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Allergic Mechanisms of Eosinophilic Oesophagitis

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Abstract

Eosinophilic oesophagitis (EoE) is characterized by oesophageal dysfunction and oesophageal eosinophilia refractory to proton-pump-inhibitor treatment. EoE is a food allergy, as elimination of food trigger(s) abrogates the disease, while trigger(s) reintroduction causes recurrence. The allergic mechanism of EoE involves both IgE and non-IgE processes. There is a break in oral tolerance, the immune mechanism allowing enteric exposure to food and micro-organisms without causing deleterious immune responses. Changes in life-style, alterations in gut flora and use of antibiotics may be increasing disease prevalence. Mouse models of EoE and human studies revealed the role of regulatory T-cells and iNKT-cells in the pathogenesis. Th2-cytokines like IL-4, IL-5 and IL-13, and other cytokines like TGFβ and TSLP are involved. Perhaps no one cytokine is critically important for driving the disease. Control of EoE may require a pharmaceutical approach that blocks more than one target in the Th2-inflammatory pathway.

Keywords

eosinophilic oesophagitis; allergic mechanism; antigen sensitization; oral tolerance; pathogenesis; t-helper lymphocyte type 2 immunity; food allergy; barrier dysfunction

Introduction

The concept of eosinophilic oesophagitis (EoE) as a food allergy seems foreign to many patients, and even physicians, since EoE does not exhibit the typical symptoms associated with allergic reactions, like hives, swelling, pruritus, wheezing or anaphylaxis. Instead, it causes symptoms of oesophageal dysfunction such as dysphagia, food impaction, vomiting and pain. The National Institute of Allergy and Infectious Disease expert panel defines food allergy as “an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food” [1]. According to this definition, EoE is unambiguously a food allergy because elimination of the food trigger abrogates the disease, while reintroduction causes disease recurrence [2,3]. Histologically, EoE is characterized by

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significant oesophageal eosinophilia (>15 eos/HPF) refractory to treatment with proton-pump-inhibitors (PPIs) [4].

Oesophageal eosinophilia was first described by Dobbins and colleagues in 1977 in a patient with concurrent eosinophilic gastroenteritis and a normal pH study [5]. Landres and co-workers, in 1978, reported the first case of eosinophilic infiltration isolated to the oesophagus with associated oesophageal dysfunction [6]. The absence of acid reflux, based on a negative pH study, suggested factors other than gastroesophageal reflux disease (GERD) were operative. Two case series, published in 1982 and 1985, concluded GERD was the underlying cause of EoE [7,8].

This paradigm of oesophageal eosinophilia as a result of GERD shifted in 1993 when Attwood and colleagues retrospectively compared patients with oesophageal eosinophilia who had normal and abnormal 24-hour pH studies [9]. They concluded that patients with significant oesophageal eosinophilia, dysphagia, and a normal pH study represented a distinct clinical group caused by factors other than GERD. This non-GERD trigger of oesophageal eosinophilia remained unknown until Kelly and colleagues, in 1995, published convincing evidence that food proteins caused the disease [2]. They showed elimination of food proteins from the diet by administrating amino-acid based elemental diets significantly reduced PPI-refractory oesophageal eosinophilia and improved clinical symptoms. Moreover, re-introduction of the food proteins caused recurrence of the symptoms. Markowitz and colleagues replicated these observations in 2003 with a larger cohort [10]. Recent clinical trials with empirical elimination diet [11] and skin testing-directed elimination diet [3] further support EoE as a food allergen-driven disease. Although there is overwhelming evidence that food allergens drive EoE, not all patients achieve histological and/or symptomatic remission with elimination diets. This discrepancy may result from non-compliance to treatment or other allergic triggers (e.g. aeroallergens).

This review discusses our current understanding of the allergic mechanism involved in EoE. Also delineated are potential therapeutic targets and opportunities for future research.

IgE or non-IgE mediated?

Food allergy is classified based on the mechanism of antigen recognition: IgE-mediated (immediate type) or non-IgE-mediated (delayed type). Food allergy is usually caused by IgE-mediated reactions. IgE-mediated food allergy is characterized by a reproducible, rapid onset of symptoms after ingesting the offending food. The classic example is the immediate development of hives, swelling, and wheezing after consuming peanuts in an individual with IgE-mediated peanut allergy. To trigger an IgE-mediated food allergic reaction, an individual must first be exposed to the food antigen and become *sensitized* by producing antigen-specific IgE antibodies. During sensitization, activated antigen-presenting cells (APCs) prime the native T-cells to differentiate into Th2-cells, which provide signals necessary to induce B-cell class-switching to generate IgE. These antigen-specific IgE molecules attach to the surface of mast cells. Upon re-exposure to the offending substance, the allergen crosslinks the IgE molecules on the mast cells causing rapid release of their preformed inflammatory mediators. This response is followed by subsequent *de novo* synthesis and

release of lipid mediators, cytokines and chemokines that orchestrate a late phase immune response in which inflammatory cells such as eosinophils infiltrate tissue.

