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Review Article

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Eosinophilic Esophagitis Pathogenesis: All Clear?

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Abstract
Background: Eosinophilic esophagitis (EoE) is a food- and aeroallergen-driven, type 2-mediated chronic inflammation that develops in genetically predisposed individuals with an impaired esophageal epithelial barrier. How pollutants, including detergents, the esophageal microbiome, immunity, and genetics trigger the multifaceted pathophysiology of EoE is not clear. ***Summary:*** This review summarizes and discusses recent findings concerning the possible contribution of the environment/exposome, the esophageal microbiome, genetics, immunity, and epithelial barrier integrity to developing esophageal type 2 inflammation and fibrosis in EoE. After summarizing the current literature, we formulate research questions that we consider relevant to EoE. ***Key Messages:*** The anticipated progress in preclinical EoE animal models, primary cell culture technologies, sequencing technologies, and clinical trials, driven by academic research and the pharmaceutical industry, is poised to revolutionize our understanding of EoE. These advancements may uncover novel pathways that can be targeted for EoE treatment, inspiring hope for improved patient quality of life.

Introduction

Eosinophilic esophagitis (EoE) is a food- and aeroallergen-driven, type 2 chronic inflammation characterized by >15 eosinophils in a genetically predisposed individual triggered by environmental factors (shown in Fig. 1 [1]). Increasing numbers of publications since the first description of EoE by Atwood and Straumann in 1993 [2, 3] have implicated the rise in EoE incidence and prevalence due to the exposure to detergents [4], changes in the microbiota composition [5, 6], impaired epithelial integrity [7], and type 2 inflammation [8] with many of the past findings being associative. The field moves with sophisticated studies and the implementation of meticulous clinical trials [9] from associations toward translational/mechanistic advances in the pathophysiology of EoE. This movement, escorted by the development of novel technologies, such as organoid cell culture [10] and high-throughput sequencing technologies [11], will push the field forward to understand the complex mucosal immune system of the esophagus and the development of EoE, resulting in novel therapies for EoE.

The esophageal mucosal immune system can be pharmacologically manipulated to treat EoE. A recent example is the introduction of the monoclonal antibody dupilumab into the clinic, which targets the alpha chain shared by the IL-4 and IL-13 receptors [9]. Further advances in EoE research are essential in light of the possible debilitating disease course with food impaction [12], perforation [13], and impaired life quality [14] for patients suffering from

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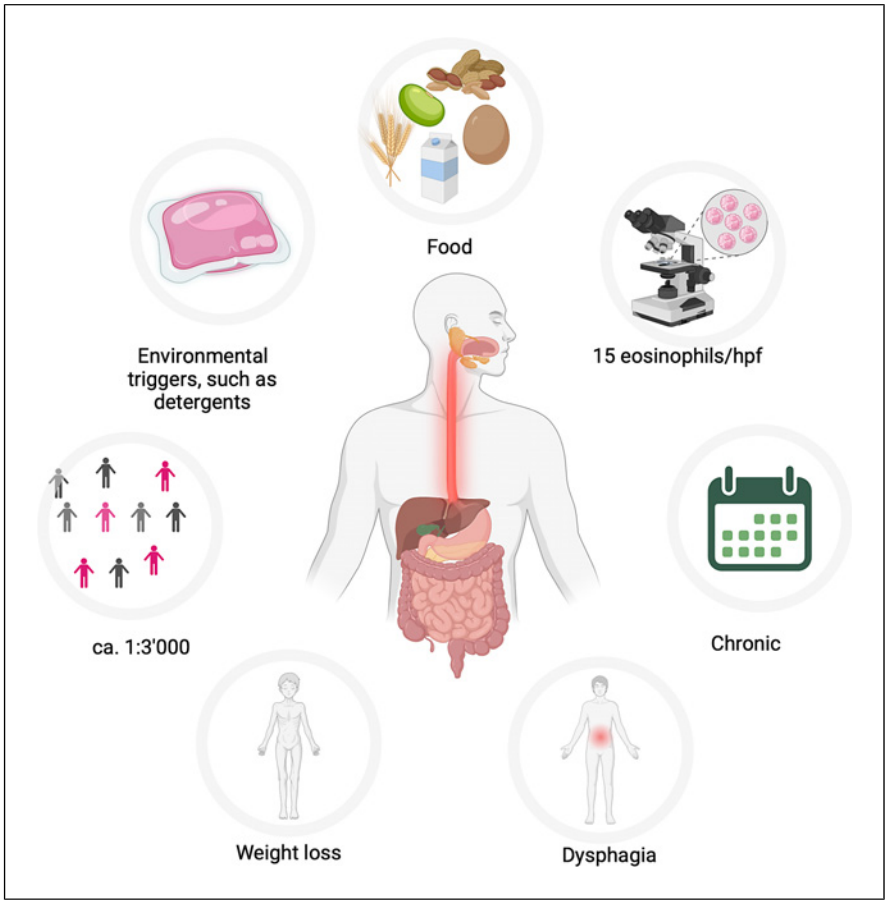

Fig. 1. The food- and aeroallergen-driven EoE is a type 2 chronic inflammation of the esophagus in a genetically predisposed individual. More than 15 eosinophils in the esophageal epithelium are the histologic criterion for diagnosing EoE triggered by environmental factors.

EoE. Genome-wide association studies (GWAS) have linked the EoE risk with single-nucleotide polymorphisms (SNPs) in genes implicated in barrier integrity and type 2 immunity [15]. The rise of the EoE prevalence in the last decades cannot be attributed to genetic predisposition alone. Studies have described associations between EoE and exposure to pollutants impairing barrier integrity, such as food emulsifiers in industrialized food, laundry, and toothpaste detergents [16]. Providing causal relationships between the exposome and EoE development is challenging, but we anticipate it will be critical to offer causal relationships to improve the care of EoE patients.

Recent years have witnessed tremendous progress in molecular biology and mucosal immunology technologies, including metagenomics for microbiome sequencing, T-cell receptor (TCR) sequencing, three-dimensional cell culture technologies, and metabolomics. In parallel, clinical trials have significantly improved by defining more stringent endpoints. These advancements will help uncover new approaches for treating EoE by restoring the disturbed epithelial barrier, targeting immune pathways, manipulating the esophageal microbiota, preventing exposure to environmental triggers, and better understanding how food-derived antigens induce EoE.

We want to emphasize that the esophageal immune system and microbiome are understudied compared to the skin and the small and large bowel [17]. We predict that the increased incidence and prevalence of EoE, with significantly impaired quality of life for affected individuals, and the opportunities for the pharmaceutical industry to develop biologics for EoE will arouse the interest of academic and pharmaceutical industry-driven research in the esophageal immune system. In this review, we aimed to summarize the current knowledge of EoE pathophysiology and discuss open questions in EoE research.

The Exposome

The incidence and prevalence of EoE are rising, as studies with children and adults in North and South America, Europe, Asia, and Australia suggest [18–22]. It

is estimated that the EoE prevalence is 32.5 in adults and 30.9 in children per 100,000 population, affecting 1 in 3,000 inhabitants in areas with a westernized lifestyle [1]. The steady increase in EoE, previously considered a rare disease, raises the question of why this dramatic increase in prevalence occurs. This increase in EoE prevalence coincides with an increase in allergies, autoimmune diseases, and inflammatory bowel disease [23]. The hygiene hypothesis proposes that reduced exposure to certain microorganisms and parasites in early childhood, as observed in westernized areas, predisposes to increased frequencies of allergies and autoimmune diseases [24]. In light of the hygiene hypothesis, an inverse correlation between EoE and gastric *Helicobacter pylori* infection has been reported [25–28]. It must be pointed out that EoE, in contrast to allergies, develops independently of IgE and depends on food and aeroallergens [29]. More importantly, epidemiological studies investigating the associations between children's exposure to microorganisms and an increased EoE risk provide conflicting results. A case-controlled study investigating associations between perinatal factors, such as preterm delivery, neonatal intensive care unit (NICU) admission, breastfeeding, antibiotics in infancy, and absence of furry pets and EoE development revealed associations between breastfeeding and early NICU admission in children with SNP in calpain-14 (CAPN14), CCL26, thymic stromal lymphopoietin (TSLP), the KLF13 region, and TGFB [30].

