peripheral blood ● Untargeted metabolomics: elevated levels of inosine and urate and reduced expression of the purine receptors P2RX7 and P2RY10 and the ectonucleotidase CD73 ● Adenosine, a purine metabolite, induced serotonin release from gastric and duodenal biopsy specimens from donors without FPIES ● Serotonin metabolite 5-hydroxyindoleacetate was significantly elevated after reaction	● Typical onset in infancy, following several ingestions of the offending food, rarely on first exposure ● Rapid-onset gastrointestinal symptoms, including repetitive emesis, lethargy, pallor, and hypotension, occurring 1-4 h (up to 6 h in adults) after ingestion of a triggering food ● Symptoms resolve within hours; patient asymptomatic and thriving in between the acute episodes ● Cutaneous and respiratory symptoms are absent ● Trigger foods differ from IgE-FA: cereal grains (eg, oat, rice, and barley), vegetables (eg, carrot, sweet potato, and green bean), fruits (eg, avocado, banana, and apple), and egg yolk; however, typical allergens such as CM, egg, peanut, tree nuts, and seafood also are reported ● Response to serotonin receptor antagonist ondansetron ● Favorable natural history
Chronic FPIES		
Chronic FPIES is associated with prolonged antigenic stimulation leading to adaptive immune dysregulation with sustained activation of the tissue-resident T cells in the gastrointestinal mucosa	Biopsy: ● Flattened villi and edema ● Increased number of lymphocytes, eosinophils, and mast cells in jejunal biopsies ● Lower expression of type 1 TGF-β receptor and higher expression of TNF-α on epithelial and lamina propria cells associated with villous atrophy	● Ongoing ingestion of high doses of food allergen over days to weeks leads to progressively worsening diarrhea, vomiting, malnutrition, dehydration, failure to thrive, anemia, metabolic acidosis, hypoproteinemia, and in severe cases shock ● Classically seen in infants fed CM or soy formula; isolated reports in adults ● Reexposure to trigger foods after period of elimination leads to an acute FPIES reaction
Atypical (IgE-positive) FPIES		
Proinflammatory state of gut immunity and allergen avoidance leads to generation of food-sIgE antibodies that do not contribute to the mechanism of FPIES reactions	● Low-grade food-sIgE sensitization detectable systemically in a minor subset of patients ● The mechanism of restricting FPIES reactions to the gut in the presence of systemic food-sIgE is unknown	● Patients with atypical FPIES are usually atopic, with associated IgE-FA to another food or AD ● Most patients with atypical FPIES continue to manifest typical delayed gastrointestinal symptoms ● A small subset has been reported to "transition" to more immediate symptoms (eg, hives, rashes, itching, or anaphylaxis); usually associated with higher food-sIgE levels
FPIES in infants with trisomy 21		
Immune dysregulation associated with trisomy 21 can lead to exaggerated inflammatory responses and more severe phenotype of FPIES	● Human chromosome 21q22.11 houses genes that encode α and β subunits of the IFN-α receptor, the second subunit of the IFN-γ receptor, and the β subunit of the IL-10 receptor ● Overexpression of chromosome 21 gene products in patients with trisomy 21 results in increased TNF-α and IFN-γ levels and decreased IL-10 in plasma that contribute to severe intestinal inflammation[92]	● 10- to 20-fold increased FPIES risk in infants with trisomy 21 compared with general population (0.51%-0.7% vs 11.6%).[86] ● Severe chronic FPIES ● Reported food triggers: CM and wheat
Adult-onset FPIES		
Breach in oral tolerance, possibly because of gut dysbiosis or hormonal changes	● Unknown, presumably similar as acute infantile-onset FPIES	● Strong predominance of female patients (70%-80%) ● Delayed, up to 6 h after ingestion; severe, debilitating abdominal pain, nausea, vomiting, and diarrhea ● Previous documented tolerance to the trigger foods ● Common triggers of acute adult-onset FPIES: shellfish and fin fish ● Reported triggers of chronic adult-onset FPIES: fish, CM, dairy, and wheat ● Guarded natural history; low rates of resolution

NK, Natural killer; *TARC*, thymus and activation-regulated chemokine.

