Mechanisms of Disease of Eosinophilic Esophagitis

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Abstract

Eosinophilic esophagitis (EoE) is a recently recognized inflammatory disease of the esophagus with clinical symptoms derived from esophageal dysfunction. The etiology of EoE is now being elucidated, and food hypersensitivity is emerging as the central cornerstone of disease pathogenesis. Herein, we present a thorough picture of the current clinical, pathologic, and molecular understanding of the disease with a focus on disease mechanisms.

Keywords

eosinophilic esophagitis; atopy; barrier dysfunction; epithelial inflammation; fibrosis

INTRODUCTION

The esophagus is normally devoid of eosinophils, but as far back as 1962, the occurrence of esophageal eosinophilia was noted. Eosinophilic esophagitis (EoE) was first described in 1977 by Dobbins et al. (1) as a variant of eosinophilic gastroenteritis, and in 1993, EoE became recognized as a separate disease state (2).

EoE remains relatively uncommon, with annual incidence rates varying between 0.1 and 1.2 cases per 10,000 persons in several studies, representing the second-most common cause of chronic esophagitis. EoE has been reported worldwide, with prevalence rates that continue to increase and reach 1:1,000 in several studies (3). This increase in prevalence is in agreement with a general trend of increasing prevalence of allergic diseases over the last half-century (4). Notably, though, the increase also appears to be a consequence of improved recognition of this disorder, at least since the mid-1980s, in part related to increasing frequency of endoscopic procedures in the pediatric population, rather than a fundamental increase in a new disease entity (5).

This disorder occurs in both the pediatric and adult populations, typically in male patients with evidence of atopy. The primary symptoms of the disorder vary with the age of the patient and progress with age in the following order: difficulty with eating, failure to thrive, vomiting, chest and/or abdominal pain, dysphagia, and food impaction (6, 7) (Figure 1).

CLINICAL ASPECTS OF EoE

Endoscopy

Endoscopically, EoE in adults is characterized by esophageal linear furrows with loss of vascularity, mucosal rings (trachealization), a small-caliber lumen, strictures, mucosal exudates, and, less commonly, polyps and ulcerations (8). The pediatric population can present with similar endoscopic features, though they may be more subtle, and up to one-third of pediatric patients with EoE have a normal endoscopy (4).

Diagnosis

The diagnosis of EoE includes assessment of food and aeroallergen sensitization and exclusion of other eosinophilic diseases of the esophagus, including gastroesophageal reflux disease (GERD) (see the sidebar entitled Differential Diagnoses for Esophageal Eosinophilia). Skin testing may assist in identification of food allergy and result in improved dietary therapy. The primary histologic feature used in diagnosing EoE is an esophageal biopsy with at least 15 eosinophils per high-power field; this is referred to as the peak eosinophil count. Other histopathologic changes consistent with EoE include basal layer hyperplasia, papillary lengthening, and lamina propria fibrosis (8). In addition, the high level of esophageal eosinophilia should be resistant to a proton-pump inhibitor (PPI) trial of 8 weeks (4). Although PPI-responsive esophageal eosinophilia has been thought to be an acid-induced disease, there is emerging evidence that this disease entity may be a subtype more closely aligned with EoE (9). Histologic response to dietary antigen elimination and/or to topical corticosteroids may suggest EoE but is not considered a diagnostic criterion.

Recently, the EoE diagnostic panel (EDP), a set of 94 genes differentially expressed in the esophagus of EoE patients, was introduced (10). The EDP identifies EoE with ~96% sensitivity and ~98% specificity in adult and pediatric patients and distinguishes patients with EoE in remission from non-EoE controls, as well as identifies patients who have been exposed to swallowed glucocorticoids. The EDP demonstrates predicative capacity for patients with subclinical histology (1–14 eosinophils per high-power field), suggesting that these patients should be tightly monitored as an EoE high-risk population and indicating the prospective utility of the EDP as a prognostic approach in personalized medicine. The EDP has the potential to overcome the limitations of histologic analysis, as it provides potentially deeper insight into tissue processes that are not visible microscopically or that may be microscopically patchy, highlighting the transformative value of using molecular parameters rather than histology for the diagnosis of inflammatory diseases. Furthermore, the EDP has the capacity to reveal EoE pathogenesis that could vary from patient to patient, forming the basis for practicing personal medicine. Notably, the EDP has a high performance after only one distal esophageal biopsy—compared with conventional histology, which currently requires at least four biopsies according to consensus recommendations (4, 10).

GERD has symptoms that closely overlap with those of EoE, but EoE is an antigen-driven disorder whose symptoms and pathology are responsive to either dietary control or steroid therapies. Additionally, these disorders are distinct in their gene expression profiles, heritability, genetic underpinnings, and linkage with atopy. However, EoE and GERD are not mutually exclusive and may coexist in *the* same patient (Table 1).

Therapy

Disease remission typically occurs with treatment, which may include dietary exclusion, topical corticosteroids, or both. Topical steroids represent the principal drug-based therapies in current use for EoE. Oral steroids are effective for acute, severe, or difficult-to-control EoE (4). Allergen avoidance by dietary measures is successfully used for the treatment of EoE (11). Elemental formulas represent the most effective therapy in terms of both histologic and symptomatic response, with a response rate of 97%. The empiric elimination diet may also be recommended for patient care. In this diet, foods commonly associated with immunoglobulin E (IgE)-mediated food allergy (typically the top six foods: milk, egg, wheat, soy, fish/shellfish, and nuts) are eliminated regardless of allergen test results. Multiple empiric elimination diet studies have reported similar response rates of about 75% for both histology and symptoms. The high variability and low predictive value of skin prick tests (SPTs) and serum IgE measurements, as demonstrated in these studies, suggest that the clinical utility for standardized assessment of food-specific reactivity in patients with EoE remains to be determined. Antigen-directed diets appear to be as effective as the empiric elimination diet. There is controversy over whether an antigen-directed diet leads to a less restrictive diet; however, as the six-food elimination diet is difficult to achieve and maintain because it is highly restrictive, antigen testing may retain its value to specific patients as both a means to design patient-specific elimination diets and as a guide for the food reintroduction process (11).

In difficult-to-treat and oral steroid–dependent cases, antimetabolite therapy (e.g., azathioprine and 6-mercaptopurine) has also been shown to be effective (12). Another secondary therapy for EoE is esophageal dilation, a mechanical procedure with proven efficacy in improving symptoms related to strictures and luminal narrowing in the majority of patients with EoE (13). Notably, however, endoscopic dilation has no effect on the underlying inflammatory process (14), so patients often must undergo subsequent procedures.

Prognosis

Currently, therapy for EoE is chronic, with relapse of disease occurring rapidly after the discontinuation of either dietary or drug-based therapies (15). Though the natural history of EoE has not been fully studied, children with EoE are more likely to have a parent with a history of esophageal strictures and/or a formal diagnosis of EoE, and biopsies of these parents have often revealed EoE. Furthermore, pediatric patients diagnosed with EoE by retrospective biopsy analysis are at increased risk of developing persistent disease characterized by dysphagia, food impaction, a need for esophageal dilation, and food allergy (5, 16). Thus, if left untreated, EoE is likely to progress to esophageal scarring and dysfunction. The development of Barrett esophagus in EoE has not been found, although

this has not been vigorously studied. EoE increases the risk of developing other forms of eosinophilic gastrointestinal disorders such as eosinophilic gastritis. Thus, routine endoscopic surveillance of the entire gastrointestinal tract, guided by symptoms, is recommended.