Although EoE patients do not exhibit the typical IgE-mediated food allergic reactions; their oesophageal lining, and only their oesophageal lining, acquires the characteristic elements of an IgE-mediated response such as dendritic cells (DCs), antigen-specific IgE, class-switched B-cells [12], tryptase-positive mast cells [13] and Th2-cytokines [14,15]. Yet serum levels of allergen-specific IgE and the results from skin prick testing (SPT) correlate poorly with the food trigger(s). Furthermore, systemic blockage of IgE-antibodies fails to eradicate oesophageal eosinophilia both in murine models [16] and in human clinical trials [4]. IgE-deficient (Igh-$7^{-/-}$) and B-cell deficient mice develop experimental EoE [16,17], suggesting IgE may not be required to induce or maintain EoE. Collectively, these observations from human and mice studies suggest there are other non-IgE-mediated pathways important in the EoE pathogenesis. This is consistent with the categorization of EoE as a mixed IgE- and non-IgE-mediated food allergy in the recent guidelines [1].

Oral tolerance

We encounter millions of foreign antigens through our skin, gastrointestinal and respiratory tract. One of the key functions of our immune system is to distinguish pathogenic from non-pathogenic foreign antigens allowing an appropriate response. We do not develop allergic reactions to foods that we consume under normal circumstances because our immune system is tolerant to these foreign, but non-pathogenic food antigens. This is called oral tolerance [18].

Food allergy results from loss of oral tolerance. Clinical studies point towards antibiotic use during infancy, caesarean delivery, pre-term birth and lack of breast-feeding as early-life risk factors predisposing people to EoE [19]. Early-life exposures help shape our microbiome, which plays a critical role in development of oral tolerance [20,21].

$Foxp3^{+}$ regulatory T-cells (Tregs) help maintain oral tolerance [22,23]. They regulate the pro-inflammatory pathway and maintain immune homeostasis. EoE patients have fewer Tregs in their oesophageal tissue compared to healthy controls, and corticosteroid treatment does not correct this deficiency [24]. This imbalance between Tregs and effector T-cells may be partially responsible for breaking oral tolerance in susceptible individuals. How to restore oral tolerance is an area of active research.

Sensitization

Antigen sensitization is a prerequisite for breaking oral tolerance. Various murine models of EoE show allergic sensitization can occur via the airway [25], skin [16,26] or gastrointestinal tract [27,28]. The route of allergic sensitization in human EoE is largely unknown, but clinical observations provided some insight. Multiple reports describe new-onset EoE in paediatric and adult patients undergoing oral immunotherapy (OIT) for IgE-mediated food allergies [29]. During OIT, increasing doses of food antigens are reintroduced to restore oral tolerance. These patients have IgE-mediated food allergy, but do not have EoE prior to starting OIT. While undergoing desensitization, they become susceptible to EoE.

This observation suggests that allergic sensitization for EoE can occur orally, and that mechanisms of antigen sensitization in EoE may differ from that of IgE-mediated food allergy.

Other studies suggest that sensitization to food allergens in EoE results from aeroallergen inhalation [30]. While airway and skin are routes of sensitization to trigger experimental EoE in mice [16,25,26], there is limited human data supporting this hypothesis. Yet, the majority of EoE patients have respiratory allergies [4]. It is proposed that food allergen sensitization in EoE patients mostly results from cross-reactivity to birch pollens via PR-10 proteins (based on component-resolved diagnostics from a preliminary human study) [30].

Epithelial production of IL-33 and thymic stromal lymphopoietin (TSLP) have become key areas of interest in allergic sensitization [22]. TSLP is a key cytokine in antigen sensitization that promotes Th2-cell development [16]. Genetic studies link EoE susceptibility to TSLP variants [31,32], and an *ex-vivo* study showed TSLP enhances the basophil response in oesophageal biopsies of human subjects with EoE [16]. Furthermore, TSLP is necessary for development of EoE in mice, which can be prevented with antibody-mediated TSLP neutralization [16].

