

# Mechanisms of gastrointestinal allergic disorders

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**Gastrointestinal (GI) allergic disease is an umbrella term used to describe a variety of adverse, food antigen-driven, immune-mediated diseases. Although these diseases vary mechanistically, common elements include a breakdown of immunologic tolerance, a biased type 2 immune response, and an impaired mucosal barrier. These pathways are influenced by diverse factors such as diet, infections, exposure to antibiotics and chemicals, GI microbiome composition, and genetic and epigenetic elements. Early childhood has emerged as a critical period when these factors have a dramatic impact on shaping the immune system and therefore triggering or protecting against the onset of GI allergic diseases. In this Review, we will discuss the latest findings on the molecular and cellular mechanisms that govern GI allergic diseases and how these findings have set the stage for emerging preventative and treatment strategies.**

## Introduction

Adverse reactions to food involve both immune-mediated and non-immune-mediated responses. Among these responses, there has been increasing attention to gastrointestinal (GI) allergic diseases, a spectrum of disorders classified by IgE-mediated, non-IgE-mediated, and mixed IgE-mediated and non-IgE-mediated mechanisms. Loss of tolerance to harmless food antigens results in initiation of immune hypersensitivity, and failure to terminate immune responses leads to chronicity (1, 2).

Basic and translational studies have uncovered several common pathways in GI allergic diseases. First, although not formally demonstrated for each of these diseases, a breakdown of immunologic tolerance appears to be a key feature. Loss of tolerance can stem from a number of mechanisms, including alterations in the immune surveillance system (e.g., dysregulation of antigen processing and change in Treg function). Second, a biased type 2 immune response is also a key factor in disease onset, manifestations, and maintenance. Several allergic GI diseases involve imbalanced Th2 effector cell responses compared with responses of other T cell types (i.e., Treg, Th1, Th17) as well as increased Th2 cytokine production. The Th2 response increases IgE and mast cell, basophil, and eosinophil production and activation. Third, an impaired epithelial barrier is an apparent mechanism, resulting in increasing encounters of food antigens with immune cells, priming a break in immune tolerance and initiation of epithelial innate immune responses that further prime for Th2 responses.

Finally, cooperating environmental and genetic factors influence these pathways and therefore promote or protect against allergic GI diseases.

## Immunologic basis of GI allergic disease

*Cells and loss of tolerance.* Allergic diseases involve the interplay of a constellation of cells, including mast cells, basophils, eosinophils, lymphocytes, and constitutive tissue cells such as epithelial cells and antigen-presenting cells. These cells and their orchestrated interactions are normally involved in protective immunity to certain pathogens, typically parasites (3). A summary of the immunologic basis of food allergic subtypes is presented in Table 1.

Under healthy homeostatic conditions, remaining unresponsive to food is a primary objective of the immune system. Such immune tolerance is generated by relocation of antigen from the gut lumen to the lamina propria by specialized M cells, myeloid cells, and goblet cells. Goblet cells have a key role in the development of intestinal tolerance, serving as a passage for antigen transit from the lumen to tolerance-inducing dendritic cells (DCs) (4, 5). The intestine's mucus layer not only provides a physical barrier but permits tolerance-inducing DCs to sample bacteria (6). Following transmission of antigen to the lymphoid tissue and subsequent antigen presentation, tolerogenic T cells return to the intestine (2). Tregs require the transcription factor forkhead box P3 (FOXP3) and secrete IL-10 and TGF- $\beta$ . IL-10 is a key regulatory cytokine that is also produced by DCs and a number of other T cells. IL-10 terminates allergen-specific Th2 responses and induces Treg differentiation (7). Tolerance-regulating Tregs have an essential role in downregulating Th2 cells and inhibiting IgE-mediated mast cell activation, thus preventing inflammatory responses and maintaining physiologic homeostasis at mucosal surfaces (8). Interestingly, the chronic allergic disease eosinophilic esophagitis (EoE) is characterized by increased TGF- $\beta$ . TGF- $\beta$  is produced by many cell types in the esophagus, including eosinophils and mast cells, and promotes tissue fibrosis, epithelial-mesenchymal transition, and smooth muscle contraction; therefore, TGF- $\beta$  likely has a dual pathogenic and immune-regulatory role in EoE rather than a sim-

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ple protective role (9). The esophagus of EoE patients contains persistent Tregs (10, 11); whether these Tregs actively produce TGF- $\beta$  and whether they possess a protective or proinflammatory role require further investigation.

It is interesting that breast milk contains immunoregulatory mediators including TGF- $\beta$  and that TGF- $\beta$  supplementation induces tolerance in a murine model of food allergy (12). Following epicutaneous sensitization and oral challenge in pregnant mice, the offspring evidenced attenuation of food anaphylaxis, specific IgE production, and intestinal mast cell numbers. This mechanism is mediated by induction of allergen-specific Tregs and transfer of maternal IgG complexes with the antigen in breast milk by the neonatal crystallizable fragment receptor, FcRN, expressed by DCs (13). Interestingly, human breast milk containing IgG-allergen immune complexes induces tolerance in humanized FcRN mice (13).

**Barrier.** Atopic diseases tend to occur in a chronological sequence termed the atopic march, in which the initial manifestation of atopic disease in early childhood is often in the skin (i.e., atopic dermatitis [AD]), followed by the staggered development of food anaphylaxis, EoE, allergic rhinitis, and allergic asthma (2, 14). Support for this theory is derived from the finding that a defective skin barrier is an established risk factor for food anaphylaxis and EoE (15, 16). Several mouse studies have shown that epicutaneous exposure to allergens causes allergic sensitization, IgE production, Th2 responses, and food anaphylaxis (17–19). Impaired skin barrier, as measured by transepidermal water loss, correlates with the development of food anaphylaxis at the age of 2 years (20).

