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Recent advances in the pathological understanding of eosinophilic esophagitis

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Abstract

Eosinophilic esophagitis (EoE) is a chronic allergen-mediated inflammatory disease of the esophagus. This inflammation leads to feeding difficulties, failure to thrive and vomiting in young children, and causes food impaction and esophageal stricture in adolescents and adults. In the twenty years since EoE was first described, we have gained a great deal of knowledge regarding the genetic predisposition of disease, the inflammatory mileu associated with EoE and the long term complications of chronic inflammation. Herein, we summarize the important breakthroughs in the field including both *in vitro* and *in vivo* analysis. We discuss insights that we have gained from large scale unbiased genetic analysis, a multitude of genetically and chemically altered mouse models of EoE and most importantly, the results of clinical trials of various pharmacologic agents. Understanding these successes and failures may be the key to developing more effective therapeutic strategies.

Keywords

Eosinophilic Esophagitis; Fibrosis; TSLP; T cells; IL-13

Introduction

The incidence of Eosinophilic Esophagitis (EoE) is increasing like most atopic disease. EoE is indeed now considered a classic chronic atopic disorder that is allergen driven and immune mediated which results in a mixed inflammatory infiltrate in the esophagus including: eosinophils, mast cells, basophils, and Th2 cells[1-3]. Accumulating evidence is showing that genetics and epithelial dysfunction are driving the accumulation of the cell infiltrate. In genetically predisposed individuals the disrupted barrier has increased

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expression of thymic stromal lymphopoietin (TSLP) and induces Th2 type inflammation, in which innate (eosinophils, basophils, mast cells, invariant natural killer T cells [iNKTs]) and adaptive (Th2 cells) immune cells play a synergistic role in protracting the chronic inflammation and inducing fibrosis. These invading cells trigger diverse cytokine production, including but not limited to eotaxin-3, interleukin (IL)-4, IL-5, IL-13, transforming growth factor (TGF)-β, tumor necrosis factor (TNF)-α, and TSLP[1-3] leading to the migration of eosinophils. Eosinophils secrete cytokines and molecules that further disrupt the esophageal layer leading to tissue damage, esophageal dysmotility and fibrosis of the esophagus.

Food allergens and environmental triggers have been shown to play a causative role in EoE, and strict elimination diets and steroids are the main stays of therapy. While these therapies induce symptomatic and histologic remission, there are concerns about long-term steroid usage such as cataracts, adrenal insufficiency, infection, growth retardation, and bone mineralization. Furthermore, diet elimination therapy is fraught with compliance and contamination issues as well as decreased quality of life[4, 5].

In this review we hope to provide an in depth examination of pathophysiologic mechanisms and hope to provide new insight into potential therapeutic and diagnostic strategies.

Genetic Risk Factors of EoE

Accumulating evidence shows that EoE, like many other atopic diseases, is multifactorial and complex disease, whose inheritance does have a strong genetic component albeit not the classical Mendelian pattern [6, 7]. Indeed in up to 10% of patients with EoE, one of parents has a history of esophageal strictures and biopsy-proven EoE. EoE also shows an extremely high sibling risk ratio compared to other atopic diseases. A recent paper has tried to tease out these genetic and environmental risk factors comparing a twin cohort and a Nuclear-Family cohort with EoE[8]. Having a monoszygotic twin with EoE carried the highest risk of developing EoE at 41% rate, while the rate was 21% for dizygotic twins and only 2.4% in the Nuclear-Family cohort. This data confirm three important points: 1) EoE is multifactorial and complex disease, whose inheritance does not follow the classical Mendelian Traditional Mendelian inheritance patterns: dominant, recessive, and X-linked patterns. In dominant inheritance, transmission between an affected parent and a child is approximately 50%; however, in the Nuclear-Family cohort, only 2.4% of the probands have an affected parents. Autosomal-recessive inheritance often has children with unaffected parents, but approximately 25% of probands' siblings are affected whereas here about 3.5% percent of brothers and 1.3% of sisters were affected. Finally both mothers (0.6%) and fathers (2.4%) transmitted the disease to their offspring, excluding the X-linked inheritance pattern. 2) There is a strong genetic component with sibling risk ratio of about 60 (i.e. there is a 60 times risk of developing a similar disease in other siblings). This is high compared to asthma, where the sibling risk ratio is only 2. Moreover, monozygotic twins develop EoE twice as as much as dyzigotic twins (41% vs 24%). 3) Environment and genetics together play a major role in EoE development, as 24% in dizygotic twins but only 2.4% of siblings develop EoE. Siblings and dyzigotic twins theoretically have an equivalent DNA risk factors, but a perhaps there is an increase in environmental exposures in the dizygotic twin.

