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The Immunologic Mechanisms of Eosinophilic Esophagitis

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Abstract

Eosinophilic esophagitis (EoE) is a chronic allergic inflammatory disease that is triggered by food and/or environmental allergens and is characterized by a clinical and pathologic phenotype of progressive esophageal dysfunction due to tissue inflammation and fibrosis. EoE is suspected in patients with painful swallowing, among other symptoms, and is diagnosed by the presence of 15 or more eosinophils per high-power field in one or more of at least four esophageal biopsy specimens. The prevalence of EoE is increasing and has now reached rates similar to those of other chronic gastrointestinal disorders such as Crohn's disease. In recent years, our understanding of the immunologic mechanisms underlying this condition has grown considerably. Thanks to new genetic, molecular, cellular, animal, and translational studies, we can now postulate a detailed pathway by which exposure to allergens results in a complex and coordinated type 2 inflammatory cascade that, if not intervened upon, can result in pain on swallowing, esophageal strictures, and food impaction. Here, we review the most recent research in this field to synthesize and summarize our current understanding of this complex and important disease.

Keywords

Eosinophilic esophagitis; Food allergy; Immunology; Inflammation

Introduction

Eosinophilic esophagitis (EoE) is a chronic allergic inflammatory disease of the esophagus that, if left untreated, can result in significant impairment in the quality of life due to pain on swallowing (odynophagia), food impaction, esophageal stricture formation, and in rare extreme cases, esophageal rupture [1–5]. Histopathologically, EoE is characterized by

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esophageal epithelial barrier defects and eosinophil infiltrates [6]. Clinically, EoE is suspected in patients with symptoms of esophageal dysfunction and/or fibrosis. In children, symptoms often mimic those of gastroesophageal reflux disease but do not respond to gastric acid suppression. Older children and adults often present with symptoms of odynophagia and food impaction caused by progressive esophageal fibrosis [7, 8]. Diagnosis is made by the presence of 15 or more eosinophils per high-power field in one or more of at least four esophageal biopsy specimens obtained via esophagogastroduodenal endoscopy, while the patient is being treated with an optimal anti-gastroesophageal reflux disease (GERD) therapeutic regimen [9, 10••].

The first case of EoE was described in 1968. Since then, the rates of EoE diagnosis in western countries have grown considerably to match those of other gastroenteropathies such as Crohn's disease [11–16]. EoE is most common in Caucasian males and can occur sporadically or in families [11, 17–21]. The sibling risk recurrence ratio for EoE is higher than that of other allergic conditions; however, twin studies have shown the environment to be a contributor in addition to familial predisposition [22•, 23]. Both sporadic and familial EoEs seem to have similar pathologic and molecular phenotypes, suggesting that the inflammatory phase of the disease is conserved between these two groups [24]. When an EoE diagnosis is made, it is imperative that measures be taken to eliminate or control esophageal inflammation for both symptomatic relief and the prevention of fibrotic complications such as esophageal stricture and food impaction [5].

Most EoE patients have comorbid allergic conditions (allergic rhinitis, asthma, immunoglobulin E (IgE)-mediated food allergies, atopic dermatitis, etc.), suggesting that these conditions are pathophysiologically related [25]. In addition, reactions to food allergens alone are not solely responsible for the inflammation observed in EoE as some EoE patients with concurrent allergic rhinitis display seasonal exacerbations of esophageal eosinophilia [26]. Consistent with EoE falling on the allergic spectrum, the inflammation observed in EoE responds to allergen avoidance and/or topical steroid applications. Elemental diets have been shown to be highly effective in inducing histologic and clinical remission in children and adolescents with EoE, though adherence to these diets is poor [27–30]. Alternative diets have been examined such as empiric elimination diets, based on the most commonly identified etiologic foods, and allergy testing-directed diets [29, 31–34]. Subsequent examination of these two approaches has shown them to be equally effective in inducing disease remission; there is no added benefit to skin testing over empiric elimination of commonly allergic foods [28]. Orally administered topical steroids are an alternative therapy for EoE that are highly effective with resolution rates up to 80 % depending on the dose, but with potential side effects [35–43]. Together, these observations highlight the need for new and improved therapeutic approaches to prevent and treat this growing disease.

Recent discoveries in animal models and human subjects have advanced our understanding of the immunologic mechanisms underlying EoE, and have led to exciting new therapeutic prospects. We review the most up-to-date research available spanning the disciplines of basic science, translational, and clinical research. This review is organized into three sections: "Genetics, Epigenetics, and Transcriptional Analyses," "Cytokines, Chemokines, and Other Molecules, " and "Pathologic and Protective Cell Populations." In addition to reviewing

immunologic discoveries in patients and animal models, we touch on new immune-directed therapies for EoE that are currently under investigation. We conclude by providing a unifying theory for the pathogenesis of EoE. We hope that this review will provide a framework for clinicians and scientists interested in improving our understanding of EoE pathogenesis and developing new preventative and therapeutic strategies for this important condition.