High-throughput approaches including whole-transcriptome and whole-exome sequencing and genome-wide association studies (GWAS) have revealed that impaired barrier influences the development of GI allergic diseases. First, loss-of-function mutations in the epidermal barrier gene *FLG* (encoding filaggrin) increase the risk for AD, peanut sensitization, peanut allergy, and EoE (21, 22). Filaggrin is a structural protein with key roles in skin homeostasis, including regulation of the physical strength of the epithelium, barrier function, hydration, pH, and antimicrobial protection (23). Up to half of European AD patients have loss-of-function genetic variants in *FLG*, which is the most significant known genetic risk factor for AD (23). Second, patients with EoE exhibit a marked decrease in the esophageal cadherin desmoglein-1 (*DSG1*) compared with control individuals. In vitro, loss of *DSG1* in esophageal epithelial cells causes impaired epithelial barrier, indicating that *DSG1* may have a key role in epithelial integrity (24–26). Mutations that decrease *DSG1* expression stimulate production of Th2 cytokines, including thymic stromal lymphopoietin (TSLP), and associate with severe atopy, including food anaphylaxis, EoE, and metabolic wasting known as severe dermatitis, multiple allergies, and metabolic wasting (SAM) syndrome (discussed in the next section) (27). Third, the cysteine protease calpain-14 (*CAPN14*) also mediates esophageal barrier function and contributes to the pathology of EoE. Overexpression of *CAPN14* in esophageal epithelial cells decreases *DSG1* expression and impaired barrier function. *CAPN14* is induced by IL-13, and silencing of *CAPN14* prevents IL-13-mediated *DSG1* loss. Whether *CAPN14* directly cleaves *DSG1* is yet unknown (28). Fourth, loss of expression of the serine protease inhibitor *SPINK7*, as occurs in EoE, is sufficient to induce epithelial barrier impair-

ment, including increased proteolytic activity with inflammatory consequences (29). Additional examples of dysregulated barrier genes are found among the epidermal differentiation complex (EDC) genes clustered on chromosome 1q21, including the genes *FLG* and *IVL*, which are markedly decreased in EoE (30).

The above data substantiate that impaired barrier function can enhance the development of the atopic response, probably via two mechanisms: (a) penetration of the tissue by unwanted antigens that subsequently encounter antigen-presenting cells, and (b) epithelial “damage sensing,” whereby pathogenic insults activate protease-activated receptors (PARs) and pattern recognition receptors (including TLRs) on epithelial cells (31–33). This activation deploys innate immune responses. For example, double-stranded RNAs and proteolytic allergens upregulate TLR-mediated and/or PAR2-mediated TSLP induction in keratinocytes (34, 35).

Several studies reveal that barrier proteins have the potential to modulate immune reactions. For example, *SPINK7* inhibits the serine protease urokinase-type plasminogen activator (uPA), which can activate eosinophils by cleaving uPAR expressed on their cell surface, which likely occurs in EoE (29). A summary of barrier regulatory molecules and their regulation in an allergic response is illustrated in Figure 1.

## Heritability of GI allergic disorders

Studies on cohorts of twins and triplets with a confirmed GI allergic disorder in at least one sibling estimate that the heritability is typically very high (>50%) regardless of the type of GI allergic disease. The genetic component’s contribution to this heritability is variable between specific diseases (36, 37). In EoE, heritability is high (with sibling risk ratios approaching 50-fold risk), but a twin study revealed that genetics only contribute about 15% (38). This is most highlighted by the 10-fold higher rate of concordance between dizygotic twins than between non-twin siblings, implicating early-life exposures as the main environmental driver (38, 39).

**Common genetic variant analysis of food allergy.** GWAS focusing on common genetic variants (>5% prevalence in the general population) have identified several genes involved in barrier function that associate with susceptibility to food anaphylaxis (21, 40). For instance, genetic variants in *FLG* associate with food anaphylaxis and EoE susceptibility (22, 40), and downregulation of *FLG* directly contributes to EoE by contributing to impaired esophageal epithelial barrier function (29, 30, 41).

Recently, the *SERPINB* gene cluster on chromosome 18q21.3 was identified as a novel locus associated with food anaphylaxis (21). In addition, whole-exome sequencing analysis of EoE patients identified rare damaging mutations in the *SERPINB3* gene (42), suggesting critical involvement of this family of protease inhibitors in the pathogenesis of allergic diseases. Because these proteins are mainly localized to the epithelium and function as protease inhibitors, they likely regulate barrier integrity.

EoE’s strong genetic association with variants at 2p23 helped mechanistically explain the tissue specificity of this disease. This locus contains the *CAPN14* gene, whose esophagus-specific expression and involvement in EoE are discussed above (22, 28, 43, 44).

Other variants emphasize type 2-skewed pathways in the onset of food allergic disorders. The first evidence was the genetic linkage of the Th2 cytokine cluster at 5q31–33 with serum

