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Pathophysiology of Eosinophilic Esophagitis

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Abstract

Eosinophilic esophagitis (EoE) is an emerging disease that is distinguished from gastroesophageal reflux disease (GERD) by the expression of a unique esophageal transcriptome and the interplay of early life environmental factors with distinct genetic susceptibility elements at 5q22 (*TSLP*) and 2p23 (*CAPN14*). Rare genetic syndromes have uncovered the contribution of barrier disruption, mediated in part by defective desmosomes and dysregulated transforming factor beta (TGF- β) production and signaling, to EoE pathophysiology. Experimental modeling has defined a cooperative role of activated eosinophils, mast cells, and the cytokines IL-5 and IL-13, mediated by allergic sensitization to multiple foods. Understanding these processes is opening the way to better treatment based on disrupting allergic inflammatory and T helper type 2 cytokine-mediated responses including anti-cytokine therapeutics and dietary therapy.

Keywords

Allergy; Desmosome; Genetics; Inflammation

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Eosinophilic esophagitis (EoE) is a chronic, T helper type 2 (Th2)–associated inflammatory disease characterized by predominant and marked eosinophilic inflammation of the esophagus (a peak count of 15 eosinophils per high-power field of esophageal biopsy tissue [eos/hpf]); the diagnosis has been traditionally limited to patients who have persistent esophageal eosinophilia after a documented proton-pump inhibitor (PPI) trial¹ but it has recently been recommended that PPI responsiveness is not part of the diagnostic criteria but rather an appropriate and effective treatment for some patients (Molina-Infante J Gut 2016 and Lucendo United European Gastro Journal 2017). The disease is associated with upper gastrointestinal symptoms that vary with age and can include fibrostenotic complications. EoE is triggered by allergen exposure, typically food allergens, and is responsive to topical glucocorticoids and dietary elimination therapy (Figure 1). The pathogenesis of EoE is being extensively studied, and there have been recent advances concerning the genetic and environmental contributors, as well as the cellular and molecular etiology. This has led to numerous new therapies targeting these molecular pathways, which are currently being tested for disease treatment. Herein, we will focus on recent advances concerning the pathogenesis of EoE.

Genetic etiology

The prevalence of EoE is approximately 1/2000 and has a known male predominance, with a male-to-female ratio approaching 3:1.^{2,3} EoE has a strong heritability pattern, with familial associations having relative risk ratios as high as 64-fold amongst brothers.⁴ Proband concordance in monozygotic twins is 58%, substantiating a genetic etiology.⁵ Several different studies, including candidate-gene identification and genome-wide association studies (GWAS) have identified multiple genes that are likely contributing to the development of EoE. These genes include thymic stromal lymphopoietin (*TSLP*), calpain 14 (*CAPN14*), *EMSY*, *LRRC32*, *STAT6* and *ANKRD27* (Table 1). However, it is important to note that dizygotic twins have a 36% concordance, whereas non-twin siblings have a 2.4% concordance; the stark difference demonstrates the substantial influence of a shared twin environment, likely via epigenetic mechanisms, at least partially.⁵ Consistent with this, the strongly associated EoE genes *CCL26* (encoding eotaxin-3, a potent eosinophil chemoattractant and activating factor induced by IL-3) and *CAPN14* (encoding CAPN14) are under epigenetic regulation.^{6,7}

A section of the human genome, known as the EoE transcriptome, has a conserved expression in the esophagus of patients with EoE; this region is not dysregulated in patients with gastroesophageal reflux disease (GERD).⁸ The most highly expressed gene, compared to controls, is the IL-13–induced gene *CCL26*.^{8,9} The EoE transcriptome is distributed throughout the genome, but the strongest “hot spot” for transcriptional changes occurs at 1q21, which encodes for the epidermal differentiation complex (EDC). This region contains genes that are involved in squamous epithelial cell differentiation, such as filaggrin; these genes are notably downregulated in EoE, consistent with a loss of epithelial cell differentiation and impaired barrier function.^{10,11}

GWAS have identified *TSLP* as a major candidate gene. *TSLP* is released by activated epithelial cells and has an important role in promoting Th2 differentiation by inducing the

Th2-polarizing capacity of dendritic cells.¹² Levels of TSLP are significantly higher in patients with atopic diseases, including EoE.¹³ *CAPN14* encodes a proteolytic enzyme that is specific to the esophagus and is induced by IL-13.¹⁴ Unlike *TSLP*, which is associated with multiple allergic disorders, *CAPN14* may account for the tissue specificity of esophageal disease in EoE, as *CAPN14* invokes a pathway that alters basic epithelial cell functions including barrier integrity.¹⁴ *STAT6* has been shown to be important for Th2 development and is a signaling intermediate for IL-4 and IL-13 post IL-4 receptor alpha (IL-4Ra) engagement. *LRRC32* is a TGF-beta binding protein, and *EMSY* is involved in transcriptional regulation.

Taken together, this genetic profile supports a microenvironment predisposed to develop allergic and eosinophilic inflammation of the esophagus (Table 1). It is notable that the genes implicated in EoE are distinct from those involved in GERD and inflammatory bowel disease and are much closer to those involved in allergen sensitization and squamous epithelial cell dysfunction.