Genetics, Epigenetics, and Transcriptional Analyses

The genetic associations and epigenetic changes observed in EoE have been nicely reviewed recently [44]. While not the focus of this review, these studies have provided important launching points for subsequent experimental approaches in mice and humans designed to elucidate the immunologic mechanisms of EoE. As such, we will touch on them briefly here. Early single-gene association studies identified polymorphisms that were more frequent in EoE patients. These include mutations in the untranslated region preceding the chemokine (C-C motif) ligand 26 (CCL26), which encodes the potent eosinophil and basophil chemotactic eotaxin-3, as well as mutations in the epidermal barrier gene filaggrin and in the promoter of the transforming growth factor beta 1 (TGF-β1) gene [35, 45–47]. More recently, genome-wide association studies have identified several loci that have a strong association with EoE. Variants in the 5q22 locus, which includes the gene which encodes thymic stromal lymphopoietin (TSLP), are associated with EoE, and *TSLP* is overexpressed in esophageal biopsies from individuals with EoE compared to unaffected individuals [48, 49]. Additionally, variants in a region on 2p23 which includes the gene *CAPN14* (that encodes a member of the calcium-dependent, non-lysosomal cysteine protease family) are associated with EoE [50•, 51•]. *CAPN14* is also up-regulated in the esophagus in active EoE, and after exposure of epithelial cells to interleukin (IL)-13 [50•]. Additional associations have been reported for variations in *c11orf30* which encodes EMSY, the gene encoding signal transducer and activator of transcription (STAT)6, and *ANKRD27* whose product regulates the trafficking of melanogenic enzymes to epidermal melanocytes [51•].

There is limited data about the role of epigenetic regulation in EoE pathogenesis, and most of our understanding in this regard stems from detailed studies of the *CCL26* locus. Firstly, it seems that IL-13 promotes the activation of *CCL26* via two STAT6 binding sites in the *CCL26* promoter [52]. This signaling cascade increases acetylated histone 3 and opens the CCL26 promoter for transcription [53]. These findings may be relevant to recent observations that omeprazole blocks STAT6 binding to the *CCL26* promoter, possibly explaining why patients with esophageal eosinophilia are at least in part responsive to PPI therapy (PPI-REE patients) [54, 55]. Secondly, it has been shown that portions of the *CCL26* promoter are hypomethylated in esophageal epithelial cells derived from EoE patients, and that the methylation status of the *CCL26* promoter dictates the propensity for STAT6 to bind to the site [56]. Together, these findings indicate that both histone acetylation and DNA methylation are mechanisms of transcriptional regulation of the *CCL26* locus and that dysregulation in either system may contribute to EoE susceptibility in some patients.

MicroRNAs (miRNAs) are short, non-coding RNAs that influence the expression of genes by binding to complementary sequences in the 3' untranslated region of the target messenger

RNA (mRNA) sequence and interfering with translation and/or promoting degradation of the transcript. miRNAs have been shown to play a role in multiple human inflammatory disease states including EoE [57]. Examination of miRNA expression patterns in patients with EoE revealed dysregulation of miRNAs involved in tissue remodeling and inflammation [58, 59]. Dysregulated miRNA expression is largely reversible in patients who respond to glucocorticoid treatment, suggesting that the altered miRNA expression patterns observed contribute to EoE pathogenesis [60]. Consistent with this, two of the most upregulated miRNAs observed in patients with active EoE, miR-21 and miR-223, have been shown to have functions that would support a pathologic role in EoE. miR-21 is implicated in eosinophil survival, allergic inflammation, and TGF-β-stimulated tissue fibrosis [61–63]. Similarly, miR-223 has been implicated in regulating IL-5 expression and eosinophil development [64]. Other miRNAs are downregulated in EoE. For example, miR-357, a microRNA that is suppressed by IL-13, shows significantly lower expression in patients with active EoE [59]. Together, these findings identify altered miRNA expression as a key phenotype of EoE and identify potential pathologic roles for some transcripts.

Through the utilization of PCR and microarray techniques, an EoE transcriptome has been identified with high resolution. In fact, the transcriptional fingerprint of EoE is becoming so well characterized that profiling of EoE-specific changes has been proposed as a new diagnostic modality, though it does not have additional diagnostic or predictive values compared to standard H&E analysis at the current time [65]. In total, more than 1600 transcripts have been identified that are dys-regulated in EoE including cytokines (*IL1B*, *IL1RN*, *IL1F6*, *IL4*, *IL5*, *IL6*, *IL8*, *IL12p70*, *IL13*, *CD40L*, *IL1a*, *IL17*, *ABCF1*), chemokines (*CCL26*, *CXCL1*, *CXCL2*, *CXCL14*, *CCL1*, *CCL23*), and receptors (*IL5RA*) [45, 66, 67]. Of these, the expression of *CCL26*, which encodes the eosinophil chemoattractant eotaxin-3, is among the most highly induced genes in the EoE transcriptome [45, 68, 69]. The role of eotaxin-3, as well as other proteins that have been identified through transcriptional analysis and implicated in the pathophysiology of EoE, will be discussed in detail in the next section of this review.

Cytokines, Chemokines, and Other Molecules

Desmoglein-1, Keratin, and Periostin

Several molecules important for epithelial integrity have been shown to be dysregulated in animal models and patients with EoE. The desmosomal cadherin desmoglein 1 (DSG1) is an intercellular adhesion molecule, belonging to the desmosomal cadherin family, that plays a critical role in maintaining suprabasal epithelial integrity [70]. There are reduced levels of DSG1 in esophageal biopsies of patients with active EoE as compared to controls, and IL-13 downregulates *DSG1* expression and promotes impaired barrier function in cultured esophageal epithelial cells [71, 72•]. Additionally, a loss of *DSG1* in cultured esophageal epithelial cells results in a transcriptional phenotype similar to that found in EoE, suggesting that many of the downstream mediators of inflammation in EoE may be a result of impaired epithelial integrity [72•]. Interestingly, homozygous mutations in *DSG1* have recently been shown to result in a loss of cell-cell adhesion, correlated with a type 2 inflammatory

response, and associated with a clinical syndrome featuring severe dermatitis, multiple allergies, and metabolic wasting [73].