**Table 1. Classifications of GI allergic diseases and their mechanism**

Disease	Antigen	Mechanism
IgE-mediated food allergy	Food anaphylaxis	<ul style="list-style-type: none"> <li>Increased Th2 cell differentiation and decreased Tregs</li> <li>Antigen encounter promotes secretion of cytokines in the type 2 family (e.g., IL-4, IL-5, IL-9, and IL-13) by Th2 cells</li> <li>Stimulated B cell class switch to IgE</li> <li>IgE binds to FcεR1 receptor on mast cells</li> <li>Food antigens induce cross-linking of mast cell-bound IgE molecules</li> <li>Mast cell degranulation with release of histamine and inflammatory mediators including proteases, de novo production of lipid metabolites of arachidonic acid, and de novo production of cytokines (IL-4, IL-13) (1, 3)</li> </ul>
	Oral allergy syndrome	Cross-reactive with fruit- or vegetable-protein epitopes
	Red meat allergy	Antigens transmitted in the saliva of ticks that have fed on mammals (2)
IgE-mediated and non-IgE-mediated (mixed) food allergy	EGIDs such as EoE	<ul style="list-style-type: none"> <li>Increased exposure to allergen and encounter with antigen-presenting cells, which lead to break of immune tolerance</li> <li>Innate response characterized by epithelial production of IL-1, IL-25, GM-CSF, IL-33, and TSLP, which promote Th2 cell recruitment and activation</li> <li>Increased IL-13 production (11, 174)</li> <li>IL-13 promotes eotaxin-3 production from epithelial cells, which recruits eosinophils (174, 175)</li> <li>IL-13 promotes CAPN14 expression to promote esophageal epithelial barrier impairment (28)</li> <li>Decreased SPINK7 expression promotes esophageal epithelial barrier impairment (29)</li> <li>Eosinophilia and tissue damage (175)</li> </ul>
		Milk, egg, wheat, fish/shellfish, peanut/tree nuts, soy
Non-IgE-mediated food allergy	Food protein-induced enterocolitis syndrome	Milk, soy, rice, oat, egg
	Food protein-induced proctocolitis	Milk, soy, wheat, egg
	Food protein enteropathy	Milk, soy, wheat, egg
	Celiac disease	Gliadin peptides (found in gluten)
		<ul style="list-style-type: none"> <li>Preliminary evidence of involvement of neutrophils, NK cells, monocytes and eosinophils, lack of IgG4, and intestinal permeability in disease propagation (177–180)</li> <li>Preliminary evidence of eosinophilic inflammation (177, 180)</li> <li>Preliminary evidence of allergen-specific suppressor CD8<sup>+</sup> T cells (180)</li> <li>TGM2 induces gluten peptide deamidation to increase affinity to HLA-DQ, which presents these peptides to CD4<sup>+</sup> T cells</li> <li>Proinflammatory T cells promote intestinal damage</li> <li>Disease-specific B cells produce autoantibodies against self-TGM2 and deamidated gluten peptides</li> <li>HLA class II genes <i>HLA-DQ2</i> and <i>HLA-DQ8</i> susceptibility (180–182)</li> </ul>

GI allergic disorders are classified by either IgE-mediated, non-IgE-mediated, or mixed IgE-mediated and non-IgE-mediated mechanisms. Loss of tolerance, resulting in initiation of immune hypersensitivity to harmless food antigens, and failure to terminate these responses, lead to chronicity of these responses. The food antigens involved in, and the mechanisms of, these diseases are summarized (1–3, 28, 29, 155, 174–187). α-gal, galactose-α-1,3-galactose; TGM2, transglutaminase 2.

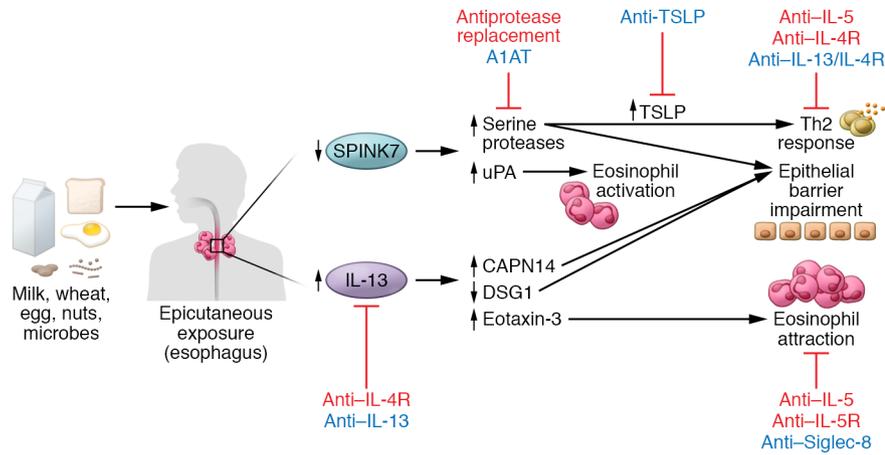
IgE levels (45). Later studies associated this locus with EoE (46), Crohn’s disease (47), psoriasis (48), eczema (49), and food anaphylaxis (21). The lead SNP at this locus, rs11949166, is located between *IL4* and the kinesin family member 3a gene (*KIF3A*), and a second, independent association is in the *RAD50/IL13* region, which also contains the well-known *IL13* coding variant (IL-13 R130Q) (21, 50–52). Consistent with these data, a gain-of-function mutation in *IL4RA* associates with atopy (52).

The 5q22 locus, encompassing *TSLP*, is associated with a number of allergic diseases, including EoE, asthma, allergic rhinitis, and AD (53, 54). Food anaphylaxis has not been linked to this region, highlighting its distinct mechanisms, as depicted in Table 1.

Other genetic variants might be linked to the breakdown of tolerance through regulation of antigen presentation; for exam-

ple, the 11q13 locus encoding *EMSY* and *LRR32* (22, 55–58) is associated with food anaphylaxis, EoE (59), AD (60), asthma (61), allergic sensitization (62), inflammatory bowel disease, and allergic rhinitis (63). *EMSY* is a transcription regulator also involved in intracellular signaling (56). *LRR32* is a leucine-rich repeat molecule expressed on the surface of Tregs that binds to TGF-β and promotes its processing. The association suggests that altered expression of *EMSY* and *LRR32* can potentially contribute to breakdown of immune tolerance (64).