Allergic milieu predisposes to eosinophilic inflammation

Multiple lines of evidence support an allergic etiology as an underlying mechanism for EoE. First, patients with EoE have a high incidence of concurrent atopic disease (Figure 1).³ Recent evidence shows that EoE is correlated with higher rates of asthma and airway hyperresponsiveness.¹⁵ Sensitization to cutaneous, ingested, and/or inhaled allergens is likely necessary in the development of EoE, and in some patients, seasonal allergens may play a role.^{16–18} Second, the success of dietary antigen elimination has provided profound insights into the role of food allergens in EoE. Removing the 6 most common food allergens leads to clinicopathologic remission in 50–75% of children and adults, and further studies and clinical experiences reveal that adding some of these allergens back into the diet leads to reoccurrence of the mucosal eosinophilia.^{19,20} Third, murine models using sensitization and challenges with oral ovalbumin, peanut, or inhaled aspergillus or dust mite antigen lead to IL-5–, IL-13–, and eotaxin-dependent esophageal eosinophilia.^{16,21–24}

The role of Th2 cytokines remains central to our understanding of EoE. Early mouse studies revealed the important nature of IL-5, a required interleukin for eosinophilopoiesis, in driving mucosal esophageal eosinophilia and in potentially mediating tissue remodeling. The clinical relevance of IL-5 is partially underscored by studies that revealed humanized anti-IL-5 antibodies significantly, but not completely, reduced esophageal eosinophilia compared to placebo; however, there was no difference in clinical symptoms between individuals treated with anti-IL-5 antibody or a placebo, suggesting an incomplete effect. Additional strategies to inhibit IL-5–induced eosinophilia include the use of the eosinophil-depleting IL-5R α antibody benralizumab, though this has not yet been formally studied in EoE.²⁵

Later studies determined the critical nature of IL-13 to EoE. IL-13 is well recognized for its role in other atopic diseases, such as asthma, atopic dermatitis, and chronic sinusitis; in both basic and clinical studies, IL-13 is shown to contribute to eosinophil chemotaxis, goblet cell hyperplasia, collagen deposition, and smooth muscle contractility. In patients with EoE, the esophagus expresses elevated levels of IL-13, and IL-13–overexpressing transgenic mice

develop an EoE-like inflammatory response in the esophagus, which has an esophageal transcriptome that partially overlaps with the EoE transcriptome.²⁶ IL-13 also promotes EoE-like changes by promoting eosinophil recruitment by inducing eosinophil-activating chemokines such as eotaxin 3; by inducing tissue remodeling, including collagen deposition and angiogenesis. IL-13 also disrupts the epithelial barrier via a mechanism involving downregulation of the desmosomal protein desmoglein 1 (DSG1); preliminary studies have shown that this process is CAPN14 dependent, as CAPN14 is markedly induced by IL-13 and dysregulated expression of CAPN14 impairs epithelial architecture and barrier formation, including promotion of DSG1 degradation.²⁷ The first clinical trial of a monoclonal antibody against IL-13 showed improved markers of esophageal barrier function and tissue remodeling and decreased inflammation.²⁸ The results of a phase 2 study of a different anti-IL-13 antibody showed a marked decrease in esophageal eosinophilia, including in cases that were previously non-responsive to steroids; in this study, endoscopic severity and symptoms also improved with active therapy.²⁹ Along these lines, blocking IL-4R α (dupilumab) may prove useful in EoE, as this strategy has shown benefit in prospective trials for atopic dermatitis; a phase 2 study of this agent in EoE is ongoing (clinicaltrials.gov NCT02379052) (Table 2).

Increasing evidence suggests that IgE does not have a prominent role in the pathogenesis of EoE. Though patients with EoE have increased levels of food-specific IgE compared to control individuals, the level of food-specific IgE is only relatively modestly increased in patients with EoE compared with patients with food anaphylaxis. In addition, elevated serum food-specific IgE does not necessarily predict EoE-triggering foods.³⁰ Consistent with these findings, anti-IgE therapy (omalizumab) in humans was neither effective in reducing levels of esophageal eosinophilia nor clinical symptoms in clinical trials.^{31,32} Recent evidence suggests a potential role for tissue-resident IgG₄, including total and food antigen-specific IgG₄, in the pathogenesis of EoE. Immunohistochemical analysis of esophageal mucosal biopsies from adult subjects revealed IgG₄ staining only in those with active EoE and not controls.³² Interesting, cases of EoE that respond to dietary treatment have elevated ratios of esophageal and plasma food-specific IgG₄ and tissue values that decrease during disease remission.³³ IgG₄ is generally thought to be a neutralizing antibody as it only weakly binds to IgG receptors, does not fix complement or engage antibody-dependent cellular cytotoxicity, and undergoes Fab-arm exchange and hence has limited ability to cross-link receptors.³⁴ It is interesting to speculate that EoE may be part of a spectrum of IgG₄-related diseases, which often involve extensive, eosinophil-associated tissue-remodeling processes.