EPIDEMIOLOGY

Age, Gender, and Family History

Research is beginning to shed light on the natural history of EoE, its strong association with specific ethnicities and the male sex, and the genetic and environmental factors involved (Figure 2). As has been noted across multiple epidemiologic studies, males comprise approximately three-quarters of all EoE cases. Interestingly, a coding variant in the cytokine receptor–like factor 2 (*CRLF2*) gene, which encodes the receptor for thymic stromal lymphopoietin (TSLP) and is located on pseudoautosomal region 1 of the X and Y chromosomes, shows a sex-specific association with EoE risk in men only. Though the mechanism is not understood, these data are intriguing because they link the male predilection for EoE with a male risk variant on sex chromosomes (8). Pediatric EoE diagnosis peaks within the first 3 years of life and presents with feeding disorder (17), most likely resulting from antigen hypersensitivity as solid foods are introduced. Most adults are not diagnosed until the third decade of life (4), presenting most commonly with dysphagia, food impaction, heartburn, or chest pain. A number of previous reports demonstrated a high preponderance of EoE in individuals with Caucasian ancestry (up to 90% of cases), though the appreciation for the racial demographics of EoE may be broadening. In a recent retrospective survey, the numbers of Caucasian and African American patients with EoE were identical. Additionally, the male gender bias found in early studies of mainly the Caucasian population persisted in the African American population. Another survey in the adult population also found similar prevalence of EoE in the Caucasian and African American populations (3). EoE often occurs in multiple family members in a non-Mendelian pattern, indicating that the heritable component of EoE is likely complex in nature. In fact, Alexander et al. (18) recently reported data on a large familial cohort. This study analyzed 914 pediatric probands (within 2,192 first-degree family members) and reported relative risk ratios for EoE in family members, which ranged from 10 to 64 depending on the relationship, with higher values for brothers (64-fold), fathers (43-fold), and men (51-fold) than sisters, mothers, and women, respectively (18); this is compared with a relative risk of 2 in siblings of patients with asthma (19). Overall, EoE is observed in 1.8–2.4% of patients' relatives, depending on their relationship and sex (18).

Environment

Environmental factors also appear to be important in establishing risk for EoE. Several early life exposures, including cesarean birth, antibiotics, and formula feeding, have been linked to increased risk of EoE (20). Also, in a recent study of a twins cohort, analysis revealed that phenotype variance among twins was accounted for more by environmental factors (81.0%) than by additive genetic heritability (14.5%) (18). It was demonstrated that environmental factors, such as food and penicillin allergies and discordant birth weight among twins, increase EoE risk and that fall birth season and breast-feeding may reduce risk. In addition,

Spergel et al. (21) found that in the United States, EoE is diagnosed more often in urban areas and in the Northeast. Supporting this, Hurrrel et al. (22) found an increasing prevalence of EoE in cold and arid climates in the United States, and seasonal variations in disease suggest environmental influences. Almansa et al. (23) studied 78 patients with EoE retrospectively and found that mere was a significant increase in diagnosis during the spring and summer months. Also, *Helicobacter pylori* infection appears to be inversely related to an EoE diagnosis (24). In line with these data, colonization by immune-shaping commensal microbiota, in the gut and also in the esophagus, could be a key determinant of environmental risk (25, 26).

Atopy

The majority (50–80%) of patients with EoE have atopy and other allergic diseases, such as atopic dermatitis, asthma, oral allergy syndrome, and allergic rhinitis, or have specific IgE to food antigens and aeroallergens (8). These clinical findings have been supported through multiple murine studies demonstrating that skin, lung, and intranasal exposure to various antigens can induce EoE-like symptoms (27−29). In addition to the aforementioned link to allergic rhinitis and aeroallergen-specific IgE, patients with EoE commonly report seasonal variations in symptoms and diagnosis (23, 30). It also seems that aeroallergens may contribute to food hypersensitivity due to cross-reactivity or cross sensitization. In a recent study, IgE antibodies against food-specific allergen components were rare in patients with EoE, but cross-reactive responses to aeroallergen IgE were common (31, 32). The allergen families predominantly responsible for this cross-reactivity were profilins, pathogenesis-related-10 proteins, and lipid transfer proteins. These proteins remain intact until being degraded in the stomach (31, 33), a process that may limit hypersensitivity responses to the esophagus. This atopic link is further supported by the striking effectiveness of elemental formulas in disease therapy. Although food elimination or elemental diet therapy can reduce or eradicate disease symptoms, relapse almost universally occurs after reintroduction of food allergens or discontinuation of treatment, again suggesting that chronic food antigen hypersensitivity is a fundamental feature of EoE. Additionally, a subset of patients with EoE (15%) have a history of food anaphylaxis (15,17, 34, 35). There are also multiple reports of patients who develop EoE while undergoing oral food immunotherapy (36). However, in a subset of patients with EoE, no allergen sensitization or history of allergic diseases can be identified, suggesting again that multiple factors (including environment and genetics) affect disease predisposition and development (8).

Other Associated Disorders

In addition to the frequent co-occurrence of EoE with atopic disorders, there has been increasing recognition of EoE in association with several Mendelian and non-Mendelian diseases (37). A few of these diseases have other associated atopic features, and as a whole, these comorbid conditions highlight important candidate genes or pathways related to EoE.

The most studied of these disease associations is that of EoE with inherited connective tissue disorders (CTD) that involve hypermobility syndromes [e.g., Loeys-Dietz syndrome (LDS), Marfan syndrome type II, and Ehlers-Danlos syndrome]. The co-occurrence of EoE with these disorders is now called EoE-CTD. EoE increases the risk for CTD approximately

eightfold. EoE and CTD share excessive production of transforming growth factor β (TGF-β) and TGF-β signaling. In fact, LDS is caused by gain-of-function mutations in the TGF-β receptors, and Marfan syndrome type II is caused by mutations in connective tissue proteins that bind to TGF-β, such as fibrillin 1 (type I). Additionally, patients with LDS have elevated IgE levels, eosinophil counts, and T helper type 2 (Th2) cell cytokines, and their naive CD4^{+} T cells skew to Th2 upon TGF-β stimulation. Ehlers-Danlos syndrome is caused by mutations in collagens, and although the syndrome has not been directly associated with excess TGF-β1 levels, direct interactions between TGF-β1 and collagen have been reported (37).

A Mendelian disease that frequently co-occurs with EoE is severe dermatitis, multiple allergies, and metabolic wasting (SAM) syndrome. SAM syndrome is caused by homozygous mutations in desmoglein 1 (*DSG1*). DSG1 is a major constituent of desmosomes, which connect the cell surface to the keratin cytoskeleton to help maintain epidermal integrity and barrier function. SAM syndrome is a rare disorder reported in only two consanguineous families and one nonconsanguineous family (38, 39). This association is interesting and substantiates further investigation of this gene, as it has been shown that DSGl is decreased in EoE and is associated with an impaired barrier phenotype (40).

Associations of EoE with a few other diseases have also been noted. Other atopic Mendelian disorders include autosomal dominant hyper-IgE syndrome, caused by loss-of-function mutations in signal transducer and activator of transcription 3 (STAT3), and a syndrome characterized by increased levels of mast cell tryptase in the blood and associated with CTD. Notably, patients with PTEN hamartoma tumor syndrome have a >200-fold increase in risk for EoE and other eosinophil-associated gastrointestinal disorders, but the mechanism of this association is unknown (37). Finally, multiple recent high-powered studies have linked celiac disease with EoE (41, 42).

METHODS TO UNCOVER MOLECULAR PATHWAYS IN EoE

Multiple cutting-edge methods have been used recently to discover molecular pathways involved in the pathophysiology of EoE (43–46). These methods include gene expression profiling of patient tissue and screening for disease risk genetic variants by genome-wide association studies (GWAS), candidate gene studies, and studies of the epigenome via microRNA (miRNA) arrays, DNA methylation profiling, and chromatin immunoprecipitation sequencing technologies. With the exception of candidate gene studies, these methods are unbiased approaches, and they are beginning to reveal many of the critical molecular pathways underlying EoE pathogenesis.

GWAS performed on both discovery and replication cohorts have identified important new candidate genes, demonstrated association with known candidates, and replicated findings from previous studies. Gene expression profiling of esophageal biopsy specimens demonstrated a striking transcript signature that distinguishes patients with EoE from healthy control subjects and from patients with chronic esophagitis (44). This signature includes 574 genes collectively termed the EoE transcriptome. Remarkably, 98% of this transcriptome normalizes with topical steroid therapy. As previously mentioned, a set of 94

signature EoE transcriptome genes (the EDP) has promise as a diagnostic tool capable of differentiating patients with EoE from those with other forms of esophagitis and patients with active EoE from those with EoE in remission (10). More recently, a more sensitive method of whole-transcriptome sequencing (RNA-seq) of biopsy transcripts identified over 1,000 new EoE-dysregulated genes not noted in the previous microarray data, providing further opportunities for insight into EoE's molecular underpinnings.

