HHS Public Access

Author manuscript

Curr Gastroenterol Rep. Author manuscript; available in PMC 2016 September 01.

Published in final edited form as:

Curr Gastroenterol Rep. 2015 September ; 17(9): 33. doi:10.1007/s11894-015-0458-9.

Do we know what causes eosinophilic esophagitis? A mechanistic update

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Abstract

The mechanisms underlying eosinophilic esophagitis (EoE) have been intensely investigated, and significant advances have been made in understanding the pathogenesis of EoE. EoE is defined as a chronic immune/antigen-mediated disease, characterized clinically by symptoms of esophageal dysfunction and histologically by an esophageal eosinophilic infiltrate. In this paper, we will review the current knowledge of EoE pathophysiology based on both animal and human data, and discuss possible etiologic mechanisms from the genetic and environmental perspectives. EoE is a Th2-predominant inflammatory process triggered by allergens. Proinflammatory cytokines and chemokines recruit eosinophils and other effector cells, such as mast cells, into the esophageal epithelium, where they cause direct damage and promote esophageal remodeling. The genetic expression profile of EoE has been described, and several single nucleotide polymorphisms have been identified and associated with EoE. While this genetic contribution is important, it is difficult to postulate that EoE is primarily a genetic disease. Given the rapid epidemiologic changes in the incidence and prevalence of EoE over the past two decades, environmental factors may be the driving force. While it is not known what causes EoE in an individual patient at a specific time, the current hypothesis is that there is a complex interaction between genetic factors and environmental exposures that remains to be elucidated.

Keywords

Eosinophilic esophagitis; pathogenesis; etiology; allergy; inflammation

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Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest

Thomas M. Runge declares no conflict of interest.

Evan S. Dellon reports research funding from Meritage Pharma, Receptos, and Regeneron; Consultant for Aptalis, Novartis, Receptos, Regeneron and Roche; Educational grant from Diagnovus, none of which pertain to this manuscript.

Introduction

Eosinophilic esophagitis (EoE) is a recently recognized disorder characterized by symptoms of esophageal dysfunction paired with esophageal eosinophilia that persists after acid suppression.[1–3] Depending on age, symptoms of EoE can include failure to thrive, abdominal or epigastric pain, difficulty feeding, heartburn, chest pain, dysphagia, or food impactions.[4] On esophageal biopsy, there is a brisk mucosal infiltration of eosinophils.[5] In contrast to the mucosa throughout the remainder of the GI tract where eosinophils are normally found, esophageal eosinophilia is always abnormal and merits evaluation.[6] Current guidelines require demonstration of at least 15 eosinophils per high-power field (eos/hpf) for diagnosis of EoE,[1, 3] but ultimately clinicians must rule out competing causes such as gastroesophageal reflux disease (GERD), proton pump inhibitor-responsive esophageal eosinophilia (PPI-REE), drugs, infection, autoimmune conditions, and primary hypereosinophilic syndromes to diagnose EoE.[4, 7]

EoE is a chronic disease, and has been reported in all ages.[1, 8–10] Males are affected 3 to 4 times more commonly than females, and EoE is also more common in whites compared to other ethnic groups.[1, 10–17] The prevalence of EoE has increased dramatically, according to multiple estimates.[18] In the general population, the rate of EoE is 0.5 to 1 case per 1000 individuals.[18–21] However, in those undergoing endoscopy for symptoms of dysphagia, the prevalence of EoE is considerably higher – as much as 12 to 23%[13, 22–24] – and in those presenting to an emergency room with food impaction, EoE is identified in at least 50%.[25–28] While the clinical presentation of EoE is now well-described, the rapid increase in both the incidence and prevalence of EoE is intriguing. While increased recognition of the disorder may be responsible for part of the increase,[18] in several studies the incidence rates outpace increases in endoscopy or biopsy rates.[11, 12, 29–31]

This rapidly evolving epidemiology raises the question of what causes EoE. Significant advances have been made in understanding the pathogenesis of EoE, which is felt to be an immune/allergen-mediated Th2 response.[32, 33] However the underlying etiology of EoE is still unknown. Given the rapid epidemiologic changes seen, environmental factors may be the driving force in those with a genetic predisposition. In this paper, we will review the current understanding of EoE pathogenesis based on both animal and human data, and discuss possible etiologic mechanisms from the genetic and environmental perspectives.