Th2 cytokines are likely produced by the recently described pathogenic effector Th2 cells (peTH2 cells), which were identified at higher numbers in the blood of patients with EoE compared to control individuals.³⁶⁻³⁷ These peTH2 cells are chemoattractant receptor-homologous molecule-positive (CRTH2+), hematopoietic prostaglandin D synthase-positive (HPSD+), and CD161^{high} CD4 T cells.³⁶⁻³⁷ CRTH2 is present on peTH2 cells, eosinophils, and basophils and is involved in the chemotaxis of these cells via its response to prostaglandin D₂. A recent clinical trial in patients with severe EoE with a CRTH2 antagonist demonstrated a statistically significant decrease, but not complete resolution, in esophageal eosinophilic inflammation.³⁸ In addition, group 2 innate lymphocytes that are

capable of expressing IL-5, -9, and -13 have been shown to be elevated in active EoE and to correlate with the degree of esophageal eosinophilia.³⁹ Another cell type that has been shown to be a source of Th2 cytokines in EoE, at least in murine models of EoE, is the invariant natural killer (iNKT) cell and their depletion attenuates experimental EoE, highlighting the potential importance of this cell as a contributor and therapeutic target.^{40–43} Mucosal mast cells influx and degranulate into the EoE esophageal epithelium and resolve following successful therapy.^{44,45} In contrast, it appears that subepithelial connective tissue mast cells are relatively static in the esophagus. Murine models demonstrate that mast cells increase smooth muscle mass.⁴⁶ In addition, via producing pro-fibrotic factors such as TGF- β 1, mast cells likely play a role in esophageal remodeling.^{47,48} A new IL-9–producing mucosal mast cell (MMC9s) described in immediate hypersensitivity may play a role in EoE, but this remains to be explored.⁴⁹

A recent advance in treating IgE-mediated food allergy is oral immunotherapy (OIT). However, 10-20% of cases will fail OIT due to recurrent gastrointestinal symptoms.⁵⁰ Recent meta-analysis has shown that EoE is observed in about 3% of esophageal biopsies from patients with OIT and abdominal symptoms were seen in 8-15%.^{51,52} In addition, recent examination of patients with IgE-mediated food allergy has shown that EoE occurs in 4.7% compared to 0.4% in the general population, indicating a link between atopic phenotypes and EoE.⁵² Since patients have a tendency to drop out of IgE desensitization trials due to abdominal pain and without undergoing esophageal biopsy, it is possible that these rates are underestimates. Conversely, because the patients are highly atopic, they might also have pre-existing undiagnosed or sub-clinical EoE that is exacerbated by the immunotherapy.⁵³ The link between OIT and EoE provides insight about the underlying pathoetiology, which undoubtedly involves food antigen–driven adaptive immune responses that involve the interplay of IgE-mediated responses (e.g., IL-4), EoE-mediated responses (e.g., IL-5 and IL-13), and checkpoints such as IgG4 and likely T regulatory cells (Figure 2).

Microbial imbalance may contribute to esophagitis

Similar to patterns in other atopic diseases, an emerging body of evidence suggests a role for intestinal dysbiosis in the pathogenesis of EoE. Host commensal populations may be skewed toward a Th2 profile by early life events such as Caesarian section delivery and antibiotic exposure during infancy, which appear to increase the risk of EoE in both children and adults.^{54–57} Of note, similar risk factors have been identified in other atopic conditions and inflammatory bowel disease.⁵⁸

Although early investigations revealed only a few bacterial populations in the esophagus, culture-independent techniques uncovered a microbial content with over 300 species. In an effort to define the role of bacteria in EoE, two recent investigations determined esophageal microbial patterns in children and adults with EoE. Collectively, the results revealed striking differences, as well as many similarities, between the oral and esophageal cavities. For instance, the *Prevotella* and *Streptococcus* genera were similar in the two sites, whereas the *Firmicutes* genus was increased in the esophagus.⁵⁹ Comparisons between active EoE and normal controls revealed increased *Proteobacteria* in subjects with active disease and *Streptococcus* in controls.⁶⁰ Ingesting EoE-triggering foods leads to changes in the

esophageal microbiome, with the emergence of *Granulicatella* and *Campylobacter* genera on mucosal biopsies.⁵⁹ An interesting observation relates to the association of herpes simplex viral infection with EoE. Case reports identify a preceding herpes simplex virus infection in some patients who go on to develop EoE; however, whether the viral infection and EoE development are related is presently unknown.⁶¹ The exact pathogenetic mechanisms that microbes contribute to the initiation, perpetuation, or even prevention of mucosal eosinophilia remain to be determined. It remains to be determined if esophageal eosinophilia leads to the changes in microbiome and/or if the dysbiosis influences EoE development.

Interestingly, commensal bacteria in a mouse model may limit food sensitization.⁶² In support of this is the observational finding of an inverse relationship between *Helicobacter pylori* infection and EoE, which has been demonstrated in several independent populations at different centers.^{63–66} This is intriguing as the rapid decrease in *H. pylori* prevalence over the past several decades matches the increase in EoE prevalence. From a mechanistic standpoint, *H. pylori* polarizes the immune system to a Th1 milieu, whereas lack of *H. pylori* results in a Th2 environment similar to what is seen in EoE.^{64,67} Despite this association, there have been no mechanistic studies that confirm a protective role of *H. pylori*. In addition, *H. pylori* infection is also protective against atopy but this effect wanes after childhood, indicating that the protective effect is complex, multifactorial and not EoE specific (Lionetti W J Gastro 2014 and Taye et al CEA and den Hollander ref).

Practical aspects of future human studies of the microbiome in EoE will need to focus on determining methods of collection of samples (e.g., mucosal biopsies or scrapings), specific host features (e.g., antibiotics, mouthwashes, PPIs), and the impact of EoE-related treatments. In addition, it is interesting to speculate that stool microbial content could have a diagnostic or monitoring role as a non-invasive tool for EoE.