Genomic studies are elucidating critical mechanisms of allergic sensitization in EoE. A large genome-wide association study (GWAS) correlated EoE susceptibility to 9 of the 22 antigen sensitization loci [32]. However, how these specific genes are involved in antigen sensitization in EoE has yet to be explored.

Sensitization may be facilitated by dysfunction in tight junctions that allow antigen penetration via the epithelial barrier [33]. EoE patients have reduced expression of desmosomal cadherin desmoglein-1 (DSG-1) in oesophageal tissues [34]. Reduction of DSG-1 weakens the oesophageal epithelial integrity and barrier function, potentiating allergic sensitization [35]. This in turn drives a Th2-response producing IL-13, which strongly down-regulates the expression of DSG-1 and propagates the local inflammatory process (figure 1).

Although the exact mechanism by which antigens are sensitized to cause EoE is unknown; genetic, epidemiologic, translational, human and animal studies are shedding light on this complicated process.

Lessons from human oesophageal biopsies

Assessment of treatment response is heavily dependent on histological evaluation of oesophagus biopsies. Patients treated with an elimination diet undergo multiple endoscopies and biopsies to identify the food(s) triggering the disease. These biopsies are taken during both disease and remission states, providing researchers the opportunity to study the allergic mechanism at tissue level.

From histological analysis of these biopsies, researchers have learned that active EoE displays a prominent eosinophilic infiltration with increased density of mast cells, basophils and lymphocytes [36]. Immunohistochemistry and/or immunofluorescence analysis further

characterized these cells, which include tryptase- and TGF-β1-positive mast cells [37], $CD8^+$ T-cells [38], $IgG4^+$ plasma cells [39] and $V\alpha24J\alpha18^+$ T-cells (a cell marker for invariant natural killer T (iNKT)-cells) [40].

However, histological analysis provides no information on cell function at the site of inflammation. Using unbiased whole-genome-wide transcript expression profile analysis of oesophageal tissues with Affymetric DNA chip, Blanchard et al uncovered 574 genes uniquely expressed in EoE [13]. The gene encoding eotaxin-3 was most highly induced. This landmark study provided a framework for investigation of inflammatory pathways critical for driving EoE. Yet, these results did not reveal the whole story, since genome-wide expression chips have modest sensitivity and cannot detect expression of potentially critical immunological cytokines produced at low levels. For example, IL-13 was not part of the initial EoE transcriptome identified by Affymetrix DNA microarray analysis. In subsequent years, higher resolution mRNA analysis techniques uncovered additional transcripts. Using human inflammatory cytokine and receptor PCR array, IL-13 and IL-5 were found to be markedly up-regulated [14]. Another key set of mRNAs, not identified by the Affymetrix DNA chip, is associated with the iNKT pathway [41]. Oesophageal tissue from patients with EoE display heightened expression of chemokine ligand 16 (CXCL16), iNKT-cell-associated cell marker Vα24, and CD1d compared to healthy control oesophageal tissue. This up-regulated gene expression was more pronounced in patients aged <6 years at diagnosis and correlated with the expression of eotaxins and periostin.

In 2010, a GWAS based on 181 patients with EoE and 1,974 controls identified an EoE susceptibility locus at 5q22, which is a gene region encoding TSLP. The association of TLSP to EoE was confirmed in 2014 with a larger cohort GWAS [32]. This GWAS also identified another EoE susceptibility locus at 2p23, encoding CAPN14, which is significantly more expressed in the oesophagus. However, the role of CAPN14 in EoE is unknown [40].

Micro-RNAs (miRNAs) are regulators of mRNA expression and translation. The first miRNA profile in EoE was reported in 2012 [42]. Lu et al found that EoE was associated with 32 regulated miRNAs and was distinguished from non-eosinophilic forms of oesophagitis. The exact functions of these regulated miRNAs also remain unknown.

Lessons from animal models

In 2001, Mishra et al developed the first murine model of EoE [25]. Mice were challenged intranasally with *Aspergillus fumigatus* and they developed the characteristic features of EoE. Rayapudi et al demonstrated indoor insect allergens could induce experimental EoE [43]. These studies raised awareness that aeroallergens may have an etiological role in EoE.