*HLA-DQ* and *HLA-DR*, encoding class II HLA molecules, are also suggested to be involved in food anaphylaxis by regulating immune tolerance (65). Antigen-presenting cells induce immune tolerance by presenting peptides to T cells via class II MHC molecules, such as HLA-DQ and HLA-DR. Two SNPs on the HLA



**Figure 1. The regulation of epithelial barrier function in EoE.** Esophageal allergic responses to food antigens are driven by barrier impairment. Decreases in the esophageal levels of the serine protease SPINK7 lead to increased serine protease activity, which impairs epithelial barrier function and in turn causes innate epithelial proinflammatory responses, including TSLP production. TSLP promotes Th2 responses. This reaction can be controlled by anti-TSLP, anti-IL-13, and/or anti-IL-4R antibodies. In addition, loss of SPINK7 promotes increased esophageal uPA activity that activates eosinophils. Antiprotease replacement of SPINK7, such as A1AT delivery, could potentially restore these pathways. Increased IL-13 promotes epithelial cells to produce eotaxin-3 that attracts eosinophils to the esophagus. Anti-IL-5, anti-IL-5R, and anti-Siglec-8 therapy reduce and/or eliminate eosinophils. IL-13 also induces decreased expression of the desmosomal protein DSG1, thereby impairing the epithelial barrier, as well as increased expression of the cysteine protease CAPN14, which also impairs the epithelial barrier. Therapeutic reagents that are FDA approved or in clinical trials are shown in red and blue, respectively.

locus on chromosome 6 significantly associate with peanut-driven allergy but not egg or cow milk allergies (65).

A recently discovered locus at 16p13, a region encoding the *CLEC16A*, *DEXTI*, and *CITTA* genes, was genetically associated with EoE (59). *CITTA* regulates the expression of class I and II MHC genes that are important in immune tolerance (66, 67). Variants in *CLEC16A* associate with IgA deficiency (68). IgA is involved in mucosal immunity, development of tolerance, and protection against infection; IgA deficiency coexists with autoimmune diseases and allergies (69). *DEXTI* has unknown function, but polymorphism in this gene is associated with autoimmunity (70).

Because many identified variants overlap between several atopic diseases, with the exception of *CAPN14*, they have poor specificity as biomarkers of allergic diseases. In addition, in allergic disorders with low prevalence rates, such as EoE (1 in 2000), even individuals carrying risk variants that increase the disorder’s odds ratio (OR) 2-fold possess relatively low risk of developing the disease.

Considering the combinatorial effect, having two or more risk variants at different loci for disease susceptibility is likely to be important. Martin et al. presented evidence of interaction between SNPs at *IL4* and *TSLP* such that *TSLP* risk variants most strongly associate with EoE when the *IL4* risk variant is present (43). Another genetic interaction is observed between variants in *TSLP* and the uPA-encoding gene, *PLAU*, in EoE (29).

**Gene-environment interactions.** Environmental factors can specifically modify disease risk in genetically susceptible subjects. For example, breastfeeding reduces EoE risk in individuals with the rs6736278 susceptibility gene variant in *CAPN14*, and neonatal intensive care unit admission significantly increases EoE risk in individuals carrying a specific risk allele in the *LOC283710/KLF13*

region (71). Moreover, an increase in peanut sensitization and allergy risk was seen in children with *FLG* loss-of-function mutations exposed to high levels of peanut allergens in household dust (72).

**Mendelian disorders inform GI allergic disease etiology.** Several monogenic disorders associated with GI allergy result from mutations in barrier genes (e.g., those that encode desmosomal junction proteins and the serine protease inhibitor SPINK5). *SPINK5* loss of function results in a rare autosomal recessive disorder termed Netherton syndrome (NS) that is characterized by defective skin cornification and Th2-skewed immune alterations (73). Loss of functional SPINK5 unleashes uncontrolled serine protease activities that promote corneodesmosome degradation and excess corneocyte desquamation, resulting in skin barrier dysfunction. NS patients develop a severe atopy syndrome involving progressive increases in serum IgE levels, hypereosinophilia, AD, and EoE. Common SNPs in the *SPINK5* locus are associated with AD severity and with food anaphylaxis (74). Generalizability

of these rare Mendelian disease observations is evidenced by the finding that both *SPINK5* and *SPINK7* expression is decreased in the esophagus of EoE patients compared with control individuals (29, 75–77) and that these are generally acquired events rather than a consequence of genetic loss of function. Mutations in *CDSN* (encoding corneodesmosin) cause peeling skin disease, with features similar to those of NS, including multiple food allergies (78). Another monogenic disorder caused by barrier impairment is SAM syndrome, which is caused by homozygous mutations in *DSG1* (27). Loss of membranous DSG1 expression impairs cell-cell adhesion, leading to acantholysis in all patients. In addition, *DSG1* deficiency stimulates production of Th2 cytokines, including TSLP, IL-5, TNF, and IL-13-induced periostin. These patients often have increased IgE levels, multiple food allergies, and EoE (27). As stated earlier, loss of *DSG1* expression occurs in non-Mendelian EoE, supporting the generalizability of this mechanism. Heterozygous missense mutations in another desmosomal protein, desmoplakin (*DSP*), also cause SAM syndrome with increased IgE levels, food allergies, hypereosinophilia, and EoE (79).