Specific genetic risk factors have been identified by two main techniques: candidate gene approach and genome wide studies. First candidate gene was first identified by a genome-wide RNA profiling of esophageal biopsies that showed that CCL-26 *(Eotaxin 3)* was overexpressed about 50-fold in patients with EoE compared with normal controls or those with gastroesophageal reflux disease (GERD). Rothenberg and colleagues then identified a single nucleotide polymorphism (SNP) in *CCL-26* as a risk factor for EoE development in a small percentage of patients[9].

Aceves and colleagues[10] showed a correlation between SNP in TGF-β gene and response to topical steroid treatment and demonstrated that CC genotype at the -509 position in the TGF-β promoter is more likely to response to the therapy. These data suggest that response to therapy maybe influenced by the genetic background. Moreover the filaggrin loss of function mutation 2282del4 is significantly overrepresented in EoE compared with control individuals (6.1% versus 1.3% respectively)[11]

The alternative approach is to look via unbiased approach giving equal weight to all genes. There are several potential approaches for genome wide approaches including looking at SNPs (Genome Wide Array Studies-GWAS), examining exons (Exon Wide Approach) or the entire genome. In EoE, there have been 3 GWAS analysis completed and no data has been published using the other two approaches. They have identified 3 genes as important candidate gene in the pathogenesis of EoE: the thymic stromal lymphopoietin (*TSLP*) gene, at 5q22, the Calpain 14 on chr2p23.1 and the *c11orf30/EMSY* gene on chr11q13.5 [6, 7, 12, 13].

TSLP

TSLP was the first ever gene to be found associated with EoE by GWAS. The relatively small population of 500 EoE children in which such association was found, confirmed the strong influence of genetics in EoE suggested by the epidemiological data[6]. The human *TSLP* gene is located on chromosome 5q22.1 next to the atopic cytokine (IL-4, IL-5, IL-13, IL-3) cluster of chromosome 5q31[14]. The same SNP in the TSLP gene has been confirmed in 2 subsequent independent studies confirming the importance of TSLP in EoE pathogenesis and its inheritance[7, 13]. Molecular studies have also shown a phenotype genotype correlation between the SNP in TSLP and EoE (detailed below). Indeed those individuals who are homozygous for the EoE risk allele (AA) showed an enhanced TSLP expression and basophil infiltration in the esophagus compared to those heterozygous (AG) or homozygous (GG) for the protective minor alleles[2].

Our group recently performed an expanded GWAS on 936 EoE patients and 4312 controls to identify potential additional targets for further biological studies as well as genetic risk factors. Such study not only confirmed the validity of previously reported *TSLP* SNP [6] but also led to the discovery of 2 novel SNP on *c110rf30 and CAPN14* [7].

In addition, Sherrill and colleagues [13] found that male patients with EoE had more often a SNP in the TSLP receptor (TSLPR) gene, which is encoded by a pseudoautosomal region on Xp22.3 and Yp11.3[13]. This finding could explain the epidemiological data that EoE is more common in males with a 3:1 ratio[15].

c11orf30 (EMSY)

The *c11orf30* gene encodes EMSY, a transcriptional regulator that was initially identified as a breast cancer 2, early onset (BRCA-2)-associated protein that is amplified in human mammary adenocarcinomas[16]. A potential role for EMSY in chromatin modulation has been proposed through its association with heterochromatin protein-1[17]. More recently, EMSY has been identified as part of a novel Akt-dependent mechanism by which interferon (IFN) regulate the expression of interferon-stimulated genes (ISGs)[18]. As IFN and ISGs play a central role in Th1 inflammation and consequent Th2 suppression it can be speculated that a dysregulation in EMSY expression could lead to allergic diseases[18]. Several other GWAS studies have found variant at the EMSY locus associated with several Th2 diseases such as seasonal allergic rhinitis[19], atopic dermatitis[20], asthma[21] and allergic sensitization[22], even if with much lower odds ratios (range 1.09 - 1.22).