Conversely, Radano and colleagues [31] found associations between caesarean sections, early antibiotic use, and EoE. Studies reporting associations between living in urban and rural areas with EoE provided inconsistent results. In a cross-sectional, case-control study of patients with esophageal biopsies in a US national pathology database, living in rural areas was associated with increased esophageal eosinophilia [30]. Another cross-sectional study with children <18 years enrolled in the US Medicaid reported that living in rural areas and areas with more neighborhood poverty had lower odd risk associations with EoE [32]. Possible confounding factors by race and ethnicity and different definitions of urban areas may have contributed to divergent results, as in the USA, more Caucasians with a higher risk of EoE live in rural areas. More detailed studies delineating environmental factors associated with EoE development are warranted to explain the increased EoE prevalence in westernized areas.

Another theory has hypothesized that an increased barrier leakiness due to pollutants is implicated in the rising prevalence of allergies, autoimmune diseases, and inflammatory bowel disease [33]. This hypothesis seems particularly relevant for EoE as the penetration of food and aeroallergens across the epithelial barrier causes EoE. Plasticizers, such as bisphenol A and phthalate added to polymers or plastics to soften them, have also been suggested to impair the epithelial barrier and be associated with type 2 inflammation [34]. It has been proposed that changes in industrialized food processing occurred parallel with the increase in EoE prevalence. Emulsifiers create stable homogenous emulsions by binding their hydrophobic ends to oils and fats and hydrophilic ends to water. They are food additives in bread, chocolate, ice cream, margarine, and processed meat. Observational studies have indicated associations between ultra-processed food and type 2 inflammation, including EoE [35]. Providing causal relationships between food emulsifiers and EoE is challenging as prospective randomized-controlled trials investigating the impact of food emulsifiers on gastrointestinal diseases must be conducted in the future.

Recently, detergents, such as sodium dodecyl sulfate (SDS), present in laundry detergents and toothpaste and used as a food additive, have been suggested to be associated with EoE. An exciting report shows that adding increasing concentrations of SDS to air-liquid interface (ALI) cultures with the telomerase-immortalized human esophageal epithelial cell line EPC2 and to mouse esophageal organoids impairs esophageal barrier integrity assessed by transepithelial electrical resistance (TEER) measurements [4]. Adding 0.5% SDS to the drinking water for 14 days elicited esophageal inflammation in 50% to 100% of C57BL/6J mice, depending on the cohort, associated with eosinophilic abscesses and spongiosis [4]. The authors used low SDS concentrations in the in vitro (200 ng/mL) and in vivo (0.5% SDS in the drinking water) experiments, which were lower than the 3% SDS in some toothpaste. However, future studies must still address whether comparable concentrations and exposure times occur in humans when exposed to SDS in detergents and hygiene products.

Studying the link between changes in food production and processing, including livestock farming and plant breeding, together with industrial food production that has occurred in parallel with the emergence of EoE, is an exciting avenue in EoE research. Considering the increasing number of observational cohort studies describing associations between changes in the food production of westernized countries, providing evidence of causal relationships between ultra-processed foods and EoE remains challenging. In the future, interventional clinical trials or

preclinical experimental systems will establish potential causal connections between environmental pollutants, dietary behaviors, and EoE.

Microbiome

The esophageal mucosal immune system has been implicated as critical for the development of EoE. Since the esophageal immune system is in continuous contact with food-derived antigens and microorganisms that colonize the surface of the epithelial cells, it is tempting to speculate that an altered esophageal microbiome is involved in EoE. A study in mice indicated regional differences in the microbiome composition between the proximal and distal esophagus, reflecting anatomic differences in the muscle composition between the proximal and distal esophagus [36]. The exposure of the distal esophagus to gastric reflux with a low pH may, in addition, also explain the differences in the microbiome composition between different esophagus segments. In the same study, germ-free animals were colonized with a microbiome from SPF animals, inducing transcriptional changes in genes involved in epithelial development, cell adhesion, nuclear body proteins, cellular respiration, and histone acetylation. This suggests that although the density of the esophageal microbiome is low compared to the large intestine, possibly explained by the rapid transit of particles through the esophagus [17], the microbiota influence tissue homeostasis and perhaps epithelial barrier integrity [36]. Challenges in obtaining samples by invasive gastroscopy, amplifying low microbe numbers before sequencing, and preventing oral and gastric cross contamination are technical hurdles to studying the microbiome's composition in the esophagus. This may explain why only a few studies have investigated associations of the esophageal microbiome with EoE. Active EoE generally leads to an increased microbial density with increased *Haemophilus* abundance [5, 37] and decreased representatives of the *Firmicutes* phylum, including *Streptococcus*, *Lactobacillus*, *Veillonella*, and *Parvimona* [6, 38]. One study reported normalization of the microbiota composition in patients on a six-food elimination diet [6]. Other studies have conversely shown increased microorganism abundance in EoE independent of the treatment and disease activity [5].

Interestingly, the esophageal microbiome correlates with the oral microbiome [6, 39, 40]. Possible explanations for the correlation between the oral and esophageal microbiome could be that oral microorganisms are constantly swallowed into the esophagus. The salivary glands produce IgA that binds to and coats microorganisms through canonical binding with their Fab fragments and other noncanonical binding modalities, including glycan regions on the Fc fragment independent of the B-cell repertoire [41]. The swallowing of IgA from the oral cavity leads to the same IgA molecules in the oral cavity and the esophagus, possibly another reason for the correlations between the oral and esophageal microbiome. These findings have to be validated in further studies, taking into account the esophageal and oral biogeography considering the proximal and distal esophagus and the soft buccal mucosa, the keratinized mucosa of the palate, gingiva, and tongue papilla, the tooth enamel, and the saliva in the oral cavity [42]. If independent studies can confirm the correlation between the oral and esophageal microbiome, these findings could open new avenues for EoE research, given the accessibility of the oral cavity. Elegant studies in ileostomy and colostomy patients providing easy access to the small intestinal microbiome without requiring ileocolonoscopy with bowel preparations have demonstrated the adaptability of the microbiome to test meals and the feasibility of investigating the adaptation of the microbiome to the diet when the microbiome is easily accessible [43]. Assuming the potential correlation of the oral and the esophageal microbiome and the easy accessibility of the oral cavity, it will be feasible to study alterations of the microbiome in response to different diets in the context of EoE by swabbing the oral cavity.

Genetics

Environmental factors partially explain the increase in EoE incidence and prevalence in the past decades. On the other hand, relatives of EoE patients have a 10- to 64-fold increased risk of developing EoE compared to the general population, implicating the importance of genetics for EoE. In monozygotic twins, the unaffected twin has a risk of 41% of developing EoE; in dizygotic twins, the EoE risk of the unaffected twins is 21%; in siblings, the EoE risk is 2.4% [44]. Nonetheless, genetic heritability appears to be a minor risk factor for EoE compared to the exposome, meaning that genetics unfolds its effects in the context of the environment. GWAS have identified SNPs with relatively low odds ratios ranging from 0.682 to 1.949 [15].

Conversely, rare Mendelian disorders, such as connective tissue disorders, including the Marfan syndrome [45], the Loeys-Dietz syndrome [46], Netherton's syndrome [47], or Erbin deficiency [48], develop EoE-like

inflammation in the esophagus [49]. For example, loss of function variants in the receptor of TGFβ (*TGFBR1* and *TGFBR2*) results in the predisposition of EoE in patients with Loeys-Dietz syndrome. Recently, the *M318R* mutation predisposing humans to allergic diseases has been introduced into the *Tgfbr1* locus of mice. These transgenic $Tgfbr1^{M318R}$ mice with the introduced point mutation driving a TGFβR1 without kinase activity develop EoE-like inflammation of the esophagus [50], indicating that inherited mutations can lead to EoE in rare circumstances.