The transcript for another molecule important for epithelial integrity, keratin, is also expressed by esophageal epithelial cells and is downregulated in patients with active EoE [74]. Conversely, the matricellular protein periostin, which interacts with several extracellular matrix proteins such as type 1 collagen and Notch1 to mediate cell migration and adhesion, is highly upregulated in patients with EoE [45, 75]. Periostin expression is thought to be induced by TGF-β and IL-13 signaling and may play an important role in promoting eosinophil adhesion. Periostin can also induce expression of TSLP, a molecule which may be central to EoE pathogenesis and is discussed in detail below [76]. Finally, periostin-deficient mice are protected against allergic inflammatory responses in the esophagus [75]. Together, these findings implicate baseline impaired mucosal integrity as a risk factor for allergen exposure and development of EoE [77]. Consistent with this hypothesis, the prevalence of EoE in patients with inherited connective tissue disorders (such as Marfan and Ehlers-Danlos syndromes) is eightfold higher than the general population [78].

Eotaxin

While many genes are known to be dysregulated in patients with EoE, the eosinophil chemoattractant eotaxin-3 is one of the best characterized. A potent eosinophil chemotactic, eotaxin-3 is expressed by endothelial cells, binds to CCR-3 on the surface of eosinophils, and causes upregulation of cell adhesion molecules and production of effector cytokines such as IL-13 [79]. A single-nucleotide polymorphism in the gene encoding eotaxin-3 (CCL26) has been shown to be associated with susceptibility to EoE [45]. Additionally, CCL26 is upregulated in the inflamed esophageal mucosa of EoE patients and is downregulated upon treatment with topical steroids [68]. Murine models have shown that overexpression of eotaxin results in recruitment of eosinophils to the mucosa of the gastrointestinal tract and mice lacking CCR-3 are protected against experimental EoE [45, 80–82]. Interestingly, expression of eotaxin-3 is only mildly elevated in patients with GERD, suggesting that analysis of eotaxin-3 expression may be able to differentiate these two conditions [69].

Several lines of investigation have interrogated transcriptional regulation of CCL26 in EoE. The CCL26 promoter is hypomethylated, and CCL26 expression is highly induced, in patients with EoE [45, 56]. Additionally, PARP14, a transcriptional cofactor from the poly(ADP-ribose) polymerase (PARP) family that facilitates CCL26 transcription via STAT6, is also dysregulated in EoE [83–85]. *PARP14* expression is increased in biopsies of children with EoE compared to controls, and CCL26 expression strongly correlates with PARP14 expression [85]. Cotransfection of an esophageal cell line with both PARP14 and STAT6 increases the activity of a *CCL26* reporter, and a PARP inhibitor attenuates IL-4 and IL-13-mediated induction of *CCL26* transcription [85]. Together, these studies have helped to identify eotaxin-3 as a molecule that is often dysregulated in EoE and that likely contributes to the exaggerated eosinophilic inflammation observed in this condition.

Histamine

The histamine receptors HR1 and HR4 have increased expression in esophageal biopsies of patients with active EoE as compared to those with inactive EoE or healthy controls. HR1 and HR4 are expressed in epithelial eosinophils from biopsies of patients with active EoE, while HR2 expression is present throughout the EoE inflamed tissue [86]. Interestingly, expression of HR2 is increased in patients with both active and inactive EoE compared to controls, suggesting that aberrant epithelial expression of HR2 may predispose individuals to the development of EoE [86]. Further investigation is needed to better elucidate the pathophysiologic implications of these observations and to determine whether antihistamines or other targeted therapies may be beneficial in the treatment of EoE.

IgE

As discussed previously, most EoE patients have comorbid allergic conditions, suggesting that these conditions share a common pathophysiologic mechanism [25]. IgE has long been known to be an antigen-specific mechanism of granulocyte degranulation, and IgE plays an important role in multiple allergic conditions including allergic rhinitis, asthma, and IgE-mediated food allergies. More recently, additional roles for IgE have been identified in immune cell development and homeostasis [87–89]. Regardless of atopic history, B cells that are class switched to the IgE isotype and IgE-bound mast cells are both increased in patients with EoE [90]. Despite these findings, eosinophilic inflammation is independent of B cells in one model of EoE and independent of IgE in another [91, 92••]. As such, the role of B cells and IgE in the pathogenesis of EoE is unclear.

Additional evidence indicates that EoE is not an IgE-mediated disease. For example, IgE-mediated food allergy and EoE seem to occur independently [93, 94]. Additionally, patients with milk-induced EoE do not outgrow their disease which is in contrast to IgE-mediated allergy where 75 % of children become tolerant by the early teenage years [7, 95, 96]. Furthermore, children who do outgrow IgE-mediated milk allergy, as well as those undergoing oral immunotherapy, are at increased risk of developing EoE once milk is reintroduced into their diet [93, 97]. Finally, food elimination diets based on IgE testing are largely unsuccessful [32–34, 98].

