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# Breaking down the complex pathophysiology of eosinophilic esophagitis

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## Abstract

Eosinophilic esophagitis (EoE) is a chronic and progressive immune-mediated disease of the esophagus associated with antigen-driven type 2 inflammation and symptoms of esophageal dysfunction. Our understanding of EoE pathophysiology has evolved since its initial recognition more than 20 years ago and has translated into diagnostic and novel therapeutic approaches that are affecting patient care. The mechanisms underlying disease development and progression are influenced by diverse factors, such as genetics, age, allergic comorbidities, and allergen exposures. Central to EoE pathophysiology is a dysregulated feed-forward cycle that develops between the esophageal epithelium and the immune system. Allergen-induced, type 2-biased immune activation by the esophageal epithelium propagates a cycle of impaired mucosal barrier integrity and allergic inflammation, eventually leading to tissue remodeling and progressive organ dysfunction. Herein, we review the current understanding of fundamental pathophysiological mechanisms contributing to EoE pathogenesis.

## Introduction

Eosinophilic esophagitis (EoE) is a chronic, progressive immunemediated disease of the esophagus associated with antigen-driven type 2 inflammation and symptoms of esophageal dysfunction.[1] EoE is a common cause of feeding dysfunction in the pediatric population[2,3] and manifests clinically with gastrointestinal symptoms that often vary based on a patient's age. Younger patients with EoE often manifest with vomiting, heartburn, abdominal pain, feeding intolerance, and/or failure to thrive, whereas adolescents and adults most often present with progressive esophageal dysfunction, including dysphagia and food impactions.[4–8] Individuals with EoE frequently report adverse symptoms related to food ingestion and have multiple immunoglobulin (Ig)E food sensitizations,[9] which can result in numerous dietary restrictions. The chronic gastrointestinal symptoms, feeding dysfunction, and restricted diets reduce patient quality of life, with EoE ranking among the lowest quality of life scores in pediatric patients with chronic disease.[10]

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Characteristic EoE endoscopic features include linear furrows, esophageal rings, white plaques, exudates, and esophageal narrowing. However, endoscopic abnormalities can be subtle, and up to 30% of children with active disease can have an endoscopically normal-appearing esophagus.[11] Furthermore, the symptoms and active eosinophilic inflammation can be discordant.[12,13] Consequently, the reference standard for EoE diagnosis and disease surveillance remains histopathologic evaluation of esophageal mucosal biopsy specimens for increased intraepithelial eosinophils, with active disease defined by a tissue eosinophil density greater than or equal to 15 eosinophils/high-power field (HPF).[1,14] Additional histopathologic features in the esophageal mucosa associated with active disease are being increasingly incorporated into histologic evaluations of esophageal tissue biopsy specimens for EoE, including epithelial cell morphology changes, basal zone hyperplasia (BZH), dilated intercellular spaces (DIS), and lamina propria (LP) fibrosis.[15,16]

Since the recognition of EoE as a distinct clinical disease in the early 1990s,[17,18] our understanding of the disease pathophysiology has advanced significantly. Mechanisms underlying disease development and progression are influenced by diverse factors, such as genetics, age, allergic comorbidities, and allergen exposures. Central to EoE pathophysiology is a dysregulated feed-forward cycle that develops between an abnormal esophageal epithelium and the immune system (Fig 1). The esophageal epithelium with impaired barrier function stimulates allergen-induced, type 2-biased immune activation. This allergic inflammation promotes further impairment of mucosal integrity and propagates chronic immune activation, tissue remodeling, and progressive organ dysfunction. Herein, we breakdown the complex pathophysiological mechanisms contributing to EoE pathogenesis.

## Genetic Contributions to Eosinophilic Esophagitis Pathogenesis

EoE pathophysiology is driven by an interplay between genetic, environmental, and immunologic components. A recent comprehensive review focused on the contributions of genetics to the etiology of EoE[19]; we refer readers to this article for more detailed discussions. A relatively strong genetic contribution to EoE is supported given the increased EoE frequency among first-degree family members.[20,21] The familial inheritance pattern of EoE is inconsistent with a Mendelian/monogenic disorder, with the exception of rare families having single-gene mutations that drive disease transmission patterns. Most frequently, EoE has a complex inheritance pattern that is influenced by the effects of multiple genetic risk loci and the host environment. Notably, disease concordance among siblings is nearly 10-fold higher among dizygotic twins than in nontwin siblings (22% vs 2.4%, respectively),[21] suggesting that shared early life environmental factors substantially influence risk of disease development. Indeed, Jensen et al[22] evaluated the role of early life factors and determined that prenatal (maternal fever, preterm labor), intrapartum (cesarean section), and early life medical treatments (antibiotics, acid suppressants) are associated with an increased risk of developing EoE.

EoE is a rare disease (prevalence of approximately 0.5–1 case per 1000 individuals[23]), resulting in genetic studies that have been relatively limited to small samples sizes. However, 5 independent genome-wide association studies (GWAS) completed with subjects with EoE

have identified numerous susceptibility loci with genome-wide significance (Table 1).[24–28] Four genetic loci (5q22 [*TSLP*/*WDR36*], 2p23 [*CAPN14*], 11q13 [*LRRC32*/*EMSY*], and 16p13 [CLEC16A/DEX1]) have been reproduced across multiple studies, with a number of other risk loci identified in single studies. Candidate gene–phenotype association studies have identified additional genetic loci that are also associated with the disease (Table 2).[24,29–37] Collectively, many of the genes identified in these different analyses seem to influence epithelial barrier function or $T_H2$-mediated immune responses, consistent with the underlying pathoetiology of EoE. Furthermore, most EoE genetic risk variants identified are located outside of gene-coding regions, suggesting a key role for genotype-dependent gene regulation in EoE.[19]

## Disease Triggers

In the past 2 decades, the incidence and prevalence of EoE have been increasing at rates that outpace increased recognition.[23] This suggests that environmental factors, rather than genetic changes, have a critical role in disease pathogenesis. EoE is an antigen-driven disease associated with exposures to food antigens and possibly environmental aeroallergens.[38,39]