More commonly than rare inherited mutations are SNPs associated with EoE with low odds ratios that, together with environmental exposures, predispose to EoE. These GWAS are a starting point for mapping the genetic landscape of EoE. Whole exome sequencing studies have yet to be performed in EoE to describe the genetic landscape in EoE. A recent metanalysis has highlighted SNPs in 13 genes associated with EoE [15]. These EoE candidate risk genes include *CAPN14*, *TSLP*, *WDR36*, *BACH2*, *TNFRSF10B*, *TNFRSF10C*, *GATA3*, *EMSY*, *LRRC32*, *ATP10A*, *CLEC16A*, *PNPLA3*, and *SAMM50* implicated for epithelial integrity and differentiation of immune cells. These GWAS thus suggest that the epithelium and immune cell differentiation are essential pathways for developing EoE.

Epithelial Barrier Integrity

GWAS have identified SNPs in genes responsible for epithelial integrity, suggesting impaired epithelial integrity is disease-inherent in EoE [15]. Conversely, immune cell-derived cytokines, such as IL-13, disturb epithelial integrity in the esophagus (shown in Fig. 2 [51, 52]). Treating EoE with elimination diets, proton-pump inhibitors, topical steroids, or monoclonal antibodies, such as dupilumab, targeting IL-4 and IL-13 signaling by binding to the IL-4Rα subunit shared by the IL-4 and IL-13 receptor could restore the impaired epithelial integrity caused by cytokine signaling [9, 51]. An intact epithelium prevents the intrusion of food antigens, providing a barrier restricting the access of potentially harmful antigens into the esophagus. This is particularly relevant for EoE as antigen deposition and penetration in and through the esophageal epithelium have been implicated in EoE [53]. Tight and adherens junctions seal the epithelium to provide the esophagus with a physical barrier adapted to the challenges of environmental signals caused by ingested food, caustic substances, infections, and refluxed gastric contents.

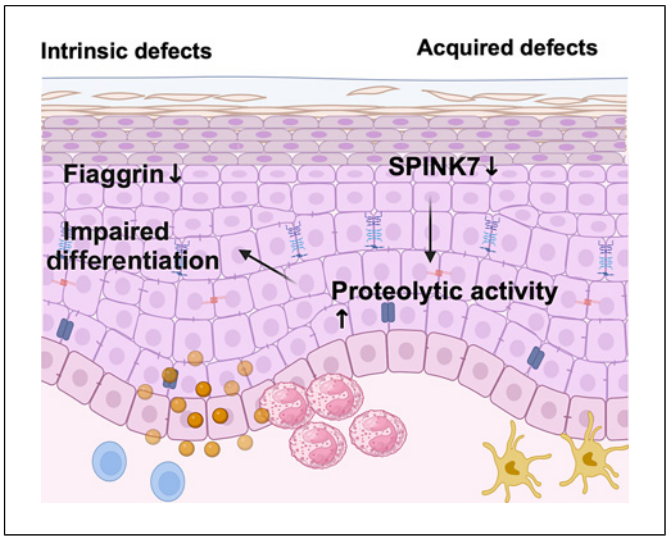

Fig. 2. GWAS have found SNPs in genes associated with epithelial integrity. These findings suggest that the impaired epithelial integrity observed in EoE is disease-intrinsic. Immune cell-derived cytokines, such as IL-13 or the IL-20 cytokine family members, impact epithelial integrity, hinting toward acquired epithelial breaches during inflammation.

The esophageal epithelium consists of nonkeratinized stratified squamous cells organized in the superficial stratum corneum, the underlying stratum spinosum, and the stratum germinativum [54]. The cells in the stratum corneum have a flat shape condensed through filaggrin (FLG) that binds to the keratins, forming the cytoskeleton of the cells. GWAS have proposed SNPs in the filaggrin genes as risk genes for EoE. As mentioned above, immune cell-derived cytokines also impair epithelial integrity. The most prominent example is IL-13, which has received much attention following the approval of dupilumab for EoE treatment.

Interestingly, stimulating esophageal epithelial cells with IL-13 leads to transcriptional changes resembling the EoE transcriptome [55]. Elegant mouse work using mouse lines with deletion of the Il13ra1 in esophageal epithelial cells indicated that IL-13, not IL-4, is the critical cytokine that alters the epithelium EoE [51]. IL-13 is also involved in epithelial-mesenchymal transition [56, 57], contributing to fibrosis development. Dupilumab, as a new therapeutic option, might prevent and even reverse fibrosis.

In addition to IL-13, transforming growth factor-β1 (TGF-β1) and oncostatin M have been suggested to be involved in esophageal barrier disturbances observed in EoE. Mediated by oncostatin M, mast cells decreased FLG, desmoglein 1, involucrin, and serine peptidase inhibitor

Kazal type (SPINK) 7 expression in the immortalized esophageal keratinocyte cell line EPC2, resulting in reduced TEER and increased epithelial permeability [58]. TGF-β1 also reduced TEER by decreasing the tight junction protein claudin-7 expression [59]. Finally, we recently added IL-19, IL-20, and IL-24 to the cytokines that induce esophageal barrier dysfunction. The IL-20 cytokine family members reduced the expression of genes and proteins involved in epithelial cell differentiation and keratinization, including FLG, in patient-derived organoids. They decreased TEER and increased epithelial permeability in patient-derived ALI cultures [52].

The epithelium also produces cytokines, triggering EoE. TSLP SNPs identified on locus 5q22 are risk gene variants for EoE [60]. Epithelial-derived TSLP activates dendritic cells and basophils to induce type 2 immunity in an antigen-induced EoE model in mice [61]. In addition, IL-33, an alarmin released by epithelial cells, acts on type 2 innate lymphoid cells in the lung or intestine [62]. It still needs to be established if this is the case in EoE. In this context, a 12-year-old boy was described as having developed EoE due to a 0.58-Mb duplication at chromosome 9p24.1 encompassing the entire IL33 gene, associated with elevated IL-33 levels [63]. Transgenic animals that overexpress secreted and active IL-33 by the esophageal epithelium spontaneously develop EoE, further supporting the relevance of IL-33 in type 2 inflammation [64]. These findings emphasize that the epithelium is actively involved in the pathogenesis of EoE by producing alarmins and cytokines that drive type 2 inflammation. The epithelium also maintains its integrity through transcription factor expression, such as hypoxia-inducible factor-1α. Hypoxia-inducible factor-1α maintains the esophageal epithelial barrier in response to inflammation-associated tissue hypoxia. It has been implicated that this process is disturbed in EoE [65].

Recently, it has been shown that a delicate balance between proteases and their inhibitors has to be maintained to secure epithelial integrity in the esophagus. Disturbance of this delicate balance is associated with the development of EoE, achieved by either the upregulation of proteases or the downregulation of their inhibitors. Elevated IL-13 increases the expression of the calcium-activated calpain protease CAPN14, degrading desmosomal proteins and impairing epithelial integrity in EoE [66]. Identifying CAPN14 by GWAS as a risk gene for EoE emphasizes the importance of this system in EoE development [67]. Reducing the SPINK family members' SPINK5 and SPINK7 expression in EoE results in the overactivation of proteases, including kallikrein 5, also contributing to epithelial barrier impairment [68, 69]. Cytokines, such as IL-13, regulate these fine-tuned relationships between proteases and their inhibitors. They are in parallel disease-inherently dysregulated, as GWAS have identified genes coding for proteases to be associated with EoE [67].

Dissecting disease-inherent mechanisms or consequences of inflammation in EoE is challenging. Animal models can provide insight into how inflammation alters epithelial integrity, which usually neglects the genetic predisposition in humans, as inbred mouse strains have the same genetic background to minimize variation between different experiments caused by various genetic backgrounds. It is also possible to stimulate three-dimensional ALI or organoid cultures derived from human esophageal biopsies or the telomerase-immortalized human esophageal epithelial cell line EPC2 to investigate the impact of immune cell-derived mediators on the intestinal epithelium. Conversely, introducing genetic mutations in transgenic animals allows the study of rare inherited mutations, as exemplified in the *Tgfbr1*^{M318R} mouse line harboring a point mutation of the *Tgfbr1* locus [50]. Genetic tools will also enable the manipulation of epithelial cell lines or primary cell cultures to investigate the impact of defined genetic alterations on epithelial integrity in EoE.