Gene-environment interactions, central to environmentally driven allergic inflammatory diseases such as EoE, are now being explored via epigenetics. Emerging epigenetic data are beginning to provide clues as to how environmental factors may be affecting genetic dysregulation in EoE, which ultimately affects disease pathophysiology (47). Remarkably, the molecular pathways involved in EoE are relatively similar between males and females, sporadic and familial cases, pediatric and adult patients, and allergic and nonallergic patients, despite varying clinical manifestations (48, 49). The candidate genes (Table 2) and associated molecular pathways discovered with these approaches are discussed with regard to EoE pathophysiology in further detail below.

IMMUNOPATHOGENESIS OF EoE

Hypersensitivity

EoE is a disease that is associated with food antigen–driven hypersensitivity, as evidenced by its response to dietary therapy. Hypersensitivity reactions can occur via multiple immune mechanisms including IgE (immediate type) and/or T cell–mediated (delayed type). Most patients with EoE develop sensitivity to foods, according to food-specific serum IgE or SPTs (17, 50, 51). Fold-induced anaphylaxis occurs in only approximately 15% of patients with EoE. Thus the role of IgE-mediated hypersensitivity remains unclear. In contrast, delayed-type, T cell-mediated reactions are increasingly understood to participate in EoE, which appears to have an immunologic response similar to delayed-type hypersensitivity characterized by Th2 responses involving interleukin 4 (IL-4), IL-5, and IL-13 and the associated eosinophilic infiltrate (52). It is currently not fully understood how allergic sensitization occurs in EoE, but mechanisms involving loss of immunologic tolerance are being elucidated. Furthermore, murine models of EoE suggest that sensitization can potentially occur through multiple modes, including epicutaneous (29, 53) and pulmonary routes (27). Below, we explore these concepts of loss of tolerance and allergic sensitization as we consider the immunologic data in EoE (Figure 3).

Innate Immune Cells in EoE

Innate immune cells are important mediators of EoE pathology. These cells include eosinophils (cells that are required for diagnosis), mast cells (sentinel Th2 cells lining the esophageal mucosa), and less studied, though not less important, cells including dendritic cells and basophils. These are individually discussed below.

Eosinophils—The esophagus is normally devoid of eosinophils, and the presence of esophageal eosinophilia is a defining pathologic feature of EoE. Despite esophageal eosinophilia not being pathognomonic of EoE, murine models demonstrate the relative

importance of the eosinophil in the disease. Mice genetically engineered to lack eosinophils have a decrease in allergen-induced basal hyperplasia and lamina propria thickness and also do not develop strictures (54, 55), yet these mice still have esophageal motility dysfunction, suggesting that the entire disease process is not fully dependent on eosinophils (54). Furthermore, mice with selective deletion of eosinophils via anti–SIGLEC F antibody treatment have decreased esophageal eosinophilia, angiogenesis, basal zone hyperplasia, and fibronectin deposition (56) in an antigen-induced model of EoE.

A number of eosinophil products have been shown to have direct effects on immune signaling and tissue dysfunction (3). The eosinophil granule proteins major basic protein (MBP), eosinophil peroxidase, and eosinophil cationic protein (ECP) are cytotoxic to epithelium at concentrations similar to those found in biological fluids from patients with eosinophilia. In vitro, the granule components of eosinophils are toxic to many tissues, including the intestinal epithelium. ECP can render cell membranes porous, and MBP increases smooth muscle reactivity via vagal muscarinic M2 receptors and can trigger mast cell and basophil degranulation. Evidence of eosinophil activation and release of granule components such as MBP has been directly observed in patients with EoE; therefore, eosinophils could exacerbate epithelial damage in EoE.

Eosinophils also have the capacity to initiate antigen-specific immune responses by acting as antigen-presenting cells (APCs). Consistent with this role, eosinophils express relevant co-stimulatory molecules (CD40, CD28, CD86, B7), secrete cytokines capable of inducing T cell proliferation and maturation (TL-2, IL-4, IL-6, IL-10, IL-12), and can be induced to express major histocompatibility complex class II molecules (57). Interestingly, experimental adoptive transfer of antigen-pulsed eosinophils induces antigen-specific T cell responses in vivo. In addition, tissue eosinophils have distinct cytokine expression patterns under inflammatory versus noninflammatory conditions. For example, esophageal eosinophils from patients with EoE express high levels of Th2 cytokines and TGF-β (3). Activated eosinophils generate a wide range of cytokines including IL-1, IL-3, IL-4, IL-5, and IL-13; GM-CSF; TGF-α and TGF-β; tumor necrosis factor α; RANTES (regulated on activation, normal T cells expressed and secreted); macrophage inflammatory protein lα; and eotaxin (3). This diverse cytokine production indicates that eosinophils have the potential to sustain or augment multiple aspects of the immune response, inflammatory reaction, and tissue repair processes.

Multiple chemotactic factors for eosinophils are important in EoE. The most studied is eotaxin-3, also known as chemokine (C-C motif) ligand 26 (CCL26). The *CCL26* gene is the most upregulated gene in the esophagus of patients with EoE (44), its expression increasing 53-fold in esophageal biopsy specimens from patients with EoE compared with normal esophageal biopsy specimens and correlating with disease activity (44). Additionally, *CCL26* expression is upregulated by 279-fold after IL-13 stimulation of primary esophageal epithelial cells grown in culture ex vivo (58), and mice lacking the eotaxin receptor, CCR3, were protected from developing experimental EoE. The esophageal epithelium is the main source of eotaxin-3 production (44), which is notably induced by IL-13 stimulation. Eotaxin-3 belongs to the eotaxin family (eotaxtn-1 to eotaxin-3) of CC chemokines and is the only family member that is upregulated in EoE. Eotaxin-3 binds CCR3 and activates G

protein signaling to drive eosinophil chemotaxis and activation. In the earliest work demonstrating genetic factors that play a role in EoE, Blanchard et al. (44) identified the first EoE risk variant in a likely candidate, eotaxin-3 (*CCL26*). The single-nucleotide polymorphism (SNP) (rs2302009) was shown to be highly associated with disease ($p <$ 0.001) in a case-control cohort. Researchers replicated this finding by genotyping rs2302009 in 117 EoE cases and 225 unrelated healthy controls, also showing a significant association with disease ($p = 6.9 \times 10^{-3}$, OR= 1.63) (44). Additionally, the observed association between rs2302009 and EoE was independent of atopic status, indicating a direct link with EoE susceptibility.

Much of what is known about the involvement of epigenetics in EoE has been attained from biochemical studies of the eotaxin-3 promoter. Lim et al. (59) demonstrated that the *CCL26* promoter is regulated by DNA methylation. Methylation occurs on cytosine nucleotides located within CpG (cytosine-guanine) dinucleotide motifs and, like other epigenetic marks, is dynamically regulated (60). Two CpG sites in the *CCL26* promoter were identified as hypomethylated in patients with EoE (59). Methylation of these sites affected both STAT6 and CBP binding to the promoter region and was remarkably stable and heritable in cell passage, remaining detectable after multiple passages. Chromatin immunoprecipitation assays by Lim et al. (61) suggest that IL-13 induces the formation of a multiprotein complex on the *CCL26* promoter that includes CBP and STAT6 and leads to increases in acetylated histone 3 and opening of the *CCL26* promoter for additional transcriptional machinery (61). PPIs have been suggested to dampen the levels of histone methylation and of STAT6 bound to the *CCL26* promoter, resulting in decreased eotaxin-3 expression (62). These findings could explain the emerging observation of PPI-responsive EoE, in which PPI therapy yields partial resolution of symptoms (63). Collectively, these findings suggest that a coordinated interaction involving DNA demethylation followed by histone acetylation occurs at the *CCL26* promoter in response to IL-13 and leads to increased eotaxin-3 expression.

Other eosinophil-directed cytokines that are likely important in EoE pathogenesis include IL-5 and prostaglandin D2 (PGD2). Eosinophils selectively express the receptor for IL-5, a cytokine that regulates eosinophil expansion and eosinophil survival and primes eosinophils to respond to appropriate activating signals. Aspects of IL-5 signaling in EoE will be discussed in the cytokine section. Additionally, PGD2, a prostanoid largely produced by mast cells, is sufficient to attract eosinophils to the esophagus (64, 65). Lastly, an orally active small-molecule inhibitor of the eosinophil and Th2 cell chemoattractant receptor, PGD2 receptor (also known as CRTH2), modestly reduces esophageal eosinophilia (65).

