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Allergic Mechanisms in Eosinophilic Esophagitis

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Abstract

Paralleling the overall trend in allergic diseases, Eosinophilic Esophagitis is rapidly increasing in incidence. It is associated with food antigen-triggered, eosinophil-predominant inflammation and the pathogenic mechanisms have many similarities to other chronic atopic diseases, such as eczema and allergic asthma. Studies in animal models and from patients over the last 15 years have suggested that allergic sensitization leads to food-specific IgE and T-helper lymphocyte type 2 cells, both of which appear to contribute to the pathogenesis along with basophils, mast cells, and antigen-presenting cells. This review will outline our current understandings of the allergic mechanisms that drive eosinophilic esophagitis, drawing from clinical and translational studies in humans as well as experimental animal models.

Keywords

Eosinophilic Esophagitis; Allergic Mechanism; Atopic; Antigen Sensitization; Th2 Immunity; Pathogenesis

Introduction

Chronic tissue infiltration of eosinophils is the hallmark of allergic inflammatory diseases, which include asthma, atopic dermatitis, and eosinophilic gastrointestinal diseases (EGIDs). Eosinophilic esophagitis (EoE), a type of EGID, is characterized by eosinophil-predominant inflammation isolated to the esophagus, the only organ in the gastrointestinal tract that is homeostatically devoid of eosinophils. There is significant evidence of a role for allergic mechanisms as the driving force in EoE. The foundation for this understanding began almost 20 years ago, when Kelly *et al*. demonstrated that children with EoE resolved inflammation and clinical symptoms on amino acid-based diets.[1] EoE is strongly linked to atopic disease and most often occurs co-morbidly with asthma, eczema, allergic rhinitis, and anaphylactic

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food allergy, and a strong family history of such disorders is equally as common.[2, 3] The tissue inflammatory response in EoE is similar to other allergic inflammatory disorders and is characterized by a dysregulated immune response with both IgE-mediated and non-IgE-mediated T-helper cell type 2 (Th2) responses. Cross-sensitization to aeroallergens appears to be common and recent literature has begun to define antigen presentation, as well as the role of mast cells and basophils. This review will examine our understanding of the allergic mechanisms involved in the pathogenesis of EoE based on clinical and translational studies in humans as well as experimental models in genetically modified animals.

Body

Clinical Associations Of Eosinophilic Esophagitis With Allergic Diseases

Despite being frequently managed by gastroenterology specialists, there are several unique features of EoE that reflect the allergic nature of this disorder. During the last few decades, the prevalence of allergic diseases has been increasing at an incredible rate: in Westernized countries over a quarter of the population now has allergic eczema, allergic rhinitis, or food allergy.[4] Paralleling this trend, epidemiologic studies show an increase in the number of children and adults with EoE.[5, 6] In 2006, the prevalence of pediatric EoE in Australia was estimated to have increased 18-fold over the previous 10 years, while a US study reported a 35-fold increase over a similar time period.[7, 8] This increasing prevalence is supported by a rising incidence; population-based data from Olmsted County, MN, USA shows the incidence of EoE increased from 0.35 to 9.45 per 100,000 persons from 1991–1995 to 2001–2005.[9] Similarly, a population-based study of pediatric and adult EoE patients in Switzerland reported increased incidence from two to six per 100,000 persons over the period from 1989 to 2004,[10] while findings from the Netherlands demonstrated an increased incidence from 0.01 per 100,000 in 1996 to 1.31 per 100,000 in 2010.[5] This worldwide increase in EoE mirrors the trends in atopic diseases, although whether this is due to a true rise in disease incidence, increased disease recognition, or improved access to endoscopy remains unclear.[11]

Beyond these parallels in disease incidence, several clinical studies have demonstrated significant co-morbidity of EoE with other atopic diseases. While the prevalence of co-morbid atopic disease varies between these studies, perhaps due to regional population differences, they demonstrate that the majority (50–80%) of patients with EoE also have atopy and other allergic diseases, including rhinitis, asthma or eczema.[12] Interestingly, while these allergic diseases can commonly be seen to follow the “atopic march”, whereby early in life appearance of eczema and food allergy are observed and predispose for rhinitis and asthma several years later, EoE displays a profoundly broad age range of onset and so seems to not adhere with this established concept. However, the strong clinical links between EoE and other well-described allergic diseases seems to imply shared pathogenic mechanisms.