Food allergens (eg, milk, egg, wheat, soy) are well-established disease triggers,[40–42] with dietary elimination of specific food allergen triggers or elemental diet therapy resulting in disease remission in most subjects.[43] Individuals with IgE-mediated food allergy (IgE-FA) have an increased risk for the development of EoE. Using a large pediatric cohort from a single academic referral center, Hill et al[44] reported that children with IgE-FA had an EoE prevalence of approximately 1 case per 20 individuals, nearly 100-fold higher than population-based estimates of 0.5 to 1 case per 1000. Furthermore, 68% of children with EoE had self- and/or parent-reported IgE-FA.[44] Pelz et al[45] also revealed that physician-diagnosed IgE-FA was common in patients with EoE, with patients with EoE and concurrent IgE-FA having distinct clinical characteristics compared with patients with EoE without IgE-FA. Interestingly, some individuals with IgE-FA may have a propensity to develop esophageal eosinophilia. Endoscopy results of patients with a history of anaphylaxis to cow's milk revealed that 38% of these individuals had esophageal eosinophilia (>15 eosinophils/HPF) at baseline, many of whom did not report chronic gastrointestinal or esophageal symptoms.[46] Similarly, endoscopy results on adults with peanut allergy found that 14% of the adult subjects had subclinical esophageal eosinophilia (>15 eosinophils/HPF).[47] Notably, individuals undergoing food oral immunotherapy (OIT) for treatment of their IgE-FA can develop EoE, with an incidence of biopsy-proven EoE ranging between 3.2% and 5.4%.[48,49] However, this incidence is likely an underrepresentation given that many patients experience gastrointestinal adverse events during OIT, but few actually undergo endoscopic evaluation.[50] A small study of adults undergoing peanut OIT revealed that most subjects developed asymptomatic esophageal eosinophilia (6 of 7 subjects [87%] with peak eosinophil counts [PECs] > 5 eosinophils/HPF; 4 of 7 subjects [57%] with PECs > 15 eosinophils/HPF) accompanied by mild endoscopic and other histologic abnormalities during their first year of therapy.[51] One subject met clinicopathologic criteria for EoE with symptoms of dysphagia and food impaction, prompting withdrawal from the study early for safety concerns. Notably, the tissue eosinophilia and other histologic abnormalities resolved

in most of the remaining subjects (4 of 6 subjects) during the second year of OIT. Larger studies are needed to determine whether individuals with IgE-FA and baseline eosinophilia represent a subpopulation of patients with food allergy with chronic mucosal inflammation and whether OIT-induced EoE is an exacerbation of this chronic disease or a new pathologic development. Together, these data establish food antigens as critical pathologic drivers of EoE and suggest that links between the immunopathogenesis of IgE-FA and EoE are likely.

Aeroallergens have also been implicated as potential EoE triggers and/or disease exacerbators, supported by the use of aeroallergens in EoE animal models,[52,53] development of denovo EoE in human subjects during sublingual immunotherapy to aeroallergens for allergic rhinitis,[54–56] and seasonal variation of EoE symptoms, food impactions, and esophageal eosinophilia.[57–62] Furthermore, retrospective review and case reports have suggested that subcutaneous immunotherapy (SCIT) may be useful for patients with EoE as an adjunctive therapy in patients with comorbid allergic rhinitis and/or asthma,[63,64] with another case report revealing efficacy of SCIT as a monotherapy to induce and maintain clinicohistologic remission of EoE.[65] Additional studies are necessary to evaluate the safety and efficacy of SCIT as an adjunctive therapy, and possibly even monotherapy, for patients with EoE and comorbid allergic rhinitis and/or allergic asthma and determine how immunomodulation to environmental aeroallergens affects disease pathogenesis.

## Esophageal Epithelial Cells and Mucosal Barrier Dysfunction

Epithelium-derived alarmin cytokines, thymic stromal lymphopoietin (*TSLP*), and interleukin (IL)-33 function as danger signals that are rapidly released into the extracellular milieu in response to tissue damage. These cytokines facilitate $T_H2$ immune responses by skewing developing adaptive responses and have direct effects on multiple allergic effector cells, including eosinophils, mast cells, and basophils.[66] GWAS implicated genetic variants in *TSLP* in EoE susceptibility.[24,25,27,28] Indeed, individuals carrying the risk allele for the *TSLP* variant most associated with EoE had elevated esophageal *TSLP* RNA expression.[24] Moreover, both *TSLP* and *IL33* gene expression were increased in esophageal biopsy specimens from children with EoE,[24,30,67–69] and mice genetically deficient in TSLPR or IL-33R/ST2 had attenuated inflammation in experimental EoE-like disease.[69,70] Finally, IL-33 protein was markedly increased within the nuclei of basal layer esophageal epithelial cells in patients with active EoE vs controls, with levels normalizing on EoE remission.[68] One mechanism by which allergenic proteins may trigger alarmin cytokine production is through a novel RipIL-33 allergen-sensing pathway in esophageal epithelial cells.[71] The RIPK1–caspase 8 ripoptosome complex in the epithelial cells functions as an allergen-sensing platform that detects diverse allergic stimuli, resulting in caspase 8-directed activation and release of IL-33 (Fig 2). This pathway may be the first molecular evidence for how food and environmental allergens trigger/promote esophageal mucosal inflammation and a novel cellular pathway for therapeutic inhibition.

The lower layers of human esophageal squamous epithelium comprise actively proliferating cells. As the epithelial cells migrate toward the luminal surface, the cells differentiate, flatten, and establish cell-cell connections to form a barrier that protects the underlying tissue from repeated exposures to exogenous antigens. In a disrupted epithelial barrier,

antigens pass through and activate the immune system. In EoE, the epithelial barrier is abnormal. The epithelium has characteristic proliferative responses, with BZH being a well-recognized histologic change associated with active EoE.[16] In-depth transcriptional and functional analyses of the esophageal epithelium have revealed profound loss of cell differentiation, with genes involved in differentiation and keratinization being the most down-regulated biological processes in the esophagus-specific transcripts altered during EoE.[72,73] Furthermore, junctional proteins (eg, E-cadherin, claudin-1, desmoglein-1) necessary to maintain barrier integrity are significantly down-regulated during EoE.[33,35,74,75]

Dysregulated epithelial protease activity has also been implicated in EoE mucosal barrier abnormalities. Several GWAS identified calpain 14 (*CAPN14*), encoding an intracellular calcium-activated protease, as the gene most highly associated with EoE.[25–28] *CAPN14* is specifically expressed in the esophagus, and overexpression and silencing experiments in cultured esophageal cells had a significant disruptive effect on epithelial barrier function.[76,77] Serine protease inhibitors (SERPINs) and serine protease inhibitors, Kazal type (SPINKs) were also among the most dysregulated peptidase families in EoE.[72] SPINK7 expression is reduced in EoE, leading to increased proteolytic activity in esophageal epithelial cells that was associated with loss of epithelial differentiation, decreased barrier integrity, and enhanced proinflammatory responses, specifically through TSLP production.[34,78]

Collectively, these data suggest that allergen-triggered, epithelial-derived alarmin cytokines and impaired epithelial cell barrier function associated with loss of cell differentiation and dysregulated endogenous proteases promote allergic inflammatory responses in the esophageal mucosa. These immune responses, as reviewed subsequently, further impair mucosal integrity to propagate chronic immune activation that leads to progressive tissue dysfunction (Fig 1).