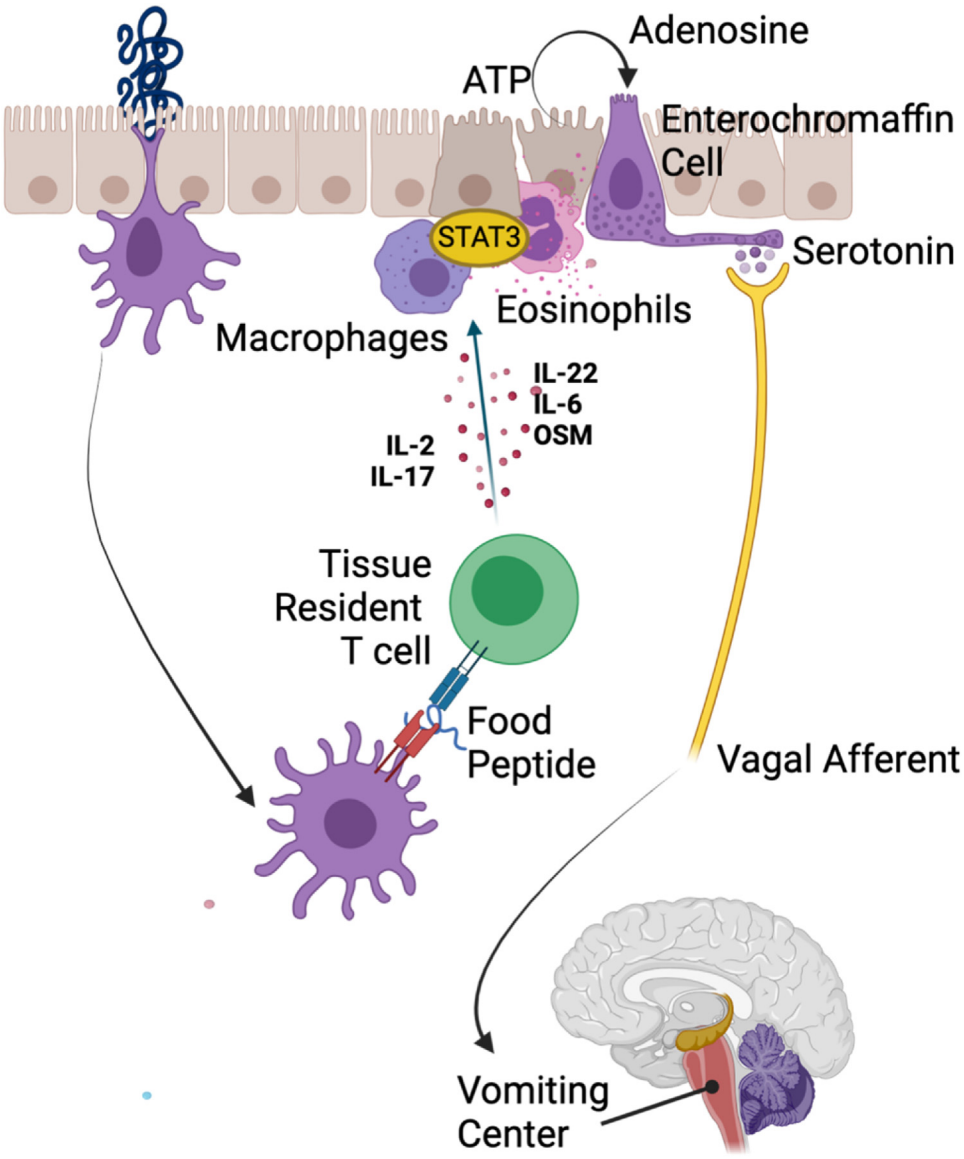

FIG 4. Model of the pathophysiology of acute FPIES. Food antigen is absorbed and activates tissue-resident T cells to make cytokines, including IL-2, IL-17, and IL-22. OSM and IL-6 are also produced, but the source may also include tissue macrophages. IL-22, OSM, and IL-6 activate STAT3, which is observed in multiple innate immune cell types. ATP can be released by activated immune cells and damaged epithelial cells, and its metabolite adenosine acts on enterochromaffin cells to drive serotonin release, linking inflammation to the vomiting, pallor, and lethargy. *OSM*, Oncostatin M; *STAT3*, signal transducer and activator of transcription 3. Reprinted with permission from Nowak-Wegrzyn.[158]

Food protein–induced enterocolitis syndrome

FPIES represents a highly distinct endotype of non–IgE-FA, characterized by immune dysregulation localized to the gastrointestinal tract.[158] Unlike IgE-FA, FPIES involves innate and adaptive immune mechanisms without detectable IgE involvement, leading to delayed, often severe, gastrointestinal symptoms triggered by specific foods.[159] The lack of systemic biomarkers and the challenges in accessing gastrointestinal tissues for analysis have historically limited understanding of its pathophysiology. However, recent insights have shed light on the immunologic underpinnings of acute and chronic FPIES (Table II).

Acute versus chronic FPIES: An endotype perspective. Acute and chronic forms of FPIES represent phenotypically and mechanistically distinct subtypes within this non–IgE-mediated endotype. These forms are defined by differences in immune activation, clinical presentation, and progression.

Acute FPIES: Transient innate immune activation. Acute FPIES is characterized by rapid-onset gastrointestinal symptoms, including repetitive emesis, abdominal pain, lethargy, pallor, and hypotension, occurring 1 to 4 hours (up to 6 hours in adults) after ingestion of a triggering food.[159,160] Acute FPIES is dominated by innate immune activation, with rapid recruitment and activation of neutrophils, monocytes, eosinophils, and natural