Eosinophil transmigration and activation

The esophageal epithelium is composed of non-keratinized, stratified squamous epithelium that is bathed by a layer of mucus and covers the rete pegs with its vascular elements. Though the normal gastrointestinal tract contains eosinophils in varying density in times of good health, the normal esophageal mucosa does not contain any eosinophils. Thus, identifying eosinophils and their progenitor cells in the esophageal mucosa indicates a pathogenic role for these cells in an inflammatory response.⁶⁸ In this realm, studies have elucidated pathogenic mechanisms related to eosinophil migration in EoE. Blanchard *et al.* identified that the *CCL26* gene is the most upregulated gene in EoE human esophageal tissue.⁸ Eotaxin 3 acts through the G-protein coupled receptor CCR3, leading to eosinophil chemotaxis. Eotaxin-3 is upregulated by IL-13, a key EoE-related cytokine in vitro, and genetic deletion of the murine eotaxin receptor gene *CCR3* leads to diminished esophageal eosinophilia in vivo. Periostin is also directly induced by IL-13 and promotes eosinophil adhesion and recruitment by direct and indirect mechanisms.⁶⁹ It is notable that periostin is one of the top upregulated genes in the EoE transcriptome. Whether transmigration across the endothelial surface follows a different pathway than other diseases is not certain. Staining studies reveal increases in vascular cell adhesion molecule 1 and CD31 expression

during active EoE. Immunostaining revealed decreased CD18 following topical corticosteroid treatment.⁷⁰

Following transmigration across the epithelial space, eosinophil activation is evidenced by the intense pattern of eosinophil-derived granule protein deposition observed in active disease. Eosinophil-derived major basic protein (MBP), eosinophil-derived neurotoxin (EDN), eosinophil cationic protein (ECP), and eosinophil peroxidase (EPO) are not only deposited in the epithelium of patients with EoE but also may carry functional consequences relevant to EoE pathogenesis.⁷¹ For instance, EDN activates dendritic cells, which promote the Th2 cell response. ECP increases membrane permeability of target cells, EPO may perpetuate tissue-injuring peroxidase formation, and MBP can disrupt epithelial barrier.^{71–73} Translational studies have also shown that measurements of these proteins in gastrointestinal secretions may be indicative of EoE activity.^{74,75}

Barrier dysfunction contributes to esophageal inflammation

The basal layer of esophageal tissues from patients with EoE becomes hyperplastic, and its integrity as a barrier structure is impaired as evidenced by dilated intercellular spaces and spongiosis.¹⁰ Using impedance monitoring, van Rhijn *et al.* demonstrated a significantly decreased esophageal barrier during active EoE compared to inactive EoE in adult subjects.⁷⁶ Ussing chamber analyses identified similar findings with mucosal biopsies.¹⁰

Ultrastructural studies show not only increased intercellular spaces but also decreased junctional proteins. It is important to note, as discussed later, that inborn errors in barrier formation predispose to EoE, indicating that intrinsic defects are contributory, at least in rare cases. Barrier dysfunction is associated with impaired epithelial turnover as hyperplastic basal cells replace the normally differentiated epithelium, which exhibit a loss of tissue identity markers.⁷⁷ This process is likely mediated by increased expression of follistatin, a natural inhibitor of bone morphogenetic protein (BMP) signaling, resulting in impaired basal progenitor cell differentiation.⁷⁸ A dysfunctional barrier could facilitate passage of allergenic molecules to a genetically predisposed microenvironment.

Mechanistically, *CAPN14* is overexpressed by the esophageal epithelia in patients with EoE, and IL-13 stimulation of esophageal epithelia results in impaired barrier function and overexpression of *CAPN14*. In vitro overexpression of *CAPN14* in esophageal epithelial cells results in diminished barrier function and architectural changes indicative of barrier impairment, such as epidermal cleaving and loss of the normal expression pattern of DSG1 and filaggrin,²⁷ a cutaneous structural protein that is important to barrier integrity and downregulated by IL-13.⁷⁹ Proof for the importance of this pathway in the pathoetiology of EoE and other atopic diseases is illustrated by the rare genetic disease, SAM (severe dermatitis, multiple allergies and metabolic wasting) syndrome, in which the desmosomal proteins DSG1 or desmoplakin (DSP) are disrupted due to homozygous loss-of-function mutations in either gene.^{80,81} Loss of DSG1 or DSP leads to weakened barrier function in squamous surfaces, providing an entry pathway for allergens. Further re-enforcing the importance of barrier function is the capability of IL-13 to downregulate formation of not only filaggrin, but also DSG1.⁸⁰ Notably, DSG1 and filaggrin are downregulated in EoE, and gene silencing of *DSG1* in esophageal epithelial cells is sufficient to induce many of the

features of EoE including acantholysis and barrier impairment.¹⁰ In addition, patients with atopic dermatitis, which often is associated with loss of function mutations in filaggrin, exhibit this impaired barrier function, emphasizing the ability of barrier impairment to predispose to atopic diseases of the squamous epithelium.⁷⁹ Notably, disruptive mutations in filaggrin are enriched in patients with EoE, independent of the presence of atopic dermatitis, indicating the direct involvement of filaggrin in EoE susceptibility.⁸²