Several immune cell types and cytokines are proved important for expression of EoE in murine models. Using lymphocyte-deficient mice, Mishra et al found that T-cells, but not B-cells, are required for the development of experimental EoE [17]. By analysing mice overexpressing IL-5, either by genetic manipulation or by IL-5 administration, researchers established the central role of IL-5 in trafficking eosinophils to the oesophagus [44]. Intra-

tracheal administration of IL-13 was shown to be sufficient to induce experimental EoE in a STAT6-dependent pathway [45]. Noti et al developed an IgE-independent murine model and showed that TSLP-regulated basophils contributed to the pathogenesis of experimental EoE [16]. In a food allergen sensitization model, Rajavelu et al found eotaxins and iNKT-cells were important for EoE development. Taken together, these mice studies have elucidated the potential routes of antigen sensitization (oral, respiratory and cutaneous), the role of different lymphocyte subsets and the importance of Th2 adaptive immunity in driving EoE. Key mouse models and their findings are summarized in table 1.

Putting the Puzzle Together

Based on the findings in human and mice, we can postulate on the allergic mechanism involved in EoE (see figure 2).

Several mechanisms have been proposed to tip the balance from tolerance to sensitization. One of them is impaired barrier function as EoE patients have barrier dysfunction of their oesophagus. This is supported by (i) histological findings of dilated intercellular spaces [46], (ii) increased oesophageal permeability [34] and (iii) decreased DSG-1 expression [47]. DSG-1 is important in maintaining barrier integrity. However, barrier disruption alone is not sufficient to induce EoE, as most patients with disorders of barrier disruption, such as inflammatory bowel disease and psoriasis, do not have higher than expected incidence of food allergy. Tregs, tolergenic DCs and IL-10 producing macrophages provide additional protection [22]. Several lines of evidence suggested that disturbance in the microbial flora (associated with early risk factors such as C-section and early antibiotic use) can impair normal development of this regulatory mechanism, leading to loss of oral tolerance [19–21]. Th2 propensity in susceptible individuals also contributes to tipping the balance from tolerance to sensitization. Th2-cytokine expression is markedly elevated in EoE [14].

Milk, wheat and eggs are the most common food triggers of EoE [48]. We do not know why these foods are more apt to trigger EoE than others, though there is evidence that certain foods process intrinsic immunological properties that can directly induce innate immune responses. For example, milk sphingomyelin can activate iNKT promoting Th2-response [49], and peanut allergen Ara h1 can directly bind to CD209 on DCs [50]. Given the limited number of foods that can trigger EoE, it is proposed there are certain intrinsic immunological properties of these food proteins that can confer allergenicity, although this remains controversial [51]. Taken together, the intrinsic properties of certain food proteins, barrier dysfunction, Th2 propensity and composition of microbiota influenced by early life events predisposing to dysregulation of the regulatory circuit, all contribute to sensitization.

APCs engulf, process and present peptides coupled to MHC class II molecules on their surface. APCs are classified into “professional” and “atypical” [52]. The professional APCs in the oesophagus are DCs, which are considered the most important APCs in EoE. DC levels are increased in the oesophagus of children with EoE compared to healthy controls [53]. Professional APCs constitutively express MHC class II structural proteins and antigen-processing machinery. By contrast, atypical APCs such as epithelial cells and eosinophils do not constitutively express MHC class II molecules, but can up-regulate the expression of

MHC class II under pathological conditions [52]. Mulder et al showed that epithelial cells from EoE biopsies expressed the MHC class II protein HLA-DR. Using a human oesophageal cell line HET-1A, they demonstrated epithelial cells can engulf, process and present antigen in an IFN-γ-dependent manner. This data supports the potential role of oesophageal epithelial cells in presenting antigen in EoE [54].

Multiple investigators have shown eosinophils from EoE biopsies express HLA-DR [55]. Le-Carlson et al demonstrated the presence of costimulatory markers on eosinophils (CD40 and CD80) and activation markers on T-cells (CD28 and CD69) within the oesophageal epithelia of patients with EoE [56]. Collectively, these data imply, but do not prove that eosinophils can present antigen to T-cells. This concept remains controversial since there is no compelling evidence eosinophils can present antigen and activate naive T-cells in an antigen-specific manner [52].

Antigens are processed and presented to naive T-cells, which are primed to mature into antigen-specific Th2-cells under the influence of Th2-cytokines. Oesophageal T-cells of EoE patients are characterized by Th2-defining cell surface markers such as CCR8 and CRTH2 [15]. The most extensively studied Th2-cytokines are IL-13, IL-5 and IL-4 (see table 2).