Hypersensitivity in Eosinophilic Esophagitis: Immediate or Delayed?

According to the NIAID-convened “Guidelines for the diagnosis and management of food allergy in the United States”,[13] food allergy was broadly defined as an abnormal immunologic hypersensitivity response to specific food proteins that leads to adverse

clinical reactions. Within this definition, EoE is clearly an example of food antigen-driven hypersensitivity. However, hypersensitivity reactions can be further classified based on the mechanisms of antigen recognition: IgE (immediate-type) or the T-cell receptor (delayed-type).

In immediate-type IgE-mediated hypersensitivity, typically associated with anaphylaxis or urticaria, cross-linking of IgE and its receptor by antigen leads to the rapid release of pre-formed mediators from mast cells and basophils. Histamine is a key molecule in this process and histamine receptors are important in regulating the physiological responses.[14] This early antigen-specific rapid response is followed by the subsequent *de novo* synthesis and release of lipid mediators, cytokines and chemokines that can drive a *late phase* response in some individuals, with infiltration of inflammatory cells, including eosinophils.

The majority of EoE patients have compelling evidence of IgE-mediated hypersensitivity to foods, as determined by elevated food-specific IgE or abnormal skin prick test (SPT), despite food-induced anaphylaxis only occurring in around 15% of these patients.[2, 15, 16] Mechanistically, it has been shown that IgE-bearing mast cells are increased in the esophageal mucosa of EoE patients, particularly those that are atopic.[17, 18] Thus, it may be that the immediate hypersensitivity response in EoE occurs in a localized fashion exclusively in the esophagus, similar to what is seen in oral allergy syndrome. While the involvement of IgE-mediated activation of mast cells in responses in the esophagus of EoE patients remains to be defined, the early phase reaction could enhance blood flow and muscle contractility via release of histamine,[19, 20] while the late phase reaction could contribute to the recruitment of eosinophils, similar to processes that have been noted in allergen-induced eosinophil recruitment in atopic dermatitis.[21]

While the role of IgE-mediated hypersensitivity remains somewhat unclear, non-IgE-mediated reactions are increasingly understood to participate in EoE. These delayed-type reactions, often referred to as T-cell mediated hypersensitivity, are characterized by the activation of antigen-specific T-cells and subsequent recruitment of inflammatory cells. Delayed-type hypersensitivity (DTH) associated with allergic inflammatory disease is classically characterized by a Th2-predominant immune response, with elevated IL-4, IL-5, and IL-13, along with eosinophilic inflammation.[22] In clinical diagnosis, patch testing, whereby antigen is applied to the skin so as to elicit a DTH-associated response, has been shown to significantly improve predictive values over SPT alone, highlighting the likely contribution of this arm of the immune response in EoE patient responses.[23] Interestingly, the IgE and T cell-mediated arms may intersect, since IgE has been shown to enhance DTH responses in mice.[24]

Allergic Sensitization

Dependent on IgE or T-cells?—The loss of tolerance and subsequent sensitization to antigen are critical events in the initiation of allergic conditions, involving coordinated involvement of antigen-presenting cells, T-cells, and B-cells, to prime the adaptive immune system for subsequent responses to antigen exposures. In particular, allergic sensitization associates with the generation of allergen-specific T helper type (Th)2 cells which proliferate and differentiate into antigen-specific effector and memory T-cells. In addition,

these Th2 cells play a critical role in B-cell production of allergen-specific IgE, through their ability to generate IL-4.

In EoE, allergic sensitization is clearly evident: regardless of atopic status, patients with EoE have increased density of B-cells and expression of IgE in the esophagus along with evidence of local class-switching.[25] Specific IgEs for foods that trigger active disease are commonly detected in EoE patients in the absence of anaphylaxis, although they may be present at low levels, perhaps reflecting local production.[26] Importantly, peripheral blood mononuclear cells from EoE patients exhibit allergen-specific cytokine responses that correlate with this elevation in specific IgE (although some patients have allergen-specific cytokine responses without elevated specific IgE, consistent with non-IgE mediated allergic sensitization).[27] In addition, mouse models of EoE-like disease, whereby sensitization is elicited via cutaneous or respiratory allergen exposure, show increased antigen-specific IgE, and a clear dependency on T-cells, but are still able to traffic eosinophils to the esophagus in the absence of either B cells or IgE.[28, 29] Thus, allergic sensitization in EoE drives the formation of allergen-specific IgE and T-cells, however they potentially exhibit, independent roles in the underlying disease pathogenesis.