Insights from animal models

Animal models have been instrumental in studying the pathogenesis of EoE, and have largely pointed to allergen-mediated inflammation as a key cause of disease. Indeed, the first animal models were created by exposing mice to food or airborne antigens.[34–36] For example, repeated exposure to *Aspergillus fumigatus* caused eosinophilic inflammation of both the airway and esophagus in mouse models.[34] This experimental EoE phenotype can also be induced by directly delivering cytokines produced by Th2 lymphocytes,[35] or by epicutaneous antigen introduction followed by a single airway challenge with the same substance.[36] Thus, this work demonstrated that EoE could be driven by an abnormal response of Th2 lymphocytes to allergic stimuli.[7, 32, 37] Normally functioning T-cells are critical in the development of EoE. Mice without normal B-cell immunity develop EoE,

while mice without B-and T-cell immunity do not.[38] In mice, deletion of central downstream mediators in the Th2 allergic cascade, such as IL-4, IL-5, or IL-13, offers protection against development of experimental EoE.[35, 39] More recently, knowledge of this physiology has allowed development of a novel mouse model where overexpression of IL-5 in the esophageal squamous mucosa leads to an EoE phenotype.[40] Animal models are also helping to elucidate the role of other, non-eosinophil, inflammatory cells in the pathogenesis of EoE, including basophils and invariant natural killer T cells.[41, 42]

EoE and allergic diseases in humans

Experience with human subjects also suggests a strong role of allergy in the pathogenesis of EoE. Most studies show that 50–80% of patients with EoE, regardless of age, have comorbid allergic diseases including food allergies, allergic rhinitis or sinusitis, atopic dermatitis, and asthma.[8, 15, 30, 43–50]

Food antigens are thought to have a central role in EoE, by both initiating and sustaining esophageal eosinophilia.[51, 52] The first study that suggested a role of food in the etiology of EoE was in 1995 by Kelly et al, where all children who received a hypoallergenic elemental formula rapidly had partial or complete remission.[53] This observation was subsequently confirmed in larger studies in children, as well as in one in adults.[54–57] Other studies found that in individuals with EoE who have a food allergy detected by skin prick or atopy patch testing, withdrawal of trigger foods caused eosinophil counts to decline and symptoms to improve, while reintroduction of the food led to increased counts and worsened symptoms.[51, 52, 58–61] However, due to limitations in the predictive power of skin testing for food allergies causing EoE, the response to food-specific allergy testing does not always correlate with identified food triggers.[62, 63, 64] Likewise, response to dietary elimination therapy in EoE is not universal.[4, 61]

Aeroallergens have been shown to play a role in EoE as well, either trigging it directly or correlating with disease activity.[65, 66, 67] There have also been a number of studies showing seasonal variation of EoE diagnosis, with more cases diagnosed in summer or fall months, again suggesting a link with environmental allergies.[11, 12, 66, 68, 69] A potential mechanism of aeroallergen-induced EoE is deposition of pollen into the nares or oropharynx, followed by swallowing of allergen-containing secretions with presentation of the antigen in the esophagus and GI tract, a physiology similar to the oral allergy syndrome,[66] as well as to murine models of EoE, as noted above. However, identifying the specific allergen or original route or timing of sensitization is not always possible. Newer diagnostic techniques, including component-resolved diagnostics, have shown that cross-reactivity with plant allergens, and birch pollen in particular, may be the driver of some food-related sensitizations.[50, 70]

Despite the relationship between EoE and these allergic diseases, it does not appear that EoE is either a classic IgE-mediated immediate response or a delayed response.[71, 72] For example, mice deficient in IgE and B cells continue to manifest experimental EoE.[38, 42] Further, while an initial clinical experience suggested that omalizumab, a monoclonal antibodies against IgE might have utility for EoE treatment,[73] a recent placebo-controlled randomized trial by Clayton et al showed that it was not effective.[74] In an adjunct

investigation exploring these negative results further, however, the investigators found strikingly elevated levels of IgG4 in EoE patients compared to normal controls.[74] While this study could not conclude that an IgG4 mechanism is causal, this observation opens a new area of mechanistic investigation related to EoE pathogenesis and diagnosis.