IL-13 is produced by Th2-cells and recruits eosinophils via an eotaxin-3 driven pathway [47]. It appears to activate the local tissue inflammatory response in Th2-associated diseases. Levels of IL-13 are increased 16-fold in the oesophagus of EoE patients [47]. It induces eotaxin-3 (*CCL26*) production from the oesophageal epithelial cells [13,57], which recruits eosinophils [26,45,57]. In addition, it recruits eosinophils by promoting fibroblasts to produce periostin [58], which increases eosinophil adhesion and TSLP levels [59]. IL-13 reduces barrier integrity by down-regulating *DSG-1*; decreased levels of DSG-1 increases periostin and TSLP [33,34,60].

TSLP is an epithelial-derived cytokine associated with multiple allergic disorders [16] and is known to promote the Th2-response [61]. TSLP levels are elevated in oesophageal tissues of patients with EoE [31], and it is required to induce experimental EoE [16]. There is evidence TSLP can activate DCs to drive the Th2-response via OX40 ligands [62], and its level is associated with heightened basophil responses in human [16]. Taken together, IL-13 perpetuates the local inflammatory process by recruiting IL-13-producing eosinophils, via stimulation of eotaxin-3 and periostin production, as well as by inducing TSLP secretion which promotes a strong Th2-response (see figure 1).

IL-5 is expressed by Th2-cells [14], eosinophils [63], basophils [64], innate lymphoid type 2 cells (ILC2) and iNKT-cells [65,66]. Its level is increased in the oesophagus of EoE patients [67]. IL-5 is involved in the differentiation and maturation of eosinophils in the bone marrow [65]. It promotes eosinophil survival [68] and migration into blood [69]. Epithelial cell-derived eotaxin-3, induced by IL-13, recruits the circulating eosinophils from the blood to accumulate in the oesophagus. In addition, IL-5 plays a role in the development, metabolism and function of basophils [70], but the exact role of IL-5-basophils axis in EoE is not defined.

IL-4 is overexpressed in oesophageal biopsies from EoE patients [12], but its exact role is not established. Although the source of IL-4 is controversial, basophils contribute significantly in initiating the Th2-inflammatory response [61]. Once the Th2-response is initiated, Th2-cells also produce IL-4 [71]. A key function of IL-4 is to induce B-cell class-switching [12], but it also plays a role in eosinophil recruitment by stimulating eotaxin-3 production from the epithelial cells [57,72].

Eosinophils are the end-effector cells of EoE. They are responsible for the injury in the oesophagus. Recruitment and migration of eosinophils from the bone marrow to the oesophagus is orchestrated by a complex network of cytokines, chemokines and lipid mediators [73]. Activated eosinophils at the site of inflammation produce a wide array of pro-inflammatory cytokines including IL-4, IL-5, IL-13, TGFβ, and TNF. These cytokines modulate the allergic response and contribute to tissue damage [14,63]. Tissue remodelling in EoE patients is largely controlled by TGFβ, which causes fibrosis and influences epithelial growth [74]. The toxic proteins, such as eosinophil peroxidase, cationic protein, neurotoxin (EDN) and major basic protein (MBP) damage the epithelium [63]. EDN skews the adaptive immunity to a Th2-response by activating DCs via the Toll-like receptor 2-myeloid differentiation factor 88 signalling pathway [75]. Leukotriene C4 increases vascular permeability, smooth muscle contraction and may therefore contribute to oesophageal dysmotility [36,63]. However, leukotriene inhibitors are ineffective in resolving inflammation in human EoE [4].

Mast cells are also increased in EoE [76] and are derived from the same $CD34^+$ progenitor cell type as eosinophils. While the oesophagus is devoid of eosinophils at baseline, mast cells normally reside in the oesophagus. Their recruitment to the oesophagus is dependent on the SCF-SCFR axis [76]. MC_{TC} (mast cells with tryptase and chymase) are the predominant mast cell-type in the oesophageal epithelium. They store and release TGFβ-1, IL-4, IL-5, IL-13, eotaxin, histamine, leukotrienes, proteases and lipid mediators when activated. The best-characterized mechanism of mast cell activation is cross-linking of their surface IgE molecules in an antigen-specific manner. Mast cells with antigen-specific IgE bound to their Fc-receptors are present in the oesophagus of EoE patients [12,38], but whether mast cells are activated in an IgE-dependent manner in EoE remains controversial, as discussed previously. Among the non-IgE mechanisms of mast cell activation, eosinophil-derived MBP seems the most relevant, although not yet proven in EoE [76]. Mast cells, through the production of TGFβ-1, play a central role in tissue remodelling and promoting aberrant smooth muscle contractility in EoE [37,77].