Tolerance—In animal models, allergic sensitization commonly occurs to an antigen for which the animal is naïve; however, in EoE where the mean age at diagnosis is 33.5 years, it is interesting to note that sensitization often occurs to antigens already in the diet or environment that have been tolerated.[30] This suggests that loss of tolerance may be critical to facilitate the subsequent immune sensitization. A number of early life risk factors have been found for EoE, including antibiotic use in infancy, cesarean delivery, preterm birth, and lack of breast-feeding,[31] all of which have been suggested by other studies to alter the development of tolerance. One critical cell type that appears to play a role in the maintenance of tolerance is the regulatory T-cell (Treg), characterized by expression of Foxp3. In EoE, an imbalance between effector and regulatory T-cells was shown by Stuck *et al*., who found the proportion of $Foxp3^{+}CD3^{+}$ T-cells was 50% reduced in EoE compared to healthy controls.[32] Using an intranasal aeroallergen-induced murine model of EoE, Zhu *et al*. found a similar alteration in the frequency of $CD4^{+}$ T cell subsets in the esophagus of allergen-challenged mice compared with saline-challenged mice.[33] Not surprisingly, it was $FOXP3^{+}$ cells that were critically reduced among these cell populations. While these studies suggest there may be a relative lack of Treg-type T-cells at the site of inflammation, it remains to be determined whether this alteration in regulatory T-cells has simply a sustaining effect in EoE or whether Treg imbalances are critical to promoting allergic sensitization.

Route of Sensitization—An interesting question that remains in EoE is the site at which allergic sensitization occurs. To date, clinical studies of early life risk factors have not supported a specific route of sensitization in EoE. However, a variety of animal models of allergic disease have demonstrated that allergic sensitization can occur via the skin, airway, or gut.[28, 34, 35] Experimental animal models of EoE suggest that sensitization may not require esophageal allergen exposure. Akei *et al*. found that epicutaneous antigen sensitization in the form of repeated allergen administration to the shaved back of mice

followed by an intranasal allergen challenge, facilitated an EoE-like disease that was IL-5-dependent and, to a lesser extent, IL-4 and IL-13 dependent.[36] More recently, Noti *et al*. 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.[28] Sensitization also appears to be effective via the lungs as repeated exposure to aeroallergens via intranasal administration led to increase antigen-specific IgG1 and was sufficient to induce eosinophilic inflammation in the esophagus.[35] Interestingly, neither intragastric nor oral administration of aeroallergens was sufficient to induce EoE-like disease. It is likely therefore that antigen sensitization can occur at several sites including lung and skin and likely depends on a variety of host and environmental factors, but will require further studies to determine what is clinically relevant in EoE.

Aeroallergens—A significant number of EoE patients show evidence of polysensitization, not just to multiple foods but also to environmental aeroallergens.[37] While the functional role of allergic sensitization to aeroallergens is not entirely clear, there is evidence both in animal models and clinically that it may participate in driving elements of the EoE disease. Several studies have described seasonal variation in a subset of patients and in whom disease worsening occurred during pollen season regardless of therapy.[38, 39] It remains unclear whether swallowed aeroallergen directly promotes active disease or inhaled aeroallergen exacerbates concomitant airway disease, as could be interpreted from the murine studies with intranasal aeroallergen. Primary allergic sensitization to aeroallergens may also contribute to food sensitization as a result of cross-reactivity or cross-sensitization. Detection of this phenomenon has become possible with the use of protein microarrays, which allow for simultaneous assessment of specific IgE antibodies against multiple recombinant or purified natural allergen components, so-called component-resolved diagnostics. Using this technique, Simon *et al*. found IgE against food-specific allergen components were rare in Swiss EoE patients while cross-reactive responses were common.[40] They noted the dominant pattern of cross-reactivity was to profilins, pathogenesis-related (PR)-10 and lipid transfer proteins (LTP). These findings were validated by a group in the Netherlands who also found that the majority of food sensitizations in EoE patients are a result of cross-sensitization to PR-10 proteins present in birch pollen.[41] Interestingly these proteins can pass through the esophagus intact, but are degraded in the stomach, which could limit inflammation to the esophagus. Thus, sensitization to aeroallergens, which can occur via the skin or airway, may be a significant factor in the development of EoE and explain some of the co-morbidity with atopic disease.