Esophageal fibrosis and strictures are a chronic feature of EoE

Emerging clinical evidence supports that the likely outcome of unbridled eosinophilia is esophageal fibrosis and stricture formation. Esophageal remodeling is defined by histologic parameters in the epithelium, including basal zone hyperplasia, dilated intercellular spaces, rete peg elongation, and desquamation, and by subepithelial lamina propria features such as increased vascularization and fibrosis.^{3,83–85} The confounding aspect of this pathogenic process is why remodeling sometimes directs mucosal healing without sequelae and other times goes on to develop clinically relevant long and short segment narrowing. In this regard, it is notable that CAPN14 has been implicated in eliciting and repairing the epithelial damage associated with EoE, suggesting that remodeling could involve a genetically controlled balance between these two processes.^{27,86} Epithelial products such as plasminogen activator inhibitor 1 (aka serpineE1) correlate with the severity of lamina propria fibrosis.⁸⁵ Such epithelial markers of subepithelial fibrosis may be clinically valuable because the size and adequacy of esophageal tissue procurement for lamina propria evaluation is variable. In addition, features of epithelial mesenchymal transition with increased vimentin-positive epithelial cells have been documented as part of the remodeling process.^{87,88} In the lamina propria, potential markers of remodeling include the pro-fibrotic factor, transforming growth factor beta (TGF- β) and its signaling molecules pSMAD2 and pSMAD3.^{23,83}

A validated endoscopic scoring system, EoE Endoscopic Reference Score (EREFS), characterizes the gross features thought to reflect remodeling, such as the presence and severity of strictures, rings, narrowing, and crepe paper esophagus.⁸⁹ Additional features, such as the endoscopic “pull” sign, which occurs during biopsy procurement, has been reported as a sign of remodeling.⁹⁰ Studies in children and adults have shown that that esophageal narrowing may be better captured by esophagram, whereas >50% of strictures may be missed by isolated endoscopic assessment.⁹¹ The ultimate consequence of esophageal remodeling and fibrosis is stiffening and dysmotility of a normally compliant tube capable of coordinated contractions that propel the food bolus distally.^{92,93} Dysmotility is alluded to by the fact that food impactions can occur in the absence of frank stricture formation. Using an endoscopic functional lumen imaging probe (EndoFLIP), strictured and non-strictured EoE esophagi have been shown to be more rigid than non-inflamed esophagi.⁹⁴ In addition, the fibrostenotic esophagus is more prone to dysmotility.⁹⁵ The natural history of untreated EoE in adults is to progressive fibrostenosis and preliminary pediatric studies show that esophageal rigidity begins in childhood.^{92,93} (Figure 1)

Using translational studies of pediatric esophageal biopsies and primary human esophageal cells, the presence of remodeling in both children and adults and the activation of the TGF- β

pathway in EoE has been elucidated.^{83,87,96–98} TGF- β has a number of molecular consequences including increasing fibrotic gene expression, altering fibroblast phenotype to myofibroblast, and increasing esophageal smooth muscle cell contraction via the expression of contractile proteins, such as the sarcoendoplasmic reticulum protein phospholamban, and via the induction of periostin.^{47,69,84,85,98,99} Further, independent of inflammation, a rigid environment increases esophageal smooth muscle cell gene expression of phospholamban and collagen I and induces smooth muscle hypertrophy.¹⁰⁰ Similar changes occur in EoE fibroblasts.⁹⁸ These data suggest that the mechanical environment significantly alters structural cell function and document an inflammation-independent pathway for esophageal remodeling.

Whether remodeling and fibrosis can be reversed may depend on patient age and/or the duration of disease.^{93,101–106} It is clear that the subset of children who respond histologically to topical corticosteroid therapy can have improvements in histologic remodeling and that this can be sustained long term.¹⁰⁷ In addition, epithelial mesenchymal transition can resolve following successful therapy.⁸⁷ Adult data show that topical steroids can improve esophageal diameter and decrease food impactions, but whether histologic remodeling or the process of fibrostenosis can be uniformly reduced remains unclear.^{104,108} Indeed, the patient with the fibrostenotic esophagus is often the most challenging to treat.¹⁰⁹ The fact that a rigid environment alone alters the function of esophageal structural cells coupled with the clinical observations of therapy-resistant disease underscores the importance of finding non-steroidal, remodeling-altering treatments.¹¹⁰

Association with other conditions provides insight into pathogenetic mechanisms

Notably, EoE has known associations with several genetic conditions (Table 3), particularly connective tissue disorders with hypermobility syndromes, such as Loeys-Dietz syndrome and Ehlers-Danlos syndrome, hypermobility type.¹¹¹ A common denominator between these two conditions is the increased production and/or signaling of TGF- β , which is thought to lead to increased contractility of smooth muscle, tissue remodeling, and Th2 responses.^{47,84} Another condition associated with increased production of TGF- β is a loss-of-function mutation in ERBB2-interacting protein (ERBIN), a protein that negatively regulates TGF- β signaling.¹¹² EoE is also associated with other syndromes including *PTEN* hamartoma tumor syndrome (PHTS), hyper-IgE syndromes, and SAM syndrome.⁸⁰ EoE has also been associated with Netherton's syndrome, which is caused by autosomal dominant mutations in the protease inhibitor *SPINK5*, which are normally expressed in the skin.¹¹³ In addition, EoE has been associated with esophageal granular cell tumors; whether this is a disease association or a concerning consequence of EoE is not certain.¹¹⁴ Finally, EoE has been associated with a number of autoimmune conditions including Hashimoto's thyroiditis, rheumatoid arthritis, celiac disease, inflammatory bowel disease, combined variable immunodeficiency, multiple sclerosis, and Sjögren's syndrome.¹¹⁵ Table 3 summarizes the known Mendelian diseases associated with EoE and attempts to synthesize what we can learn from them.

