Genome Medicine

COMMENTARY

New genetic links in eosinophilic esophagitis

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Abstract

Eosinophilic esophagitis (EoE) is increasingly diagnosed as a disorder throughout the world. It is characterized by eosinophils in the esophagus due to food allergies. Molecular analysis of esophageal biopsies and mouse models have indicated a clear role for the T helper 2 pathway, in particular interleukins 5 and 13, in this disease. Current treatment options for EoE involve avoidance of the allergens or using anti-inflammatory medications such as topical corticosteroids. In the past year, genomic research has led to the identification of single nucleotide polymorphisms in the gene encoding thymic stromal lymphopoietin (TSLP), and subsequently in the gene encoding its receptor, as disease susceptibility markers for EoE. Identification of this molecule and its receptor suggest the potential for new treatment options in the future.

Definition and prevalence of eosinophilic esophagitis

Eosinophilic gastrointestinal diseases are increasingly recognized and diagnosed disorders that include eosinophilic esophagitis (EoE), eosinophilic gastroenteritis and eosinophilic colitis. Among the eosinophilic gastrointestinal diseases, EoE has become increasingly prevalent in the United States, Switzerland and Australia [1]. Overall, EoE is a global health condition now reported on all continents except Africa, with an incidence of approximately 5 in 10,000 [1,2].

The diagnosis of EoE is based on clinicopathology and depends in part on demonstration of esophageal eosinophilia. A panel of experts proposed consensus recommendations in 2007 [1], which included the demonstration of 15 or more eosinophils in at least one high-powered field despite treatment with a proton pump inhibitor or exclusion of gastroesophageal reflux disease (GERD) by ambulatory pH monitoring. The clinical presentation of EoE varies with age: infants and toddlers often have difficulty feeding and fail to thrive, school-age children present with vomiting and epigastric or chest pain, and adolescents and adults present with dysphagia and food impaction [3].

EoE is considered a food-allergy-related disorder on the basis of several findings. Most patients are atopic individuals (that is, they have a high rate of food allergen sensitization as determined using skin prick and patch testing); in addition, EoE patients have a higher rate of food anaphylaxis than the general population [4]. Moreover, nearly all EoE patients have complete remission following introduction of an elemental formula diet that removes all allergens from the diet; conversely, the disease flares on reintroduction of specific foods [3]. Unlike classic anaphylaxis that typically involves a limited set of foods, EoE patients are often sensitized to a myriad of foods, often including food groups not typically considered to elicit anaphylaxis [4].

Mechanism of eosinophilic esophagitis

EoE seems to be similar to many other allergic diseases with a mechanism of disease mediated by T helper 2 (Th2) cells. Experimental mouse models have demonstrated key roles for adaptive immunity, Th2 cell cytokines (especially interleukin (IL)-5 and IL-13) and eosinophilic-attraction chemokines such as CCL26 (also called eotaxin-3) in the development of EoE, and also a strong connection between allergic sensitization and inflammation in the respiratory tract and skin [5,6]. IL-13 has been shown to induce many of the features of EoE in human tissue and murine systems, including the induction of CCL-26 [7]. Genome-wide profiling revealed that CCL-26 is overexpressed about 50-fold compared with normal controls or patients with GERD [6]. In addition, Rothenberg and colleagues [6] found that the EoE transcriptome was consistent across sex, age and familial or non-familial inheritance patterns and was independent of atopic status, suggesting a common disease mechanism despite phenotypic variations. A potential proposed mechanism is that Th2 cell activation leads to overexpression of CCL-26 and thereby to migration of eosinophils to the esophagus.

Work by Aceves and colleagues [8] showed that eosinophilic migration and activation in EoE lead to

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subepithelial fibrosis and to increased expression of transforming growth factor β (TGF-β) and its downstream signaling molecule phospho-SMAD2/3 compared with patients with GERD and healthy controls. In addition, esophageal biopsies demonstrated an increased expression of vascular cell adhesion molecule 1 (VCAM-1) [8]. This fibrosis may account for the esophageal dysmotility that leads to the symptoms of dysphagia and food impaction observed in adults. The chronic fibrosis and changes in inflammatory markers also parallel symptoms observed in asthma.

Genetic links in EoE

The evidence indicates that EoE has a strong familial association, with nearly 10% of parents of EoE patients having a history of esophageal strictures and about 8% having biopsy-proven EoE [5]. EoE also shows a high sibling risk ratio (λ_S) of approximately 80 compared with related atopic diseases such as asthma (λ_S about 2) [9]. The first candidate gene for EoE identified was *CCL-26*, the most overexpressed gene in the esophagus as determined by genome-wide expression profiling [6]. However, the disease-associated allele is present in only 14% of EoE patients [6].

Rather than looking at the potential pathways, Aceves and colleagues [10] examined response to topical corticosteroids - a standard therapy for the condition - in patients with EoE. A positive response was defined as residual eosinophil counts of seven or fewer eosinophils per high-power field. Responders had a reduced esophageal remodeling with decreased fibrosis, fewer TGF-β- and pSmad2/3-positive cells and decreased vascular activation following therapy with the corticosteroid budesonide. Responders were more likely to have a CC genotype at the -509 position in the TGF-β promoter than were non-responders.