Antigen Presentation in the Esophagus

Antigen presentation plays a crucial role in initiating a highly specific immune response to a foreign protein. Antigen presenting cells (APCs) engulf, process, and display peptides coupled to major histocompatibility complex (MHC) class II peptides on their cell membrane. Cell surface co-stimulatory molecules also help determine whether presented antigen provokes an immunogenic or tolerogenic T-lymphocyte response. In EoE, the mechanistic understanding of this process is quite limited, but it appears that both professional APCs such as dendritic cells (DCs) and non-professional APCs such as epithelial cells play a role.

The primary professional APC in the esophagus seems to be the Langerhans cell, a type of dendritic cell found in all squamous epithelia,[42] particularly the epidermis. Langerhans cells of the esophagus are structurally similar to those in the skin and are located along the papillae of the lamina propria and in the suprabasal region.[43] These myeloid DCs, identified by the surface marker CD1a, are increased in density in children with EoE as compared to controls and are reduced post-treatment.[44] However, there is contradictory data from a study in adults with EoE, which found no differences in CD1a density pre/post-treatment or with controls.[45] This may be due histopathologic variability or may represent a key etiologic difference between children and adults with EoE. Additionally, Langerhans cells of the upper GI tract express the high-affinity IgE receptor, FcεRI,[46] for which expression increases in active EoE.[47] IgE signaling on APCs has been proposed to enhance antigen uptake and enhance the development and activation of allergen-specific T-cells.[48] While the role of Langerhans cells in EoE is unclear, they are critical to the pathogenesis of atopic diseases such as eczema, and their close proximity to T-cells in the esophagus suggests a possible interaction and pathologic function.

Under pathological conditions, epithelial cells at mucosal surfaces act as nonprofessional APCs, and can regulate immune responses at the site of exposure. Antigen presentation by small bowel epithelium is well established and likely plays a role in food hypersensitivity.[49, 50] Mulder *et al*. found that basal epithelial cells in EoE biopsies express the MHC class II protein HLA-DR.[51] Using the human esophageal epithelial HET-1A cell line, which maintains characteristics of basal esophageal epithelium, they demonstrated the ability of these cells to engulf, process, and present antigen in an IFNγ-dependent manner, as well as stimulate T-helper cell activation. IFNγ, which is increased in biopsy tissue of EoE patients, enhanced expression of MHC class II, while IL-4 enhanced co-stimulatory molecule expression. Thus, while the esophageal epithelium is unlikely to play a role in the early initiation of an immune response, given the dependence on cytokine priming, it may potentially to play a role in perpetuating EoE-associated inflammation.

Interestingly, and rather controversially, recent literature has suggested that eosinophils may also function as APCs at the site of inflammation.[52] In asthmatics, eosinophils appear to express the MHC Class II protein, HLA-DR, dependent on stimulation by GM-CSF, as well as co-stimulatory molecules CD40, CD80, and CD86, and can traffic to regional lymph nodes after exposure to antigen bringing them in proximity to T-cells for presentation.[53, 54] Likewise in EoE, tissue eosinophils have been shown to express increased HLA-DR,[55] as well as CD40 and CD80,[56] supporting the potential capacity for antigen presentation. However, the evidence to support the ability of eosinophils to engulf and process protein antigens seems lacking and would limit their ability to function in similar ways to professional antigen presenting cells, such as DCs. One postulated mechanism, whereby MHC II loading occurs from exogenous peptides generated from the protease-rich milieu in EoE, remains to be fully established. Additionally, the nature of the interaction between T-cells and antigen-presenting eosinophils is not well understood; thus it is unclear the extent to which eosinophils act as APCs to initiate or even sustain the inflammatory process.

T-lymphocyte immune responses

Murine studies on mice lacking various components of the adaptive immune system have established a critical role for T-cells in EoE.[29] Similar to other atopic diseases, such as allergic asthma and eczema, tissue inflammation in EoE is characterized by a Th2-type inflammatory response. This was initially described by Straumann *et al*. in 2001, who observed increased T-cells and IgE^+ mast cells in esophageal biopsies of EoE patients associated with IL-5 expression in the infiltrating inflammatory cells.[57] Since that initial study, several reports have confirmed these findings and described elevated levels of IL-4 and IL-13 in biopsy samples.[25, 58, 59] Peripheral blood mononuclear cells from EoE patients also produce IL-5 and IL-13 in response to specific allergen stimulation,[27] and murine models of EoE have provided additional support that a Th2-mediated response is required for pathogenicity.[29, 36, 60] Blanchard *et al*. examined a large cohort of EoE patients and found enhanced expression of both IL-4 and IL-5 in atopic individuals with EoE compared to non-atopic.[61] In addition the study noted concerted expression of IL-5 and IL-13, suggesting a common cell type is responsible for their production.

