Genetic and Epigenetic Underpinnings of Eosinophilic Esophagitis

Joseph D. Sherrill, PhD, Marc E. Rothenberg, MD, PhD*

KEYWORDS

• Genetic variant • Thymic stromal lymphopoietin • Eotaxin-3 • Epigenetics
• MicroRNA

KEY POINTS

- Eosinophilic esophagitis (EoE) is a complex, polygenic disorder.
- Disease risk variants and an altered esophageal transcriptional profile underlie the genetic origin of EoE.
- Emerging epigenetic modifications link environmental exposures to the genetic dysregulation in EoE.

INTRODUCTION

Early evidence for a genetic origin of eosinophilic esophagitis (EoE) came in the form of several epidemiologic studies showing a high prevalence of disease in specific genders and races, with nearly three-quarters of patients being men and almost all (≈90%) being of European descent, respectively.[1] Moreover, an increased disease risk is seen among familial cases, which typically demonstrate a non-Mendelian inheritance pattern.[2] Expression profiling from esophageal biopsies acquired during routine endoscopic procedures has provided molecular insight into genetic dysregulation occurring within the inflamed esophagus. These transcriptional changes affect both coding and noncoding (microRNA) transcripts and underscore consistent, disease-specific alterations in the levels of select molecules expressed by activated immune cells and structural cells of the esophagus.[3,4] These dysregulated transcripts and associated biologic pathways represent potential targets for novel therapeutics and diagnostic methods.[5]

In addition to the genetic elements, a role for environmental factors in EoE has been established through both clinical and basic research. Patients with EoE are often

Division of Allergy and Immunology, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, 3333 Burnet Avenue, Cincinnati, OH 45229, USA
* Corresponding author. Division of Allergy and Immunology, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, Cincinnati, OH 45229.
E-mail address: marc.rothenberg@cchmc.org

Gastroenterol Clin N Am 43 (2014) 269–280
http://dx.doi.org/10.1016/j.gtc.2014.02.003 **gastro.theclinics.com**
0889-8553/14/$ – see front matter © 2014 Elsevier Inc. All rights reserved.

hypersensitized to multiple food antigens, making directed dietary modification one of the most effective therapies for EoE.[6] Several early life exposures, including Cesarean birth, antibiotics, and formula feeding, have been identified to influence the risk of pediatric EoE.[7] In addition, geographic location, industrialized environments, history of *Helicobacter pylori* infection, and seasonal variations in disease implicate environmental antigens.[8–11] These clinical findings have been supported through multiple basic research studies showing that epidermal and pulmonary exposure to various antigens can induce EoE-like symptoms in mice.[12–14] Emerging epigenetic data are now beginning to provide clues as to how these environmental factors may be intricately intertwined with the genetic dysregulation in EoE and thus act in a concerted fashion to affect disease pathophysiology.

GENETIC VARIANTS

Several candidate gene approaches have identified a handful of genetic risk variants in EoE. For instance, a common single-nucleotide variant (minor allele frequency [MAF] = 0.25 in the HapMap[15] population of European descent) located in the 3′ untranslated region of the chemokine (C-C motif) ligand 26 (*CCL26*) was overrepresented in patients with EoE in both a case-control and a family-based analysis.[4] Furthermore, 2 coding variants (R501X and 2282del4) in the epidermal barrier gene filaggrin (*FLG*), which is negatively regulated by interleukin (IL) 13 and is decreased in the esophageal mucosa of patients with EoE, associate with EoE risk.[16] Lastly, in a small cohort of patients with steroid-treated EoE, a genetic variant in the promoter of the transforming growth factor beta 1 (*TGF-β1*) gene, was associated with steroid unresponsiveness and correlated with increased TGF-β1–positive cells in the esophagus.[17] The genetic link between the TGF-β pathway and EoE identified in this study is remarkable given the evidence showing a high rate of EoE, other eosinophilic gastrointestinal disorders, and atopic disease in patients with connective tissue disorders,[18] such as Loeys-Dietz syndrome, which has been associated with variants in the TGF-β receptors 1 and 2 (**Table 1**).[19]

To identify disease risk variants in a more unbiased fashion, a genome-wide association study (GWAS) was performed in which 351 patients with EoE and 3,104 healthy controls were genotyped for more than 550,000 common variants. On chromosome 5q22, a single locus spanning the thymic stromal lymphopoietin (*TSLP*) and WD repeat domain 36 (*WDR36*) genes showed a significant association with EoE susceptibility.[20] TSLP is a potent Th2-promoting cytokine involved in the development of multiple allergic diseases.[21] Expression analyses showed increased *TSLP* in EoE and a genotypic effect of the top associated variant on *TSLP* expression, with patients carrying the risk allele having elevated *TSLP* expression.[20] In addition, *TSLP* risk genotypes correlated with increased levels of basophils, which have a key role in promoting EoE-like disease in mice, and with granulocyte-monocyte progenitor-like cells in the esophagus.[14,22]

A secondary candidate gene approach also identified variants within the *TSLP* locus that were significantly associated with EoE risk.[23] In this study assessing more than 700 variants in epithelial-derived genes linked to atopy, *TSLP* variants were the most significant genetic hits linked to EoE that, importantly, showed a stronger association with disease risk when compared with controls with atopic diseases (atopic dermatitis and asthma).[23] Moreover, a coding variant in the cytokine receptor–like factor 2 (*CRLF2*) gene, which encodes for the receptor for TSLP, showed a sex-specific association with EoE risk in men only.[23] These cumulative data support aberrant regulation affecting the TSLP pathway as a specific genetic origin in EoE. Given the

Download English Version:

https://daneshyari.com/en/article/3300834

Download Persian Version:

https://daneshyari.com/article/3300834

Daneshyari.com