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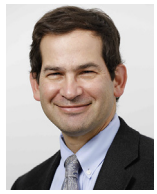
Pathophysiology of Eosinophilic Esophagitis







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Eosinophilic esophagitis is an emerging disease that is distinguished from gastroesophageal reflux disease by the expression of a unique esophageal transcriptome and the interplay of early life environmental factors with distinct genetic susceptibility elements at 5q22 (*TSLP*) and 2p23 (*CAPN14*). Rare genetic syndromes have uncovered the contribution of barrier disruption, mediated in part by defective desmosomes and dysregulated transforming growth factor beta production and signaling, to eosinophilic esophagitis pathophysiology. Experimental modeling has defined a cooperative role of activated eosinophils, mast cells, and the cytokines IL-5 and IL-13, mediated by allergic sensitization to multiple foods. Understanding these processes is opening the way to better treatment based on disrupting allergic inflammatory and type 2 cytokine–mediated responses, including anti-cytokine therapeutics and dietary therapy.

Keywords: Allergy; Desmosome; Genetics; Inflammation.

Eosinophilic esophagitis (EoE) is a chronic type 2–associated inflammatory disease characterized by predominant and marked eosinophilic inflammation of the esophagus (a peak count of ≥15 eosinophils per high-power field of esophageal biopsy tissue); the diagnosis has been traditionally limited to patients who have persistent esophageal eosinophilia after a documented proton pump inhibitor trial,[1] but it has recently been recommended that proton pump inhibitor responsiveness is not part of the diagnostic criteria but rather an appropriate and effective treatment for some patients.[1–3] The disease is associated with upper gastrointestinal symptoms that vary with age and can include fibrostenotic complications. EoE is triggered by allergen exposure, typically food allergens, and is responsive to topical glucocorticoids and dietary elimination therapy (Figures 1 and 2). The pathogenesis of EoE is being extensively studied, and there have been recent advances concerning the genetic and environmental contributors, as well as the cellular and molecular etiology. This has led to numerous new therapies targeting these molecular pathways that are currently being tested for disease treatment. Herein, we will focus on recent advances concerning the pathogenesis of EoE.

Genetic Etiology

The prevalence of EoE is approximately 1 in 2000 and has a known male predominance, with a male-to-female ratio approaching 3:1.[4,5] EoE has a strong hereditability pattern, with familial associations having relative risk ratios as high as 64-fold amongst brothers.[6] Proband concordance in monozygotic twins is 58%, substantiating a genetic etiology.[7] Several different studies, including candidate-gene identification and genome-wide association studies have identified multiple genes that are likely contributing to the development of EoE. These genes include thymic stromal lymphopoietin (*TSLP*), calpain 14 (*CAPN14*), *EMSY*, *LRRC32*, *STAT6*, and *ANKRD27* (Table 1). However, it is important to note that dizygotic twins have a 36% concordance, whereas non-twin siblings have

Abbreviations used in this paper: **CEGIR, Consortium of Eosinophilic Gastrointestinal Disease Researchers; EoE, eosinophilic esophagitis; OIT, oral immunotherapy; Th2, T-helper type 2.**

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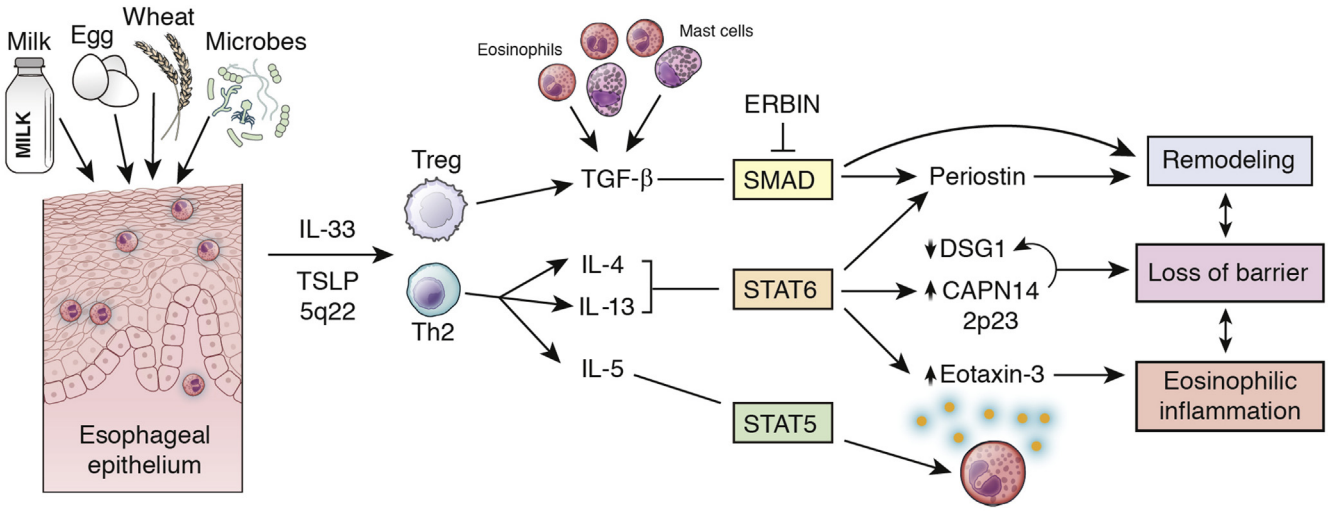