The identification of pathways that restore the epithelium offers excellent potential for the treatment of EoE. Most current therapies target inflammatory cytokines and do not primarily preserve or restore epithelial integrity. Reports suggest that vitamin D can antagonize the effects of IL-13 on the epithelium [70] and that the short-chain fatty acids butyrate and propionate can reverse the epithelial damage caused by IL-13 [71]. Given the low microbial load in the esophagus compared to the colon, it needs to be established whether butyrate serves as an energy reservoir for the esophageal epithelium as it does in the colon, where the fatty acid oxidation of short-chain fatty acids accounts for 70% to 90% of energy and 70% of oxygen consumption of epithelial cells [72]. Furthermore, 17β-estradiol also protects against IL-13-induced epithelial alterations [73]. However, taking into account the associations of elevated 17β-estradiol and frequencies of endometriosis, leiomyomata, venous thromboembolism, breast cancer, and ovarian cancer, we assume that establishing appropriate 17β-estradiol concentrations in females and males is a significant obstacle to avoid side effects. Considering the low vitamin D concentrations in many regions worldwide, testing the protective effects of vitamin D supplementation on EoE severity in interventional trials could be an exciting approach.

Immune System

EoE is a chronic type 2 inflammation of the esophagus occurring in genetically predisposed individuals exposed to unknown environmental triggers in childhood and adulthood. EoE is characterized by eosinophils (>15 eosinophils per high power field), other immune cells, including mast cells and T cells, and elevated IL-5 and IL-13 expression in the esophagus. Conversely, only a few immune cells reside in the non-inflamed esophagus, and no eosinophils are present in the esophagus, in contrast to other gastrointestinal tract segments, such as the small and large intestines. Better characterization of the esophageal immune landscape is required to understand the esophageal immune system in physiology and diseases, considering that the mucosal immunology of the esophagus is relatively understudied compared to the small and large intestine [17]. The increased eosinophil numbers in EoE imply that eosinophils are essential for the development of EoE. Clinical trials with eosinophil-depleting antibodies reduced eosinophil numbers in the esophagus as expected. Yet, they did not resolve clinical symptoms, presuming that other immune cells are involved and critical for the pathogenesis of EoE [74]. In contrast to atopic diseases, IgE does not play a significant role in the development of EoE [29]. Instead, elevated serum IgG4 levels have been described in EoE patients [75]. IgG4 has the lowest prevalence of all IgG subclasses, accounting for <5% of total IgG. Repeated allergen exposure leads to elevated serum IgG4 concentrations in patients with allergic diseases [76]. In line, high titers of IgG4 with specificity to cow milk in the serum and esophageal wall IgG4 deposits have been observed in EoE [29, 77]. Despite the unique properties of IgG4 in Fc-dependent effector functions, including complement activation, antibody-dependent cellular toxicity, and the capability of IgG4 to exchange Fab arms to bind two unrelated antigens [78], the significance of elevated IgG4 in EoE remains unclear.

There are only a few immune cells present in the healthy esophagus. A better understanding of pathways involved in homing immune cells to the esophagus promises the possibility of interfering with antibodies or small molecules. Immune-derived cytokines, including IL-13, induce the expression of chemokines, such as eotaxin-3 (CCL26), that attract eosinophils, T cells, and mast cells to the esophagus [79]. Case reports have suggested that blocking the integrin α4β7 required for immune cell homing to mucosal sites with the monoclonal antibody vedolizumab could be an option for treating EoE [80]. The sphingosine-1-phosphate 1 receptor modulator etrasimod inhibiting lymphocyte egress from lymph nodes is currently tested in the phase II VOYAGE trial (NCT04682639) for their safety and efficacy in EoE. In line with these findings, a recent manuscript reports that pathogenic effector Th2 cells in the esophagus with the GPR15 ligand GPR15L are expressed by epithelial cells in pediatric EoE patients. These findings highlight the relevance of pathways involved in lymphocyte homing to the esophagus for EoE [81]. In this study, using improved single-cell RNA-Seq platforms to profile esophageal tissue and the TCR repertoire, the authors succeeded in capturing and sequencing eosinophils that were previously missed due to the release of RNA-degrading ribonucleases by the eosinophils during the isolation process. The authors found indications for the clonal expansion of pathogenic effector Th2 cells in the esophagus that diverged from non-Th2 cells in other tissues. These clonotypes emerged in milk-reactive pathogenic effector Th2 cells in patients with milk-triggered EoE. In the future, chimeric antigen receptor T cells could eliminate the identified clones, assuming the rapidly progressing field of cellular therapies, including T cells carrying engineered chimeric TCRs directed against the T-cell clonotypes in patients with milk antigen-triggered EoE.

Considering that eggs, wheat, soy, peanuts/tree nuts, and fish/shellfish provoke EoE, it is interesting to investigate whether clonotypes generated by the antigen driving the disease occur in these patients. Nutrition influences multiple physiological processes besides T-cell immunity. A recent interventional trial assessing the impact of a ketogenic and vegan diet on immunity and the microbiota revealed that a ketogenic diet is associated with an enrichment of pathways involved in adaptive immunity. Conversely, the vegan diet was associated with enriching pathways involved in innate immunity [82]. The advancement of computational tools, including artificial intelligence, can predict three-dimensional structures of proteins to anticipate possible interactions and functions based on shape and binding sites in food-derived products, such as AlphaFold2 [83]. Biochemical studies will provide experimental validation to confirm the predictions of computational tools. This knowledge and interventional dietary trials on proteins that influence metabolic pathways will be essential in linking effective dietary interventions to EoE, offering insights into disease mechanisms and potential therapeutic targets.

Fibrosis and Strictures

The development of strictures is a devastating clinical consequence of EoE, leading to food impaction, elevated risk of esophageal perforation, and the need for repeated

endoscopic dilatations [57]. It is assumed that fibroblasts in the lamina propria beneath the epithelium release extracellular macromolecules, like collagens and glycoproteins, in response to signals derived from immune and epithelial cell, such as TGFβ, TNF, IL-4, and IL-13, to form the extracellular matrix. Eosinophils induce the production of fibronectin and collagen I by human esophageal fibroblasts and esophageal muscle cells in a TGFβ-dependent manner, demonstrated in cell culture experiments of fibroblast and muscle cells stimulated with eosinophil sonicates in the presence of a neutralizing anti-TGFβ antibody [84]. In line, findings of human fibroblast cultures obtained from pediatric EoE patients confirmed the essential function of TGFβ in the activation of fibroblasts [85], and the genetic deletion of the TGFβ signaling mediator SMAD3 attenuated esophageal remodeling in the ovalbumin-induced experimental EoE mouse model [86]. In addition, TGFβ facilitates esophageal smooth muscle cell contraction, highlighting the essential role of TGFβ in esophageal remodeling in EoE [87].

Active EoE elevates multiple cytokines, suggesting that various cytokines have overlapping and redundant functions in promoting esophageal remodeling. Reductionist approaches focusing on a single cytokine help delineate a particular cytokine's function in esophageal remodeling during EoE. At the same time, it neglects the complexity of biological systems, considering the >60 cytokines involved in mucosal immune responses. Elegant work using patient-derived three-dimensional organoids indicates that TNF and TGFβ act synergistically in inducing lysyl oxidase, a collagen cross-linking enzyme involved in esophageal remodeling [88]. It is important to note that one cytokine can induce signaling through different receptors, and multiple cytokines can signal through the same receptor. Receptor chains are also shared between different cytokine receptors, further contributing to the complexity of studying EoE. An example is the alpha chain of the IL-4 receptor shared between the IL-4 and the IL-13 receptors. The deletion of the IL-4 receptor alpha chain in squamous epithelial cells in mice reduced esophageal wall thickening and collagen deposition in the oxazolone EoE mouse model [51]. Based on these experimental findings in mice, it can be inferred that the recently approved antibody dupilumab binds to the IL-4 receptor alpha chain and will also impact esophageal remodeling in EoE.