Other monogenic disorders highlight the balance between Th2 cells and Tregs as a causative mechanism in the etiology of GI allergic diseases. Deficiency of dedicator of cytokinesis 8 (*DOCK8*) results in an autosomal recessive, combined immunodeficiency and hyper-IgE syndrome characterized by sinopulmonary infections, eczema, viral skin infections, high specific serum IgE against food allergens, increased Th2 cells, and severe atopy, including food anaphylaxis (80). CD4<sup>+</sup> T cells from *DOCK8*-deficient patients are preferentially polarized to a Th2 effector phenotype, with defective ability to polarize toward a Th17 cytokine-producing state. In the absence of *DOCK8*, impaired

**Table 2. Common genetic variants that contribute to allergic GI diseases**

Susceptibility locus	Top candidate genes involved	Atopic and immune disorders	
Loci potentially involved in barrier function	1q21.3	<i>FLG</i>	Food allergy, atopic dermatitis, allergic rhinitis, asthma, EoE
	18q21.3	<i>SERPINB7, SERPINB10</i>	Food allergy
	2p23	<i>CAPN14</i>	EoE
Loci potentially involved in Th2 responses	5q31.1–q33	<i>IL4, IL13, KIF3A</i>	Food allergy, EoE, Crohn's disease, psoriasis, eczema
	5q22	<i>TSLP, WDR36</i>	EoE, allergic sensitization, asthma, allergic rhinitis, atopic dermatitis
Loci potentially involved in immune tolerance	11q13	<i>EMSY, LRRC32</i>	Food allergy, EoE, atopic dermatitis, asthma, allergic rhinitis, allergic sensitization, inflammatory bowel disease
	6p21	<i>HLADQ, HLADR</i>	Peanut allergy
	16p13	<i>CLEC16A, DEXI, CITTA</i>	EoE, IgA deficiency, and autoimmune diseases

Susceptibility loci associated with allergic GI disorders.

STAT3 activation leads to production of Th2-biased cells at the expense of Th17 cells (81, 82). Interestingly, STAT3 mutations also result in hyper-IgE syndrome and EoE (83, 84).

Loeys-Dietz syndrome (LDS) is an autosomal dominant connective tissue disorder caused by mutations in the genes encoding the TGF- $\beta$  receptor subunits *TGFBR1* and *TGFBR2*, which result in dysregulated TGF- $\beta$  signaling. The clinical phenotype includes predisposition to atopy including asthma, food anaphylaxis, eczema, AD, allergic rhinitis, and eosinophilic GI disorders (EGIDs). Patients with LDS have increased frequency of CD4<sup>+</sup> T cells that express both FOXP3 and IL-13, and cultures of TGF- $\beta$ -stimulated CD4<sup>+</sup> T cells from patients with LDS produce increased Th2 cytokines compared with controls. These findings suggest that LDS mutations support Th2 skewing in a cell-autonomous manner (85) and highlight the key role of TGF- $\beta$ , and likely Treg dysregulation, as a pathobiologic mechanism in GI allergy including EGID.

In support of the key role of TGF- $\beta$ R1, individuals with a loss-of-function mutation in *ERBB2IP* have increased risk for food allergic diseases including food anaphylaxis and EoE. Notably, *ERBB2IP* encodes ERBB2-interacting protein (ERBIN), a known anchor protein for the TGF- $\beta$ R1 downstream signaling molecules SMAD2 and SMAD3. Both STAT3 and ERBIN form a complex with SMAD2/3, inhibit SMAD2/3 activation, and suppress TGF- $\beta$  signaling. ERBIN loss of function impairs TGF- $\beta$  signaling and increases Treg numbers. Interestingly, DSG1 and ERBIN cooperate to repress MAPK signaling and promote keratinocyte differentiation, converging multiple relevant pathways in the development

of food allergic responses (84, 86). Homozygous loss-of-function mutations in the gene *CARMIL2* result in primary immunodeficiency disorder with variable phenotypic presentations including pulmonary allergy, various bacterial and fungal infections, dermatitis, and EoE. *CARMIL2* contributes to the NF- $\kappa$ B pathway by stabilizing activated PKC $\theta$  microclusters at the immunological synapse, and loss-of-function mutations in this gene cause impaired Treg differentiation and function and cytoskeletal organization (87, 88). Summaries of genetic loci and of monogenic disorders associated with food allergic diseases are presented in Tables 2 and 3, respectively.

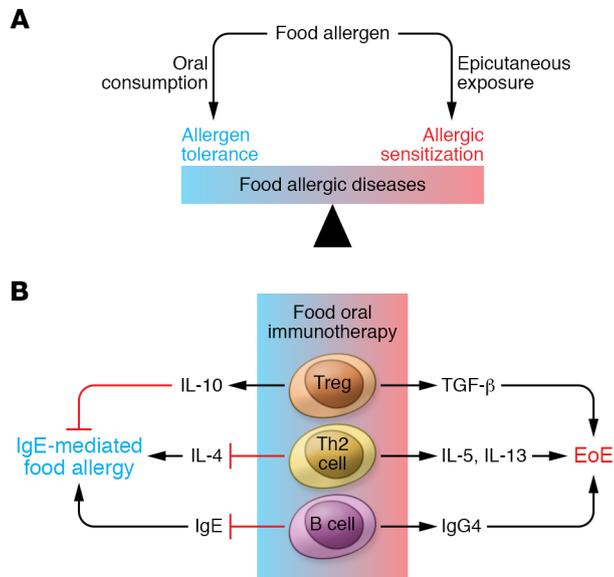
### Environmental factors that contribute to food allergic diseases

The pathoetiology of food allergic disease is likely due to a complex interplay of prenatal and postnatal environmental factors. Changes in food production, processing, and packaging (e.g., the use of pesticides, antibiotics, hormones, preservatives, heat denaturation, detergents, and chemicals) have been suggested to be linked to allergic diseases directly or indirectly (89–94).