CAPN14

CAPN14 is the 14th member of the calpain family of intracellular Ca^{2+}-regulated cysteine proteases, that has been only recently described. Calpains are known to be involved in diverse biological processes like the cell cycle, tight junction protein, cytokine regulation, and human fibroblast biology, however the specific biological function of CAPN14 is currently unknown[7, 12, 23]. Calpains can be ubiquitous or tissue-specific. CAPN14 appears to be highly and selectively expressed in the esophagus [24, 25], and upregulated by Th2 cytokines (*i.e.* IL-13[12] and IL-4[26]). More importantly, it overexpressed in EoE esophageal epithelial cells compared with controls[7, 12] making it a very promising candidate in the pathogenesis of EoE.

In conclusion, the evidence accumulated so far indicate that EoE is a multifactorial disease with a strong genetic component. The genetic background seems to point to epithelial targets as significant risk factors for the development of EoE. Indeed, many of the SNPs are in genes primarily expressed in the epithelial cells.

Microenvironment Alterations in EoE

TSLP and TSLPR

TSLP is a four-helix cytokine closely related to IL-7, a cytokine with hematopoietic function [27]–In the last several years, it has been clearly demonstrated that TSLP is a strong inducer of a Th2 cellular innate and adaptive response in both humans and mice[28]. TSLP can induce such Th2 shift either by acting on antigen presenting cells (APCs) (i.e. dendritic cells) or by directly stimulating innate and adaptive cells. For example, if primed with TSLP, APCs like $CD11c^+$ dendritic cells (DCs): a) express OX40 ligand (OX40L-CD134), which in turn promotes the development of Th2 differentiated cells; b) polarize $CRTH2^+$ T cell into Th2 effector cells; c) inhibit the production $FOXP3^+$ Tregs (T regulatory cells)[27].

TSLP can also directly activate innate and adaptive immune cells to secrete Th2 cytokines by ligation of the TSLPR: a) many of the innate immune cells involved in allergic inflammation such as innate lymphoid cells type 2 (ILC2), mast cells, NKT cells, basophils and eosinophils express the TSLPR and upon TSLP stimulation they have an enhanced Th2

cytokine[27]; b) in naïve CD4 and CD8 T cells ligation of TSLP-TSLPR induces IL-4 gene transcription, which in turn further up regulates TSLPR on CD4 and CD8 T cells, resulting in a positive-feedback loop[27, 29,30].

TSLP may favor a Th2 response against an allergen penetrated through a dysfunctional esophageal epithelial barrier in genetically predisposed individual. For example, damage through the esophagus with acid would induce TSLP, which would promote a TH2 cytokine environment, that further promotes TSLP in a positive feedback loop. Therefore, TSLP may be an ideal therapeutic target as the blockage of TSLP could lead to a selective global inhibition of the Th2 response. In the last five years, high impact publications have confirmed a role of TSLP in EoE pathogenesis. Independent groups have shown not only the genetic mutation in TSLP and TSLPR genes favor EoE development but also that TSLP is expressed in significantly higher level in patients with EoE, especially in those with active disease and those who carry the genetic risk factor[7, 31, 32]. Furthermore, Noti et al demonstrated that in an animal model TSLP blocking antibodies inhibited some of the major features of the EoE such as food impaction[2]. Animal and human studies have shown that TSLP may induce EoE by promoting Th2 cytokine production from basophils[2, 33] Therefore, TSLP may be an ideal therapeutic target as the blockage of TSLP could lead to a selective global inhibition of the Th2 response. While there have been some preliminary trials in asthma, TSLP antibodies have not been tested in EoE[34]. TSLP and its receptor appear to have an important role in EoE pathogenesis and are promising targets for the future.