Mast cells—Mast cells normally reside in the mucosa and submucosa of the esophagus. Mast cell activation classically occurs when a multivalent allergen cross-links IgE molecules bound to the high-affinity IgE receptor (FcεRI). The significant increases in mast cell degranulation and mastocytosis within the epithelium, lamina propria, and smooth muscle layer (66,67) observed in EoE can be ameliorated with steroid therapy (66), further implicating these cells in the local inflammatory milieu within the esophagus. Thus, it is likely that an immediate hypersensitivity response occurs locally in the esophagus in EoE, similar to what is observed in oral allergy syndrome.

Mast cells generate cytokines, proteases, and bioactive compounds that can activate eosinophils and lead to the fibrosis that is often apparent across the range of pediatric and adult patients with EoE (68⁻70). Murine models of EoE using mast cell–deficient mice have demonstrated reduced muscle cell hyperplasia and hypertrophy consistent with a role for mast cells in remodeling, but there was no effect on eosinophil recruitment (71).

Additionally, mast cell–specific genes, specifically carboxypeptidase 3A, high-affinity IgE receptor, and tryptase α, are abundantly represented in the EoE transcriptome, and two unique mast cell–related transcriptomes have been generated on the basis of counts of intact and degranulated mast cells. These transcriptomes demonstrate an unusual mast cell-protease profile with evidence of increased expression of carboxypeptidase A3 (25-fold increase) and tryptase, with very little or no expression of either chymase or tryptase γ1 (66).

Similar to its role for eosinophils, IL-5 may participate in increased induction of mast cells in the tissue, as CD2-IL5 transgenic mice had increased levels of esophageal mast cells (54). Furthermore, anti-IL-5 therapy in clinical trials found reduced esophageal mast cells in treated patients (72). Use of immunohistochemistry to analyze biopsies of patients with EoE enrolled in an anti-IL-5 trial (73) showed that activated MBP⁺ eosinophils and other unidentified cells that are adjacent to the tryptase⁺ mast cells in the esophagus produced IL-9. IL-9, a pleiotropic cytokine, can promote the activation and maturation of mast cells (74). Notably, the expression of the *IL9* gene transcript is elevated in the esophagus of patients with EoE (75). Other cells that have been shown to be important sources of IL-9 include T helper type 9 (Th9) cells (76), which also produce other Th2 cytokines (IL-4, BL-5, and IL-13), and innate lymphoid cells (77). The anti-IL-5 clinical trial also showed that the severity of EoE symptoms correlated with mast cell number, whereas the reduction of eosinophil numbers alone did not correlate with symptom severity (72). Because multiple studies have demonstrated a role of mast cells in regulating smooth muscle contractility and vagal nerve activity (67, 78, 79), it is reasonable to speculate that the activated mast cells in the esophagus are the primary drivers of the pathophysiology of EoE in a subgroup of patients. In summary, these studies revealed that esophageal eosinophils may promote esophageal mastocytosis via IL-9 and that this interaction between mast cells and eosinophils may regulate the severity of EoE symptoms.

Dendritic cells—The understanding of dendritic cells in EoE is limited, but there is evidence that both dendritic cells and nonprofessional APCs, such as epithelial cells (80) and possibly eosinophils, play a role (81⁻83). The primary professional APC in the esophagus seems to be the Langerhans cell, a type of dendritic cell found in all squamous epithelia (32), particularly the epidermis. Langerhans cells of the esophagus express FcεRI (84), which increases in active EoE (85). FcεRI expression on dendritic cells in human disease and mouse models of asthma and atopic dermatitis is correlated with increased Th2 effector response (86⁻88). It is possible that IgE signaling on APCs facilitates antigen uptake and enhances development of allergen-specific T cells (89). In addition to the importance of dendritic cells in sensitization, selective depletion of dendritic cells during allergen challenge in both asthma and allergic rhinitis murine models has demonstrated the importance of dendritic cells in the effector phase of these diseases (90, 91). A similar mechanism likely occurs in EoE.

Allergens can induce a Th2-mediated response, either alone (with a self-adjuvant effect) or in combination with other environmental adjuvants (viral or bacterial infections or air pollution) (92), and this effect likely occurs via communication by resident stromal cells and dendritic cells (93, 94). The stimulation of dendritic cells via environmental adjuvants may be one direct mechanism by which environment is contributing to EoE.

Basophils—Basophils are known to be important in allergic inflammation, but there is a paucity of data on basophil function in EoE. Siracusa et al. (95) showed that TSLP could lead to basophil hematopoiesis and that basophils that express the TSLP receptor are present in the esophagus of patients with EoE. Shortly following this report, Noti and colleagues (29) found that sensitization to egg or peanut protein could occur during skin inflammation or injury (tape stripping) in a TSLP-dependent, basophil-dependent, and IgE-independent manner. This study also showed increased basophil levels in EoE biopsies. TSLP is an interesting link to this basophil axis, as it is known to be an alarmin molecule released by stressed epithelium and is considered a master regulator of Th2 immune responses. TSLP has previously been linked to EoE, and further details of TSLP's role in EoE are discussed in the epithelium section below.

Adaptive Immune Cells in EoE

In addition to the innate immune system, the adaptive arm is also integral to the Th2 immune response in EoE. B cells are important mediators via IgE and IgG4 secretion. Multiple subtypes of T cells, including Th2, CD8+, and invariant natural killer T (iNKT) cells, are relevant to pathophysiology. Finally, intercellular communicators, cytokines, help orchestrate the concerted response.

B cells and IgE—Lymphocytes represent another component of the inflammatory infiltrate that is consistently elevated in patients with active EoE relative to normal controls and patients with inactive EoE (44, 82, 96, 97). A process central to the pathogenesis of many atopic disorders, including anaphylaxis, allergic bronchospasm, and urticaria, is generation of antigen-specific IgE via Th2 cell–mediated class switching of B cells. As noted above, this IgE can then bind FcεRI on mast cells and basophils to carry out its function. Allergen-specific serum IgE and SPT are commonly abnormal, providing evidence of immediate hypersensitivity in EoE, but the role of B cells in EoE is not clear. In addition to being increased in number, B cells undergo class-switch recombination and generation of IgE locally within the esophagi of both atopic and nonatopic patients with EoE (98−100). However, though B cells appear to be generating IgE in patients with EoE, in murine models of EoE utilizing B cell–deficient, IgE-deficient mice and an IgE-independent aeroantigen (*Aspergillus*), the B cell and its repertoire appear to be dispensable in initiating the primary characteristics of EoE. This suggests that IgE may play a role in maintenance rather than initiation of the disorder in humans (29, 81). In clinical studies using a monoclonal antibody directed against IgE in EoE, the use of the drug demonstrated clinical but not histologic or endoscopic improvement (101), suggesting that some acute symptoms in EoE may be associated with IgE but that the chronic inflammation may not be as dependent (29, 81). Interestingly, a recent study of anti-IgE in EoE showed a lack of response in terms of either symptoms or biopsy eosinophil count (102). This study showed that esophageal tissues from

patients with EoE had a 45-fold increase in IgG4 compared with controls and that this IgG4 could be detected extracellularly in biopsy specimens. Additionally, the study showed that patients with EoE had increased food-specific serum IgG4 in response to the foods that are most associated with EoE (milk, egg, wheat, and nuts).

T cells—Studies of mice lacking various components of the adaptive immune system have established a critical role for T cells in EoE (53, 81, 103). Similar to the case in other atopic diseases, tissue inflammation in EoE is characterized by a Th2-type inflammatory response (58, 75, 82, 98). This immune response includes an increase in both CD4+ and CD8+ T cells and an increase in the CD8+ T cell/CD4+ T cell ratio in the esophagus (96, 97). Regulatory T cells (Tregs), characterized by expression of FOXP3, are vital to maintenance of tolerance. Studies in the pediatric and adult EoE populations are in disagreement with regard to Treg numbers in EoE. Increased numbers of Tregs were seen in pediatric cases, whereas there was a relative lack of Tregs in the adult cases (104). This may point to a fundamental difference in disease processes in pediatric versus adult cases of EoE. Regardless, further studies are needed to decipher the general roles of both Tregs and T cells in EoE.