More recently, a multi-center genome-wide association study (GWAS) has identified the thymic stromal lymphopoietin (*TSLP*) gene, at 5q22, as an important candidate gene in the pathogenesis of the disease [11]. TSLP is an epithelial-derived cytokine that activates professional antigen-presenting cells, such as dendritic cells, which initiate Th2-type allergic responses [12]. The same study also found an increased expression of *TSLP* in the esophagi of patients with EoE compared with healthy controls [11].

The most recent finding by Sherrill *et al.* [13] adds to our understanding of the interaction of *TSLP* and EoE. This genomic analysis [13] focused on key allergic single nucleotide polymorphisms (SNPs) along with epithelial SNPs and compared them in atopic and healthy controls. In addition to replicating the significant association between SNPs at *TSLP* and EoE, they found that *TSLP* variants remained significant when compared with atopic controls in their study [13] or asthma controls from the previous GWAS analysis [11]. However, variations in the *TSLP* gene were not significant when compared with controls, probably because of the small number of controls used. *TSLP* has also been found to be associated with atopic dermatitis [14] and asthma [15] compared with healthy controls. The finding of *TSLP* being significant only among the atopic controls could be due either to the other studies not removing patients with EoE (which is commonly atopic) from their control group or to the possibility that *TSLP* might trigger multiple atopic diseases depending on secondary signals.

Sherrill and colleagues [13] also found a SNP in the TSLP receptor (TSLPR) gene that was associated with EoE. The gene encoding the TSLP receptor is located on the pseudoautosomal region on Xp22.3 and Yp11.3 and it was significantly associated with disease only in male patients with EoE. Given that EoE is more common among males by a 2:1 ratio [1], the finding of a SNP in the TSLPR suggests a potential mechanism for the male dominance observed in EoE. Sherrill *et al.* [13] also noted one additional finding that may suggest alternative pathways for the treatment or the pathogenesis of EoE: they observed that stimulation of primary esophageal epithelial cells with poly I:C (a double-stranded RNA mimetic) induced the expression of *TSLP* mRNA. This induction was dependent on Toll-like receptor (TLR)-3 stimulation. TLR-3 recognizes double-stranded RNA, which is found in some viruses such as reoviruses. These results suggest a second hit for the development of EoE with a viral trigger and allergen exposure. In the lung and skin TSLP is produced primarily by epithelial cells in response to Th2 cytokines or TLR3 agonists, and it subsequently targets dendritic cells to secrete Th2-inducing activity, including Th2 cytokine and chemokine production.

These findings [13] suggest a unique potential mechanism for the induction of EoE. Could food allergens trigger the TLR-3 receptor, inducing TSLP and causing the activation of the Th2 pathway, leading to eosinophilic inflammation in the esophagus? Or is there a 'second hit', a virus that makes susceptible people develop EoE?

Potential pathways for treatment

The current treatment options for EoE involve the avoidance of the trigger (foods) and the treatment of the underlying inflammation with topical corticosteroids [1]. Treatment with food avoidance is highly successful, with rates close to 100% with elemental diets (amino acid formulas) [1]. However, these formulas are unpalatable and lead to low quality of life. Eliminating foods on the basis of allergy testing or empirical elimination leads to resolution of esophageal eosinophilia in 50 to 80% of patients, depending on the diet and the age of the patient

and reduction of symptoms in over 90% of the patients [3]. These diets are also difficult to maintain and many patients refuse to continue them. Treatment with topical steroids can work for 50 to 80% of patients, but there are also some drawbacks. Topical corticosteroids can lead to localized yeast infections and have potential long-term side effects, including growth suppression and osteopenia (low bone density); however, these have not been studied or seen in short-term studies. Other treatments currently being investigated include anti-immunoglobulin (Ig)E, anti-IL-5, anti-IL-13 and chemoattractant homologous receptor expressed on Th2 cells (CRTH2) antagonist or topical corticosteroids [16-18].

The recent identification of TSLP and its receptor as key components in the EoE pathogenesis [13] suggests that blockage of the TSLP-TSLP receptor activation could provide an attractive approach to treating the cause of EoE. In addition, the new finding that TLR-3 induces TSLP suggests that a second hit (a virus) may trigger this pathway. If a particular virus or microorganism unique for EoE were identified, this would allow the development of a preventive strategy. This is unlikely to occur in the near future, but treatment with TLR-3 antagonists or blocking downstream signaling already represent hope for the treatment of EoE.

Abbreviations

CCL-26, chemokine (C-C motif) ligand 26; EoE, eosinophilic esophagitis; GWAS, genome-wide association study; GERD, gastroesophageal reflux disease; SNP, single nucleotide polymorphism; TGF-β, transforming growth factor; Th2, T helper 2; TLR, Toll-like receptor; TSLP, thymic stromal lymphopoietin.

Competing interests

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