## Eosinophilic Esophagitis Immunopathogenesis

**Interleukin-13 and Interleukin-4—**IL-13 has a central role in EoE pathogenesis, directing eosinophil-predominant inflammatory responses and characteristic histologic changes to the epithelium associated with barrier dysfunction (Fig 2).[31,33,79–82] IL-13 is produced in the esophagus by infiltrating immune cells, including eosinophils, T helper 2 ($T_H2$) lymphocytes, and mast cells.[83–85] IL-13 is highly up-regulated in human esophageal tissue during EoE, and treating cultured primary esophageal epithelial cells with IL-13 alone induces a gene program that largely overlaps with the esophageal transcriptome from EoE biopsy specimens.[80] IL-13 stimulation of cultured human epithelial cells also promotes barrier dysfunction and reduces epithelial cell differentiation in the absence of eosinophils.[31,33] Furthermore, IL-13 induces expression of CCL26 (eotaxin-3), which promotes eosinophil chemotaxis and recruitment into the tissue.[80] Murine models support a prominent role for IL-13 in disease, as esophageal eosinophilic inflammation is induced directly by intranasal or intratracheal IL-13 administration,[79] and IL-13 overexpression drives esophageal eosinophilia, epithelial hyperplasia, and esophageal remodeling (fibrosis, angiogenesis).[81] Conversely, IL-13–deficient mice fail to develop esophageal eosinophilia in

an aeroallergen-induced EoE model.[53] These studies provided the rationale for monoclonal antibodies (mAbs) targeting IL-13 in human clinical trials for EoE, which revealed therapeutic efficacy in reducing EoE histologic and endoscopic signs, but limited efficacy in reducing clinical symptoms.[86,87] Collectively, these studies implicate IL-13 as a central immune mediator in the observed immunologic and histologic changes characteristic of active EoE.

IL-4 promotes differentiation of $T_H2$ cells and regulates eosinophil trafficking by inducing eosinophil chemotaxins and eosinophil adhesion molecules.[88,89] *IL4* expression is also increased in EoE by disease activity.[82] Notably, dupilumab, a fully human mAb targeting the IL-4Rα chain, which antagonizes both IL-4 and IL-13 signaling, was found to have efficacy in improving histologic, endoscopic, and symptomatic measures in phase 3 clinical trials. Consequently, the US Food and Drug Administration approved dupilumab in May 2022 as the first therapeutic for treating EoE in adolescents aged 12 years and above and adults.[90,91]

**CCL26 and Interleukin-5—**Mechanistic studies have implicated CCL26 (eotaxin-3) and IL-5 as additional immune mediators that affect eosinophil function during EoE. CCL26 is a chemokine that causes eosinophil chemotaxis by CCR3, the CCL26 receptor. Notably, *CCL26* is the most highly up-regulated gene (53 fold) in the EoE transcriptome and *CCL26* expression significantly correlates with disease activity.[30] Furthermore, CCR3-deficient mice are protected from developing experimental EoE. CCL26 production is produced mainly by the esophageal epithelium and induced by IL-13 stimulation.[80]

IL-5 is an important cytokine in eosinophil development and function, promoting eosinophil maturation, proliferation, activation, and survival. In allergen-induced EoE, disease can be induced in wildtype, but not IL-5–deficient, mice and treating wild-type mice with IL-5–neutralizing antibody blocks both allergen– and IL-13–induced EoE.[52,53,92,93] These data supported human trials targeting eosinophils through IL-5 inhibition in individuals with EoE.[94–97] Mepolizumab and reslizumab are humanized mAbs that neutralize IL-5 by binding and preventing cytokine-receptor interaction. These biologic medications reduce both blood (>90%) and tissue (55%) eosinophil levels in human EoE.[94,96,97] However, neither medication induced complete histologic remission (PECs < 15 eosinophils/HPF) in most individuals, and there was no significant clinical improvement in the symptoms. It remains unclear whether the incomplete histologic response and poor clinical improvement reflect eosinophil persistence in the tissue or evidence that symptoms are driven by other cell populations. Ongoing trials with biologics targeting and more completely depleting tissue eosinophils (eg, benralizumab, lirentelimab) through antibody-dependent cell cytotoxicity may further clarify our understanding of IL-5 and eosinophils' role in disease pathogenesis and the effectiveness of therapeutic strategies specifically targeting this immune axis.

**Eosinophils—**Eosinophils are pleotropic cells often residing within the mucosal tissues with known effector functions in allergic inflammation, immunoregulation, and tissue remodeling and repair. Eosinophil infiltration into the esophageal tissue was recognized early in the study of EoE as a fundamental pathologic and diagnostic feature of the disease.[17,18] Although not pathognomonic for EoE, intraepithelial eosinophils are absent within the esophageal mucosa of healthy individuals,[98] and their migration into the

epithelium implies underlying tissue pathology. In human EoE, esophageal eosinophil levels correlate with disease severity by endoscopy,[99,100] histopathologic severity (eg, epithelial hyperplasia, DIS),[12,30,99,101] and tissue remodeling and fibrosis.[102,103]

Although esophageal mucosal eosinophils are a disease hallmark, the mechanisms by which eosinophils contribute to pathophysiology are not fully understood. Eosinophils generate and release reactive oxygen species and toxic granule proteins (eg, major basic protein, eosinophil peroxidase, eosinophil cationic protein) that damage the esophageal epithelium and potentially decrease epithelial barrier function. Indeed, degranulating eosinophils and extracellular granule proteins are observed in human EoE.[30,94,104] Major basic protein can also increase smooth muscle reactivity through the muscarinic M2 receptors[105] and activate mast cells and basophils[106] also present in the tissue during EoE.[107,108] Esophageal eosinophils from human subjects with EoE also express high levels of $T_H2$ cytokines that sustain and augment allergic inflammatory responses (eg, IL-4, IL-5, IL-13, IL-9) and produce profibrotic factors (eg, transforming growth factor beta [TGF-β]) that promote tissue remodeling and fibrosis.[84,109] Eosinophils also generate leukotrienes that contribute to smooth muscle proliferation and hyperresponsiveness, which could promote esophageal dysfunction.