Conclusion, and Future Clinical and Research Directions

Variable symptoms and responses to treatments suggest EoE represents a group of heterogeneous diseases of the oesophagus, rather than a single disease. Three key points are known about EoE pathogenesis: it (1) is Th2-mediated, (2) requires loss of oral tolerance and (3) is characterized by eosinophil recruitment to the oesophagus.

Due to engagement of multiple compensatory inflammatory pathways in EoE, therapeutic trials using agents designed to block multiple components of the Th2 pathway are likely to

display efficacy. Biologics neutralizing single agents like IL-5, IL-13, CRTH2 and IgE show limited efficacy in EoE [78]. Therapeutics targeting multiple pathways are necessary and finding these is an active and on-going field of research. A clinical trial with Dupilumab, targeting both IL-4 and IL-13, is underway. Recently, JAK1/3-inhibitors have shown promising effects in a murine model of asthma [79]. This finding may present a novel therapeutic approach for EoE.

Strengthening oral tolerance also may be an effective strategy in preventing and/or treating EoE. The rapid increase in the prevalence of EoE cannot be explained by changes in genetic susceptibility [80]. Risk factors that may predispose to EoE include use of antibiotics during infancy, caesarean delivery, premature birth and lack of breast-feeding. These circumstances correlated with changes in the gut microbiota and with dysregulation of Tregs and iNKT-cells. Mice studies show that manipulating the microbiota can restore oral tolerance [20,21]. Changes in microbiota are associated with various human diseases, but its role in EoE remains to be elucidated. Successful modulation of the microbiota to treat human disease is feasible as demonstrated by the efficacy of faecal transplant in the treatment of refractory *Clostridium difficile* [81]. Future research should explore the role of the microbiota in the pathogenesis of EoE, and whether manipulation of microbiota can restore oral tolerance, prevent and/or treat EoE.

Eosinophilic infiltration in the oesophagus is the hallmark histologic feature of EoE. Eosinophils cause tissue damage, remodelling and fibrosis. They produce various mediators that propel the Th2-pathway to perpetuate the local inflammatory cycle. The fact that eosinophils only affect the oesophagus in EoE suggests there are oesophagus-specific chemotactic signals that may offer opportunities for therapeutic intervention.

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Research agenda

1. Restoring oral tolerance via modulation of microbiota may prevent/treat EoE. We need a better understanding of how the microbiota contributes to the risk of EoE development and loss of oral tolerance.
2. Simultaneous blockade of more than a single target in the Th2 pathways may be required to abrogate the disease, due to the compensatory inflammatory processes in EoE.
3. Targeted disruption of eosinophil trafficking to the oesophagus may abate EoE without systemic side effects. Oesophagus-specific chemotactic signalling pathways needs to be better defined.