Cells and cytokines involved in the inflammatory cascade in EoE

Regardless of whether an allergic response is induced by food or environmental allergens, the result is a cascade of Th2 inflammation leading to esophageal eosinophilia.[75, 76] Th2 cells express specific markers on their surface and secrete a characteristic combination of cytokines, including IL-4, IL-5, and IL-13.[77, 78] Levels of each of these cytokines have been shown to be elevated in patients with EoE.[33, 77, 79–82] IL-5 promotes proliferation and maturation of bone marrow eosinophils, readying them for activation by local cytokines.[39] IL-13 is thought to affect the epithelial barrier of the GI tract, increasing permeability to inflammatory cells such as eosinophils, basophils, and mast cells.[83, 84] In addition, through activity on periostin (an extracellular matrix protein), IL-13 promotes eosinophil accumulation into affected tissues.[85] Both IL-5 and IL-13 stimulate esophageal epithelial cells to produce eotaxin-3, a chemokine that recruits and activates eosinophils.[32] IL-4, which is also elevated in EoE, is known in other atopic diseases to cause T cells to differentiate into Th2 cells, and can also stimulate eotaxin-3 release.[86]

Targeting these cytokines for EoE therapies has yielded mixed results, but focusing therapeutics on these pathways may be promising. Anti-IL-5 therapies have been shown to reduce esophageal and peripheral eosinophilia but not significantly improve symptoms.[87–90] However, these agents also decreased levels of mast cells in those who responded to treatment, indicating additional study is warranted.[91] A pilot study of an anti-IL-13 monoclonal antibody found that it decreased eosinophil counts by 60%, while decreasing also production of eotaxin-3, periostin, and other mediators of allergic inflammation,[92] but further confirmation is required. Studies evaluating anti-IL-4 agents in asthma and atopic dermatitis have shown promise, and are planned in EoE.

The multiple cytokines and chemokines triggered by the Th2 immunologic cascade in EoE subsequently involve a number of effector cells. Eosinophils are the hallmark cell, and are recruited to the esophagus by eotaxin-3 as well as chemoattractant proteins such as CRTH2, ICAM-1, and CCR3.[93–95] Once in the esophagus, they are activated and release granule proteins as well as cytokines that facilitate and precipitate inflammation.[96–99] These granule proteins, including major basic protein, eosinophil-derived neurotoxin, eosinophil cationic protein, and eosinophil peroxidase, are directly cytotoxic.[97, 100, 101] These proteins also increase smooth muscle activity,[102, 103] insert pores into target cells,[104] and trigger degranulation of mast cells and basophils.[105] Moreover, eosinophils are involved in esophageal remodeling in EoE as a consequence of producing transforming growth factor-β (TGF-β). This results in epithelial proliferation, epithelial-mesenchymal transition, and deposition of collagen and fibrosis of the esophagus.[106–109]

In addition to eosinophils, there are other effector cells. In particular, mast cells have been implicated in EoE. The number of mast cells is increased in EoE compared to controls and to patients with GERD.[33, 82, 110, 111, 112–115] Mast cell-associated genes, including

carboxypeptidase A3, tryptase, and the histamine receptor, are upregulated in EoE,[114, 116] and mast cells also produce TGF-β, compounding the remodeling effects from the eosinophil as noted above.[103]

Recently, basophils have been linked to EoE pathogenesis. Eosinophils and basophils both arise from a common progenitor cell.[117] This cell of eosinophil/basophil lineage (Eo/B) is committed to the eosinophil pathway by expression of IL-5 in the bone marrow.[118] Patients with any atopic disease have higher levels of these Eo/B progenitor cells.[119] A recent study showed that both thymic stromal lymphopoietin (TSLP) and basophils were required to precipitate an allergen-induced EoE phenotype, and without basophils present, the disease improved.[42]