Closing

The recent formation of the Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR), which is part of the Rare Diseases Clinical Research Network (RDCRN) of the NIH, will undoubtedly lead to better understanding and treatment of EoE and related rare eosinophil-associated gastrointestinal diseases. CEGIR is focused on defining the natural history of eosinophilic gastrointestinal disorders, developing disease criteria, identifying improved dietary intervention strategies, and training the next generation of clinical and research leaders in the field. In the short time since EoE has received attention (i.e., the last two decades), there has been much progress in understanding its pathogenic bases. We have furthered the perspective that EoE is unlike GERD and inflammatory bowel disease but rather closely aligned with an allergic etiology and thus involves the interplay of a different set of experts and clinical interventions than is typically encountered in the gastroenterology practice. Accordingly, this review article integrated the input of experts in gastroenterology and allergy, consistent with the composition of CEGIR. Collectively, we are establishing that EoE is a unique disease process, characterized by the expression of a marked esophageal transcriptome that provides deep insight into the effector phase of the disease. Transcriptome analysis from only a single biopsy has similar sensitivity and specificity as histologic characterization,^{116,117} and the routine usage of this test has the potential to transform clinical care.^{118,119} We have reviewed the likely importance of the interplay of early life environmental factors and distinct genetic susceptibility elements, with a focus on 5q22 (*TSLP*) and 2p23 (*CAPN14*), the two loci that have been genetically replicated and most studied in the context of EoE. We have shown that rare genetic syndromes can predispose to EoE and provide valuable insight into disease mechanisms that may not only be operational in the rare disease but also informative for the common patient. These studies have uncovered the contribution of barrier disruption, mediated in part by defective desmosomes and dysregulated TGF- β production and signaling. Experimental modeling has defined a cooperative role of activated eosinophils, mast cells, and the cytokines IL-5 and IL-13, likely mediated by allergic sensitization to multiple foods. Figure 3 synthesizes our understanding of the pathophysiology of EoE. Understanding these processes is opening the way to better treatment based on disrupting allergic inflammatory and Th2 cytokine-mediated responses including anti-cytokine therapeutics and dietary therapy.

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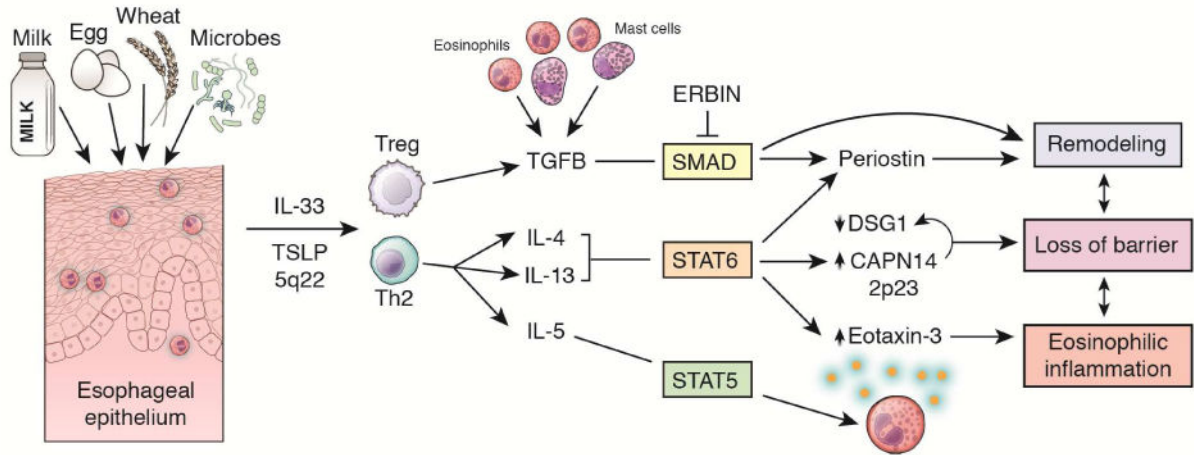


Figure 1. Clinical, pathologic, and therapeutics of EoE

Allergens drive eosinophilic esophagitis (EoE); however, current (glucocorticoid and dietary therapy) and future interventions can treat the disease. The presenting symptoms are shown, leading to esophageal inflammation, remodeling, rigidity, and dysfunction.