Omalizumab is a humanized mouse monoclonal antibody that binds to the IgE molecule rendering it inactive. Omalizumab has been shown to influence allergic cell populations and improve outcomes in asthma and chronic urticaria and is being investigated in other atopic conditions [99]. Additionally, omalizumab has been studied in multiple times in the context of EoE. While one open-label, single arm, non-blinded study showed a positive effect of omalizumab therapy in a subset of EoE patients, several other studies have shown no effect [100]. In a small study of 2 patients, omalizumab therapy had no effect on esophageal eosinophils while in another 16-week open-label study of nine subjects with allergic eosinophilic gastroenteritis omalizumab treatment resulted in reduced peripheral blood, duodenal, and antral eosinophil counts but modestly increased esophageal eosinophils [101, 102]. Finally, in a prospective, randomized, double-blind, placebo-controlled trial of adults with EoE, omalizumab did not alter symptoms of eosinophilic esophagitis or esophageal eosinophil counts compared to placebo [103•]. Together, these findings indicate that IgE is

unlikely to play a formative role in the pathogenesis of EoE and that omalizumab is not an effective therapeutic strategy for EoE.

IL-4

Interleukin (IL)-4 is critical for the development of T helper type 2 (Th2) cells and contributes to many type 2 inflammatory responses [104]. Several studies in humans and mice have shown that EoE is characterized by a type 2 allergic inflammatory response. Esophageal biopsies and blood samples of patients with active EoE have increased levels of the type 2 prototypical cytokines and chemokines including IL-4, IL-5, and IL-13 [67, 105–107]. IL-4 also induces secretion of eotaxin-3 by esophageal epithelial cells in vitro [108]. However, the presence of IL-4 is not necessary for the development of esophageal inflammation in some animal models of EoE, suggesting that IL-4-independent mechanisms of allergic inflammation may be more relevant in these cases [109].

IL-5

IL-5 has long been known to promote eosinophil development, activation, survival, and recruitment to sites of inflammation [110]. Patients with EoE are more likely to have polymorphisms in the gene encoding IL-5, higher numbers of circulating IL-5^+ $CD4^+$ T cells, and higher esophageal tissue levels of IL-5 and its receptor IL-5-R compared to controls [67, 68, 107, 111, 112]. Furthermore, IL-5 expression in the esophagus of patients with EoE is downregulated with topical steroid treatment, supporting a pathologic role for this cytokine [67, 68, 107, 111]. Animal studies have shown us that non-specific overproduction of IL-5 results in eosinophil accumulation in the esophagus, a phenomenon which is potentiated by eotaxin. Furthermore, epicutaneous antigen exposure primes the immune system for subsequent eosinophilic inflammation in the esophagus upon airway antigen exposure in an IL-5-dependent manner [113]. Conversely, eosinophil accumulation and fibrosis in the esophagus in response to oral or intranasal allergen administration is attenuated in the absence of IL-5 [80, 81, 114–116]. These findings suggest that IL-5 is both sufficient and necessary for eosinophil trafficking to the murine esophagus in some experimental contexts and that IL-5 and eosinophils contribute to the esophageal fibrosis observed in these experimental systems.

As IL-5 is dysregulated in patients with EoE and contributes to some experimental models of EoE, IL-5 blockade was suggested as an attractive potential therapeutic strategy for EoE. Mepolizumab and reslizumab are humanized monoclonal IgG1 antibodies targeted against IL-5 that have been studied in multiple disease contexts from hypereosinophilic syndrome to eosinophilic granulomatosis with polyangiitis [117–119]. In two small studies in adults, mepolizumab therapy caused reductions in peripheral blood and esophageal eosinophilia and a variable degree of resolution of EoE-related symptoms with overall improvement in quality of life scores [120, 121]. One double-blind, randomized, prospective study of 59 children with EoE showed that treatment with mepolizumab reduced esophageal eosinophils, but only to a peak level of 40 eosinophils/hpf which is above the threshold for EoE diagnosis [122]. In a larger double-blind, randomized, placebo-controlled trial of reslizumab in 227 children and adolescents with EoE, there was also a partial reduction in esophageal eosinophils, but again not to normal levels [123]. Importantly, improvements in

symptoms in this study were equivalent in all groups including the placebo [123]. Together, these findings suggest that IL-5 blockade may not be a useful therapeutic strategy in EoE possibly due to redundant pathways for eosinophil recruitment and activation.

IL-13

IL-13 is one of the prototypical type 2 cytokines and is integral to multiple aspects of human physiology and disease [124]. Polymorphisms in the gene encoding IL-13 have also been shown to be genetically associated with EoE in a phenome-wide association study [112]. There are several mechanisms by which IL-13 has been proposed to contribute to EoE pathogenesis including upregulation of periostin, induction of AMCase expression, and influencing genes important for epithelial integrity [47, 75, 125]. Esophageal epithelial cells express the IL-13 receptor, and IL-13 induces dysregulated gene expression in the esophageal epithelium, such as overexpression of eotaxin-3, that mimics the transcription profile observed in esophageal biopsies of EoE patients [71]. Mouse models have shown that *IL-13* overexpression in the lung, but not the esophagus, results in an EoE-like disease state that is partially dependent on eotaxin-1 but not eosinophils [126]. Intratracheal IL-13 also induces features of experimental EoE in mice in a IL-5-, eotaxin-1-, and STAT6-dependent manner. Importantly, IL-13-deficient mice are protected from the development of experimental EoE in some but not all model systems of EoE and anti-IL-13 treatment in mice reduces esophageal eosinophilia [109, 113, 115, 127, 128].