Invariant natural killer T (iNKT) cells are also thought to have a role in EoE pathogenesis. These are a subset of T-cells that respond to lipid antigens and coordinate downstream responses to allergic stimuli.[120, 121] At diagnosis, component markers of the iNKT cascade are significantly elevated in EoE patients, indicating a greater susceptibility to allergic stimuli.[122] As noted above, mice without critical components of the iNKT pathway do not develop EoE.[123]

As the resident cells of the esophagus, esophageal epithelial cells are not innocent bystanders in EoE pathogenesis. Barrier function, normally maintained by tight junctions, adherens junctions, and desmosomes,[124] is compromised in EoE, due to breakdown of these critical proteins.[37] In addition, subtypes of dendritic cells reside in the esophagus which can act as antigen presenting cells and link innate and adaptive immunity in the tissue.[82] Further, esophageal epithelial cells are the primary producers of eotaxin-3.[100]

The cascade of inflammatory cytokines and cells in the esophagus of EoE patients results in the clinical phenotype of EoE. Symptoms of dysphagia and food impaction, as well as structural changes of the esophagus noted on upper endoscopy such as esophageal strictures and narrowing, can be attributable to esophageal remodeling. In animal models, collagen and fibronectin deposition cause esophageal strictures, whereas mice without IL-5 have significantly fewer fibrotic changes.[125, 126] Similarly, IL-13 induces remodeling in mice, in an eosinophil-independent fashion.[127] In humans, eosinophils and mast cells in the esophagus produce TGF-β, a protein critical for wound healing and tissue repair.[106–109, 128] In normal healing tissue, this process is essential. However, in EoE, excessive tissue fibrosis from unbridled inflammation leads to fibrostenotic disease complications.[109, 129, 130] Further, a number of proteins unique to mast cells such as histamine, tryptase, and chymase cause contraction and hypertrophy of smooth muscle,[103, 109] which have a role in esophageal dysmotility and smooth muscle abnormalities that occur in EoE.[103, 109] These changes can be demonstrated clinically using a functional luminal imaging probe (FLIP).[131, 132] In EoE, esophageal compliance is significantly impaired in EoE patients compared to controls,[132] and improved compliance after treatment leads to fewer significant clinical events such as food impaction.[133]

New insights from genetic studies

Recently, there have been rapid advances in the understanding of the potential genetic contribution to EoE pathogenesis. Initial observations suggested that EoE (or clinical features of EoE) could run in families, with approximately 8% of parents of EoE patients being diagnosed themselves with EoE, and about 10% of patients with EoE having parents with esophageal strictures. Subsequent studies reported families with multiple individuals affected by EoE.[5, 134–137] One way to measure genetic risk is with the sibling risk ratio (λs) which compares the risk of developing a disease in a sibling versus the risk in the general population; λs>1 suggests an increased risk. The λs for asthma is approximately 2.[134] By comparison, the estimated sibling recurrence rate in EoE is approximately 80, indicating a potentially significant role of genetics in the disease.[116] This was investigated in more detail in a recent large study focusing on families with multiple EoE members and also on twins with EoE.[138] Here, the sex-adjusted rate of EoE in first degree relatives in the nuclear family cohort was 2.3%, with recurrence risk ratios ranging from 10 to 64, depending on the family relation. Interestingly, in the twin cohort, there was approximately 58% concordance in monozygotic twins compared to 36% in dizygotic twins, with a genetic heritability of 14.5%. This suggested that shared environmental context rather than shared genetics was responsible for the majority of the increased risk seen in relatives.[138]