killer cells.[161] Peripheral blood neutrophilia is a hallmark feature, peaking 4 to 6 hours after symptom onset and correlating with the clinical severity of the reaction.[162]

Cytokine profiling during acute reactions has identified a strong innate inflammatory signature, including elevated levels of IL-6, IL-10, IL-22, and oncostatin M.[161] These cytokines, released downstream of innate immune activation, drive systemic inflammation and amplify myeloid and lymphoid signaling via the STAT3 pathway, as confirmed by mass cytometry and RNA sequencing.[163,164] Elevated levels of IFN-γ–inducible protein 10 and IL-10 indicate both inflammatory and regulatory components in the acute response.[165] Antigen specificity of acute FPIES suggests that innate immune activation is driven by an adaptive component and is supported by activation of the T_H17 pathway.

Hypothetical mechanism of acute FPIES. Recent metabolomic analyses have implicated the purine signaling pathway in acute FPIES.[164] Elevated levels of inosine and adenosine, key metabolites in purine metabolism, were detected during acute reactions. Adenosine has been shown to induce serotonin release from enterochromaffin cells, triggering vagal nerve activation and driving hallmark symptoms such as emesis and lethargy. Increased blood levels of 5-hydroxyindoleacetate (serotonin metabolite) during reactions further support this mechanism (Fig 4). Reduced expression of purine receptors (such as P2RX7 and P2RY10) and ectonucleotidases (such as CD73) in symptomatic patients suggests that purine metabolism exacerbates inflammatory and gastrointestinal responses.

Chronic FPIES: Prolonged adaptive immune dysregulation. Chronic FPIES arises from repeated ingestion of large doses of triggering foods, such as CM or soy formula in infants, leading to progressively worsening diarrhea, vomiting, and malnutrition over days to weeks. Unlike the transient inflammation of acute FPIES, chronic FPIES is hypothesized to involve adaptive immune responses, characterized by sustained activation of the tissue-resident T cells in the gastrointestinal mucosa.