Experimental findings in mice and humans suggest that IL-13 may also be sufficient and necessary for EoE-like inflammation in some cases, leading to the hypothesis that anti-IL-13 treatment may be a useful therapeutic modality. Anti-IL-13 treatment in adult patients with EoE normalized expression of EoE disease-related transcripts, decreased esophageal eosinophil counts (though not to normal levels), but only resulted in a non-significant trend towards improved symptoms [129]. Therefore, while animal and translational studies support a role for IL-13 in the pathogenesis of EoE, further study is needed to determine whether IL-13 blockade will ultimately become a useful therapy for EoE patients.

IL-15

IL-15 is a cytokine with a structural similarity to IL-2 that binds to and signals through a complex composed of the IL-2/IL-15 receptor beta chain (CD122) and the common gamma chain (CD132). Produced predominantly by monocytes, macrophages, and dendritic cells, IL-15 plays an important role in antiviral immunity by supporting the development, survival, proliferation, and activation of multiple lymphocyte lineages including natural killer cells [130]. Additionally, IL-15 has recently been shown to support type 2 allergic inflammatory responses. For example, mast cells express a distinct receptor for IL-15 (IL-15RX) which signals through the JAK2/STAT5 pathway and murine mast cells treated with IL-15 engage the IL-2/IL-15Rγ chain causing phosphorylation of Tyk2/STAT6 and the production of IL-4 [131, 132].

Both *IL-15* and *IL-15Ra* transcripts are elevated in esophageal biopsies of patients with EoE compared to controls [133]. *IL-15* transcripts are also elevated in the esophagus of mice with experimental EoE, IL-15-mediated signaling causes $CD4^+$ T cell proliferation and

production of IL-5 and IL-13, and IL-15-deficient mice are protected against experimental EoE [133]. Finally, coculture with IL-15 causes primary esophageal epithelial cells to increase the expression of eotaxin proteins which could promote eosinophil chemotaxis [133]. Together, these findings support a tentative role for IL-15 in contributing to EoE pathogenesis and identify one potential mechanism by which IL-15 may promote esophageal eosinophilia.

IL-18

IL-18 is a cytokine with structural homology to IL-1 that is produced by both immune and non-immune cells and mediates both immunity and pathologic inflammation in various contexts [134]. While originally characterized for its role with IL-12 in stimulating Th1 cell differentiation, IL-18 is also known to influence type 2 inflammation as polymorphisms in IL-18 are protective for some atopic conditions and IL-18 promotes allergic inflammation in some animal models [135, 136]. Recently, a role for IL-18 in the pathogenesis of EoE has also been postulated. Esophageal biopsies of patients with EoE showed higher expression levels of *IL-18* mRNA and a higher proportion of IL-18Rα$^+$ cells, and IL-18 can influence IL-5 and IL-13 cytokine production by invariant natural killer T cells (iNKTs) providing one potential pathologic mechanism for this cytokine [137]. Further research may continue to elucidate a role for IL-18 in EoE pathogenesis.

TGF-β and Tumor Necrosis Factor Alpha

TGF-β1 is a member of the transforming growth factor beta superfamily of cytokines. It is a secreted protein that performs many cellular functions including the control of cell growth, proliferation, differentiation, and apoptosis [138]. TGF-β is also a potent stimulator of the synthesis of extracellular matrix proteins and plays a prominent role in the development of tissue fibrosis [139]. Tumor necrosis factor alpha (TNF-α) is an inflammatory cytokine that is produced by multiple immune cell types and has many roles including mediating the activation and survival of eosinophils [140, 141].

Both TGF-β and TNF-α are thought to play a role in EoE pathogenesis. Polymorphisms in the promoter for TGF-β1 are associated with EoE susceptibility, and TGF-β1$^+$ cells are overrepresented in the esophagus of patients with EoE [35, 77]. Similarly, TNF-α is upregulated in EoE and is highly expressed by epithelial cells of the esophagus in patients with active disease [45, 105]. TGF-β1 is produced by eosinophils and mast cells and promotes collagen production and tissue fibrosis by signaling through the Smad3 pathway [142–144]. Consistently, Smad3-deficient mice are protected against esophageal fibrosis and angiogenesis [145]. It is thought that the inflamed epithelial cells prime esophageal fibroblasts to secrete the profibrogenic cytokines IL-1β and TNF-α, which in turn promote epithelial-to-mesenchymal transition and esophageal fibrosis [142, 146]. In one study, coculture of primary epithelial or muscle cells derived from patients with EoE with eosinophils caused increased cell line secretion of fibronectin and collagen I, a response that was inhibited by blocking TGF-β1 [147]. Coculture of eosinophils with cultured muscle cells also resulted in reduced contractility, an observation that may be the result of TGF-β1-induced phospholamban expression [147, 148].

As the aforementioned studies suggest, TGF-β and TNF-α may promote esophageal fibrosis in EoE. Based on these observations, it was hypothesized that blockade of TNF-α with infliximab (a chimeric IgG1 mAb directed against TNF-α) could be beneficial in the treatment of patients with EoE. In a small study of three adult patients, infliximab therapy did not influence esophageal inflammation or symptoms [149]. However, given the limited size of this study, it is reasonable that further investigation may support a role for TNF-α blockade in EoE therapy.