In the context of this background of heritability, a number of studies have focused on looking at the specific genetic factors related to EoE. Blanchard and colleagues first elucidated this by reporting gene expression profiles of patients with EoE, compared to patients with GERD and healthy controls.[139] Using array techniques and measuring RNA expression, they characterized the EoE transcriptome, a set of several hundred differentially expressed genes (either up- or down-regulated). Moreover, pathway analysis showed that genes were clustered into categories such as cytokines, epithelial/barrier function, mast cell-related genes, and cell growth and differentiation. They also found that CCL26, the gene which encodes eotaxin-3, was the most up-regulated gene in EoE, and that there was a single nucleotide polymorphism (SNP) in this gene associated with EoE. This finding has now been replicated in multiple studies,[139–142] confirming the central role of eotaxin-3 in EoE. The EoE transcriptome has recently been updated and expanded using whole genome sequencing techniques.[143]

Transcriptome analysis also showed the importance of genes related to IL-13, which is increased by more than a factor of 15 in EoE patients compared to healthy individuals.[80] IL-13 stimulates the esophageal epithelium to produce eotaxin-3,[32, 80, 116, 139] and recruits other inflammatory cells including mast cells, lymphocytes, and eosinophils.[80] Additional genes of interest have also been identified, including filaggrin (FLG). Filaggrin is a barrier protein important in skin structure and function.[32, 78] IL-13 is known to downregulate filaggrin expression, which may affect the esophageal mucosa, causing abnormal antigen exposure to esophageal epithelial cells.[78] This dysregulation is associated with susceptibility to EoE.[83, 139]

Finally, genome-wide association studies (GWAS) have identified novel genetic loci in EoE. There three that have been published to date. In the first, Rothenberg and colleagues found a

SNP on chromosome 5q22 that codes for TSLP.[144] TSLP regulates allergic responses mediated by T-helper cells and has been implicated in other allergic diseases.[144, 145] As IL-13 has been shown to upregulate TSLP production, and IL-13 has been associated with EoE, TSLP may be the mediator of this response,[144] and may also be related to basophil function in EoE.[42] The more recent GWAS have identified additional novel loci, some of which are associated uniquely with EoE and some of which are associated with both EoE and other atopic diseases.[146, 147] Kottyan et al replicated the association with the 5q22 locus, and also found a locus spanning the CAPN14 gene, which is expressed in the esophagus but expressed with varying frequency in control and EoE subjects.[146] The role of CAPN14 in EoE has yet to be elucidated, but it may explain the esophageal specificity in EoE. Sleiman et al also replicated the association with TSLP and CAPN14, but identified c11orf30 and STAT6, which are involved in general allergic pathways, as well as ANKRD27, which is involved in melanocyte pathways.[147] This role of these genes in EoE has yet to be determined.

Environmental risk factors and EoE

While there is clearly a genetic contribution to the pathogenesis of EoE, as evidenced by the familial and genetic studies discussed above, it is difficult to postulate that EoE is primarily a genetic disease. The shifts in EoE epidemiology over the past two decades, with a steadily increasing incidence and prevalence, are too fast for a genetic cause and argue instead for an environmental etiology.[18] Correspondingly, and as already noted, data from a study of twins found that the environmental contribution far outweighed the genetic one.[138] While the true environmental “cause” of EoE has not yet been determined, and there may be multiple factors at play, there are a number of possibilities.

Aeroallergens could have a central role. Aeroallergens such as pollen have been linked with developing EoE in humans, and differential exposure to pollen early in life could play a role in EoE risk.[65–67] This relationship has also been defined in mouse models of disease.[34, 35] Pollen and aeroallergens could also explain varying rates of EoE diagnosis by season, with highest rates during times of high aeroallergens, such as summer or fall.[11, 12, 18, 68, 69, 148] These associations, however do not explain why EoE has become so frequently seen over the past two decades, but other environmental factors may have a role. One study showed that the prevalence of esophageal eosinophilia varied by climate zone, with cases more commonly identified in cold and dry climates.[149] This relationship has also been seen in other allergic and autoimmune disorders.[149] Esophageal eosinophilia was also found to be more common in rural areas than in urban zones.[150] This could be another link between aeroallergens, environmental factors, and EoE, but was counterintuitive given that studies in asthma and atopic dermatitis have found the opposite relationship. However, other studies in EoE have also found a rural predisposition.[151, 152] Again, this work does not point to a specific etiology, and identification of the initial trigger of EoE is often extremely difficult, but in some cases a substantial allergen exposure has been identified as the seminal clinical event in development of EoE.[65]