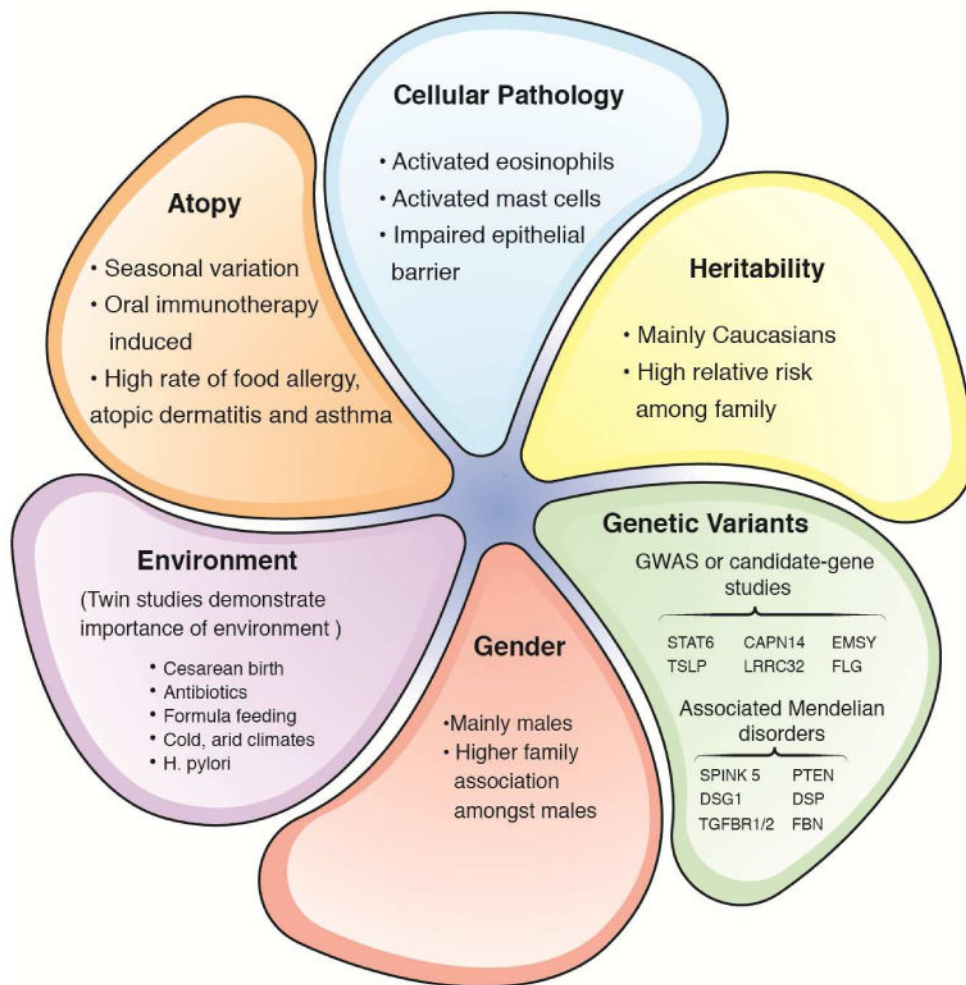


Figure 2. Pathophysiologic overview of EoE

Environmental factors, including foods and the microbiome, interact with the esophageal epithelium to elicit production of the pro-atopy cytokines IL-33 and TSLP. Activated T regulatory and Th2 cells secrete bioactive cytokines including TGF-β, IL-4, IL-13, and IL-5, which elicit barrier disruption, tissue remodeling, and eosinophilic inflammation.