TSLP

As discussed previously, variants at chromosome 5q22 encompassing the *TSLP* and *WDR36* genes are strongly associated with EoE [49]. *TSLP* is overexpressed in esophageal biopsies from individuals with EoE as compared to unaffected individuals, while *WDR36* expression is unaltered, implicating the 5q22 locus (and *TSLP* in particular) in the pathogenesis of EoE [48]. Animal models also support a role for TSLP in EoE pathogenesis [150•]. In a murine epicutaneous sensitization model of EoE, esophageal inflammation is dependent in part of TSLP and basophils, but independent of IgE. In the same study, elevated *TSLP* expression and exaggerated basophil responses were observed in esophageal biopsies of patients with EoE, and a gain-of-function polymorphism in TSLP was found to be associated with increased basophil responses in EoE patients [92••]. Further investigation may continue to elucidate a role for TSLP in EoE pathogenesis.

Prostaglandin 2

Prostaglandin D2 (PGD2) is a prostanoid that is produced by mast cells and promotes allergic responses. Introduction of exogenous prostaglandins results in eosinophil infiltration into the esophagus of animal models, while prostaglandin antagonists protect against EoE-like inflammation [151]. Chemoattractant receptor expressed on Th2 cells (CRTH2) is the receptor for PGD2 and mediates chemotaxis of Th2 cells, eosinophils, and basophils [152]. One study examined the utility of a CRTH2 inhibitor in treating EoE. In this randomized, double-blind, placebo-controlled trial of 26 adult EoE patients that were dependent or resistant to corticosteroids, 8 weeks of anti-CRTH2 therapy resulted in reduced esophageal eosinophil load compared to treatment with a placebo. Assessments of disease activity also improved, which correlated with reduced extracellular deposits of eosinophil peroxidase and tenascin C (which are markers of esophageal remodeling), suggesting that anti-CRTH2 therapy may have utility in refractory EoE patients [153].

Pathologic and Protective Cell Populations

Antigen-Presenting Cells

Classically, $CD4^+$ T helper cells are known to be activated by professional antigen-presenting cells (APCs) such as dendritic cells, macrophages, and B cells [154]. Additionally, non-professional APCs are now known to be able to process and present antigens to T cells in certain settings [155]. The roles of professional and non-professional APCs in processing and presenting antigen to T cells in EoE are only beginning to be understood. In models of EoE, epithelial cells have been shown to express MHCII and can induce T helper cell lymphocyte proliferation in vitro [156]. Additionally, eosinophils seem

to express some of the molecules necessary for T cell activation though it has not been shown that eosinophils act as APCs in models of EoE [157]. Despite these advances, questions remain to be answered. For example, it is unclear at present where APCs encounter antigen to promote adaptive responses in EoE. Potential locations include the esophageal epithelium, the lamina propria, or organized lymphoid structures. Additionally, it is not clear which APCs are most critical to initiating adaptive response in EoE. Further investigation is therefore warranted.

Basophils

Basophils are a long-known innate granulocyte that circulate in the blood and were initially regarded as a redundant granulocyte population lacking unique functions. However, the past decade of research has revealed an important pathologic role for the basophil in multiple inflammatory disease states [158]. In particular, basophils have been shown to be activated by key allergic signals such as TSLP and to respond to allergen exposures by homing to lymphatics or sites of tissue inflammation where they can help to initiate and propagate allergic responses [88, 159]. As discussed previously, mouse models suggest that TSLP and basophils contribute to an epicutaneous sensitization model of EoE [92••]. Consistently, altered *TSLP* and basophil responses are present in patients with EoE [92••]. Together, these findings support a tentative role for basophils in EoE pathogenesis.

Eosinophils

The presence of eosinophils in the esophageal mucosa of patients is the classic observation from which EoE derives its name. Highlighting the perceived importance of eosinophils in EoE pathogenesis, the diagnosis of EoE requires the presence of 15 or more eosinophils per high-power field in one or more of at least four esophageal biopsies [9, 10••]. However, eosinophils in the esophagus is not pathognomonic for EoE as many other conditions such as GERD, proton pump inhibitor-responsive esophageal eosinophilia, drugs, infection, autoimmune conditions, and primary hypereosinophilic syndromes have a similar histopathologic appearance [160, 161]. One commonly considered differential diagnosis for EoE is GERD, and as such, it is imperative that a patient is being treated with an optimal anti-GERD therapeutic regimen prior to considering a diagnosis of EoE. However, recent findings that a subset of patients with esophageal eosinophilia have improvement or resolution of disease with PPI therapy alone has led some investigators and clinicians to examine the relationship between EoE, esophageal eosinophilia, and GERD. Specifically, proton pump inhibitor-responsive esophageal eosinophilia is an active area of research [162]. Nevertheless, it is likely that the underlying inflammatory mechanisms of GERD and EoE are distinct and that the presence of eosinophils in the esophagus represents a common inflammatory endpoint [163, 164].