While much of the focus has been on the Th2 cell in EoE, Th1-associated cytokines are also an important part of the inflammatory response, and likely play a critical role in pathogenesis. This includes TNF, which is expressed by esophageal epithelial cells,[57] and is involved in remodeling,[62] and IFNγ, which is expressed by T-cells following stimulation with IL-15,[63] and is involved in priming the epithelium for antigen presentation.[51]

IL-4—Critical to the initiation of a Th2 response, IL-4 promotes differentiation of naïve T-helper cells into Th2 cells as well as B-cell class-switching to produce IgE. While the initial source of IL-4 in atopic disease is not entirely clear, recent work has proposed that TSLP-elicited basophils may be important.[28, 64, 65] In the esophagus, IL-4 not only sustains the Th2 response, but also contributes directly to recruitment of eosinophils by stimulating eotaxin production in esophageal epithelial cells.[66] Th2 cells are considered to be an important source of IL-4 in EoE, which is enhanced by IL-15 stimulation.[63] Countering this concept, IL-4 expressions levels correlate poorly with the other Th2-associated cytokines, IL-5 or IL-13,[59] and suggest other cells may be relevant sources.

IL-5—Of the Th2 cytokines, IL-5 is the most well studied in EoE and appears to be central to the disease. In the GI tract, $IL\text{-}5^+$ allergen-specific T-cell responses differentiate EGIDs from IgE-mediated immediate hypersensitivity, characterized by $IL\text{-}5^-$ Th2 responses.[67] IL-5 is produced primarily by Th2 cells, although additional sources include mast cells and eosinophils. It acts on the bone marrow to stimulate eosinophil proliferation and differentiation and regulates survival and activation of eosinophils.[68] Mice lacking IL-5 fail to recruit eosinophils to the esophagus in intranasal aeroallergen-induced EoE, whereas mice transgenic for IL-5 under the control of the T-cell specific CD2 promoter (CD2-IL5) develop chronic esophageal eosinophila and mastocytosis.[69, 70] Trafficking of eosinophils by IL-5 likely occurs by priming of eosinophil responses to chemokines such as eotaxins (CCL11, CCL24 and CCL26), or by up-regulating homing receptors.[60] IL-5 also has a role in tissue remodeling, since mice with CD2-IL-5 mediated esophageal eosinophilia have increased collagen accumulation in the lamina propria and extended stromal papillae,

whereas IL-5 deficient mice do not in similar model studies.[60, 70] Although clinical and murine studies has shown a central role for IL-5 in the allergic mechanisms of EoE, and there is variable down-regulation of IL-5 expression following treatment with fluticasone,[71] anti-IL-5 biologic therapy has shown limited clinical efficacy,[72] suggesting that, while IL-5 plays an important role in EoE disease, blocking IL-5 may not be sufficient to prevent the immunopathology of EoE in humans.

IL-13—IL-13 is a pleotropic cytokine that exerts pathologic effects when excessively produced by activating local tissue inflammatory responses; its cellular sources include Th2 cells and activated eosinophils.[27, 57, 73] In EoE, active inflammation is self-perpetuating as infiltrating eosinophils secrete IL-13 which acts to enhance further recruitment of eosinophils to the esophagus by inducing STAT6-dependent eotaxin expression in the epithelium.[74–76] The critical interaction between IL-13 and the esophageal epithelium in driving EoE was highlighted by Blanchard *et al*. who found a significant overlap between the transcriptome of primary esophageal epithelial cells treated with IL-13 and total RNA from EoE patient biopsies, which was reversible with steroid therapy.[58] IL-13 also recruits eosinophils by promoting fibroblasts to produce periostin, which increases eosinophil adhesion to fibronectin.[77] Intra-tracheal IL-13 was sufficient to induce experimental EoE in mice in an eotaxin/IL-5/STAT-6 dependent manner,[74] but was not required, as intranasal aeroallergen-induced EoE had only mildly reduced esophageal eosinophilia in IL-13 deficient mice,[36, 78] which may be due to exaggerated Th17 responses.[79] IL-13 also plays key roles in barrier function, by downregulating genes involved in the epithelial cell differentiation, such as desmoglein-1, filaggrin, and involucrin,[76, 80] and eosinophil-independent tissue remodeling by promoting collagen deposition, angiogenesis, and epithelial hyperplasia.[81] IL-13 is a prominent T-cell mediator in EoE pathogenesis with broad function, and may be predicted as a likely factor that prevented efficacy from targeted IL-5 therapy. Ongoing clinical trials with anti-IL-13 will serve to better understand its role in pathogenesis and relevance as a therapeutic target.