Recently, the importance of iNKT cells in EoE pathophysiology has begun to be elucidated. A study of early-onset EoE has suggested that insufficient immune imprinting by environmental microorganisms results in an esophageal increase of CXCL16, an iNKT cell chemokine (105). iNKT cells respond to lipid and glycolipid antigens presented by CD1d molecules (106, 107). It has been previously shown that mucosal iNKT cell tolerance to later environmental exposures is formed at an early age (26) and that if this tolerance does not develop, these cells can mediate allergic sensitization and tissue inflammation (108). iNKT cells from peripheral blood of pediatric patients with EoE have been shown to be activated by milk sphingolipids (109). Additionally, CD1d-deficient mice were protected from EoE disease induction (110).

Cytokines

The Th2 cytokines (IL-4, IL-5, and IL-13) are elevated in patients with EoE (75, 82), as well as in murine models of EoE (111). IL-4 induces naive Th cells into Th2 cells and activates B cell class switching to produce IgE, thus initiating a Th2-mediated immune response. It appears that TSLP-elicited basophils, Th2 cells, and iNKT cells are important sources of IL-4 in EoE (82, 112−114). IL-5 is one of the most well-studied Th2 cytokines in EoE and seems to be central to the disease. IL-5 is produced by Th2 cells, mast cells, and eosinophils. IL-5 regulates eosinophil expansion and eosinophil survival and primes eosinophils to respond to appropriate activating signals (115). EL-5 overexpression in mice induces EoE, and IL-5 neutralization completely blocks allergen- or IL-13-induced EoE in mice (116). However, anti-IL-5 therapy in humans has notyet been shown to be effective at ameliorating clinical aspects of the disease, although esophageal eosinophilia improves (117).

Among the Th2 cytokines, EL-13 plays a unique role in EoE. Highlighting its importance, a recent study found the genetic locus of STAT6, a downstream transcription factor of the IL-13 signaling pathway (118), to have a major genetic association in EoE. IL-13 is

overproduced in the esophagus of patients with EoE. In addition, in experimental systems—such as IL-13 lung transgenic systems—IL-13 induces EoE and tissue remodeling with features both dependent and independent of eosinophils (119). Ex vivo microarray analysis showed that treatment of biopsy-derived primary esophageal epithelial cells with IL-13, which is upregulated at the mRNA level in patients with EoE, can largely recapitulate the EoE transcriptome (58). Th2 cells and activated eosinophils are important sources of EL-13 in EoE (82, 120, 121). IL-13 also recruits eosinophils by increasing an eosinophil chemokine, eotaxin-3, and by promoting fibroblasts to produce periostin (POSTN), which increases eosinophil adhesion to fibronectin (122). IL-13 induces tissue remodeling by promoting collagen deposition, angiogenesis, and epithelial hyperplasia (119). The esophageal remodeling in this model occurs independently of eosinophilia and is inhibited by the type 2 IL-13 receptor (119). IL-13 is also important in barrier function. It has been shown to down-regulate *DSG1*, filaggrin (*FLG*), and involucrin, genes important in epithelial differentiation and barrier function (40, 123). Mice treated with anti-IL-13 antibody demonstrated improvement in esophageal inflammation (124); furthermore, a Phase II, double-blind, randomized control trial has shown the safety and efficacy of an anti-IL-13 antibody (QAX576, Novartis, Switzerland), which produced improvement in both esophageal eosinophilia and disease-related transcripts, as well as a trend for improved symptoms (125). These studies demonstrate that IL-13 is a central mediator and link between the immunologic and histologic changes that are germane to EoE, largely through its effects on the esophageal epithelium.

IL-15 appears to mediate CD4^{+} T and iNKT cells (114) and drive the synthesis of Th2 cytokines IL-5 and IL-13, all four of which are believed to play significant roles in EoE (55, 58, 114, 123). IL-15 has also been demonstrated to be elevated in patients with EoE, as well as in the *Aspergillus*-driven experimental model of EoE.

ESOPHAGEAL TISSUE IN EoE

Apart from the inflammatory response, the resident tissue of the esophagus itself plays a fundamental role in the pathophysiology of disease. Genetic variants associated with both barrier function and immune signaling have been linked to the epithelium. Finally, both the lamina propria and smooth muscle are key tissue types that produce symptoms of EoE via fibrosis and dysmotility, respectively. The contributions of these tissue types are explored in more detail below.

Epithelium

The epithelium is a protective barrier and key interface for immune signaling. In addition to genetic variants in barrier function and immune signaling being linked to the epithelium, it is also a source of disease biomarkers, including transcript and miRNA such as *CCL26* and miR-375.

Barrier—The esophagus is composed of stratified squamous epithelium. In contrast to the skin, the esophagus lacks a cornified layer but does have a mucus layer that provides additional protection. This esophageal epithelium is composed of a proliferating basal layer of one to three cells in depth and a differentiating suprabasal layer migrating toward the

esophageal lumen (126). The epithelium forms a protective barrier against environmental antigen exposure that, when compromised, can lead to antigen hypersensitivity and exacerbated immune responses (127). The structure of the epithelium is disrupted in EoE, and a similar disruption occurs in an in vitro esophageal epithelium model when stimulated with IL-13. These structural changes include basal cell hyperplasia, dilated intracellular spaces, and impaired barrier function (128−130). These changes may be linked to derangements in processes such as epithelial differentiation and epithelial barrier formation, including cellular junction formation.

The epidermal differentiation complex (EDC) on human chromosome lq21 is a cluster of genes that regulates terminal differentiation (131). The EDC locus contains the highest density of dysregulated genes in the EoE transcriptome (123). *FLG*, involucrin and several small proline-rich repeat family members (2C, 2D, and 3) are expressed in esophageal epithelial cells and are downregulated in response to IL-13 ex vivo (123), suggesting a homeostatic role for the EDC in the esophageal epithelium. FLG dysfunction has been associated with defects in epidermal barrier function in patients with atopic dermatitis (132,133), a disease that frequently co-occurs with EoE. It is also important to note that 2% of the EoE transcriptome is not fully reversible after disease remission (58). Interestingly, these transcripts include genes whose protein products are involved in regulating homeostatic and pathogenic responses in the epithelium, such as cadherin-like 26 (*CDH26*), uroplakin 1B, *POSTN*, and *DSG1* (58).

The epithelial barrier gene *FLG* represents yet another genetic locus linked with numerous allergic diseases, including EoE. FLG has been shown to play an important role in barrier function of the skin (134, 135). *FLG* is negatively regulated by IL-13 and is decreased in the esophageal mucosa of patients with EoE, and two coding variants (R501X and 2282del4) in *FLG* associate with EoE risk irrespective of atopic status (123).

Sherrill et al. (40) reported that expression of DSG1 is decreased in active EoE (22-fold) compared with healthy control subjects and that *DSG1* deficiency in an esophageal epithelial in vitro model leads to impaired barrier function and acantholysis and intraepidermal clefting. This impaired barrier function was also seen in EoE patient biopsies compared with controls. DSGl is a transmembrane desmosomal cadherin component and facilitates the calcium-dependent homotypic interactions between adjacent cells that impart both structure and mechanical strength to the epithelium. Notably, DSGl autoantibodies are found in pemphigus foliaceus and pemphigus vulgaris, squamous epithelial diseases that demonstrate decreased cellular adhesion resulting in epidermal blistering, with some patients displaying eosinophilic infiltration (136). Additionally, two recent reports have shown that families with recessive mutations in *DSG1* have a severe allergy phenotype, including one patient with EoE (38, 39). Collectively, these findings substantiate the significance of alterations in DSGl in a spectrum of human diseases, including EoE. Therefore, it appears that tissue-specific decreases in DSGl may be pathogenic in EoE. Other junctional proteins, including E-cadherin and claudin-1, are also reduced in EoE (137). Thus, in active EoE, the mucosal integrity is altered due to defects in desmosomal and tight junction adhesion proteins. These findings place the esophageal epithelium as a central location for the basic defect in EoE and

as one essentially involved in the Th2 cytokine signaling cascade, as IL-13 promotes germane EoE-related responses directly in esophageal epithelial cells.