The association of chemicals like bisphenol A (BPA) and phthalates with food allergy has been controversial (90). BPA is an endocrine disruptor with estrogenic activity that is commonly used as a component in polycarbonate plastic and epoxy resins. The main exposure to BPA is through food and beverages. Two studies demonstrated that BPA exposure altered the development of oral tolerance and decreased Treg number in mice (95, 96). Pre-

**Table 3. Monogenic disorders associated with allergic GI disorders**

	Gene name	Disease	Atopic manifestation
Barrier	<i>SPINK5, CDSN</i>	Netherton syndrome	Increased IgE levels, food allergy, atopic dermatitis, EoE
	<i>DSG1, DSP</i>	SAM syndrome	Increased IgE levels, multiple food allergies, EoE
T helper responses	<i>DOCK8</i>	Hyper-IgE syndrome	Eczema, increased IgE, food allergy
T regulatory responses	<i>TGFBR1, TGFBR2</i>	Loeys-Dietz syndrome	Asthma, food allergy, eczema, atopic dermatitis, allergic rhinitis, EGIDs
	<i>ERBB2IP</i>		Food allergy, EoE
	<i>STAT3</i>	Hyper-IgE syndrome	Increased IgE, food allergy, atopic dermatitis, eczema
	<i>CARMIL2</i>	Immunodeficiency disorders	EoE, dermatitis, recurrent skin and chest infections



**Figure 2. The effects of different allergen exposure paths on GI allergic diseases.** (A) The dual allergen exposure hypothesis suggests that (a) environmental exposure to antigens in early life, specifically via the skin, increases the risk of developing food allergic disease later in life by inducing allergic sensitization, and (b) oral consumption of high amounts of antigen in early life decreases the risk of developing food allergic disease later in life by inducing immune tolerance. (B) OIT induces Treg expansion and release of IL-10. IL-10 promotes Treg cell differentiation and inhibits Th2 cell differentiation. As a result, less IL-4 is produced, which decreases IgE isotype switch recombination in local B cells and Th2 cell differentiation. OIT-induced TGF- $\beta$  production by Tregs is also considered pathogenic in EoE and promotes tissue fibrosis, epithelial-to-mesenchymal transition, and smooth muscle contraction. OIT, at least in the setting of EoE, does not effectively dampen Th2 cell production of IL-5 and IL-13, which promote EoE. Increased IgG4 production by B cells is thought to be protective against IgE-mediated allergic GI diseases but might be pathogenic in EoE.

natal exposure of rats to BPA resulted in decreased Tregs and DCs in the spleen and mesenteric lymph nodes (97). In addition, glycosylated proteins, found in many foods particularly after super-high heating, such as microwave cooking, frying, and barbecuing, have been suggested to serve as alarmins that promote type 2 responses (94). Finally, exposure to certain drugs during infancy, particularly histamine 2 receptor antagonists and proton pump inhibitors, also increases risk for food anaphylaxis and EoE (71, 98, 99).

Past assumptions were that early exposure to food was a risk factor for the development of food allergy. However, current evidence supports that early exposure to food antigens is likely protective, at least for the development of food anaphylaxis (100, 101). The dual allergen exposure hypothesis suggests that epicutaneous exposure to antigens induces allergic sensitization, particularly in individuals with impaired skin barrier, whereas oral consumption of high amounts of antigen induces tolerance (Figure 2A). Several studies on peanut allergy showed striking results. Du Toit et al. (102) reported that the prevalence of peanut allergy in infants in the United Kingdom is 10-fold higher than the prevalence of peanut allergy in infants in Israel. This study revealed a link between early consumption of food antigens and tolerance induction, suggesting that the dramatic increase in infant peanut consumption in Israel is the main reason for the low prevalence of peanut allergy (102,

103). The dual allergen exposure hypothesis has been solidified by the Learning Early About Peanut Allergy (LEAP) study, a controlled clinical study that aimed to determine the best strategy to prevent peanut allergy in children. The study found that infants that had a negative skin-prick test to peanut were at higher risk for developing peanut allergy at 60 months of age if they avoided peanut consumption than if they were peanut consumers. In the group of infants that had a positive skin-prick test to peanut, the peanut-avoiding children were 3 times more likely to have peanut allergy at the age of 60 months than were peanut consumers (104). This study showed that peanut consumption can be protective even in high-risk infants who were environmentally exposed and sensitized to peanut. This protective effect remained even if the children who consumed peanut avoided peanut for the following 12 months (105). These findings have now been put into clinical practice by recommendation of peanut consumption in the first year of life (106).

Variance in the rates of allergic GI disease are found by geography and ethnicity. For example, non-US-born children who migrate to the US have decreased risk of food allergy independent of ethnicity (107). Similarly, Asian children who migrate to Australia have decreased risk to develop nut allergy (108). In contrast, among US-born children, the children of immigrants were at the highest risk for food anaphylaxis (107). Ethnic minorities in developed countries tend to have a higher rate of allergic sensitization. Higher levels of food-specific IgE have been observed in black children than in white children (109). These differences are probably attributable to differences in genetics and lifestyle.

Vitamin D deficiency has been associated with increased risk of peanut sensitization, peanut allergy, and IgE-mediated egg allergy (110, 111). The mechanism is thought to be mediated by vitamin D-driven suppression of IgE production and the promotion of tolerogenic DC and Treg maturation, which induces immune tolerance. In contrast, several studies have shown that excess vitamin D consumption increases the risk for allergies (112). Further studies are needed to establish the driving mechanisms, the dose response, and timing relationships.

**Microbial dysbiosis.** Decreased exposure to pathogens, such as *Helicobacter pylori*, has been reported to contribute to the development of allergies (113). Preterm delivery, cesarean section, and antibiotic use in infancy, which affect/alter the microbiome, are more common in EoE than control groups (71, 99). A large study in Japan revealed that food allergy risk is decreased with increasing birth order, possibly reflecting exposure to more infections from siblings (114, 115). Having a dog is a protective factor against IgE-mediated food allergy and EoE (71, 115). Living on a farm is associated with decreased rates of food allergy sensitization in children (116). These data substantiate a key role for exposure, particularly related to dysbiosis, in the etiology of GI allergic diseases.