Not all EoE features associate with eosinophilic inflammation, however. In experimental EoE, eosinophil-deficient mice have reduced stricture formation and decreased epithelial BZH and LP thickness but still develop esophageal motility dysfunction.[93,110] In humans with EoE, esophageal eosinophilia dissociates from symptoms of esophageal dysfunction and endoscopic abnormalities,[12,99,100,111] some of which correlate with tissue mast cell levels.[111] Furthermore, individuals with an EoE-like disease have similar clinical features, response to steroid therapy, and strong familial association with EoE but have no tissue eosinophilia by histopathology.[112] Interestingly, these individuals had reduced CCL26 and increased esophageal lymphocytic infiltrates compared with individuals with EoE. Finally, EoE endotypes (see subsequent discussion) had variable degrees of histologic, endoscopic, and clinical abnormalities, but their classification was independent of PECs.[113]

A review by Doyle et al[114] proposed a model whereby eosinophils have divergent roles in EoE pathogenesis by disease stage (ie, early vs established disease). Given that eosinophils have homeostatic roles in the gastrointestinal tract, their appearance at early stages of EoE may reflect functions to protect/restore a damaged epithelial barrier. In later stages of disease, these cells may become activated and promote tissue damage, thereby perpetuating inflammation and fibrosis.

**Mast Cells—**Mast cells are tissue-resident immune cells that have central roles in allergic inflammatory responses. Mast cells are normally present within the esophageal mucosa during homeostasis and predominantly reside in the LP. During active EoE, mast cells infiltrate and expand within the esophageal epithelium, where they become activated and degranulate.[83,108,115–117] Clinically, mast cell numbers correlate with patient-reported pain symptoms.[111,118] A clinical trial of anti–IL-5 therapy in children with EoE revealed that the severity of reported pain during EoE correlated with esophageal mast cell, not eosinophil, levels.[109] A recent study corroborated these findings and suggested that a relationship

between mast cells and the molecular expression of esophageal TRPV1, an ion channel serving as a detector of painful stimuli on sensory neurons, may contribute to the mast cell–pain association in EoE.[118] Notably, mast cell infiltration into the epithelium persists despite treatment-induced resolution of tissue eosinophilia, and mast cell levels correlate with persistent symptoms and endoscopic (furrowing, rings) and histologic abnormalities (BZH, DIS).[83,111,117]

Mast cells are equipped with effector mechanisms that contribute to disease pathogenesis. They prominently produce esophageal IL-13,[83] cytokines that activate eosinophils (IL-3, IL-5, granulocyte-macrophage colony-stimulating factor), and inflammatory mediators, including histamine, prostaglandins, leukotrienes, and thromboxanes, which increase vascular permeability and smooth muscle contraction.[119] In experimental EoE, mast cell infiltration into the esophageal muscle layers associates with smooth muscle hypertrophy, increased contractility, and decreased relaxation responses partially mediated by TGF-β1 expression.[110,115,120] Mast cells also promote fibroblast activation and collagen secretion.[120,121]

Single-cell RNA sequencing (scRNA-seq) analysis of the esophageal mast cell population in human EoE reveals a heterogeneous population with cell subsets associated with distinct spatial compartments that fluctuate by EoE disease status.[83] During homeostasis, a resident mast cell population with a quiescent phenotype is present in the LP. During active disease, 2 additional mast cell populations emerge in the intraepithelial compartment; these populations assumed a proinflammatory state and expressed proliferation-associated genes. Notably, one of these populations persists during disease remission, poised to reinitiate inflammation.

Collectively, these data emphasize the importance of mast cells in EoE disease pathogenesis. Future diagnostic testing methods for clinical and outcomes–based research will need to consider this effector cell population when assessing disease activity and remission.

**T Lymphocytes—**Accumulating evidence suggests that effector $T_H2$ cells producing cytokines IL-4, IL-5, and IL-13 have central roles in EoE pathogenesis. T cells infiltrate the esophageal mucosa during active EoE, and their levels are elevated in individuals with active disease vs inactive disease or normal controls.[30,122–124] Although levels of both esophageal CD4+ and CD8+ T cells increase,[85,123–125] allergen-induced EoE models in mice revealed that CD4+ T cells were pathogenic but that CD8+ T-cells were dispensable.[125]

Wen et al[85] analyzed human tissue-residing CD3+ T cells using scRNA-seq and revealed a prominent polyclonal memory CD4+ T cell population expressing IL-4, IL-5, and IL-13 that correlated strongly with esophageal tissue eosinophilia. Subsequently, Morgan et al[126] used scRNA-seq and TCR sequencing to further characterize the esophageal T cell population during active EoE vs remission and confirmed that a pathogenic memory effector $T_H2$ cell population was enriched in the esophagus of individuals with active EoE. This pathogenic $T_H2$ population expressed distinct gene signatures associated with gene up-regulation of $T_H2$ cytokines and eicosanoid prostaglandin D2 (PGD2) synthesis. Notably, PGD2 signals through the chemoattractant receptor-homologous molecule expressed on $T_H2$

cells (CRTH2) expressed on $T_H2$ CD4+ cells, eosinophils, and basophils and stimulates these cells' recruitment into the tissue.[127,128] Signaling through CRTH2 also stimulates eosinophil activation,[128–130] proinflammatory cytokine production in $T_H2$ cells,[131] and basophil activation.[132]

Altogether, these data reveal that pathogenic effector $T_H2$ cells infiltrate the esophagus during active disease and release inflammatory mediators capable of (1) promoting inflammation through the recruitment and activation of eosinophils, basophils, and additional pathogenic $T_H2$ cells and (2) inducing epithelial cell changes that contribute to loss of barrier integrity.