Recently, the largest and most comprehensive GWAS in patients with EoE identified calpain 14 (*CAPN14*) as the gene most highly associated with EoE (41). This finding was soon replicated in a separate GWAS (118). CAPN14 is a member of the calpain family—a group of intracellular, calcium-activated proteases. CAPN14 was shown to be specifically expressed in the esophagus, dynamically regulated as a function of disease activity and genetic haplotype and after exposure of esophageal epithelial cells to IL-13, and located in an epigenetic hot spot modified by IL-13 (41). Recently, it has also been shown that CAPN14 has a significantly disruptive effect on the esophageal epithelial barrier, and its expression and activity appear to lead to cleavage of DSG1 (138), providing a unifying mechanism that connects genetics with an essential disease susceptibility mechanism.

MicroRNAs—A select set of miRNAs—short, noncoding RNAs that fine-tune the expression of target genes by repressing translation through binding complementary sequences in the 3′ untranslated region of target mRNAs (139)—has been shown to be dynamically altered in the esophageal mucosa of patients with EoE. The miRNA signature associated with EoE includes 21 upregulated and 11 downregulated miRNAs, and this dysregulation is largely reversed with steroid therapy (140,141). Some of these miRNAs have been shown to correlate with esophageal eosinophil levels in patients with EoE (140) and regulation of IL-13-induced transcriptional responses (142). These findings identify miRNAs as potential biomarkers for EoE diagnosis and steroid responsiveness.

Epithelial inflammatory response—Besides its barrier function, the esophageal epithelium can also induce inflammation. As noted above, the epithelium is a potent reservoir of cytokines and lipid mediators (143). IL-13 stimulates esophageal epithelial cells to produce eotaxin-3 (44), which signals eosinophils to traffic to the esophagus. Esophageal epithelial cells also express Toll-like receptors (144, 145) and produce proinflammatory cytokines in response to both pathogen-associated and danger-associated molecular patterns (82, 144). EoE-derived epithelial cells can produce RANTES (CCL5), a chemotactic factor for T cells, eosinophils, and basophils (109), and CXCL16 (105), which may play a role in the migration and activation of iNKT cells in EoE. In addition, others have found that esophageal epithelial cells may function as nonprofessional APCs (80). Resident innate immune cells are also present within the esophageal epithelium at baseline (97, 105), and their roles in EoE are being actively investigated (105).

Multiple GWAS (41,45,118) and candidate gene studies (46) have implicated genetic variants of *TSLP* in genetic susceptibility for EoE. These variants encode an epithelial protein expressed in response to cytokines (146), noxious substances (147), and mechanical stress (148). TSLP has been termed a master regulator of Th2 responses (149) and has been shown to target dendritic cells and promote their Th2-polarizing ability (150). It also exerts effects on nearly every cell type involved in Th2 inflammation, including eosinophils (151) and mast cells (152). *TSLP* is increased in the esophageal tissue of patients with EoE (45, 46). Patients carrying the risk allele for the variant most associated with EoE have elevated *TSLP* expression (45). TSLP has recently been shown to be key in the development and

maintenance of EoE in a murine model and is associated with an increased number of basophils in the esophageal tissue (29). In addition, *TSLP* risk genotypes correlate with increased levels of basophils (29). Effects in the TSLP signaling pathway as a result of variants either increasing *TSLP* gene expression or altering receptor function could potentially amplify innate inflammatory responses to food antigens—the exact processes involved in allergen sensitization that underscore the EoE phenotype.

Lamina Propria in EoE

The lamina propria is important for the inflammatory response as it is a site of considerable inflammatory infiltration. It is also an important site for the major symptoms of EoE because of the fibrotic response leading to fibrostenosis and dysphagia. This fibrotic response includes key mediators and processes such as TGF-β, POSTN, and epithelial-to-mesenchymal transition (EMT), which are further reviewed below.

Fibrotic remodeling—On the basis of the paradigm of other eosinophilic inflammatory conditions, the natural history of EoE has been described as a progression from an inflammatory to a fibrostenotic disease (153). Fibrotic remodeling, including metaplasia of the mucosal glands, smooth muscle hypertrophy, angiogenesis, and subepithelial collagen deposition or fibrosis, occurs in pediatric (69, 70) and adult (154, 155) patients with EoE. The myofibroblast, which shares properties of smooth muscle cells and fibroblasts, is the key effector cell in fibrosis. The myofibroblast contracts the extracellular matrix and secretes extracellular matrix components, including type 1 collagen (156).

Esophageal remodeling is associated with stricture formation and, as a result, dysphagia and food bolus impaction (153, 157). In fact, EoE is currently the leading cause of emergency endoscopy for esophageal food impaction in adults (158). Both histopathologic fibrosis (154) and gross fibrostenosis increase with age (155). Symptoms of fibrosis range from signs of progressive solid food dysphagia to food impaction.

Esophageal inflammation leads to deposition of subepithelial fibrous tissue and tissue remodeling correlated with eosinophil degranulation (69). In fact, eosinophil-released MBP has been found to increase the expression of FGF9 in biopsies of patients with EoE (159). Additionally, eosinophils secrete high levels of CCL18, the expression of which is highly increased in EoE (154). Both of these cytokines, FGF9 and CCL18, are important in fibroblast activation and extracellular matrix deposition.

TGF-β1 is a key cytokine for epithelial growth, fibrosis, and tissue remodeling and is reportedly generated not only by mast cells but also by eosinophils and epithelial cells of patients with EoE. Its expression is elevated in esophageal biopsy samples of patients with active EoE relative to control patients (55, 70, 117, 155). Furthermore, the number of TGF-β1-positive cells is increased in biopsy samples from patients with EoE relative to either control patients or patients with GERD (70). TGF-β stimulates myofibroblast differentiation (67) and expression of various genes responsible for the fibroblast phenotype, including α smooth muscle actin, collagen, and *POSTN* (122). Moreover, TGF-β has recently been shown to stimulate esophageal smooth muscle contractility and potentially contribute to esophageal dysmotility in patients with EoE (67). Also, in a small cohort of patients with

steroid-treated EoE, a genetic variant in the promoter of *TGFB1* was associated with steroid unresponsiveness and correlated with increased TGF-β-positive cells in the esophagus (43). Remarkably, there is a high rate of EoE with CTD (160), such as Marfan syndrome, Ehlers-Danlos syndrome, and LDS, which has been associated with variants in TGF-β receptors 1 and 2 (161). In addition toTGF-β, IL-4, IL-5, and IL-13 have been shown to mediate the remodeling processes (55, 162, 163).

POSTN, which functions as a cell adhesion molecule that regulates extracellular matrix deposition (164, 165), is dramatically upregulated (approximately 52-fold) in patients with EoE; both TGF-β and IL-13 are able to induce POSTN expression in primary esophageal fibroblasts and epithelial cells. Studies of POSTN-deficient mice have demonstrated that POSTN facilitates eosinophil recruitment into the esophagus (122), increasing eosinophil adhesion to fibronectin.

Epithelial-to-mesenchymal transition—EMT is a process in which epithelia lose epithelial markers (e.g., E-cadherin and keratins 8 and 14) and acquire markers of mesenchymal cells (e.g., α smooth muscle actin, vimentin, fibronectin, and N-cadherin), which share features of both fibroblasts and smooth muscle cells (myofibroblasts) and participate in the synthesis, deposition, and degradation of extracellular matrix along with the contraction of wound tissue (166⁻168). TGF-β, MMP-9, IL-13, and MBP released by eosinophils or damaged epithelium may induce EMT and contribute to fibrosis (167,169). The extent of EMT in patients with EoE correlates with eosinophils, TGF-β, and fibrosis (169). The dedifferentiation of epithelial cells in EoE appears to be effected by another TGF-β superfamily member, bone morphogenetic protein, and one of its inhibitors, follistatin (170). Follistatin is increased in EoE, increases with IL-13, and correlates with basal cell hyperplasia and loss of differentiation markers (171).

Fibrosis response to therapy—It appears that both swallowed topical corticosteroids (43, 172) and elimination diets (173) can prevent and even reverse the esophageal remodeling process in children; however, there is conflicting evidence in adults (154). This difference may be due to either the populations studied or the differences in topical steroid formulations. Thus, untreated eosinophilic inflammation leads to esophageal remodeling with stricture formation, and the use of early, consistent anti-inflammatory therapy may protect against this outcome.