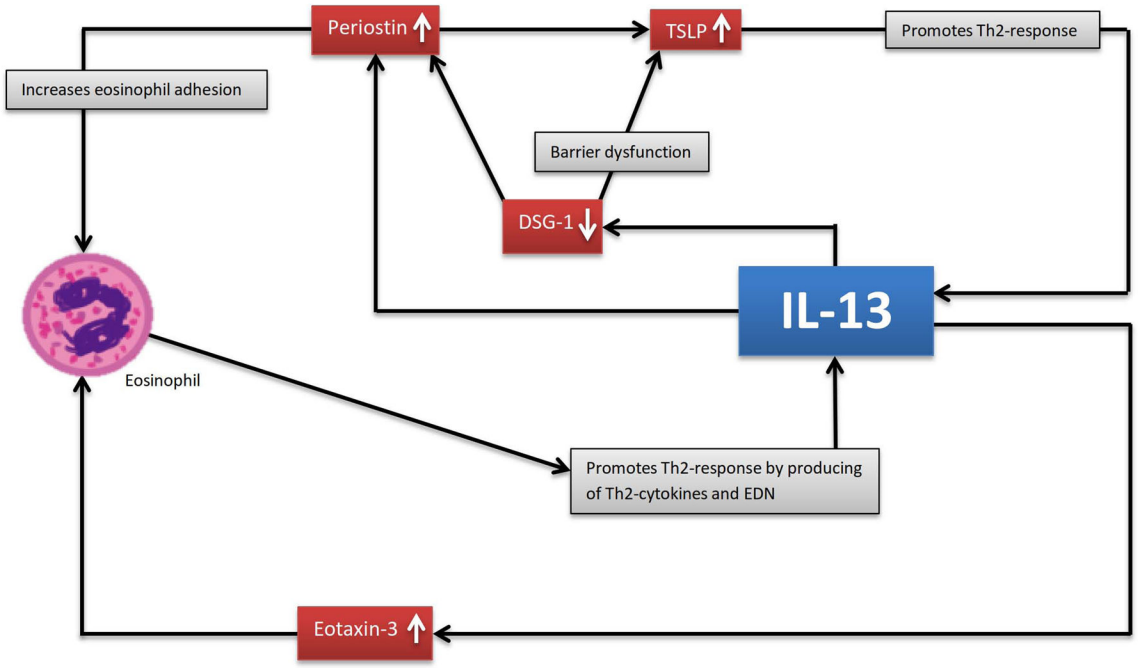

FIGURE 1. Self-perpetuated inflammatory cycle mediated by IL-13

IL-13 up-regulates periostin, while down-regulating DSG-1. Down-regulation of DSG-1 enhances the production of TSLP and periostin. Up-regulation of periostin further enhances the expression of TSLP, which is a strong driver of the Th2-response that propels the IL-13 inflammatory cycle. IL-13 stimulates the oesophageal epithelial cells to express eotaxin-3. Both eotaxin-3 and periostin recruit eosinophils to the site of inflammation; eotaxin-3 as a chemo-attractant, while periostin increases eosinophil adhesion. Eosinophils produce IL-13 and release EDN to activate DCs to prime Th2-differentiation.