In general, it is believed that the progressive fibrostenotic EoE depends on the disease duration, as a delay in EoE diagnosis increases the risk for stricture formation [89]; a recent mouse study pointed to the possibility that aging predisposes to fibrosis development. Klochkova and colleagues [90] applied an ovalbumin-induced EoE model to young animals (3 months old) and aged mice (18 months old). The authors did not find significant differences in lamina propria and epithelium eosinophil numbers per high power field, indicating that young and aged mice have comparable inflammation degrees. The aged animals exhibited increased lamina propria thickening, suggesting a more progressive fibrosis development could occur in older individuals. The epithelial cells of the aged mice produced more fibroblast-stimulating factors, including basal fibroblast growth factor and osteopontin. This study highlights that in addition to disease duration and chronicity, individual patient-intrinsic factors, such as age, influence fibrosis development.

Experimental Models and Trials to Study EoE

Animal Models

After considering genetic predisposition, environmental factors, including exposure to detergents, the richness and complexity of the esophageal microbiota, dietary-derived factors, and the complexity of the immune system and epithelial biology, there is a need to standardize experimental systems and choosing the appropriate system for the relevant scientific questions. As Albert Einstein has coined, "Researchers have to make things as simple as possible. But not easier." Discussions include patient-derived cell cultures, experimental animal models, and interventional trials to offer insights into disease mechanisms and reveal new therapeutic targets through standardizing experimental systems. Genetic modifications allow the study of the impact of one specific gene on disease development, and clinical trials in a well-defined patient cohort provide the possibility to investigate the effect of a defined target on EoE. It is too simplistic not to anticipate that the different genetic backgrounds of individuals will not influence the trial outcome and that different environments, including the microbiotas in different *vivaria*, do not influence the results achieved in transgenic animal models of the same genetic backgrounds [91]. Several animal models have been proposed for studying EoE, each with specific advantages and disadvantages (shown in Table 1). Generally, experimental EoE can be induced in animals through exposure to detergents, *Aspergillus fumigatus*, or sensitization to model antigens, including ovalbumin, peanut extracts, or oxazolone, followed by a subsequent challenge with the same antigen [97, 98]. These inducible

Table 1. EoE animal models

Model	Features	Mouse	Sensitization	Challenge	Reference
Ovalbumin	Esophageal eosinophilia, mainly subepithelial	BALB/c and C57BL/6	1 mmol MC903 in 100% EtOH applied to the skin of ears followed by 10 µL of 5 mg/mL OVA for 14 days	1.5 g OVA/L in drinking water for 4 days. On days 15 and 17, the mice are additionally challenged with 50 mg OVA in 100 µL water	[61]
Aspergillus fumigatus	Esophageal eosinophilia type 2 inflammation	BALB/c	100 µg *A. fumigatus* on the backs of mice for 1 week; after 2-week rest period two sensitization over the course of 4 weeks	25 µL of 1 mg/mL *A. fumigatus* as nasal drips	[92]
Peanut extracts		BALB/c	200 µg peanut extract with 1 mg of alum on day 0 and day 14 by intraperitoneal injection	100 µg peanut extract alone on days 21, 23, 25, 27, 29, 31, 33, intragastrically	[93]
SDS	Patchy eosinophilia in the esophagus	C57BL/6	N/A	0.5% SDS in the drinking water ad libitum for 14 days	[4]
Intratracheal IL-13 instillation	Esophageal eosinophilia	BALB/c	N/A	Three doses of 10 µg recombinant IL-13 by nasal drip	[94]
Transgenic animals overexpressing IL-13 in the lungs	Esophageal eosinophilia	CC10-iIL-13 mice on BALB/c background	N/A	N/A	[95]
IL-5 overexpression in esophageal eosinophilia	Eosinophilia in hematopoietic, peripheral, and esophageal compartments	IL-5 transgenic mice on C57BL/6 background	N/A	N/A	[96]
IL-33 overexpression by the esophageal epithelium	Epithelial basal zone hyperplasia, eosinophilia, increased mast cells, Th2 cells, and type 2 cytokines	EoE33 mice were generated by expressing the saIL-33 by squamous epithelial cells on C57BL/6J background	N/A	N/A	[64]
Missense knock-in mutation in the mouse Tgfbr1	Esophageal eosinophilia	Heterozygous $Tgfbr1^{M318R}$ mouse line on C57BL/6 background	N/A	N/A	[50]

N/A, not applicable; sail-33, secreted and active IL-33; Tgfbr1, transforming growth factor, beta receptor I.

models mimic human disease by resembling histological features of human EoE, such as eosinophil infiltration in the mucosa and submucosa. It needs to be pointed out that the models with exposure to *A. fumigatus* [99], ovalbumin [61], or oxazolone sensitization [51] are immune-mediated after a sensitization phase. The applications of detergents, such as SDS, destroy the integrity of the epithelium [4], whereas, in the latter models, the

esophageal epithelium stays intact during the disease induction. The ovalbumin and peanut extract models are IgE-mediated, opposite to human EoE, which is considered IgE-independent. The advantages of these models are the defined onset of the disease, the possibility to investigate the disease course after genetic deletion of defined genes in mice, and the opportunity to test potential drug candidates for the treatment of EoE.

Conversely, EoE can spontaneously develop in animals after genetic modifications, as discussed in the *Tgfbr1*^{M318R} mouse line [50], by overexpressing IL-33 in the esophageal epithelium [64], or by installing cytokines, such as IL-13, in the airways [100], thus mimicking rare mutations in humans associated with EoE. These mouse lines predict the function of defined genes or their mutations in EoE and help delineate pathways relevant to EoE.

Patient-Derived Three-Dimensional Cell Cultures

Mouse models most commonly used in immunology research do not fully recapitulate the human immune system, as these organisms had to adapt to different ecological niches during evolution [101]. In contrast to humans, mice have significant bronchus-associated lymphoid tissue, possibly reflecting the higher exposure to airborne antigens in their environmental niche by living on the ground. Moreover, the peripheral blood of humans is enriched in neutrophils in contrast to mice, which have more lymphocytes in the peripheral blood [101]. Advances in primary cell-derived three-dimensional culture models help translate the findings from experimental mouse models into patient-based models and test their relevance for human EoE. In particular, patient-derived organoids and ALI cultures allow studying the effects of immune-derived cytokines, growth factors, and other mediators on the esophageal epithelium. Kasagi and colleagues [10] with human esophageal organoids derived from the immortalized human esophageal squamous epithelium cell line EPC2-hTERT and patient-derived cells together with Zhang et al. [102] using induced pluripotent stem cell-derived esophageal organoids discovered the significance of TGFβ and bone morphogenetic protein (BMP) inhibition for esophageal progenitor cell development and the crucial role of Notch signaling in the differentiation of the stratified squamous epithelium. Organoids are powerful tools for studying tissue architecture and the expression of potential target genes after stimulation with cytokines. Because of their three-dimensional growth with an inner keratin core, TEER or macromolecule flux cannot be measured in organoids, limiting their use in functional studies investigating epithelial barrier integrity.

Conversely, ALI cultures modeling epithelial differentiation are obtained by growing EPC2-hTERT or primary patient-derived esophageal keratinocytes on semipermeable Transwell membranes followed by differentiation and stratification through increased Ca^{2+} concentration (1.8 mM) in the culture medium and subsequent removal of the medium from the upper Transwell chamber [55]. These ALI systems can be used to investigate the effects of cytokines, such as IL-13 or members of the IL-20 cytokine family, on epithelial integrity [7, 52]. Combining patient-derived organoids and ALI cultures to investigate tissue architecture and integrity of the epithelial barrier in EoE will be applied in EoE studies. We expect to witness a rise in publications using patient-derived three-dimensional cell culture to deduce the effects of immune mediators on the esophageal epithelium.