Losartan, an angiotensin II receptor blocker and FDA-approved antihypertensive medication, may reduce TGF-β responsiveness via an effect either on signaling or on transcription of TGF-β and its receptor (174); thus, losartan is a potential treatment for EoE. A Phase II trial to evaluate losartan therapy in patients with EoE is currently under way (175).

Smooth Muscle

EoE is associated with esophageal dysmotility and dysphagia, which may be related to motor dysfunction of the esophagus rather than to physical narrowing. Esophageal ultrasound shows dysfunctional muscularis mucosa in EoE (176). Tissue remodeling also involves both morphologic and functional changes in smooth muscle components. In fact, esophageal muscle cells respond to various profibrogenic stimuli. Eosinophils and mast cells

infiltrate the submucosal and myenteric neuronal plexus and the smooth muscle, respectively, in EoE (67, 177). Additionally, both eosinophils and mast cells and their secreted mediators affect smooth muscle function and innervation (176,178−181). Particularly, TGF-β has been shown to increase smooth muscle contractibility over time (67) but decrease its force of contraction (178). Thus, TGF-β may be a key mediator of esophageal dysmotility in EoE.

CONCLUSION

In a relatively short period of time, diligent investigation of both patient cohorts and animal models and the utilization of cutting-edge technology (e.g., GWAS, expression arrays, and epigenetic studies) to investigate the pathophysiology of EoE have led to tremendous strides in piecing together the features of this enigmatic disease (Figure 4). Disease pathophysiology is associated with allergic hypersensitivity to food, heritability via genetic risk variants [e.g., 5q22 (*TSLP*) and 2p23 (*CAPN14*)], and early-life environmental risk factors. On the molecular level, activation of innate epithelial inflammatory pathways (TSLP and eotaxin-3), impaired barrier function (mediated by loss of DSG1 via IL-13 and CAPN14 mechanisms), and allergic inflammation likely mediated by eosinophils and mast cells, which produce increased TGF-β, lead to fibrosis and dysmotility that together contribute to the major symptom of dysphagia. Collectively integrating these data, we propose a two-hit mechanism for the etiology of EoE that involves allergic sensitization and esophagus-specific pathways including CAPN14.

Further dissection of the molecular mechanisms of EoE represents a promising area for translational research aimed at discovering novel therapies, noninvasive diagnostics, and biomarkers for therapy response. A better understanding of EoE-specific pathways (e.g., calpain proteases) and how early-life exposures (e.g., altered microbiome) increase susceptibility to EoE is predicted to impact future treatment. Notably, oral desensitization trials for food anaphylaxis have demonstrated that a major side effect of therapy includes the possible development of EoE. This finding demonstrates an entangled relationship between IgE-mediated food allergy and the chronic, Th2 cell–associated inflammation of EoE (36). A better understanding of the factors involved in the balance between anaphylaxis and EoE may lead to tolerance-inducing protocols for treatment and to an eventual cure for EoE. Though the findings from the early-stage clinical trials for IL-5 (mepolizumab and reslizumab) and IL-13 (QAX576) mentioned in this review did not meet primary end points, they did demonstrate tissue responses, provide needed insight into the pathology of disease, and prompt further studies of these and related biological agents. Additional agents in development for treatment of EoE include inhibitors of TSLP (e.g., AMG 157), CCR3, eotaxin (e.g., bertilimumab), and IL-4Rα (the common receptor for IL-4 and IL-13; e.g., dupilumab). Other agents include eosinophil-depleting antibodies, such as those against IL-5Rα (e.g., benralizurnab) or sialic acid–binding Ig-like lectin 8 (182). A molecular diagnostic test for EoE that is now clinically available could improve diagnosis and clinical monitoring, patient-specific therapy, and predictive and personalized medicine approaches to EoE. Additionally, therapeutic agents such as drugs and microorganisms are easy to deliver to the esophagus. Therefore, it may one day be possible to prevent EoE in individuals with high risk for this disease. We hope that this review will aid basic scientists and clinical

investigators alike in their future endeavors to continue to advance the field, thereby promoting research that has the potential to change the natural course of this disease and, in turn, countless patients' lives.

Acknowledgments

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DIFFERENTIAL DIAGNOSES FOR ESOPHAGEAL EOSINOPHILIA

There are several differential diagnoses for esophageal eosinophilia, as eosinophil activation and accumulation is a triggered immune response to a variety of stimuli. Thus, diagnosis of eosinophilic esophagitis (EoE) includes exclusion of other eosinophilic diseases of the esophagus (e.g., GERD) and of other more general immune system–inducing conditions (e.g., infection):

- EoE
- Proton pump inhibitor–responsive esophageal eosinophilia (PPI-REE)
- Celiac disease
- Crohn's disease
- Infection
- Hypereosinophilic syndrome
- Achalasia
- Drug hypersensitivity
- Vasculitis
- Pemphigoid vegetans
- Inherited connective tissue disease
- Graft-versus-host disease
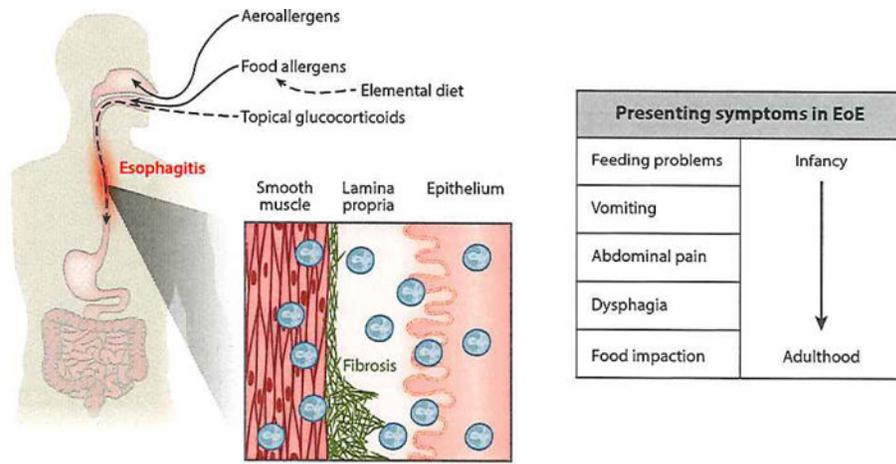- Gastroesophageal reflux disease