Mast Cells

Mast cells are tissue-resident granulocytes that bind IgE to their surface and, when activated, release histamine and other allergic mediators [165]. Mast cell-associated genes are upregulated in adult EoE, and mast cells are present in increased numbers in esophageal biopsies from both pediatric and adult EoE patients [105, 143, 166, 167]. Implementation of a selective food elimination diet or topical corticosteroid therapy results in downregulation

of mast cell-associated genes and significantly reduces epithelial mast cell numbers [143, 166–168]. Furthermore, therapy with mepolizumab, a humanized monoclonal antibody directed against human IL-5, results in decreased numbers of esophageal mast cells in pediatric but not adult EoE patients [121, 169]. Tissue mast cells are not thought to be directly responsive to IL-5 signaling, and it has therefore been hypothesized that the effects of mepolizumab on tissue mast cells are indirect and perhaps mediated through reduction in IL-9^{+} eosinophils [169]. The precise role of mast cells in EoE pathogenesis is yet unclear.

Th2 Cells

The eosinophilic inflammation observed in EoE is thought to originate as a result of antigen-specific differentiation of T helper type 2 cells. While in some cases of EoE one or more allergenic food triggers can be identified, the analysis of human Th2 cell subsets in this condition is surprisingly limited with only one study demonstrating an increased percentage of IL-5-expressing CD4^{+} T cells in the peripheral blood of patients with active EoE [111]. Animal models support a role for the adaptive immune system in EoE pathogenesis. In a mouse model of EoE, B and T cell populations, as well as eosinophils, were found in increased numbers of experimental animals as compared to controls. Additionally, oral sensitization of mice with peanut protein results in EoE-like inflammation, the production of peanut-specific IgE, and the secretion of IL-4, IL-5, and IL-13 in splenocyte cultures stimulated with peanut protein [170]. Furthermore, eosinophil accumulation in the esophagus of experimental animals is absent in *RAG1*-or *FOXN1*-deficient mice that are deficient in B and T cells or T cells, respectively, but not in *IgH6*-deficient mice that are deficient in B cells. Moreover, CD8-deficient mice develop experimental EoE while CD4-deficient mice are partially protected from esophageal inflammation. Taken together, these studies support a role for antigen-specific adaptive immune responses, and Th2 cells in particular, in EoE pathogenesis [91].

Regulatory T Cells

Regulatory T cells (Tregs) are a subset of T lymphocytes that play an important role in the prevention and control of many autoimmune and allergic diseases [171]. Tregs are reduced in biopsies of adults with EoE as compared to controls, a finding that is irrespective of steroid therapy [172]. In contrast, Tregs seem to be increased in esophageal tissue of children with EoE [173, 174]. In animal models of EoE, epicutaneous immunotherapy (EPIT) induced Tregs in the spleen and expression of *FOXP3* in the esophagus that correlated with reduced eosinophilic infiltration, while depletion of CD25 cells abrogated Tregs induction and resulted in increased esophageal inflammation. Transfer of Tregs isolated from mice who had undergone EPIT prevented peanut-induced eosinophil infiltration and eotaxin expression in the esophagus of mice [175]. Interestingly, patients with the autosomal recessive form of hyper-IgE syndrome caused by mutations in the *DOCK8* gene have defective regulatory T cells and often develop EoE [176, 177]. Together, these findings show that Tregs are dysregulated in patients with EoE and that they can protect against an EoE-like disease in some cases.

iNKTs and Innate Lymphoid Cells

iNKTs are a subset of lymphocytes which can produce type 2 cytokines in response to certain stimuli and have been postulated to play a pathogenic role in some atopic diseases [178]. Recently, patients with EoE were found to have reduced peripheral blood iNKTs, and increased esophageal iNKTs, compared to controls. Interestingly, iNKTs from patients with active EoE expand more readily and were found to produce more IL-13 in response to stimulation when compared to controls [179].

Innate lymphoid cells (ILCs) are another type of innate lymphocyte population that play important roles in mouse models of infection, inflammation, and tissue repair and can be dysregulated in specific disease states [180]. Group 2 ILCs (ILC2s), a lineage-negative lymphocyte which express CRTH2, are induced by IL-33 and TSLP to produce large amounts of Th2 cytokines, and are enriched in biopsies of patients with active EoE [181]. Further research is warranted to determine whether either of these innate lymphocyte populations play a prominent role in EoE pathogenesis.

Commensal Bacteria

Commensal bacteria that colonize the intestine and other mucosal sites are now widely regarded as integral to promoting normal human physiology. Commensals are now known to influence broad aspects of the mammalian immune system and have been identified as key modifiers in multiple human disease states including allergy [182]. Despite these advances, studies of how commensals contribute to, or are modified in EoE, are comparably lacking. It is known that patients with EoE have dysregulated commensal bacterial populations compared to healthy controls [183]. Additionally, the total bacterial load is increased in patients with EoE compared to healthy subjects [184]. With regards to specific bacteria, *Haemophilus* is present in a higher proportion in subjects with untreated EoE [184]. Together, these findings indicate that EoE is associated with commensal bacterial dysbiosis. Whether microbial dysbiosis is a marker of, or a contributor to, the inflammation observed in EoE is yet to be determined.