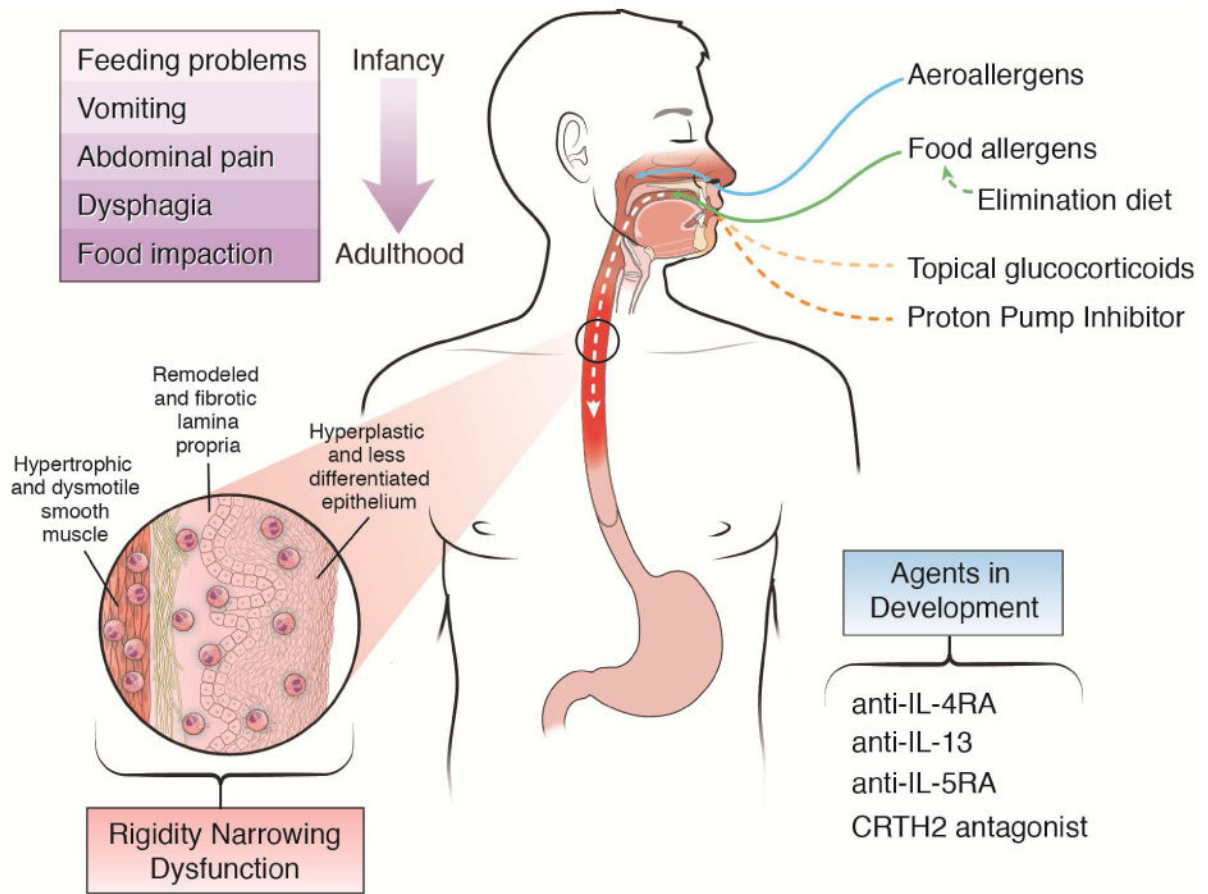


Figure 3. Factors that contribute to the development of EoE

Table 1
EoE genetic risk loci (statistically significant and replicated)

Genetic risk loci	Genes encoded	Odds ratio for most associated SNP at each locus	Genetic mechanism	Pathogenic mechanism
2p23	<i>CAPN14</i>	1.98	Promoter variant leads to genotype-dependent expression of CAPN14, likely involving epigenetic mechanism	CAPN14 is a proteolytic enzyme specific to the esophagus that is induced by IL-13 and involved in epithelial homeostasis and repair
5q22	<i>TSLP WDR36</i>	0.74	Multiple risk alleles associated with genotype-dependent expression of TSLP	TSLP induces Th2 cell development and activates eosinophils and basophils
11q13	<i>LRRC32 EMSY</i>	2.49	Not yet described	LRRC32 is a TGF-beta binding protein. EMSY is involved in transcriptional regulation.
12q13	<i>STAT6</i>	1.5	STAT6 is the primary mediator of IL-4 and IL-13 signaling	STAT6 is a downstream signaling mediator of IL-4R α and important for Th2 development
19q13	<i>ANKRD27 PDCD5 RGS9BP</i>	1.6	Not yet described	ANKRD27 inhibits the SNARE complex; PDCD5 is involved in apoptotic pathways. RGS9BP is not expressed in the esophagus or by immune cells.

Abbreviations: EoE, eosinophilic esophagitis; SNP, single-nucleotide polymorphism; TSLP, thymic stromal lymphopoietin. Risk shown is positive and hence adjusted for being a common or rare allele.

Table 2
Emerging Therapies in EoE

Emerging Therapies	Type	Mechanism
RPC4046	Anti-IL-13 antibody	IL-13 regulates multiple genes within the EoE transcriptome including eotaxin 3, desmoglein 1, periostin, and filaggrin
OC000459	CRTH2 inhibitor	CRTH2 is important for chemotaxis of eosinophils
Reslizumab/Mepolizumab	Anti-IL-5 antibody	IL-5 specifically stimulates expansion of eosinophils
Dupilumab	Anti-IL-4R α antibody	IL-4 α is a high-affinity receptor for IL-4, which induces Th2 cell differentiation
Benralizumab	Anti-IL-5R α antibody	IL-5R α is the high-affinity receptor for IL-5, which stimulates expansion of eosinophils

Abbreviations: CRTH2, chemoattractant receptor-homologous molecule

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Table 3
Mendelian diseases associated with EoE

Mendelian disease associated with EoE	Inheritance	Genetic mutation	Plausible etiologic mechanism
Hyper-IgE syndrome	Atopic dermatitis	Deleterious mutations in signal transducer and activator of transcription 3 (<i>STAT3</i>)	Dysregulated response to IL-6 and possibly IL-5
Hyper-IgE syndrome	Allergic rhinitis	Loss-of-function mutations in dedicator of cytokinesis 8 (<i>DOCK8</i>)	Loss of T cell homeostasis; lack of durable secondary antibody response against specific antigens
Ehlers-Danlos syndrome, hypermobility type	Atopic dermatitis	Unknown – other subtypes of Ehlers-Danlos syndrome are caused by mutations in collagen genes	Disrupted joint and skin development; increased activity of transforming growth factor beta (TGF- β) due to altered binding by extracellular matrix
ERBIN Deficiency	Atopic dermatitis	Loss-of-function mutation in ERBB2-interacting protein (<i>ERBIN</i>)	Increased TGF- β pathway activation in T cells with increased Th2 responses
Loeys-Dietz syndrome (LDS)	Allergic rhinitis	Mutations in TGF- β receptors 1 and 2 (<i>TGFBR1</i> and <i>TGFBR2</i> , respectively)	Enhanced TGF- β signaling
Netherton's syndrome	Allergic rhinitis	Loss-of-function mutations in skin protease inhibitor, kazal type 5 (<i>SPINK5</i>)	Unrestricted protease activity of kallikrein 5 and 7 (KLK5, KLK7)
PTEN hamartoma tumor syndrome (PHTS)	Atopic dermatitis	Mutations in phosphatase and tensin homolog (<i>PTEN</i>)	Inhibited regulation of the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) signaling pathway
Severe atopy syndrome associated with metabolic wasting (SAM) syndrome	Allergic rhinitis	Homozygous mutations in desmoglein 1 (<i>DSG1</i>) or desmoplankin (<i>DSP</i>)	Disrupted epithelial barrier