It is notable that germ-free mice are more susceptible to Th2 responses (117–119). Azad et al. demonstrated that microbiome dysbiosis in early infancy is associated with food sensitization later in life (120). In another study, the intestinal microbiota of infants with milk allergy was significantly different from that of control infants (121). Animal studies suggest that gut colonization of commensal microbes in early life influences tolerance versus allergic sensitization to environmental exposures encountered later in life via several

mechanisms. In the GI tract, dietary fiber is converted to short-chain fatty acids (mainly acetate, butyrate, and propionate) through the actions of commensal anaerobic bacteria. The receptors for these metabolites (GPCRs such as GPR43/FFAR2, GPR41/FFAR3, and GPR109A/HCAR2) are expressed by Tregs, Th2 cells, neutrophils, macrophages, DCs, mast cells, epithelial cells, and adipocytes in the intestine and particularly the colon (11, 122). Butyrate and propionate regulate differentiation of colonic Tregs that suppress inflammatory and allergic responses (123, 124). Acetate regulates gut epithelial integrity (125). Short-chain fatty acids influence the severity of allergic inflammation in the lungs by regulating DCs and Th2 cells (126). Alterations in the intestinal microbiome homeostasis regulate the epithelial inflammasome pathway and IL-18 production, which can be protective processes against intestinal damage and colitis (127). Dietary fiber and microbiota also promote chromatin changes by regulating histone acetylation and methylation in multiple host tissues (122). Barletta et al. showed that probiotic supplementation in a murine model ameliorates peanut allergy by increasing TGF- $\beta$  levels (128). Atarashi et al. successfully isolated Treg-inducing bacterial strains from the healthy human indigenous microbiota. Inoculation of these bacteria into germ-free mice revealed multiple strains of clusters IV, XIVa, and XVIII of Clostridia that induced Treg expansion and antiinflammatory cytokine production (129). Colonization of germ-free mice with feces from healthy or cow's milk-allergic (CMA) infants revealed that the CMA-colonized mice had increased anaphylactic responses compared with healthy-colonized mice and exhibited differential gene signature in the ileal epithelium. In the same paper, the authors also identified the clostridial species *Anaerostipes caccae* as a protecting species against an allergic response to food (130). Though the effect of probiotic supplements on AD and eczema in clinical trials seems promising (131), their effect on GI allergy remains controversial (132, 133). Zmora et al. investigated the murine and human mucosa-associated microbiome along the GI tract with and without supplementing with multiple strains of bacteria (mainly from the genera *Lactobacillus* and *Bifidobacterium*) and reported that humans can be clustered into two groups: permissive or resistant to mucosal probiotic colonization (134). In addition, the use of empiric probiotics after the use of antibiotics could delay the gut microbiome and transcriptome reconstitution, whereas fecal microbiome transplantation induced rapid microbiome reconstitution (135). These studies raise the hypothesis that probiotic treatment may be more beneficial as a patient-tailored therapy than as an empiric one-for-all approach. Further studies are required to identify specific strains and, particularly, certain species of the genus *Clostridium*, which will be adjusted to the host microbiome in a personalized manner. Perhaps healthy dietary guidelines can protect from GI allergic diseases by promoting a balanced GI microbiome.

### Oral immunotherapy and the mechanism of desensitization

Food allergen immunotherapy is a process by which an atopic individual is exposed to initially small but gradually increasing quantities of allergens in order to achieve tolerance or

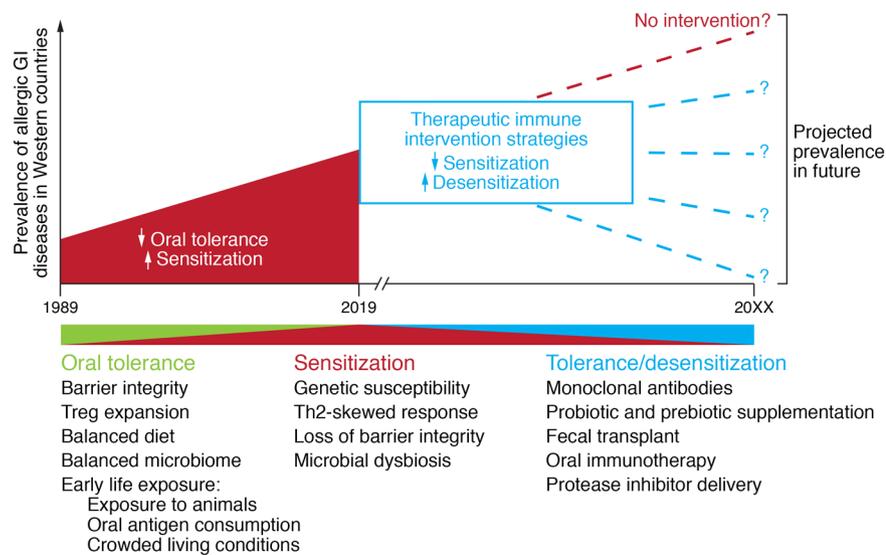
sustained unresponsiveness of the immune system, thereby decreasing the probability of an allergic reaction toward the allergen (136). The exposure to antigens can be epicutaneous, sublingual, or oral. The mechanisms by which immunotherapy is mediated are under extensive investigation. The reduction in sensitivity after immunotherapy is associated with a decreased ratio of IgE/IgG2a and increased antigen-specific IgG4 and IgA antibodies (137), decreased mast cell and basophil reactivity, and increased Tregs (138).

The extent of protection following immunotherapy is highly variable. Epicutaneous immunotherapy in a murine peanut allergy model revealed hypermethylation of the *Gata3* promoter and hypomethylation of the *Foxp3* promoter in Tregs, leading to a decrease in Th2 cells and an increase in Tregs, respectively. This was associated with sustained protection from food anaphylaxis (139).