Figure 1. Pathophysiologic overview of EoE. Environmental factors, including foods and the microbiome, interact with the esophageal epithelium to elicit production of the proatopy cytokines IL-33 and TSLP. Activated T regulatory and T helper type 2 cells secrete bioactive cytokines including TGF-β, IL-4, IL-13, and IL-5, which elicit barrier disruption, tissue remodeling, and eosinophilic inflammation.

a 2.4% concordance; the stark difference demonstrates the substantial influence of a shared twin environment, likely via epigenetic mechanisms, at least partially.[7] Consistent with this, the strongly associated EoE genes *CCL26* (encoding eotaxin-3, a potent eosinophil chemoattractant and activating factor induced by IL-3) and *CAPN14* (encoding CAPN14) are under epigenetic regulation.[8,9]

A section of the human genome, known as the EoE transcriptome, has a conserved expression in the esophagus of patients with EoE; this region is not dysregulated in patients with gastroesophageal reflux disease.[10] The most highly expressed gene, compared with controls, is the IL-13–induced gene *CCL26*.[10,11] The EoE transcriptome is distributed throughout the genome, but the strongest "hot spot" for transcriptional changes occurs at 1q21, which encodes for the epidermal differentiation complex. This region contains genes that are involved in squamous epithelial cell differentiation, such as filaggrin; these genes are notably down-regulated in EoE, consistent with a loss

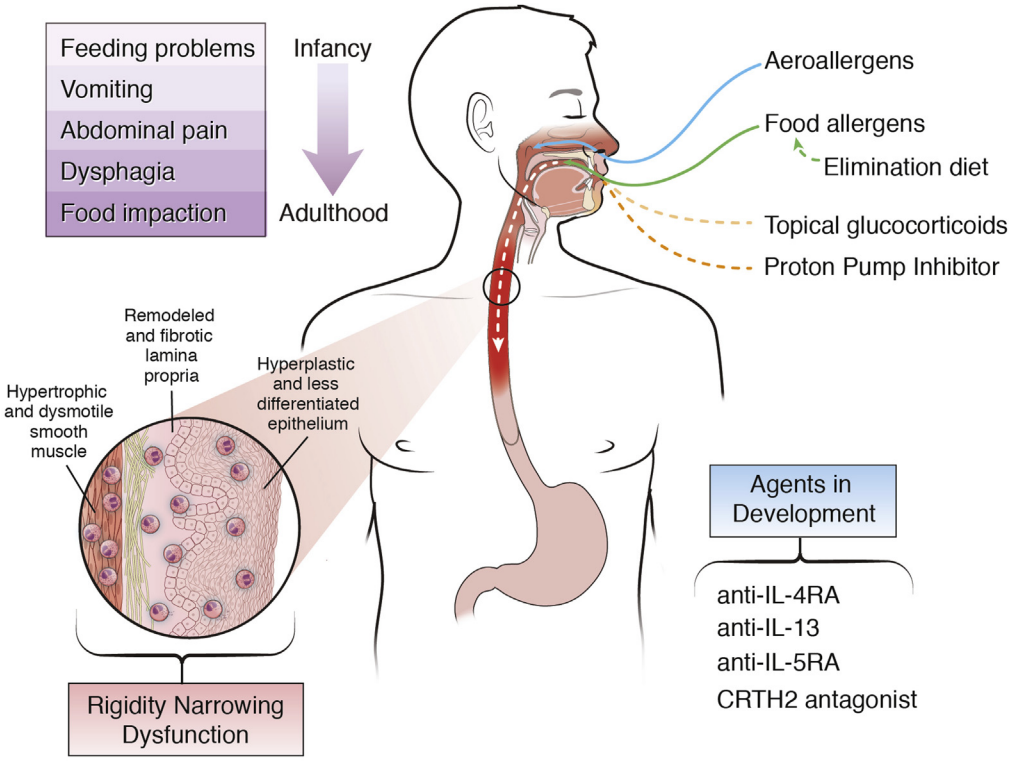

Figure 2. Clinical, pathologic, and therapeutics of EoE. Allergens drive EoE; current (glucocorticoid and dietary therapy) and future interventions can treat the disease. The presenting symptoms are shown, leading to esophageal inflammation, remodeling, rigidity, and dysfunction.