**Additional Allergic Effector Cells—**Additional allergic effector cells with potential roles in EoE include basophils, type 2 innate lymphoid cells (ILC2s), and dendritic cells (DCs). Basophil levels are increased in the blood and esophageal biopsy specimens of human active EoE.[69,107,133] Although the role of basophils in disease pathogenesis remains unclear, a mouse model of EoE-like disease revealed that allergic inflammation depended on TSLP and basophils,[69] suggesting a possible TSLP-basophil axis in EoE pathogenesis. ILC2s are tissue-resident immune cells that are activated by the epithelial alarmins IL-33 and TSLP and capable of robust IL-4, IL-5, IL-9, and IL-13 production.[134] Doherty et al[135] revealed that levels of esophageal ILC2s were increased in individuals with active EoE vs remission or controls and that tissue ILC2 levels correlated strongly with tissue eosinophilia. DCs normally reside in the esophageal epithelium,[123,124] but DC levels increase during EoE.[123] TSLP and IL-33 promote DC-mediated $T_H2$ cell polarization,[136] suggesting that DCs may be involved in promoting $T_H2$ cell accumulation and polarization in the esophageal mucosa. Additional research will be necessary to better understand the contributions of these allergic effector cells to the pathogenesis of EoE.

**Immunoglobulins (Immunoglobulin E, Immunoglobulin G4)—**EoE is associated with other atopic diseases with known IgE-mediated pathophysiology, including food allergy, allergic rhinitis, and asthma.[39] Elevated total serum IgE level and specific IgE sensitization to food or environmental allergens are common in individuals with EoE.[5,9,137,138] Moreover, IgE production in the esophageal mucosa has been observed in children with EoE.[139] However, human studies treating EoE with omalizumab, a humanized anti-IgE mAb, have not supported a significant role for IgE in disease pathogenesis. In one non–placebo-controlled study, anti-IgE therapy significantly reduced esophageal tissue IgE levels but was only marginally effective at inducing remission (33% of subjects).[140] In a double-blind, placebo-controlled study, omalizumab did not differ from placebo in inducing histologic remission or symptom improvement.[141] Collectively, these data suggest that IgE sensitization associates with EoE but is not directly involved in pathogenesis.

Interestingly, several lines of evidence implicate the antibody subclass IgG4 in EoE pathogenesis. Adults with EoE had a 45-fold increase in esophageal IgG4 levels vs controls, with no significant increase in other IgG subclasses.[141] IgG4 deposits were noted in the esophageal tissue in 76% of adults with EoE vs 0% of controls.[142] Furthermore, adults with EoE had elevated levels of serum total IgG4 and food-specific IgG4 vs controls.[143] Children with active EoE had increased esophageal levels of IgG4-positive

plasma cells,[144] and elevated esophageal IgG4 levels correlated with disease activity as assessed by histopathology and transcriptomic features.[145] Finally, individuals with EoE who were treated with topical steroids or responsive to 6-food elimination diet therapy had reduced serum and esophageal IgG4 levels.[143,146] Additional studies are necessary to clarify the specific role of IgG4 in disease pathogenesis.

**Interferons (Interferon Alfa, Interferon Gamma)—**As noted previously, studies of EoE immunopathology strongly support a critical role for type 2 inflammatory networks. However, levels of type 1 inflammatory signals, including IL-1 and IL-6, and type I and II interferons (IFNs) are elevated in the esophagus of individuals with EoE.[82,147,148] Ruffner et al[147] found a strong IFN-responsive gene signature (IFN-α– and IFN-γ–responsive genes) in transcriptomic analyses of esophageal biopsy tissue from both adult and pediatric patients with EoE and revealed that blood CD4+ T cells from children with EoE produce IFN-γ on activation with EoE-causal allergens. Previous studies have also detected IFN-γ expression in CD8+ T cells that are enriched in EoE biopsy tissues,[85,148] suggesting that they could also contribute to the increased IFN-responsive gene signature in EoE esophageal tissue. Together, these data highlight a potential role for non–type 2 inflammatory networks in EoE immunopathology, but additional studies using animal models and human tissue are needed to clarify the cellular participants in the IFN response and the role that these cytokines may play in pathogenesis.

## Tissue Fibrosis and Remodeling and Transforming Growth Factor Beta

Natural history studies suggest that EoE progresses from an early eosinophil-rich, inflammatory disease to a fibrostenotic disease associated with subepithelial collagen deposition, smooth muscle hypertrophy, and angiogenesis.[4,23] Indeed, endoscopic features of fibrostenotic disease and histopathologic fibrosis increase with age, which is associated clinically with worsening dysphagia, stricture formation, and food impactions.[4,6,7,149] However, tissue remodeling is variable; not all adults with longstanding inflammation develop fibrostenotic disease, whereas some children with EoE develop tissue fibrosis at a young age.[5,7,150] Consequently, which individuals will develop fibrostenosis remains unclear, although a fibrostenotic endoscopic phenotype has been associated with a distinct EoE endotype by esophageal gene expression.[4,113]

TGF-β promotes esophageal remodeling by inducing fibroblast activation and secretion of extracellular matrix (ECM) proteins (eg, collagen, fibronectin),[151–153] including smooth muscle proliferation, hyperplasia, and contractility.[154] TGF-β level is increased in EoE esophageal biopsy specimens and produced by infiltrating eosinophils and mast cells.[103,115] TGF-β also promotes epithelial-mesenchymal transition (EMT), during which epithelial cells acquire myofibroblast characteristics and lose certain epithelial cell features,[155,156] allowing these cells to participate in ECM synthesis and deposition. Treatment of adult patients with EoE using an anti–IL-13 antibody significantly reduces EMT markers in the esophageal tissue, suggesting that targeting this immune pathway may reduce the fibrotic response in patients with active EoE.[157] In a retrospective study in children with EoE, EMT markers correlated strongly with eosinophil counts and were reversible after treatment.[156]

Recent studies have begun to shed light on some of the molecular components involved in EoE fibrostenosis. Shoda et al[158] used a set of 94 esophageal mRNAs dysregulated in EoE to compare children and adults with fibrostenotic vs nonfibrostenotic EoE phenotypes and associated loss of esophageal tetraspanin 12 (TSPAN12) expression in endothelial cells with EoE tissue fibrostenosis. Notably, IL-13 reduces TSPAN12 expression, which promotes endothelial production of profibrotic mediators (eg, endothelin-1) capable of increasing ECM production by fibroblasts. A proteomic study revealed that fibroblasts from human EoE secrete a unique ECM proteome, identifying thrombospondin-1 (TSP-1) expression specifically in the EoE ECM.[159] Notably, TSP-1 was capable of inducing fibroblast collagen I production,[159] suggesting a profibrotic role in EoE.