B-lymphocytes and IgE

Formation of antigen-specific IgE is a principal effector function of Th2 cells, which promote class switching in B-cells by stimulation with IL-4. IgE can bind to its high affinity receptor, FcεRI, on the surface of mast cells and basophils, where subsequent engagement with polyvalent antigen triggers hypersensitivity responses as described above. This process is central to the pathogenesis of many atopic disorders including anaphylaxis, allergic bronchospasm, and urticaria. Additionally, there are a number of antigen-independent immune functions of IgE, which include enhancement of mast cell survival, maintenance of mast cell location, and dendritic cell migration.[82] Clinical studies have documented the presence of allergen-specific IgE in patients with EoE, and skin prick testing (SPT) is commonly abnormal, providing evidence of immediate hypersensitivity to a variety of foods, and specific IgE has been suggested to contribute to symptoms.[40] Interestingly, a clinical study of omalizumab, a monoclonal antibody directed against IgE, in the treatment of EoE, found clinical but not histologic or endoscopic improvement.[83] This may have pathogenic implications, as it suggests that some acute symptoms in EoE may be associated with IgE-mediated activation of mast cells or basophils.[18] However, many patients have no

evidence of food-specific IgE, nor abnormal SPT, and as described previously, experimental studies in mice have demonstrated that eosinophil recruitment is IgE-independent, indicating a critical need for more translational and murine studies to fully understand the contribution of IgE to disease pathogenesis.

Eosinophils

Both acute and chronic allergic reactions are associated with tissue eosinophilia. Antigen-driven recruitment of eosinophils occurs through critical mediators like IL-5 and the eotaxin family of chemokines, as well as lipid mediators like prostaglandin D2 (PGD2). At the site of inflammation, eosinophils become activated where they modulate immune responses and can damage the surrounding tissue.[84] Activation promotes secretion of various mediators that have been linked to EoE, including cytokines such as IL-4, IL-5, IL-13, and transforming growth factor (TGF)-β, chemokines such as CCL5/RANTES and CCL11/eotaxin-1, and lipid mediators such as leukotriene C_4.[59, 85] These molecules have profound effects on the inflammatory response that include upregulation of adhesion molecules, enhanced cellular trafficking and activation, and regulation of vascular permeability and muscle contraction. In addition, eosinophils secrete toxic granule protein that damage gut epithelium, including eosinophil peroxidase, eosinophil cationic protein, eosinophil-derived neurotoxin, and major basic protein, all of which have been shown to be increased in EoE tissues.[86]

The regulation over eosinophil recruitment to the esophagus seems similar to other atopic inflammatory diseases and largely associated with the chemotactic effects of the eotaxin proteins, which are critical for maintenance of tissue eosinophilia. In EoE, eotaxin-3 (CCL26) was shown to be the most highly expressed gene in the esophagus, and expression levels strongly correlated with disease severity.[87] Eotaxin-deficient mice have been described as having markedly impaired esophageal eosinophilia,[88] even when overexpression of IL-5 is genetically introduced.[60] Interestingly, the relative increase in esophageal eosinophils in these IL-5 transgenic/eotaxin-deficient mice, when compared to control mice, suggest that additional chemotactic factors participate. This may include histamine, generated from mast cells or basophils, as thioperamide, a non-selective blocker of the histamine 3- and 4-receptor, inhibited eosinophil infiltration to the esophagus in an allergen-inhalation model of EoE in guinea pigs.[89] In addition PGD2, a prostanoid largely produced by mast cells, is sufficient to drive eosinophils to the esophagus since injection of a PGD2 agonist into the esophagus led to rapid recruitment of eosinophils in guinea pigs, and pretreatment with a selective antagonist limited this experimental EoE-like disease.[90] Also, in adults with corticosteroid-resistant EoE, treatment for 8 weeks with OC000459, a selective antagonist of CRTH2, the receptor for PGD2, led to reduced tissue eosinophilia and clinical symptoms.[91]