Histologic studies in chronic FPIES reveal villous atrophy, epithelial edema, and increased infiltration of lymphocytes, eosinophils, and mast cells.[166] Elevated TNF-α expression in the intestinal mucosa correlates with villous atrophy severity. Chronic antigen exposure may drive T_H-cell activation, particularly T_H17 responses. Levels of IL-17A, IL-22, and thymus and activation-regulated chemokine are elevated in peripheral blood following an isolated food allergen ingestion during OFC and are likely to be further augmented during chronic exposure.[167-169]

γδ T cells, a nonconventional T-cell subset, are prominently activated during acute reactions, as evidenced by increased expression of CD69 in peripheral blood.[170] However, the antigen specificity of T-cell responses in FPIES remains elusive, without clear evidence of antigen-specific proliferation in PBMCs, suggesting a localized antigen-driven response in the gut. Reexposure to triggering foods after elimination results in acute FPIES symptoms, highlighting the potential for tissue-resident memory T-cell involvement in bridging acute and chronic forms. Adaptive immune imprinting in chronic cases may sensitize the gut to exaggerated innate responses on reexposure.

Triggers and humoral responses. FPIES triggers vary with age and geography. Common triggers in children include low-protein foods such as rice, oats, sweet potato, and banana, whereas seafood is the predominant trigger in adults.[160,171] Despite the term "food protein" in its name, it is possible that components other than proteins may act because FPIES triggers in foods with low protein content that are uncommon IgE-FA allergens (eg, oat and sweet potato). Humoral immune responses are minimal, with no significant allergen-specific IgA, IgG, or IgE to food proteins (eg, casein and whey proteins) detected in plasma.[165,172] Children with atypical FPIES may show low-level sIgE, but this is considered an epiphenomenon unrelated to the core pathophysiology.

Neuroimmunology: Emerging importance in FA

Recent insights into FPIES pathophysiology highlight the central role of neuroimmune interactions in FA, with crosstalk between the immune and nervous systems in the gut linking immune activation to the symptom of vomiting.[158] However, the relevance of neuroimmunology extends beyond FPIES. Enteric neurons release neuropeptides such as substance P, calcitonin gene-related peptide, and vasoactive intestinal peptide, which amplify mast cell degranulation and the release of histamine and other proinflammatory mediators.[173,174] This cascade exacerbates T_H2-driven inflammation, contributing to acute allergic symptoms such as vomiting, abdominal pain, and diarrhea. In addition, the vagus nerve, a key regulator of gut homeostasis, influences intestinal permeability and immune responses. In FA, dysregulation of vagal signaling impairs mast cell stabilization, promoting heightened inflammatory reactions and further disrupting the intestinal barrier.

Emerging research highlights novel mechanisms by which sensory neurons directly interact with allergens, such as through transient receptor potential (TRP) ion channels.[174,175] TRPV1, a receptor involved in pain and inflammation, is hyperactivated in allergic states, linking neuronal excitation to enhanced immune responses. Chronic activation of these pathways may perpetuate local inflammation, eosinophil recruitment, and tissue remodeling. These findings underscore the potential of targeting neuroimmune pathways, including TRP channels and neuropeptide signaling, as therapeutic strategies to reduce FA severity and improve disease management.

Conclusions

Traditional classification of FA has recognized the fundamental role of food-sIgE antibodies in immediate hypersensitivity reactions, thus providing an initial endotypical framework. Major progress has been made in characterizing the endotype of IgE-FA with novel diagnostic tests on the basis of individual major allergens, individual IgE-binding epitopes, and functional *in vitro* assays. Therapies targeting IgE and signaling pathways in effector cells have been developed. Ongoing investigations focus on defining endotypes of severe food-induced anaphylaxis, persistent versus transient FA, and responsiveness to immunotherapy. In contrast, non–IgE-FA remains poorly understood and is an area of major unmet need regarding prevention, management of acute reactions, and therapeutics.

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