Anti- Interleukin-5 (IL-5)

Interleukin-5 is the major growth factor essential for the differentiation, activation and survival of eosinophils[35]. IL-5 is a glycoprotein with a molecular weight of 40–50 kDa [36, 37]. IL-5 is similar to other hematopoietic cytokines such as IL-3 and granulocyte-macrophage colony-stimulating factor (GM-CSF) [36, 37]. IL-5 exerts its effects by binding to its receptor IL-5R, which is composed of 2 chains: the IL-5Rα subunit, which specifically binds only IL-5 and IL-5Rβ common (βc) signaling subunit, which can also recognize IL-3 and GM-CSF[37, 38] Cells that can produce IL-5 are eosinophils, basophils, CD34+ progenitor cells, Th2 cells, mast cells, iNKT cells and non-B/non-T cells, which most have been implicated in the pathogenesis of EoE.

Patients with EoE, have high esophageal tissue levels of IL-5 and its receptor, IL-5R [39, 40]. Furthermore, studies using an animal model of EoE, showed that IL-5 deficient mice will not develop EoE, whereas overexpression of IL-5 was conducive to a more severe eosinophilic infiltration in the esophagus[41-44]. Blockade of IL-5 by two humanized monoclonal antibodies against IL-5 (Mepolizumab (SB240563) and Reslizumab (Sch55700) have been tried in double blind placebo controlled studies for EoE[45, 46]. Mepolizumab blocks binding of human IL-5 to the IL-5Rα subunit [45, 46] whereas reslizumab neutralizes IL-5 prior to binding IL-5R [46]. In both pediatric and adult placebo controlled studies, there was a significant reduction in the number of the eosinophils infiltrating the esophagus, but there was no difference in any clinical outcome between active and placebo groups possibly due to the fact that esophageal eosinophil levels did not completely return to normal (zero

eosinophils) in any treated group[45, 46]. Specifically, in the pediatric study 226 EoE children were randomly assigned to receive 1, 2, or 3 mg/kg intravenous (IV) reslizumab or placebo monthly for 4 months. At the end of the study children treated with reslizumab had an esophageal eosinophil but the physician's global assessment scores significantly improved in all treatment groups, including the placebo group[47].

Similarly in 11 adults with active EoE, mepolizumab significantly reduced eosinophils count by histology but did not significantly improve the clinical manifestations[48]. In such study patients randomly received two IV infusions of 750 mg of Mepolizumab (n = 5) or placebo (n = 6) 1 week apart.

These results may indicate that IL-5 maybe important in driving eosinophilic infiltration, but that other redundant Th2 cytokines are also driving the local Th2 inflammation and reduction of IL-5 only is not enough for treatment of disease.

IL-13

Among Th2 cytokines in EoE, IL-13 has been shown to play a major role in EoE pathogenesis[41, 49]. IL-13 is elevated in the biopsies of patients with EoE especially those with active disease[39]. In animal models, the level of IL-13 was associated with disease activity. Transgenic mice expressing higher levels of IL-13 or those who had IL-13 given intratracheally had stronger eosinophilic infiltration in the esophagus and the converse was true with decreased eosinophilia in IL-13 deficient mice[41, 50]. Blanchard et al. showed that IL-13 promoted eosinophilic infiltration by inducing eotaxin-3 a potent chemotactic mediator for eosinophils[51]. IL-13 is also able to induce a significant barrier dysfunction by downregulating numerous epidermal differentiation complex genes, such as filaggrin and SPRR3 esophageal epithelial cells and in EoE biopsies specimens compared with healthy controls. Decreased filaggrin expression was uniformly seen in all EoE cases *in vivo*. Furthermore, the expression of the EDC genes filaggrin and involucrin was strongly inhibited by IL-13. These results suggest that the epithelial response in EoE involves a cooperative interaction between IL-13 and expression of epidermal differentiation complex genes[11]. Animal models also showed that inhibition of IL-13 by anti-IL-13 showed promising results in an EoE animal model[49] with decrease inflammation and fibrosis.

Given the evidence of the prominent importance of IL-13 in EoE pathogenesis, anti-IL13 antibodies are currently in trial for EoE [49]. In a double blind placebo controlled study with anti-IL13 (QAX576),[52] adult patients with EoE received 3 monthly doses of IV QAX576 (6 mg/kg) or placebo. The treated group tolerated the antibody and had a significant reduction of esophageal eosinophilia, markers of Th2 inflammation and epithelial dysfunction compared to the placebo treated group. However, there was no statistically significant clinical improvement and there was persistent inflammation of eosinophils. Therefore, the clinical significance of such treatment remains to be established.