The eosinophil is critical to many aspects of the histopathology of EoE. Mice deficient in the eosinophil lineage have a significant reduction in basal layer and lamina propria collagen thickness and fail to develop esophageal strictures as detected by barium esophagram.[69, 70] Notably, these mice still maintain evidence of esophageal motility dysfunction, suggesting that this aspect of the disease is eosinophil-independent.[69] In oral ovalbumin-induced EoE in

mice, antibody targeting of Siglec-F, the mouse homolog of Siglec-8, which is highly expressed on eosinophils, and which mediates their apoptosis and clearance, reduced esophageal eosinophilia associated with reduced angiogenesis, basal zone hyperplasia, and fibronectin deposition.[92] These studies implicate the eosinophil as a critical damage-inducing mediator of EoE.

Mast cells

Despite being derived from the same $CD34^+$ progenitor cell type as eosinophils, mast cells are normally resident in the mucosa and submucosa of the esophagus. Their best-characterized function involves crosslinking of IgE, which binds to the high-affinity receptor, FcεRI, and becomes activated after engagement with antigen. Similar to eosinophils, mast cells store and produce an abundant number of inflammatory mediators that might participate in the pathogenesis of EoE. This includes TGF-β1, Th2 cytokines IL-4, IL-5, and IL-13, as well as eotaxins, histamine, leukotrienes, lipid mediators, and proteases, which can collectively contribute to fibrosis, tissue inflammation and/or recruitment and activation of eosinophils.[93]

Mast cells are considered to be a major player in allergic disease, although the exact nature of their role EoE pathogenesis remains unclear. Numerous studies have observed an increase in mast cell density in biopsies from EoE patients,[18, 57, 87] and this correlates with both eosinophil density and basal zone hyperplasia and is responsive to swallowed steroids.[45] Mast cells activation occurs locally in EoE, as ultrastructural changes in cytoplasmic granules are detectable by electron microscopy,[18] and genes such as carboxypeptidase A3, tryptase and histamine decarboxylase are elevated in esophageal tissue, and normalize with therapy.[94] In the smooth muscle of patients with EoE, mast cell numbers are increased and express TGF-β1, which is capable of enhancing muscle contraction, suggesting a potential role in symptoms.[85] Atopic EoE patients can be distinguished from non-atopic patients by the presence of IgE on esophageal mast cells, suggesting mast cell activation may occur by alternate mechanisms in non-atopic patients.[17]

Mechanistically, the role of mast cells in EoE has been studied in mice and, similar to humans, there is an increase in density paralleling the increase in eosinophils.[69, 78, 88, 95, 96] In the intranasal aeroallergen-induced model of EoE, the increase in esophageal mast cells was time- and challenge-dependent. While mast cell-deficient mice had reduced muscle cell hyperplasia and hypertrophy in this model, consistent with a role in remodeling, interestingly there was no effect on eosinophil recruitment.[96] Likewise, eosinophils are not required to recruit mast cells to the esophagus, but IL-5 seems to participate in recruiting mast cells, as CD2-IL5 transgenic/eosinophil-deficient mice had similar elevations esophageal mast cell density as controls.[69] This was supported clinically by sub-analysis of a trial of mepolizumab in children, which also found reduced esophageal mast cells in treated patients.[97] Thus it appears that mast cells have a multifunctional role in EoE, contributing to symptoms, remodeling, and tissue inflammation.

Basophils

Despite an abundance of work defining the role of basophils in allergic inflammation, there have been limited studies investigating their pathogenic function in EoE. Recently, their potential involvement was demonstrated using a novel murine model of EoE, whereby mice are sensitized to food antigen via the skin and EoE-like disease is initiated by repeated oral challenge with antigen.[28] In this model, antigen-specific IgE is detectable, but the mice develop EoE-like inflammation that is IgE-independent. Instead, the authors show that EoE responses were associated with a significant expansion of basophils, driven by exposure to epithelial-derived TSLP, along with a Th2 response that was dominated by IL-4. They establish that depletion of basophils or deficiency of TLSP signaling resulted in loss of responses and included translational studies also demonstrating increased TSLP and basophils in EoE patient biopsies. This new model provides unique insight into the mechanism by which IgE-independent allergic sensitization to antigen can facilitate eosinophil recruitment to the esophagus driven by basophils.