Conclusions

EoE is the result of a complex and coordinated inflammatory response to allergens in a patient’s environment. We have reviewed the most recent research in this field to provide an overview of what is currently known about the immunologic mechanisms underlying this condition. It is known that there are a number of genetic and epigenetic factors that predispose to the development of EoE. Additionally, gastric acid is clearly damaging to the esophageal mucosa and may predispose to inflammation and/or allergen exposure. Once the cycle of inflammation is established, it is likely that impaired mucosal integrity promotes further allergen exposure that may compound the degree of inflammation (Fig. 1). What is not well understood is where the initial antigen-APC-T cell interaction occurs (whether it be at the epithelium, within the underlying lamina propria, or in a more organized lymphoid structure) and how the inflammatory cycle is initiated. It will be important to elucidate these aspects of EoE pathogenesis as intervening upon them (for example, via intervention at the

point of the APC or upon innate cytokines such as TSLP that can influence adaptive responses) may provide for new preventative or therapeutic strategies.

Once the inflammatory cycle is initiated, several key cell types (including Th2, iNKT, and ILC2 cells) likely provide an important source of pro-inflammatory type 2 cytokines including IL-4, IL-5, and IL-13 (Fig. 2). Interactions between these cytokines and the esophageal epithelial cell is important for subsequent upregulation of additional cytokines, chemoattractants, and other molecules which recruit inflammatory effector cell types such as eosinophils, mast cells, and basophils. This inflammatory response disrupts normal epithelial integrity through down-regulation of cell adhesion molecules such as DSG1 and keratin and upregulates profibrotic molecules such as TGF-β, IL-1β, and TNF-α. Tregs may be important in trying to control this inflammation, but prolonged exposure to allergen can lead to the development of odynophagia, fibrosis, esophageal strictures, and in rare and extreme cases, esophageal rupture [1–5]. Given that the current therapeutic approaches available to clinicians and families have significant side effects, and at times cases of refractory EoE can occur, it is important that we continue to strive to develop new and innovative preventative and therapeutic strategies for this important and growing disease.

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Abbreviations

EoE	Eosinophilic esophagitis
Th	T helper cell
GERD	Gastroesophageal reflux disease
Ig	Immunoglobulin
CCL	C-C motif ligand
TGF-β	Transforming growth factor beta
TSLP	Thymic stromal lymphopoietin IL, Interleukin
DSG	Desmosomal cadherin desmoglein
miRNA	MicroRNA
STAT	Signal transducer and activator of transcription
CD	Cluster of differentiation
PARP	Poly(ADP-ribose) polymerase

TNF-α	Tumor necrosis factor alpha
PGD	Prostaglandin
CRTH2	Chemoattractant receptor expressed on Th2 cells
ILCs	Innate lymphoid cells
iNKTs	Invariant natural killer T cells
APC	Antigen-presenting cell
MHC	Major histocompatibility complex
HR	Histamine receptor

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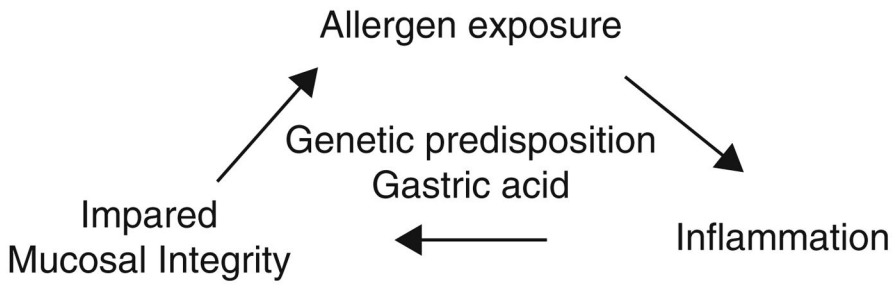

Fig. 1.
The inflammatory cycle of EoE

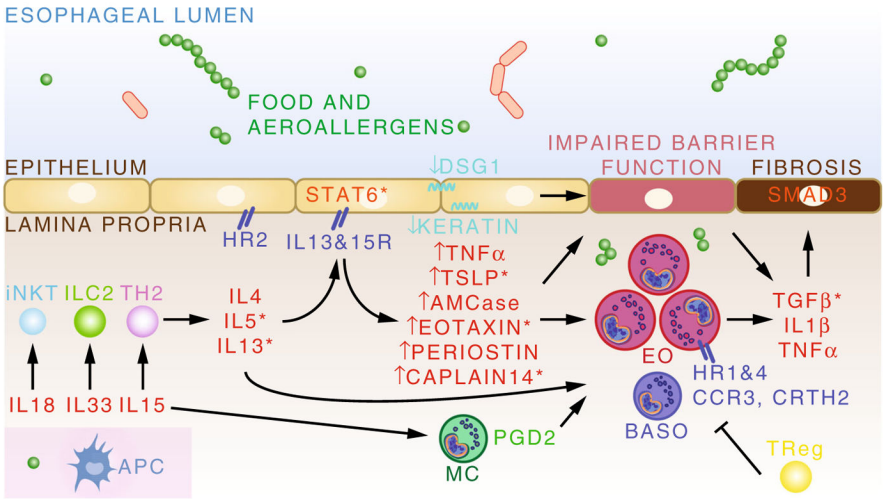

Fig. 2.

The inflammatory mechanisms of EoE. Allergen interaction with antigen-presenting cells (*APC*) leads to innate and adaptive lymphocyte responses and characteristic type 2 cytokine production. Signaling in the esophageal epithelial cells broadens the inflammatory response through production of effector and chemoattractant molecules which mediate recruitment and activation of eosinophils (*EO*), mast cells (*MC*), and basophils (*BASO*). Downregulation of cell adhesion molecules contributes to impaired mucosal integrity. Ultimately, persistent inflammation results in the development of esophageal fibrosis