Mast Cells

Activated mast cells and mast cell products have been described in the esophageal biopsies obtained active EoE subjects by several independent groups.[53, 54] Corticosteroid, anti-IL-5, anti-IL-13 and dietary treatment for EoE decrease esophageal epithelial mast cell numbers

and correlates with decreased tissue eosinophilia, suggesting an important role of mast cells in EoE pathogenesis.[54-57]. Mast cell may promote not only inflammation but also fibrosis in EoE pathogenesis, by secreting factors such as TGF-β, a pro-inflammatory cytokine that induce esophageal smooth muscle contraction,[54] and mast cell tryptase, which promotes proliferation and collagen secretion.

Mast cell infiltration has been noted in the epithelium, lamina propria and muscularis of the esophagus in EoE[3, 58]. In fact presence of mast cells may assist differentiating EoE from PPI-REE and GERD as they are more abundant in EoE compared to these other disorders[59]. Mast cells also produce histamine, which acts by increasing vascular permeability allowing for granulocyte migration into effected tissues. Yu et al showed that mast cell migration into the esophageal tissue precedes eosinophil migration in a guinea pig model of EoE. A histamine receptor antagonist, attenuated both mast cell and eosinophil migration in this model[60], suggesting that granulocyte recruitment is in part due to a histamine mediated pathway. This, however, is in contrast to Niranjan et al, who showed in an *aspergillus* model of EoE that mice deficient in mast cells continue to have the same degree of eosinophilic infiltration as wild type mice[61].

In addition, our group has recently reported that histamine receptors (HR)-1, HR2, and HR4 are increased in active EoE patients compared to inactive and controls. Histamine stimulation of esophageal epithelial cells *in vitro* has been shown to induce GM-CSF, TNF, and IL-8. These effects were inhibited by HR1 antagonists, but not HR2 anatgonists[62]. The effect of mast cell derived factors on epithelial function is currently unknown.

Basophils

Basophils are less than 1% of white blood cells population, but they play a major role in type I allergic responses because of their ability to secrete histamine and various cytokines. Recent studies however have shown that basophils may be important in non-IgE mediated food allergy such as EoE. It has been demonstrated that a secondary sub-population of basophils that are TSLP-dependent and IL-3 independent exist. They are highly expressed in patients with active EoE and secrete high levels of Th2 cytokines.[63] Further studies have shown that the TSLP-basophil axis is essential for the development of an EoE-like disorder in mice, as inhibition of either TSLP or basophils with appropriate antibodies resulted in a significant reduction of major EoE experimental manifestation, like food impaction.[2] Together, these studies show that TSLP mediated basophil response might play an important role in the pathogenesis of EoE in humans.

IgE

The role of IgE in EoE is unclear. But, several lines of evidence in human and animals indicate that it does not plan a role. In Noti's mouse model of EoE in which the development of EoE-like features was dependent upon both TSLP and basophils, but independent of IgE responses.[2] Wild type and IgE deficient mice developed similar levels of esophageal inflammation upon antigen challenge, on the other hand TSLP or basophil blocking antibodies against ameliorated the EoE-like disease when administered after the onset of disease. The use of omalizumab (anti-IgE) has no effect on histological or clinical symptoms

in EoE in most studies.[64] Indeed in a double blind placebo controlled study on the use of omalizumab in 15 patients with EoE failed to show any significant clinical improvement or histological improvement[65]. The use of skin testing or specific IgE (tests for measuring IgE to foods) to identify causative allergens work in less than 20% of patients[2, 66]. A recent study on the use of IgE microarray to direct elimination diet was suspended as blatantly not effective[67]. Finally, oral immunotherapy is effect in treating up to 80% of patients with IgE-mediated food allergy, but has no effect in EoE, in fact, it can cause EoE in patients.[68] Similarly, in the natural history of individuals with food allergy, individual can outgrow IgE mediated food allergy to an individual food then develop EoE to the food.[66] These studies indicate that EoE is a Th2 disease that is not dependent on IgE.