Figure 1.
The clinical manifestations of eosinophilic esophagitis (EoE). Both aeroallergens and food allergens have been implicated in EoE. Elemental diet and topical glucocorticoids reverse both symptoms and microscopic features of the disease. The presenting symptoms are age dependent.
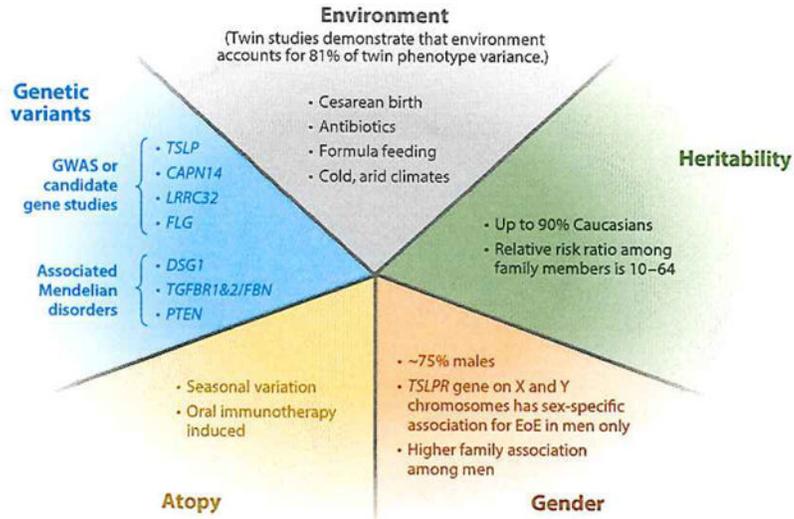
Figure 2.
Risk factors for EoE. The main categories of risk are environmental exposure and genetic predisposition. Genetic predisposition can be described through multiple subcategories including genetic variants, atopy, gender, and heritability. Abbreviations: EoE, eosinophilic esophagitis; GWAS, genome-wide association study.
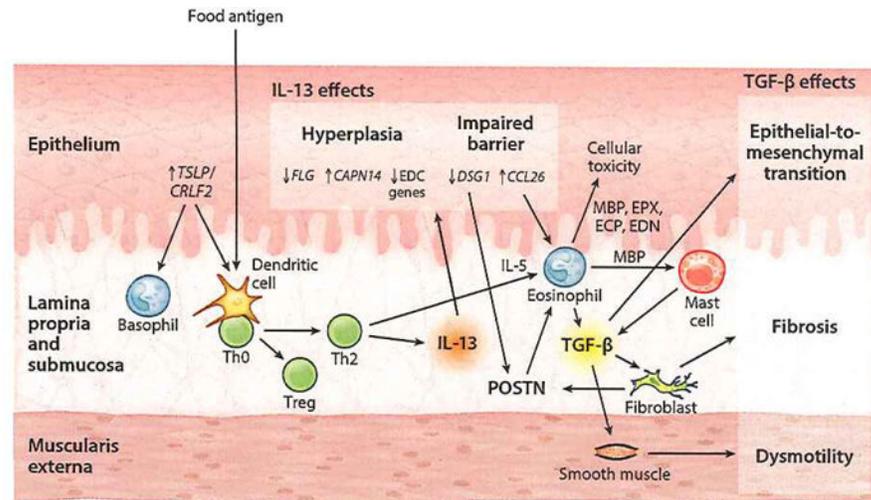
Figure 3.
Pathophysiology of EoE. TSLP is released from the epithelium and activates basophils and food antigen–presenting dendritic cells to induce Th2 polarization of naive CD4^{+} T cells. These Th2 cells then secrete JL-13 that increases CCL26, CAPN14, and periostin (POSTN) expression and decreases *DSG1, FLG*, and DC gene expression in the epithelium. Decreased DSG1 level impairs barrier function, thereby forming a propagation loop by allowing further penetration of food antigen, and also leads to increased POSTN levels. The increased CCL26 and POSTN promote eosinophil recruitment from the bloodstream. The accumulating activated eosinophils cause epithelial cell cytotoxicity. TGF-β released by both eosinophils and mast cells increases POSTN expression and stimulates fibrotic response and smooth muscle dysmotility. Abbreviations: CAPN14, calpain 14; CCL26, chemokine (C-C motif) ligand 26; CRLF2, cytokine receptor-like factor 2; DSG1, desmoglein 1; ECP, eosinophil cationic protein; EDC, epidermal differentiation complex; EDN, eosinophil-derived neurotoxin; EoE, eosinophilic esophagitis; EPX, eosinophil peroxidase; FLG, filaggrin; IL, interleukin; MBP, major basic protein; TGF-β, transforming growth factor β; Th0, naive T helper; Th2, T helper type 2; Treg, regulatory T cell; TSLP, thymic stromal lymphopoietin.
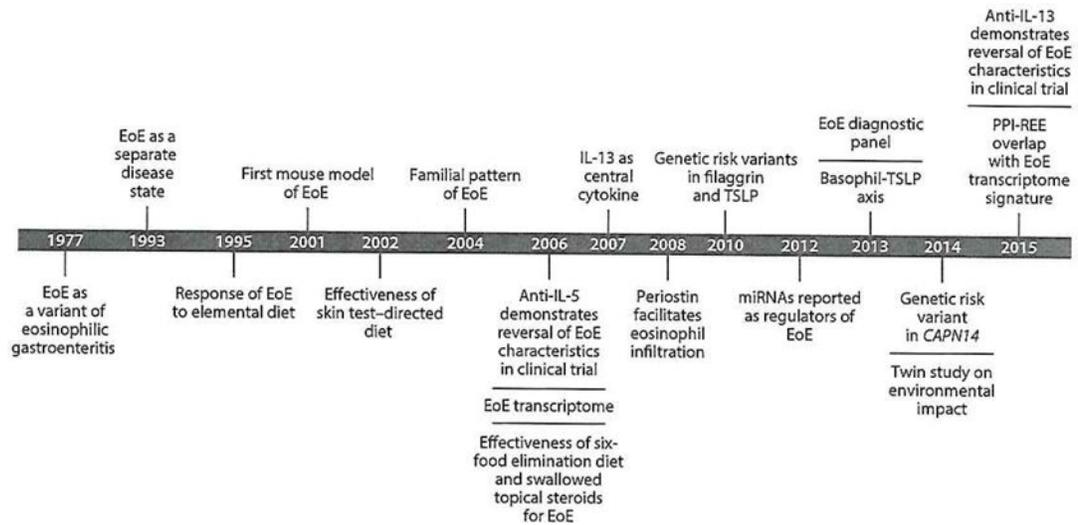
Figure 4.
Timeline of EoE research. EoE has been studied over the last 20 years, with the majority of findings occurring within the last decade. These findings have advanced clinical and mechanistic insights into disease epidemiology, pathogenesis, and treatment. Abbreviations: CAPN14, calpain 14; EoE, eosinophilic esophagitis; IL, interleukin; TGF-β, transforming growth factor β; TSLP, thymic stromal lymphopoietin; miRNAs, microRNAs; PPI-REE, proton-pump inhibitor-responsive esophageal eosinophilia.

Table 1

Features of EoE and GERD

Associated features	EoE[a]	GERD[a]
Clinical		
Atopy	Yes	No
Food sensitivity	Yes	No
Gender preference	Male	No
Food impaction	Common	Uncommon
Procedural findings		
pH probe	Neutral	Acidic
Endoscopic furrowing	Yes	No
Endoscopic rings	Sometimes	No
Decreased luminal distention	Yes	Unknown
Radiographic small caliber	Sometimes	No
Histopathology		
Proximal disease	Yes	No
Distal disease	Yes	Yes
Epithelial hyperplasia	Severe	Moderate
Eosinophils/HPF	15	<15
EoE diagnostic panel positive[b]	Yes	No
Treatment effectiveness		
H-2 blockers	No	Yes
Proton-pump inhibitors	Partial	Yes
Glucocorticoids	Yes	No
Food elimination	Yes	No
Elemental diet	Yes	No

[a]EoE and GERD can co-occur in the same patient.

[b]First approximation.

Abbreviations: EoE, eosinophilic esophagitis; GERD, gastroesophageal reflux disease; HPF, high-power field; H-2, histamine receptor 2.

Table 2

Genes associated with EoE

Gene	Approach	Modification	Associated Mendelian disease	Plausible biological mechanism
CCL26	Candidate gene	SNP in 3′UTR		Enhancement of activity or expression of eotaxin-3
TGFB1	Candidate gene	SNP in promoter		Increase in expression and steroid resistance
FLG	Candidate gene	Nonsense and missense mutations		Impairment of barrier function
TSLP	GWAS	SNP in promoter and introns		Increase in expression of potent Th2-polarizing cytokine; association with basophil responses
CRLF2	Candidate gene	Missense SNP		Male-specific association; TSLP receptor increase; TSLP signaling
DSG1	Mapping/sequencing	Missense SNP	SAM	Impairment of barrier function; increase in production of TSLP and periostin
TGFBR1/TGFBR2/FBN	Phenotype association	Missense SNP	LDS and MF	Increase in TGF-β levels and/or signaling and Th2 cell skewing
CAPN14	GWAS	SNP in promoter, introns and intergenic		Regulation of expression of calpain-14, a calcium-activated intracellular regulatory protease
LRRC52	GWAS	SNP in introns and intergenic		Altered TGF-β signaling, as LRRC32 (also known as GARP) is a membrane-bound TGF-β binding protein
PTEN	Phenotype association	Missense SNP	PHTS	Gain of function of phosphatase activity; regulation of eosinophil responses

Abbreviations: *CAPN14*, calpain-14; *CCL26*, chemokine C-C motif ligand 26; *CRLF2*, cytokine receptor-like factor 2; *DSG1*, desmoglein-1; *FBN*, fibrillin; *FLG*, filaggrin; GARP, glycoprotein-A repetitions predominant protein; GWAS, genome-wide association study; LDS, Loeys-Dietz syndrome; *LRRC32*, leucine rich repeat containing 32; MF, Marfan syndrome; PHTS, *PTEN* hamartoma tumor syndrome; *PTEN*, phosphatase and tensin homolog; SAM: severe dermatitis, multiple allergies and metabolic wasting syndrome; SNP, single-nucleotide polymorphism; TGF-β, transforming growth factor β; Th2, T helper type 2; *TSLP*, thymic stromal lymphopoietin.