Clinical Trials

Insights into the pathophysiology of EoE will be gained from experimental models with targeted genetic manipulation and patient-derived cell culture models, reducing the complexity of biological systems and focusing on networks between the immune system and the epithelial compartment. These systems will provide information on single pathways while, at the same time, neglecting the multidimensional framework of EoE encompassing the role of genetics, the environment, dietary factors, and the complexity of the immune system. Clinical trials that test the targeting of specific pathways with monoclonal antibodies will ultimately prove the significance of a pathway for EoE (shown in Table 2). The approval of dupilumab for the treatment of EoE highlights the importance of preclinical translational research that has elucidated the significance of IL-13 in the development of EoE [9]. Clinical trials with negative results also give exciting insights into EoE. The anti-IgE antibody omalizumab did not improve symptoms or esophageal eosinophilia, highlighting that EoE occurs independently of IgE, contrary to typical IgE-mediated food allergies [29]. Interestingly, different clinical trials and clinical case series testing and describing the anti-IL5 antibodies mepolizumab and reslizumab as well as the anti-IL-5Rα antibody benralizumab showed improvements of eosinophilia but did not result in full resolution of clinical symptoms [74, 107, 108]. Considering that >15 eosinophils/hpf are one criterion for EoE diagnosis, the results of these clinical trials open up questions on the function and importance of eosinophils in EoE. Other immune cells, including T cells, are possibly involved in EoE. These studies

Table 2. Clinical trials in EoE

Intervention	Target	Outcome	Reference
Dupilumab	Anti-IL4Rα antibody	Histologic remission in 60%	[9]
Mepolizumab	Anti-IL5 antibody	Improvement of eosinophilia (<5 Eos/HPF) but did not reach primary endpoint	[74, 103]
Reslizumab	Anti-IL-5 antibody	Histologic improvement, but no symptoms	[104]
Benralizumab	Anti-IL-5Rα antibody	Heterogenous	[105]
Infliximab	Anti-TNF antibody	Not effective	[106]
Omalizumab	Anti-IgE	No change in symptom or eosinophils	[29]

underscore the need to better comprehend and characterize the functionality of immune and mesenchymal cells in the esophagus, including fibroblasts and the epithelium, to understand their role in EoE.

A recent trial comparing a one-food elimination diet versus a six-food elimination diet for the treatment of EoE reported histological remission rates in 34% in the one-food elimination diet (cow milk) versus 40% in the six-food elimination diet (cow milk, eggs, wheat, soy, peanuts/tree nuts, and fish/shellfish) [109]. The remission rates in this randomized prospective trial are lower than in a recent metanalysis that suggested remission rates ranging from 67.9% with a six-food elimination diet to 56.9% with a four-food elimination diet, and 42.1% with a two-food elimination diet and 54.1% with a one-food elimination diet [110]. However, another trial with children comparing a one-food elimination diet with a four-food elimination diet resulted in comparable remission rates as the latter study that compared the one-food elimination diet with the six-food elimination diet [111]. Maladherence to the diet, differences in the defined endpoints, or the possibility that additional proteins contribute to the disease development is possible explanation for the divergent results in different trials. Elemental diets that remove all potential food allergens from the food have an efficacy of 71%, stressing that host variables and environmental factors also contribute to EoE [112, 113].

We look forward to advancements in TCR sequencing and the identification of protein-binding sites for food-derived molecules on receptors with AlphaFold2, which will provide exciting insights into EoE pathophysiology in the future. The rapidly increasing TCR engineering technologies could provide opportunities to eliminate T-cell clones with high avidity and functionality to food-derived antigens.

Conclusions/Future Perspectives

This review discusses the established aspects of EoE pathophysiology and addresses the following open points that will expand our understanding of the disease.

1. Information on environmental factors associated with EoE needs to be more consistent. Some reports describe an association between breastfeeding and NICU admission with EoE, while other studies describe an association between caesarean sections and early antibiotic use with EoE. Conflicting results exist whether living in rural areas is associated with an increased risk of EoE or not. More epidemiological studies are needed to adjust possible confounders to reveal environmental triggers associated with EoE. These possibilities could be tested in experimental EoE models with germ-free animals or mice with low-diversity microbiota.
2. The exposure to environmental pollutants, such as the detergent SDS present in laundry detergents and toothpaste, has been proposed to be associated with EoE. The recently developed mouse model in which SDS given in drinking water induces EoE [4] can reveal causal relationships suggested by previous epidemiological studies. This mouse model complements previously established inducible experimental models in which the disease occurred after sensitization to allergens and a subsequent challenge. These models will allow us to test relations between risk genes and potential pollutants in EoE pathophysiology.
3. GWAS are powerful tools to identify risk genes associated with EoE. The biology of the >13 risk genes and the significance of individual SNPs not necessarily located in the coding regions of the identified gene or not necessarily resulting in a loss of function of the protein is challenging. Whole exome sequencing studies have not yet been performed in EoE. We anticipate that whole exome sequencing studies and the generation of mutants

with the CRISPR/Cas9 technology will help elucidate the function of the identified risk genes. This will be a critical first step in personalizing the treatment according to the disturbed pathway in individual patients.

4. The validation of potential correlations between the oral cavity and the esophageal microbiome provides excellent opportunities for future research, given easy accessibility to the oral cavity. Considering that a one- or six-food elimination diet has multiple yet not-defined effects on the microbiome, the metabolome, and the immune system with potential relevance to EoE, this could give insights into the molecular effects of dietary therapies and the reason why they do not work for everyone with EoE.
5. An impaired epithelial barrier characterizes EoE. GWAS have identified risk genes associated with EoE that are implicated in epithelial barrier integrity, pointing to an underlying barrier defect in EoE. Conversely, immune-mediated cytokines, including IL-13 and IL-20 cytokines, can impair epithelial barrier integrity, suggesting that the impaired barrier is a consequence of inflammation. Strategies to repair an impaired barrier could be the treatment of inflammation with antibodies such as dupilumab or by applying nutritional supplements, for instance, butyrate or vitamin D, as suggested by experimental data.
6. The esophageal immune system is understudied. Characterizing the immune landscape in the esophagus in healthy individuals and EoE by mass cytometry or single-cell RNA sequencing will help comprehend and appreciate the esophagus's immune system. Advances in TCR sequencing will also give information on food-derived peptides recognized by the TCR. Progress in TCR engineering could help eliminate T-cell clones involved in EoE development.
7. Tissue remodeling, fibrosis development, and strictures are devastating consequences of EoE. Limited information is available on pathways involved in the fibrosis development in EoE. More importantly, how tissue remodeling, fibrosis, and strictures can be pharmaceutically resolved is of significant interest to patients with long-standing EoE suffering from complications that demand repetitive dilatation.

Advances in technologies and clinical trials have improved our understanding of EoE and led to the development and approval of therapies, such as orodispersible budesonide formulations and dupilumab. Type 2 chronic inflammation triggered by food and aeroallergens develops in a genetically predisposed individual exposed to environmental factors impacting the esophageal epithelial barrier. Future studies will uncover the multifaceted interplay between environmental factors, the esophageal microbiome, the epithelium, and the immune system.

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Conflict of Interest Statement

None of the authors have a conflict of interest related to this article.

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References

1 Biedermann L, Straumann A. Mechanisms and clinical management of eosinophilic oesophagitis: an overview. Nat Rev Gastroenterol Hepatol. 2023;20(2):101–19. https://doi.org/10.1038/s41575-022-00691-x

2 Attwood SE, Smyrk TC, Demeester TR, Jones JB. Esophageal eosinophilia with dysphagia. A distinct clinicopathologic syndrome. Dig Dis Sci. 1993;38(1):109–16. https://doi.org/10.1007/BF01296781

3 Straumann A, Spichtin HP, Bernoulli R, Loosli J, Vögtlin J. [idiopathic eosinophilic esophagitis: a frequently overlooked disease with typical clinical aspects and discrete endoscopic findings]. Schweiz Med Wochenschr. 1994;124(33):1419–29.