Food-based allergens can be thought of as a form of environmental exposure, and as discussed above, foods can cause EoE and allergen-free diets can improve EoE from a

clinical and histological standpoint.[47, 51–53] Less is known about why foods that have been tolerated by humans for thousands of years now trigger EoE. Multiple potential routes of sensitization combined with cross-reactivity of aeroallergens could explain some of the differences, as could differences in farming practices, genetic modification of foods, food packaging, and antibiotic or hormone use in food supplies, but further work into this area is warranted.[18, 153]

Other possible environmental shifts could also have a role in EoE pathogenesis. The rise in EoE diagnosis is temporally associated with a decline in *Helicobacter pylori* prevalence.[154] In a large study analyzing both esophageal and gastric biopsy specimens, esophageal eosinophilia was inversely related to the presence of *H. pylori.*[155] This relation has since been reported in other studies of EoE,[156–158] and the decreasing prevalence of *H.pylori* has also been associated with the increase of other atopic disorders.[18]

Even if environmental risk factors are responsible for a large fraction of a person's risk for EoE, changes to the genome and transcriptome of those with EoE may open the door for environmental allergens to have a more potent effect. Yamazaki et al found that after an initial sensitization with aeroallergens or food allergens, monocytes of patients with EoE undergo increased production of Il-13 and Il-5 compared to healthy people.[159] Finally, it is possible that a genetic predisposition interacts with environmental factors at an early age, setting the stage for subsequent development of EoE. In an initial study of early life exposures as risk factors for EoE, Jensen et al showed that antibiotic use during the first year of life was a strong risk factor for EoE.[160] In a different study, breastfeeding and penicillin allergies were also identified as early life factors that could potentially be associated with increased EoE risk.[138] These findings raise the question of the role of the human microbiome in EoE.

Conclusions

Tremendous advances have been made in recent years in understanding the pathogenesis of EoE. EoE is defined as an immune/allergen-mediated disease. Food and/or environmental allergen triggers stimulate a Th-2 inflammatory response, where multiple cytokines, including IL-5 and IL-13 stimulate the esophageal epithelium to produce eotaxin-3, recruiting eosinophils to the esophageal. The eosinophil is the key effector cell, causing direct cytoxic damage to the esophagus and disrupting mucosal barrier function, as well as releasing profibrotic mediators. Mast cells are also recognized to play an important role, particularly in synergy with eosinophils in promoting esophageal remodeling. Additional cell types have been recently recognized to be involved, including basophils and iNKT cells. This inflammatory milieu is associated with dysregulated gene expression, which can be largely reversed with successful treatment. Knowledge of these genetic changes, analysis of families in which multiple members have EoE, and performance of GWAS have led to the identification of SNPs that are associated with EoE, as well as novel loci and mechanisms to explore. This has also lead to the understanding of the importance of environmental factors in the development of EoE, though these are just beginning to be explored.

Do we know what causes EoE? The simple answer is no. We do not know why an individual patient develops EoE at a certain time. In the context of the rapidly evolving epidemiology of EoE, with increasing incidence and prevalence, the current hypothesis is that individuals with a genetic predisposition must have an appropriate environmental exposure. In some cases these might be food or aeroallergens. However, the complex interactions between allergic, genetic, and environmental pathways and exposures require additional investigation. Continued exploration of genetic changes that may predispose to allergic sensitization, and how genes and the immune system interact with changes in the modern environment will help further define the cause of EoE. Such work has the potential to yield both targets for future therapy as well as preventative measures that may reduce the risk of developing EoE.

Acknowledgments

Financial support: This research was supported, in part, by NIH awards T32DK007634 (TR), K23DK090073 (ESD), and R01DK101856 (ESD).

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