**Phenotypic Variability and Eosinophilic Esophagitis Endotypes—**EoE is increasingly recognized as a heterogeneous disease with phenotypic variability in clinical presentation by age, race, sex, symptoms, endoscopic and histologic abnormalities, comorbidities, disease triggers, and treatment response.[160–162] Males have a higher risk for active disease, food impactions, and strictures, and African Americans exhibit classic EoE endoscopic findings but are less likely to present with dysphagia.[163–167] Although most individuals with EoE have atopy,[39,168] a subset of patients have no allergic comorbidities, and several non-atopic diseases associate with EoE, including inflammatory bowel disease and connective tissue disorders.[169,170] Furthermore, differential responses to therapy have been recognized (eg, response to proton pump inhibitors, swallowed steroids, or dupilumab).[90,171]

Greater understanding of the disease pathogenesis and clinical heterogeneity has driven efforts to begin characterizing EoE cases by the distinct molecular mechanisms driving disease development and progression (ie, endotypes). Using a machine-learning approach to evaluate histologic, endoscopic, and molecular disease features, Shoda et al[113] identified 3 discrete EoE endotypes. EoE endotype 1 (EoEe1) is associated with a normal-appearing esophagus, relatively mild histologic and molecular changes, and steroid responsiveness. EoE endotype 2 (EoEe2) is associated with pediatric onset, the highest degree of endoscopic and histologic severity for inflammation, highest expression of inflammatory cytokines (eg, IL-4, TSLP), and steroid-refractory disease. EoE endotype 3 (EoEe3) is associated with adult onset, the highest degree of endoscopic and histologic severity for fibrostenotic components, and lowest expression of epithelial differentiation genes. Using unsupervised clustering of transcriptional responses from tissue biopsy specimens, Dunn et al[172] found heterogeneity in genes associated with type 2 immunity among EoEe1-e3, suggesting that these endotypes could be further subdivided. Notably, none of the endotypes were differentiated by tissue eosinophil levels, reaffirming that the underlying differences in pathophysiology extend beyond eosinophil-directed immunopathogenesis. Longitudinal studies are necessary to determine whether these endotypes associate with distinct disease mechanisms or represent a disease continuum. Aligning specific molecular signatures to individuals with distinct clinical phenotypes and longitudinal outcomes may eventually enable physicians to begin targeting specific effector pathways to individualize therapeutic approaches for EoE.

## Conclusion

EoE is a chronic inflammatory disease of the esophagus associated with clinical and molecular heterogeneity and characterized by epithelial barrier defects, eosinophilic $T_H2$-predominant inflammation, and tissue remodeling leading to progressive esophageal dysfunction (Fig 2). Dysregulated epithelial and immune cell responses are central to disease pathogenesis and generate a feed-forward cycle leading to chronic inflammation. Although research efforts in the past 2 decades have drastically improved understanding of EoE, many knowledge gaps remain, including the precise steps underlying development of EoE and how the different elements of pathogenesis influence one another and the natural history of disease. Additional basic and clinical research is necessary to develop methods that efficiently identify allergen exposures that are clinically relevant in individual patients, further understand the underlying mechanisms by which food and possibly aeroallergens are driving disease pathogenesis, and determine the role of the gastrointestinal microbiome in establishing, furthering, and/or mitigating EoE pathophysiology, as Benitez et al[173] revealed that the microbiome was altered by the presence and activity of EoE (microbiota in EoE further reviewed in Busing et al[174] and Mennini et al[175]). Prospective studies will be needed to further define how specific therapeutic interventions modulate disease pathogenesis over time and determine which molecular components drive the disease in specific individuals. Ultimately, an improved understanding of EoE pathogenesis will lead to identification of molecular pathways important for the disease that will improve biomarker development, assignment of disease endotypes, and novel treatments for the disease.

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**Key Messages**

- Eosinophilic esophagitis (EoE) is a chronic inflammatory disease of the esophagus associated with clinical and molecular heterogeneity.
- EoE pathophysiology is characterized by epithelial barrier defects, eosinophilic $T_H2$-predominant inflammation, and tissue remodeling leading to progressive esophageal dysfunction.
- Dysregulated epithelial and immune cell responses are central to disease pathogenesis and generate a feed-forward cycle leading to chronic inflammation.
- Improved understanding of EoE pathogenesis has led to identification of disease pathways that have identified novel pathways for disease treatment.