4 Doyle AD, Masuda MY, Pyon GC, Luo H, Putikova A, LeSuer WE, et al. Detergent exposure induces epithelial barrier dysfunction and eosinophilic inflammation in the esophagus. Allergy. 2023;78(1):192–201. https://doi.org/10.1111/all.15457

5 Harris JK, Fang R, Wagner BD, Choe HN, Kelly CJ, Schroeder S, et al. Esophageal microbiome in eosinophilic esophagitis. PLoS One. 2015;10(5):e0128346. https://doi.org/10.1371/journal.pone.0128346

6 Benitez AJ, Hoffmann C, Muir AB, Dods KK, Spergel JM, Bushman FD, et al. Inflammation-associated microbiota in pediatric eosinophilic esophagitis. Microbiome. 2015;3:23. https://doi.org/10.1186/s40168-015-0085-6

7 Sherrill JD, Kc K, Wu D, Djukic Z, Caldwell JM, Stucke EM, et al. Desmoglein-1 regulates esophageal epithelial barrier function and immune responses in eosinophilic esophagitis. Mucosal Immunol. 2014;7(3):718–29. https://doi.org/10.1038/mi.2013.90
8 Straumann A, Bauer M, Fischer B, Blaser K, Simon HU. Idiopathic eosinophilic esophagitis is associated with a t(h)2-type allergic inflammatory response. J Allergy Clin Immunol. 2001;108(6):954–61. https://doi.org/10.1067/mai.2001.119917
9 Dellon ES, Rothenberg ME, Collins MH, Hirano I, Chehade M, Bredenoord AJ, et al. Dupilumab in adults and adolescents with eosinophilic esophagitis. N Engl J Med. 2022;387(25):2317–30. https://doi.org/10.1056/NEJMoa2205982
10 Kasagi Y, Chandramouleeswaran PM, Whelan KA, Tanaka K, Giroux V, Sharma M, et al. The esophageal organoid system reveals functional interplay between notch and cytokines in reactive epithelial changes. Cell Mol Gastroenterol Hepatol. 2018;5(3):333–52. https://doi.org/10.1016/j.jcmgh.2017.12.013
11 Gurtner A, Borrelli C, Gonzalez-Perez I, Bach K, Acar IE, Núñez NG, et al. Active eosinophils regulate host defence and immune responses in colitis. Nature. 2023;615(7950):151–7. https://doi.org/10.1038/s41586-022-05628-7
12 Alhmoud T, Ghazaleh S, Ghanim M, Redfern RE. The risk of esophageal food impaction in eosinophilic esophagitis patients: the role of clinical and socioeconomic factors. Clin Exp Gastroenterol. 2022;15:153–61. https://doi.org/10.2147/CEG.S364994
13 Arias-González L, Rey-Iborra E, Ruiz-Ponce M, Laserna-Mendieta EJ, Arias Á, Lucendo AJ. Esophageal perforation in eosinophilic esophagitis: a systematic review on clinical presentation, management and outcomes. Dig Liver Dis. 2020;52(3):245–52. https://doi.org/10.1016/j.dld.2019.10.019
14 Jensen ET, Chaiboonma K, Ayala O, Proia A, Aceves SS. Sleep, anxiety, somatization, quality of life, and resilience in pediatric patients with eosinophilic esophagitis. Clin Transl Gastroenterol. 2024;15(3):e00672. https://doi.org/10.14309/ctg.0000000000000672
15 Kottyan LC, Trimarchi MP, Lu X, Caldwell JM, Maddox A, Parameswaran S, et al. Replication and meta-analyses nominate numerous eosinophilic esophagitis risk genes. J Allergy Clin Immunol. 2021;147(1):255–66. https://doi.org/10.1016/j.jaci.2020.10.018
16 Celebi Sözener Z, Cevhertas L, Nadeau K, Akdis M, Akdis CA. Environmental factors in epithelial barrier dysfunction. J Allergy Clin Immunol. 2020;145(6):1517–28. https://doi.org/10.1016/j.jaci.2020.04.024
17 Kaymak T, Hruz P, Niess JH. Immune system and microbiome in the esophagus: implications for understanding inflammatory diseases. FEBS J. 2022;289(16):4758–72. https://doi.org/10.1111/febs.16103
18 Kapel RC, Miller JK, Torres C, Aksoy S, Lash R, Katzka DA. Eosinophilic esophagitis: a prevalent disease in the United States that affects all age groups. Gastroenterology. 2008;134(5):1316–21. https://doi.org/10.1053/j.gastro.2008.02.016
19 Prasad GA, Alexander JA, Schleck CD, Zinsmeister AR, Smyrk TC, Elias RM, et al. Epidemiology of eosinophilic esophagitis over three decades in olmsted county, Minnesota. Clin Gastroenterol Hepatol. 2009;7(10):1055–61. https://doi.org/10.1016/j.cgh.2009.06.023
20 Hruz P, Straumann A, Bussmann C, Heer P, Simon HU, Zwahlen M, et al. Swiss Eo Esg: escalating incidence of eosinophilic esophagitis: a 20-year prospective, population-based study in olten county, Switzerland. J Allergy Clin Immunol. 2011;128:1349–50 e1345.
21 van Rhijn BD, Verheij J, Smout AJ, Bredenoord AJ. Rapidly increasing incidence of eosinophilic esophagitis in a large cohort. Neurogastroenterol Motil. 2013;25(1):47–52.e5. https://doi.org/10.1111/nmo.12009
22 Arias Á, Pérez-Martínez I, Tenías JM, Lucendo AJ. Systematic review with meta-analysis: the incidence and prevalence of eosinophilic oesophagitis in children and adults in population-based studies. Aliment Pharmacol Ther. 2016;43(1):3–15. https://doi.org/10.1111/apt.13441
23 GBD 2017 Inflammatory Bowel Disease Collaborators. The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990-2017: a systematic analysis for the global burden of disease study 2017. Lancet Gastroenterol Hepatol. 2020;5(1):17–30. https://doi.org/10.1016/S2468-1253(19)30333-4
24 Strachan DP. Hay fever, hygiene, and household size. BMJ. 1989;299(6710):1259–60. https://doi.org/10.1136/bmj.299.6710.1259
25 Ronkainen J, Talley NJ, Aro P, Storskrubb T, Johansson SE, Lind T, et al. Prevalence of oesophageal eosinophils and eosinophilic oesophagitis in adults: the population-based kalixanda study. Gut. 2007;56(5):615–20. https://doi.org/10.1136/gut.2006.107714
26 Dellon ES, Peery AF, Shaheen NJ, Morgan DR, Hurrell JM, Lash RH, et al. Inverse association of esophageal eosinophilia with helicobacter pylori based on analysis of a us pathology database. Gastroenterology. 2011;141(5):1586–92. https://doi.org/10.1053/j.gastro.2011.06.081
27 Furuta K, Adachi K, Aimi M, Ishimura N, Sato S, Ishihara S, et al. Case-control study of association of eosinophilic gastrointestinal disorders with helicobacter pylori infection in Japan. J Clin Biochem Nutr. 2013;53(1):60–2. https://doi.org/10.3164/jcbn.13-15
28 von Arnim U, Wex T, Link A, Messerschmidt M, Venerito M, Miehlke S, et al. Helicobacter pylori infection is associated with a reduced risk of developing eosinophilic oesophagitis. Aliment Pharmacol Ther. 2016;43(7):825–30. https://doi.org/10.1111/apt.13560
29 Clayton F, Fang JC, Gleich GJ, Lucendo AJ, Olalla JM, Vinson LA, et al. Eosinophilic esophagitis in adults is associated with igg4 and not mediated by ige. Gastroenterology. 2014;147(3):602–9. https://doi.org/10.1053/j.gastro.2014.05.036
30 Jensen ET, Kuhl JT, Martin LJ, Langefeld CD, Dellon ES, Rothenberg ME. Early-life environmental exposures interact with genetic susceptibility variants in pediatric patients with eosinophilic esophagitis. J Allergy Clin Immunol. 2018;141(2):632–7.e5. https://doi.org/10.1016/j.jaci.2017.07.010
31 Radano MC, Yuan Q, Katz A, Fleming JT, Kubala S, Shreffler W, et al. Cesarean section and antibiotic use found to be associated with eosinophilic esophagitis. J Allergy Clin Immunol Pract. 2014;2(4):475–7.e1. https://doi.org/10.1016/j.jaip.2014.02.018
32 McGowan EC, Keller JP, Dellon ES, Peng R, Keet CA. Prevalence and geographic distribution of pediatric eosinophilic esophagitis in the 2012 us medicaid population. J Allergy Clin Immunol Pract. 2020;8:2796–8.e4. https://doi.org/10.1016/j.jaip.2020.04.009
33 Akdis CA. Does the epithelial barrier hypothesis explain the increase in allergy, autoimmunity and other chronic conditions? Nat Rev Immunol. 2021;21(11):739–51. https://doi.org/10.1038/s41577-021-00538-7
34 Robinson L, Miller R. The impact of bisphenol a and phthalates on allergy, asthma, and immune function: a review of latest findings. Curr Environ Health Rep. 2015;2(4):379–87. https://doi.org/10.1007/s40572-015-0066-8
35 Eussen S, Wielders S, de Rooij WE, Van Ampting MTJ, Van Esch B, de Vries JHM, et al. Dietary composition of adult eosinophilic esophagitis patients is related to disease severity. Immun Inflamm Dis. 2024;12(3):e1206. https://doi.org/10.1002/iid3.1206
36 Brusilovsky M, Bao R, Rochman M, Kemter AM, Nagler CR, Rothenberg ME. Host-microbiota interactions in the esophagus during homeostasis and allergic inflammation. Gastroenterology. 2022;162(2):521–34.e8. https://doi.org/10.1053/j.gastro.2021.10.002
37 Ravi A, Marietta EV, Alexander JA, Murray JA, Katzka DA. H influenzae lps colocalization with toll-like receptor 4 in eosinophilic esophagitis. J Allergy Clin Immunol Glob. 2023;2:100151. https://doi.org/10.1016/j.jacig.2023.100151