Multiple case reports and meta-analysis of oral immunotherapy (OIT) reveal that immunotherapy for IgE-mediated food allergy may cause development of EGIDs (140–144). In murine models of EoE, epicutaneous allergen exposure primes for EoE (145), whereas epicutaneous immunotherapy induces a persistent resolution of esophageal eosinophilia (138), suggesting the skin's potential to positively or negatively modify EoE-related responses. During OIT, Treg-mediated Th2 immunity in mice is modified, likely concentrated on inhibiting IL-4- and IgE-mediated responses but not sufficiently inhibiting IL-5- and IL-13-mediated responses. During experimental OIT, the induced Treg response is sufficient to repress IL-4/IgE but not experimental EoE development. It is unknown whether OIT-associated EoE is due to the unmasking of preexisting, lower-grade esophageal eosinophilia or the initiation of new esophageal disease. Interesting observations have shown that IgG4 levels are increased in EoE (146–149). IgG4 is thought to be a neutralizing antibody because it binds weakly to activating Fc $\gamma$  receptors. Treg-derived IL-10 and TGF- $\beta$  likely regulate IgG4 production, connecting these pathways. During early life, food-specific IgG4 increases with continual peanut exposure; notably, a similar IgG4 increase occurs during OIT. Why the EoE response occurs only in a subset of OIT-treated patients may be genetically dictated. Figure 2B summarizes what OIT teaches us about the mechanism of EoE and IgE-mediated food allergy.

### Prevention and therapies

The most common approach to treat GI allergies is food allergen avoidance. Dietary treatment requires strict guidelines and educational interventions, especially in EoE, in which multiple foods drive disease and patients often have to remove the top six food allergen groups (milk, wheat, soy, egg, nuts/tree nuts, and fish/shellfish). Self-injectable epinephrine can prevent fatal consequences in life-threatening IgE-mediated food allergy. Because a dry, impaired skin barrier may increase the risk for GI allergic diseases, a few studies have examined whether treating eczema may decrease the risk of food anaphylaxis (150). Consistent, routine application of emollients has been shown to prevent AD (151, 152). Lowe et al. showed that prevention of eczema using lipid replacement therapy reduced food sensitization in a pilot trial (153). Likewise, in support of the dual allergen hypothesis, oral consumption of food allergens early in life prevents IgE



**Figure 3. Factors that contribute to immunologic tolerance, sensitization, and desensitization.**

Immune tolerance toward an antigen breaks down when a danger signal is produced instead of a tolerance signal. Long-lasting adaptive immune responses are influenced by a sequence of environmental and genetic factors. The increase in the prevalence rate of allergic GI diseases over the past several decades is mainly attributed to changes in environmental factors. Future studies that will decipher the pathways toward sensitization and desensitization will provide the bases for therapeutic immune intervention.

sensitization and food anaphylaxis, at least in the case of peanut allergy (100, 104, 105, 115).

Other treatment options that currently exist include corticosteroids, mast cell inhibitors, H2 antagonists, and leukotriene receptor antagonists. For diseases such as EoE, topical esophageal delivery of swallowed corticosteroids can be effective (154). However, EoE reoccurs nearly universally after cessation of therapy.

Non-IgE-mediated food allergies are typically resolved between 1 and 3 years of age, and the serotonin 5-HT<sub>3</sub> receptor antagonist ondansetron has proven beneficial in some cases (155).

Anti-human IgE antibody (anti-IgE; omalizumab) was the first biologic agent approved for treating asthma. Omalizumab treatment with allergen immunotherapy helps to potentiate increases in Treg activity by reversing the Th2 cell-like program (156). Using allergen OIT with anti-IgE antibodies in clinical studies showed promise, although not in all studies (157–160). Anti-IL-5 antibodies (mepolizumab, reslizumab) have been FDA-approved for treating eosinophilic asthma (161), and several clinical trials support their effectiveness for EoE, although while esophageal eosinophilia improved, clinical symptoms were only modestly improved compared with typical improvements seen with topical glucocorticoids or dietary elimination therapy (162–164). Treatment of EoE with anti-IL-13 antibodies (QAX576 and RPC4046) produced favorable early results (165–167). Early phase II trials of anti-IL-4R $\alpha$  (dupilumab) also yielded positive results (168), substantiating preclinical models based on IL-13-driven EoE-like responses (169, 170). Ongoing clinical studies are evaluating the effectiveness of targeting the IL-5 receptor IL-5R $\alpha$ , anti-Siglec-8 (an eosinophil and mast cell inhibitory receptor), and anti-IL-4R $\alpha$  for a number of GI allergic diseases, including EGIDs and food anaphylaxis. The effect of anti-TSLP treatment (AMG157) on EoE or IgE-mediated food allergy is unknown. However, in a study of asthma, AMG157 treatment showed positive results, especially for asthma that remained uncontrolled despite treatment (171). IL-33 was shown necessary for sensitization to peanut allergens and allergic responses

in mouse models of food anaphylaxis (172). Encouraging preliminary findings from a clinical trial of anti-IL-33 in peanut allergy have been recently presented (available at <https://www.anaptysbio.com/pipeline/etokimab/>) (173).

## Future directions

It is now understood that oral tolerance under healthy conditions is characterized by barrier integrity and Treg expansion promoted by early-life exposures through diet and microbiome composition. In contrast, loss of tolerance is characterized by loss of barrier integrity, microbial dysbiosis, and exaggerated type 2 immunity influenced by genetic susceptibility elements (including common variants as well as rare mutations associated with Mendelian diseases). Treatment is focused on promoting antigen desensitization and restoring long-term oral tolerance, currently centered around oral immunotherapy approaches, but future strategies include administering concurrent biologic therapies (e.g., monoclonal antibodies), manipulating commensal organisms through probiotics, prebiotics, and fecal transplantation, and reestablishing the protease/antiprotease balance (Figure 3). Currently, there is an unmet need to find more diagnostic markers and inhibitory strategies for GI allergic diseases. Better identification of individuals with increased risk of disease susceptibility will help future prevention of disease onset. Additional translational research will likely help in developing new treatment strategies and tailored medicine.

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