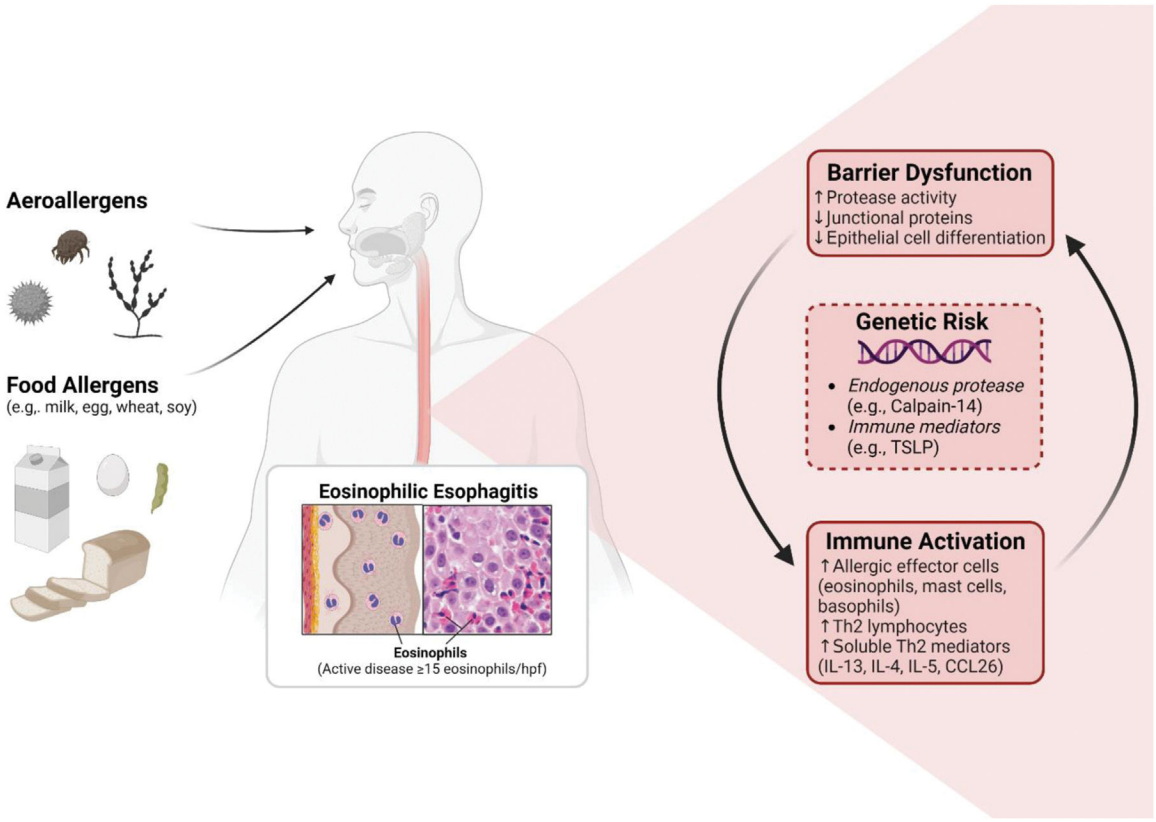


**Figure 1.**

EoE is an allergen-driven, chronic inflammatory disease of the esophagus. Impaired epithelial barrier function and dysregulated immune cell responses influenced by genetic polymorphisms are central to EoE pathogenesis, generating a feed-forward cycle leading to loss of immunologic tolerance to exogenous allergens and chronic eosinophilic inflammation. Created with BioRender.com. EoE, eosinophilic esophagitis; HPF, high-power field; IL, interleukin; $T_H2$, T helper 2 cells; TSLP, thymic stromal lymphopoietin.

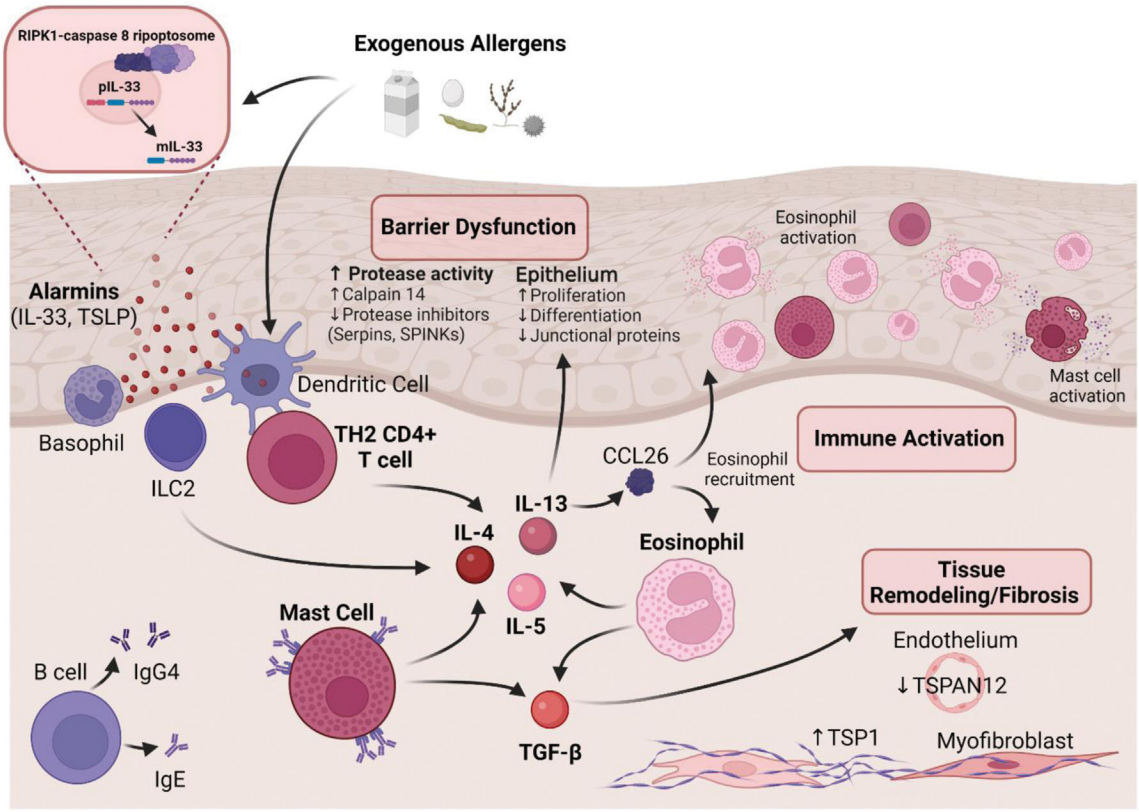


**Figure 2.**

EoE pathophysiology model. Exogenous allergens trigger epithelial-derived cytokine TSLP and IL-33 production, the latter through activating the intracellular allergen sensor RIPK1-caspase-8 ripoptosome. An impaired mucosal barrier from dysregulated endogenous proteases and an abnormal epithelium allow translocation of food antigens to the dendritic cells, which process and present them to the CD4+ T cells. TSLP and IL-33 influence the dendritic cells to mature $T_H2$-biased effector T cells and stimulate ILC2s; both populations secrete cytokines IL-4, IL-5, and IL-13, which recruit and activate mast cells, eosinophils, and basophils. Mast cells and eosinophils propagate allergic inflammation through cytokine and inflammatory mediator production (eg, PGD2, leukotrienes, granule enzymes), leading to immune cell activation and epithelial changes that further impair barrier function. A feed-forward cycle develops, causing chronic inflammation that stimulates tissue remodeling/fibrosis through the cytokine TGF-β, epithelial-mesenchymal transition, and pro- and anti-fibrotic mediator (TSPAN-12, TSP1) modulation. Created with BioRender.com. EoE, eosinophilic esophagitis; IL, interleukin; ILC2, type 2 innate lymphoid cell; PGD2, prostaglandin D2; TGF-β, transforming growth factor beta; $T_H2$, T helper 2 cells; TSLP, thymic stromal lymphopoietin.