Microbial Alterations in EoE

Recent evidence suggests that dysbiosis may contribute to the pathogenesis of a variety of diseases including inflammatory bowel disease, asthma, eczema, and irritable bowel disease[69, 70]. Recent studies have shown that antibiotic exposure in early childhood causes a 6-fold increase in the odds of developing EoE compared to those unexposed. Other factors such as ceasarian birth and formula feeding have less significant trends[71]. These population studies suggest that there may be a role for microbes in pathophysiology of EoE.

Until recently, nothing was known about the esophageal microbiota in EoE. Two independent groups evaluated the bacterial composition of the esophagus in both control and EoE patients. Both studies show a predominance of the genus Streptococcus in the healthy esophagus. Harris et al, using the esophageal string test to sample bacterial colonies, found that the EoE esophagus had significantly increased Haemophilus species. Furthermore, they found that EoE subjects returned to Streptococcal enrichment when in remission. On the other hand, Benitez et al, using esophageal biopsies found a predominance of Firmicutes in the normal esophagus, and an enrichment of Neisseria and Corynebacterium in patients with active EoE. However, no significant difference between active and inactive EoE subjects was found. Variations between these two studies may be due to geographic factors. Harris et al showed that subjects in Aurora, Colorado and Chicago, Illinois had distinct esophageal microbiota, which could account for the differences between Benetiz and Harris. Further studies will be needed to investigate whether the observed EoE relevant microbiota is a cause of or a result of allergic inflammation.

PPI-REE (Proton Pump Inhibitor Responsive Esophageal Eosinophilia)

Although EoE is defined by a failed proton pump inhibitor (PPI) trial (8 weeks of treatment with (20-40 mg of available agents twice daily for adults or 1 mg/kg -10-30 mg of available agents twice daily for pediatric subjects), another form of esophageal eosinophilia that is clinically indistinguishable from EoE is emerging. This eosinophilia has clinical manifestation similar to EoE but it is responsive to PPI monotherapy (PPI responsive, PPI-REE). The frequency of PPI-REE among all patients with esophageal eosinophilia (≥15 eosinophils/hpf) is substantial, ranging from 10% to 50% in different studies[72]. PPI-REE is more similar to EoE than GERD, because (1) tissue eosinophilia of patients is higher than the one found in patients with GERD; (2) rate of atopy, food allergy, or both, is similar to

patients with EoE and much higher than in GERD; and (3) there is a Caucasian male predominance similar to the one observed in EoE. Recently Wen et al[72] have demonstrated that untreated PPI-REE has a molecular signature that overlaps with that of EoE. Indeed, patients had a similar overlapping transcriptomes between for genes important for eosinophil chemotaxis (eotaxin 3, CCL26), barrier molecules (desmoglein 1, DSG1), tissue remodeling (periostin, POSTN), and mast cells (carboxypeptidase A, CPA3). This suggests two scenarios: 1) these two diseases are part of the same spectrum of a T_h2-associated disease process in nearly all patients or 2) the esophageal transcriptome is more characteristic of eosinophilic inflammation than the true disease process in EoE. However, the authors also identified a candidate gene that was significantly expressed in EoE patients but not in PPI-REE ones: KCNJ2 a gene that encodes the potassium channel Kir2.1, which is abundant in gastrointestinal mucosa and co-localizes with the H1-K1-ATPase/proton pump.

Even if it is not understood how a PPI relieves inflammation in PPI-REE a number of hypothesis have been made including (1) inhibition of acid and related inflammation; (2) the anti-inflammatory effects of PPI, such as inhibition of eotaxin-3 and signal transducer and activator of transcription 6 (STAT-6); and (3) food allergens less available to be presented to the immune system in absence of acidity[72].