Summary

Eosinophilic esophagitis is a chronic inflammatory disease isolated to the esophagus that impacts both children and adults. Animal models as well as studies in patients have helped to uncover various aspects of its pathogenesis, although many questions remain. EoE appears to share a significant clinical link with other atopic diseases and there is strong evidence that it is caused by immune dysregulation secondary to allergic sensitization to dietary and/or aeroallergens. While the role of IgE remains unclear, EoE is dominated by T-lymphocyte mediated pathology with significant participation from mast cells, basophils, epithelial cells, and dendritic cells, summarized in Figure 1. What remains poorly understood is how the disease develops and while there is some literature to suggest a role for loss of tolerance, further translational research is necessary to better characterize this aspect of the disease. As the complex immune mechanisms that govern EoE are uncovered, novel diagnostic and treatment options will move from bench to bedside.

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Key Points

1. Eosinophilic esophagitis shares a clinical link with other atopic diseases and is caused by immune dysregulation secondary to allergic sensitization to dietary and/or aeroallergens.
2. Allergic sensitization, which may occur via multiple routes, drives the formation of allergen-specific IgE and T-cells that appear to participate in the esophageal hypersensitivity response.
3. Loss of tolerance is likely critical to pathogenesis, and may be secondary to regulatory T-cell imbalance.
4. Eosinophilic esophagitis is dominated by T-helper lymphocyte type 2-mediated eosinophil-predominant inflammation with key contributions from mast cells, basophils, epithelial cells, and dendritic cells.

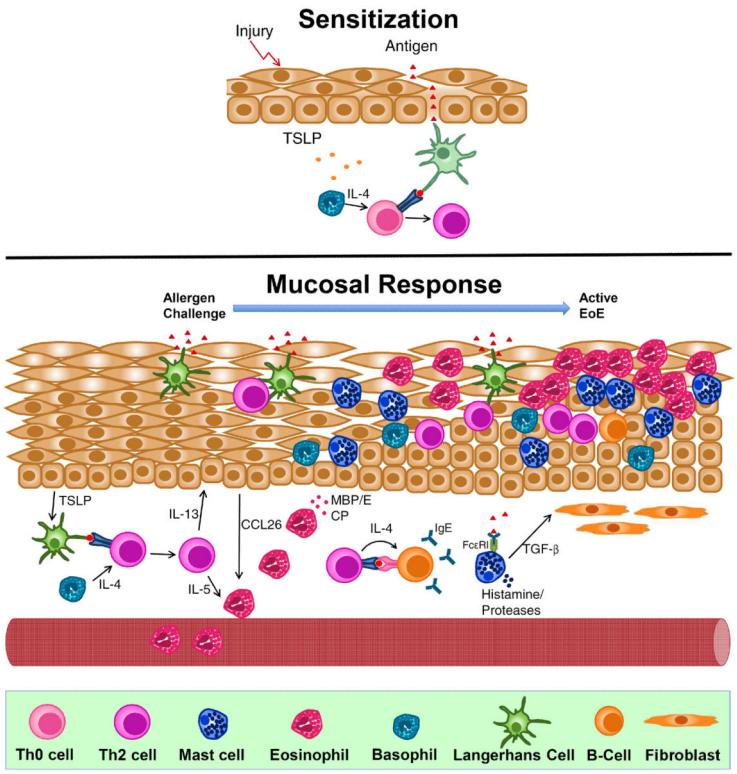

Fig 1.

Proposed allergic mechanisms involved in the pathogenesis of Eosinophilic Esophagitis (EoE). TOP: Proposed mechanism of allergic sensitization in EoE. In the presence of epithelial injury, TSLP production is elicited from epithelium. This primes basophils to produce IL-4 which promotes allergic sensitization after antigen presentation to a naïve T-cell which generates antigen-specific Th2 cells. BOTTOM: Proposed mucosal response in EoE. Subsequet antigen challenge leads to recruitment and expansion of Th2 cells which secrete IL-5 and IL-13, both critical in the recruitment of eosinophils and remodeling of the esophagus. Th2 cells locally promote class-switching of B-cells to produce antigen-specific IgE, which binds to the surface of mast cells. Activation of mast cells leads to the releast of pro-inflammatory mediators such as TGF-β, which promotes remodeling and enhances muscle cell contractility.