## Table 1

Statistically Significant EoE Genetic Risk Loci Identified by GWAS

| EoE Risk Locus (chromosome location) | Candidate genes at or near risk variants | Known function/putative mechanism in EoE pathogenesis | References |
|---|---|---|---|
| Established risk loci using independent cohorts | | | |
| *2p23.1* | *CAPN14* | CAPN14 is an intracellular calcium-activated protease specifically expressed in the esophagus. *CAPN14* expression is increased during active EoE and is upregulated by IL-13. Overexpression and silencing of *CAPN14* in cultured esophageal cells have a disruptive effect on epithelial barrier function. | Kottyan et al,[25] 2021<br>Chang et al,[26] 2022<br>Kottyan et al,[27] 2014<br>Sleiman et al,[28] 2014 |
| *5q22.1* | *TSLP*<br>*WDR36* | TSLP is an epithelium-derived alarmin cytokine that induces allergic Th2 immune responses and has direct effects on multiple allergic effector cells, including eosinophils, mast cells, and basophils. | Rothenberg et al,[24] 2010<br>Kottyan et al,[25] 2021<br>Chang et al,[26] 2022<br>Kottyan et al,[27] 2014<br>Sleiman et al,[28] 2014 |
| *11q13.5* | *LRRC32*<br>*c11orf30/EMSY* | *LRRC32* encodes a TGF-β-binding protein that is involved in regulatory T-cell-mediated suppression of colitis. *LRRC32* is upregulated by IL-13. EMSY is involved in epithelial cell differentiation. Both *LRRC32* and *EMSY* are expressed in esophageal epithelial cells. | Kottyan et al,[25] 2021<br>Chang et al,[26] 2022<br>Sleiman et al,[28] 2014 |
| *16pl3.13* | *CLEC16A*<br>*DEX1* | *CLEC16A* and *DEX1* are expressed in esophageal epithelial cells. Many cells of the immune system also express CLEC16A. Expression of *CLEC16A* is upregulated by IL-13. The function of CLEC16A and DEX1 proteins in EoE remains unclear. | Kottyan et al,[25] 2021<br>Chang et al,[26] 2022<br>Kottyan et al,[176] 2019 |
| Suggestive risk loci identified by single GWAS | | | |
| *8p23.1* | *XKR6* | Unknown | Kottyan et al,[27] 2014 |
| *15ql3.3* | between *LOC283710* and *KLF13* | Unknown | |
| *12q13.3* | *STAT6* | STAT6 is a transcription factor activated by IL-4 and IL-13 and has a role in the development of $T_H2$ cells and promotes type 2 immune responses. STAT6 also induces *CAPNI4* expression. | Sleiman et al,[28] 2014 |
| *19q13.11* | *ANKRD27* | ANKRD27 inhibits the activity of the SNARE complex, which could impact vesical trafficking and wound healing. May have a role in mucosal barrier integrity. | |
| *10p14* | *ITIH5* | ITIH5 is a serine protease inhibitor from a class of protease inhibitors that have been implicated in mucosal protease dysregulation and decreased epithelial barrier function in the esophagus. | Kottyan et al,[25] 2021 |
| *2q12.1* | *TMEM182* | Unknown | Chang et al,[26] 2022 |
| *5q31.1* | *RAD50* | Unknown | |
| *6p22.3* | *SOX4* | Unknown; involved in immune-associated pathways. | |
| *8q22.1* | *MATN2* | Involved in inflammatory responses, macrophage M2 polarization, and T cell differentiation. | |
| *10q21.1* | *PRKG1* | PRKG1 is involved in inflammatory signaling pathways. | |
| *11p15.4* | *RHOG* | Ras homolog gene family, member G (Rho G) is a member of the Rac subfamily of Rho GTPases that are highly expressed in lymphocytes. | |
| *11q13.4* | *SHANK2* | Unknown | |
| *13q12.13* | *GPR12* | Unknown | |
| *15q22.2* | *RORA* | Unknown; involved in immune-associated signaling pathways. | |
| *15q23* | *SMAD3* | Unknown; involved in immune-associated signaling pathways. | |

| EoE Risk Locus (chromosome location) | Candidate genes at or near risk variants | Known function/putative mechanism in EoE pathogenesis | References |
|---|---|---|---|
| *18q12.2* | *GALNTI* | Unknown | |

Abbreviations: CAPN14, calpain 14; EoE, eosinophilic esophagitis; GWAS, genome-wide association study; ITIH5, inter-alpha-trypsin inhibitor heavy chain 5; PRKG1, protein kinase CGMP-dependent 1; $T_H2$, T helper 2 cell; TGF-β, transforming growth factor beta; TSLP, thymic stromal lymphopoietin.

**Table 2:**

Additional EoE Genetic Risk Loci Identified by Phenotype Association

| Gene associated with EoE risk | Known function/putative mechanism in EoE pathogenesis | Reference |
|---|---|---|
| *CCL26* | *CCL26* encodes eotaxin-3, which is a chemokine that promotes eosinophil chemotaxis and recruitment into the tissue and is induced by IL-13. | Blanchard et al,[30] 2006 |
| *CRLF2* | *CRLF2* encodes the TSLP receptor | Sherill et al,[177] 2010 |
| *FLG* | FLG is important for maintenance of esophageal barrier function. | Blanchard et al,[31] 2010 |
| *DSG1* | DSG1 is a major constituent of desmosomes; important for maintenance of esophageal barrier function. | Samuelov et al,[32] 2013<br>Sherill et al,[33] 2014 |
| *IL5* | IL-5 is a cytokine important for eosinophil development and function, promoting eosinophil maturation, proliferation, activation, and survival. | Namjou et al,[29] 2014 |
| *IL13* | IL-13 is a cytokine with central role in EoE pathogenesis, directing eosinophil-predominant inflammatory responses and characteristic histologic changes to the esophageal epithelium associated with barrier dysfunction. | Namjou et al,[29] 2014 |
| *STAT3* | STAT3 is a transcription factor involved in signaling pathways for multiple cytokines. Abnormalities in STAT3 signaling can lead to dysregulated responses to IL-6 and possibly IL-5, leading to enhanced type 2 immune responses. | Arora et al,[37] 2017 |
| *SPINK5* | SPINK5 is a serine peptidase inhibitor downregulated in EoE. SPINK5 targets serine proteases and inhibits their proteolytic function. Loss leads to unrestricted protease activity, impaired epithelial barrier function and proinflammatory immune responses. | Paluel et al,[36] 2017 |
| *DSP* | DSP is a member of the plakin protein family and a critical component of desmosome structures in the epithelium; DSP is highly expressed in the esophagus and is important for maintenance of esophageal barrier function. | Shoda et al,[35] 2021 |
| *PPL* | PPL is a member of the plakin protein family and a critical component of desmosome structures in the epithelium; PPL is highly expressed in the esophagus and is important for maintenance of esophageal barrier function. | Shoda et al,[35] 2021 |

Abbreviations: DSG1, desmoglein 1; DSP, desmoplakin; EoE, eosinophilic esophagitis; FLG, filaggrin; IL, interleukin; PPL, periplakin; SPINK5, serine peptidase inhibitor kazal type 5; TSLP, thymic stromal lymphopoietin.