Barrier Function

Epithelial barrier function is altered in EoE. Recent studies demonstrate that there is increased passage of small molecules through the mucosa of patients with EoE compared to control patients[73, 74]. Furthermore, there are increased dilated intercellular spaces in patients with EoE when compared to control. This is thought to be due to decreased expression of intracellular adhesion molecules. Ultrastructural analysis of EoE biopsies by electron microscopy has shown decreased desmosomes in patients with active EoE[75] and further *in vitro* analysis has revealed that knock down of desmoglein-1 in particular leads to decreased cell adhesion[32]. Immunohistochemical analysis reveals that active EoE biopsies have decreased filaggrin, zona occludens-1, and claudin 1[76]. In one study filaggrin staining was positive in 88% of controls, 100% of reflux biopsies, and in 86% of EoE samples obtained from patients in remission, but negative in all EoE samples obtained from patients with active disease[77]. In another recent study the expression of filaggrin was reduced and cytokines (TSLP, IL-25, IL-32, IL-33) were elevated in EoE as compared to normal esophageal tissues[78]. These data overall suggest that active inflammation due to IL-13 and TSLP may inhibit filaggrin and further impair the epithelial barrier function[77].

In addition to these increased intracellular spaces, basal cell hyperplasia is a key histologic feature of the active EoE esophagus[1]. Disruption of the balance of epithelial differentiation may contribute to disruption of the barrier function. Bone morphogenetic protein (BMP) is a cytokine has been shown to promote esophageal squamous cell differentiation[79]. In both a murine model of EoE and in EoE patient biopsies, there is enhanced expression of follastatin, a BMP inhibitor, suggesting a role for this pathway in the reactive epithelial changes seen in EoE.

Moreover, it is now clear that the esophageal epithelium is more than just a physical barrier; it is also the organ that most likely drives the Th2 inflammation characteristic of EoE. Esophageal epithelial cells can be activated by danger signals. They express TLRs[80, 81], (PAMPs) pathogen associated molecular patterns and (DAMPs) danger-associated molecular patterns and can produce significant amounts of pro-inflammatory cytokines in response to stimuli that activate such receptors [80]. We and other have also demonstrated that EoE-derived epithelial cells can produce the eosinophilic and T-cell chemokine, such as Eotaxin 3 and RANTES (CCL5)[82] which may play a role in the migration and activation of IL-13 producing iNKT cells in EoE. Finally there are evidence that esophageal epithelial cells may also function as nonprofessional antigen presenting cells, as they are able to internalize and process chicken egg ovalbumin, and can and activate T cells upon antigen priming.[83]

Fibrosis

Recent studies have shown that EoE affects both the motility and distensibility of the esophagus[84, 85]. Retrospective studies have shown that the duration of untreated EoE positively correlates with stricture formation, and currently the mean delay in diagnosis for adults with EoE is 7 years[86]. Due to this delay in diagnosis many patients present with fibrotic disease however little is known about the pathophysiology of fibrosis in EoE.

Similar to the esophageal epithelium, the lamina propria and muscularis mucosa both undergo eosinophilic infiltration[87, 88]. Esophageal fibroblasts and smooth muscle cells display enhanced fibrillogenesis and altered contractility in response to both TGF-β and eosinophil sonicates in *ex vivo* cultures. This suggests that esophageal inflammation in the lamina propria and muscularis mucosa may effect esophageal function through enhanced collagen deposition and altered contractility.

TGF-β is considered the key cytokine of in esophageal fibrosis in EoE. Immunohistochemical evaluation showed that there is enhanced TGF-β staining in the lamina propria of EoE patients compared to controls and furthermore and co-localizes with eosinophils[87]. Furthermore, canonical TGF-β signaling has been linked to murine fibrosis in EoE with decreased lamina propria thickness in SMAD3 deficient mice.

The epithelium may also contribute to fibrosis in EoE. Biopsies of patients with EoE have enhanced epithelial staining of mesenchymal markers, vimentin and smooth muscle actin, when compared to control patient biopsies[8990]. In fact prolonged exposure of in vitro esophageal epithelial cells to both TGF-β and TNF-α cause cells to contract, to migrate and to secrete collagen[91]. While these in vitro studies suggest that epithelial cells undergo epithelial to mesenchymal transition, further in vivo lineage tracing studies will need to be done to determine the true origin of these fibroblast-like cells.