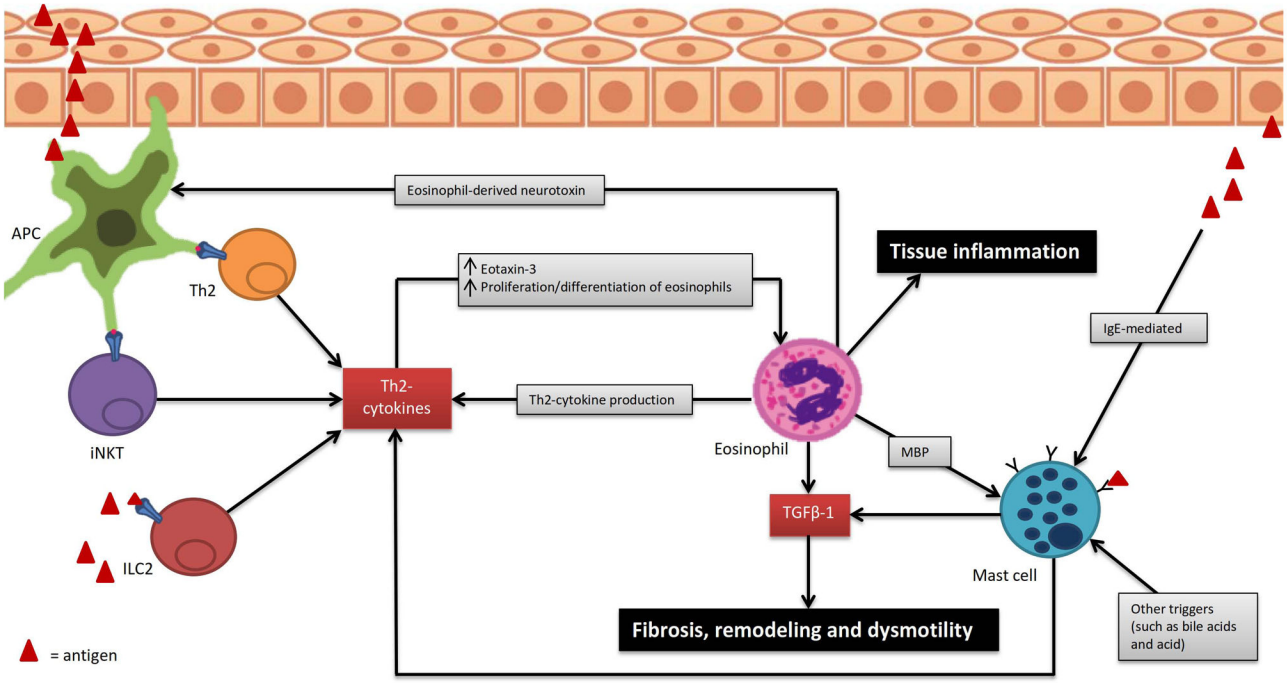

FIGURE 2. Proposed allergic mechanisms of EoE

Antigen is presented by APCs, which promotes a Th2-response in EoE. Th2-cytokines are primarily produced by Th2-cells, but can be produced by ILC2, iNKT-cells, eosinophils and mast cells. IL-5 increases the proliferation and differentiation of eosinophils in the bone marrow, maintains their survival and facilitates their migration into the blood. IL-13 stimulates eotaxin-3 production from the epithelial cells, which recruits circulating eosinophils to the oesophagus. Eosinophils produce Th2-cytokines propagating the inflammatory cycle. They release cytotoxic granules causing tissue injury. They activate DCs via EDN to prime Th2-cells and possibly iNKT-cells. Eosinophils activate mast cells via MBP. Mast cells can also be activated by antigens cross-linking their surface IgE. Activated mast-cells release IL-13, IL-5 and TFGβ-1. Together, mast cells and eosinophils cause fibrosis, remodelling and dysmotility in a TGFβ-1 mediated pathway.

TABLE 1

Lessons learned from mouse models.

Key findings	Reference
First murine model of EoE. EoE induced by intratracheal administration of *Aspergillus fumigatus*.	Mishra 2001 [25]
EoE induced by intratracheal IL-13. Mechanism is dependent on IL-5, eotaxin-1, and STAT6.	Mishra 2003 [45]
Mice were sensitized epicutaneously to develop experimental EoE. First evidence that antigens could be sensitized via the skin in EoE.	Akei 2005 [26]
Mice deficient in the eotaxin-3 receptor (CCR3−/−) could not develop EoE.	Blanchard 2006 [13]
T-cells, but not B-cells, are required to trigger EoE.	Mishra 2007 [17]
IL-5-deficient mice or eosinophil-lineage deficient mice had significantly less tissue remodelling.	Mishra 2008 [82]
EoE was induced intranasally by cockroach and dust mite allergens in an eotaxin and IL-5 mediated pathway. Mice deficient in eotaxin-1/2, CCR3 or IL-5 failed to develop EoE.	Rayapudi 2010 [43]
Administration of anti-Siglec-F antibodies significantly decreased eosinophilic inflammation.	Rubinstein 2011 [28]
Mice were sensitized intraperitoneally, and then challenged intranasally or intragastrically with corn or peanut to induce EoE. Disease process is dependent on eotaxin and iNKT-cells.	Rajavelu 2012 [83]
IgE is not required to generate experimental EoE. EoE is TSLP and basophil dependent.	Noti 2013 [16]
Mast cell-deficient mice model had reduced hyperplasia and hypertrophy, but showed no difference on eosinophil recruitment to the oesophagus.	Niranjan 2013 [84]

TABLE 2

Cytokines and cells involved in EoE mechanism.

Cytokines and cells	Origin	Key function(s) in EoE
TSLP	Epithelial cells	• Prime basophils and DCs to initiate Th2-response
Th2-cells	Lymphocyte progenitor cells in the bone marrow	• Induce class-switching of B-cells • Produce cytokines (i.e. IL-4, IL-5, IL-13) • Recruit eosinophils
B-cells	Lymphocyte progenitor cells in the bone marrow	• Produce antigen specific-IgE and IgG4
Mast cells	Myeloid progenitor cells in the bone marrow	• Activated through IgE-dependent, -independent mechanism or other triggers • Produce inflammatory mediators (i.e. TGFβ-1 and Th2-cytokines), contribute to recruitment of eosinophils, fibrosis, inflammation and dysmotility
Eosinophils	Myeloid progenitor cells in the bone marrow	• Produce Th2-cytokines, toxic granule proteins, lipid mediators, chemokines and TGFβ-1 • Critical in damage-inducing mechanism of EoE
Basophils	Myeloid progenitor cells in the bone marrow	• Primed by TSLP • Produce IL-4 to promote Th2-differentiation
ILC2	Lymphocyte progenitor cells in the bone marrow	• Produce Th2-cytokines
IL-4	*Origin unclear;* basophils, Th2-cells	• Promote Th2-differentiation • Promote B-cell class-switching
IL-5	Primarily produced by Th2 cells, also by eosinophils and mast cells	• Stimulate eosinophil differentiation and proliferation in the bone marrow • Traffick eosinophils to the oesophagus
IL-9	*Origin unclear;* eosinophils, ILC2 cells	• Mast cell growth and survival factor
IL-13	Primarily produced by Th2 cells, also by eosinophils and mast cells	• Down-regulate DSG-1, resulting in impaired barrier function • Stimulate production of eotaxin-3 and periostin by epithelial cells
IL-33	Epithelial cells	• Involved in sensitization process
Eotaxin-3	Epithelial cells	• Chemo-attractant for eosinophils
Periostin	Epithelial cells	• Promote eosinophil recruitment and adhesion