Expert Commentary

In the twenty years since the first report of Eosinophilic Esophagitis[92], we have seen EoE evolve from a relatively unknown and underdiagnosed entity to a well described and accurately diagnosed disease process. With the help of clinical guidelines[1], making an accurate diagnosis and initiating therapy have become easier. However, over the last twenty years, we continue to rely on two main therapeutic interventions: corticosteroids and diet

intervention. While our use of these therapies has grown more sophisticated with topical steroids and six food elimination diets[93, 94], these shotgun approaches do not reflect our overall knowledge of the pathophysiology of this disease. We have made great strides to understand the genetic and inflammatory factors that contribute to EoE, however, many of the targeted therapies (anti-IL-5 and anti-IgE), have been unsuccessful. These therapeutic failures likely are a reflection of the complexity of EoE. There are many redundant pathways in action and there may not be just one anti-inflammatory agent that will eliminate the multitude of inflammatory mediators. Looking outside of the anti-inflammatory box towards novel pathophysiologic mechanisms such as improving barrier defects and dysbiosis, may provide insight towards adjunctive therapies that could improve clinical outcomes.

Five-Year View

Over the next 5 years, it is our hope that with all of this knowledge, we will be able to diagnose and monitor EoE more accurately and with less invasive testing modalities. It is our hope that there will be improved therapies that are more patient friendly and that lead to improved quality of life. One significant breakthrough is the exploration of alternative, noninvasive, methods of sampling esophageal tissue. For example, the esophageal string-test (EST) is an absorbent string that is swallowed in a capsule[95]. After the string has been in the esophagus overnight, it is removed and an array for eosinophil granular proteins is performed. With these methods, active EoE patients were able to be distinguished from inactive, GERD, and normal patients. Similarly, Cytosponge is another noninvasive method and is mesh attached to a string that is swallowed in a capsule. As the sponge is pulled up through the esophagus and it collects esophageal mucosa for histologic evaluation. Histologic evaluation of the sponge tissue accurately diagnosed EoE 83% of the time in a small cohort of adult patients[96].

Ongoing research will hopefully to a better understanding the natural history of EoE. We are now more attuned to the fibrostenotic potential of this disease. Routine biopsies may fail to obtain lamina propria and muscularis for complete analysis so early stage fibrosis may be missed. The use of the endoluminal functional imaging probe (EndoFLIP) may allow practitioners to evaluate the distensibility of the esophagus for the first time[85].

Various novel therapies are being considered for the treatment of EoE including the use of novel monoclonals against Th2 pathway or novel desensitization routes. As our understanding of the pathobiological processes involved in EoE continues to grow, it will be important to continue translating these basic science advances to patient care.

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Abbreviations

EoE	Eosinophilic Esophagitis
TSLP	thymic stromal lymphopoietin
TSLPR	thymic stromal lymphopoietin receptor
iNKT	invariant natural killer T cells
TGF	transforming growth factor
IL	interleukin
TNF	tumor necrosis factor
TLR	toll like receptor
Treg	T regulatory cells
DC	dendritic cells
ILC2	innate lymphoid cell type 2
APC	antigen presenting cell
SNP	single nucleotide polymorphism
BRCA	2-breast cancer 2, early onset-associated protein
IFN	interferon
ISG	interferon-stimulated gene
NK	natural killer cells
dsRNA	double strand RNA
PPI-REE	Proton Pump Inhibitor Responsive Esophageal Eosinophilia
TCR	T cell receptor
HR	histamine receptor
GERD	gastroesophageal reflux disease
GWAS	genome wide array study
miRNA	micro RNAs
PPI	proton pump inhibitor
BMP	Bone morphogenetic protein

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❖ Papers of interest

• Papers of considerable interest

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Key Issues

- Eosinophilic Esophagitis is a TH2 mediated allergen driven disease, however, IgE is not necessary.
- TSLP and CAPN14 are linked to the disease pathogenesis by genetic and mechanistic studies.
- Persistent disease leads to fibrosis of the esophagus, but, the exact mechanism is not known.
- Current treatment is based on food allergen avoidance and steroid use, but it is very specific and it manages but doesn't cure the disease
- Biological aim at blocking key cytokines in EoE pathogenesis (anti-IL-5, IL-13) have not been lead to complete resolution of disease, most likely due to the fact that many Th2 cytokines have redundant functions
- Newer therapeutic agents are necessary.
- The new advancement in understanding EoE pathogenesis, may lead to the development of new therapeutic targets