38 Kashyap PC, Johnson S, Geno DM, Lekatz HR, Lavey C, Alexander JA, et al. A decreased abundance of clostridia characterizes the gut microbiota in eosinophilic esophagitis. Physiol Rep. 2019;7(20):e14261. https://doi.org/10.14814/phy2.14261
39 Hiremath G, Shilts MH, Boone HH, Correa H, Acra S, Tovchigrechko A, et al. The salivary microbiome is altered in children with eosinophilic esophagitis and correlates with disease activity. Clin Transl Gastroenterol. 2019;10(6):e00039. https://doi.org/10.14309/ctg.0000000000000039
40 Angerami Almeida K, de Queiroz Andrade E, Burns G, Hoedt EC, Mattes J, Keely S, et al. The microbiota in eosinophilic esophagitis: a systematic review. J Gastroenterol Hepatol. 2022;37(9):1673–84. https://doi.org/10.1111/jgh.15921
41 Pabst O, Slack E. Iga and the intestinal microbiota: the importance of being specific. Mucosal Immunol. 2020;13(1):12–21. https://doi.org/10.1038/s41385-019-0227-4
42 Baker JL, Mark Welch JL, Kauffman KM, McLean JS, He X. The oral microbiome: diversity, biogeography and human health. Nat Rev Microbiol. 2024;22(2):89–104. https://doi.org/10.1038/s41579-023-00963-6
43 Yilmaz B, Fuhrer T, Morgenthaler D, Krupka N, Wang D, Spari D, et al. Plasticity of the adult human small intestinal stoma microbiota. Cell Host Microbe. 2022;30(12):1773–87.e6. https://doi.org/10.1016/j.chom.2022.10.002
44 Alexander ES, Martin LJ, Collins MH, Kottyan LC, Sucharew H, He H, et al. Twin and family studies reveal strong environmental and weaker genetic cues explaining heritability of eosinophilic esophagitis. J Allergy Clin Immunol. 2014;134(5):1084–92.e1. https://doi.org/10.1016/j.jaci.2014.07.021
45 Abonia JP, Wen T, Stucke EM, Grotjan T, Griffith MS, Kemme KA, et al. High prevalence of eosinophilic esophagitis in patients with inherited connective tissue disorders. J Allergy Clin Immunol. 2013;132(2):378–86. https://doi.org/10.1016/j.jaci.2013.02.030
46 Frischmeyer-Guerrerio PA, Guerrerio AL, Oswald G, Chichester K, Myers L, Halushka MK, et al. TGFβ receptor mutations impose a strong predisposition for human allergic disease. Sci Transl Med. 2013;5(195):195ra194. https://doi.org/10.1126/scitranslmed.3006448
47 Paluel-Marmont C, Bellon N, Barbet P, Leclerc-Mercier S, Hadj-Rabia S, Dupont C, et al. Eosinophilic esophagitis and colonic mucosal eosinophilia in netherton syndrome. J Allergy Clin Immunol. 2017;139(6):2003–5.e1. https://doi.org/10.1016/j.jaci.2016.10.045
48 Polivka L, Hadj-Rabia S, Bal E, Leclerc-Mercier S, Madrange M, Hamel Y, et al. Epithelial barrier dysfunction in desmoglein-1 deficiency. J Allergy Clin Immunol. 2018;142(2):702–6.e7. https://doi.org/10.1016/j.jaci.2018.04.007
49 O'Shea KM, Aceves SS, Dellon ES, Gupta SK, Spergel JM, Furuta GT, et al. Pathophysiology of eosinophilic esophagitis. Gastroenterology. 2018;154(2):333–45. https://doi.org/10.1053/j.gastro.2017.06.065
50 Laky K, Kinard JL, Li JM, Moore IN, Lack J, Fischer ER, et al. Epithelial-intrinsic defects in TGFβR signaling drive local allergic inflammation manifesting as eosinophilic esophagitis. Sci Immunol. 2023;8(79):eabp9940. https://doi.org/10.1126/sciimmunol.abp9940
51 Avlas S, Shani G, Rhone N, Itan M, Dolitzky A, Hazut I, et al. Epithelial cell-expressed type ii il-4 receptor mediates eosinophilic esophagitis. Allergy. 2023;78(2):464–76. https://doi.org/10.1111/all.15510
52 Kaymak T, Kaya B, Wuggenig P, Nuciforo S, Göldi A; Swiss EoE Cohort Study Group SEECS, et al. Il-20 subfamily cytokines impair the oesophageal epithelial barrier by diminishing filaggrin in eosinophilic oesophagitis. Gut. 2023;72(5):821–33. https://doi.org/10.1136/gutjnl-2022-327166
53 Ravi A, Marietta EV, Geno DM, Alexander JA, Murray JA, Katzka DA. Penetration of the esophageal epithelium by dust mite antigen in patients with eosinophilic esophagitis. Gastroenterology. 2019;157(1):255–6. https://doi.org/10.1053/j.gastro.2019.02.042
54 Blevins CH, Iyer PG, Vela MF, Katzka DA. The esophageal epithelial barrier in health and disease. Clin Gastroenterol Hepatol. 2018;16(5):608–17. https://doi.org/10.1016/j.cgh.2017.06.035
55 Kc K, Rothenberg ME, Sherrill JD. In vitro model for studying esophageal epithelial differentiation and allergic inflammatory responses identifies keratin involvement in eosinophilic esophagitis. PLoS One. 2015;10(6):e0127755. https://doi.org/10.1371/journal.pone.0127755
56 Gann PH, Deaton RJ, McMahon N, Collins MH, Dellon ES, Hirano I, et al. An anti-il-13 antibody reverses epithelial-mesenchymal transition biomarkers in eosinophilic esophagitis: phase 2 trial results. J Allergy Clin Immunol. 2020;146:367–76.e3. https://doi.org/10.1016/j.jaci.2020.03.045
57 Muir AB, Wang JX, Nakagawa H. Epithelial-stromal crosstalk and fibrosis in eosinophilic esophagitis. J Gastroenterol. 2019;54(1):10–8. https://doi.org/10.1007/s00535-018-1498-3
58 Kleuskens MTA, Bek MK, Al Halabi Y, Blokhuis BRJ, Diks MAP, Haasnoot ML, et al. Mast cells disrupt the function of the esophageal epithelial barrier. Mucosal Immunol. 2023;16(5):567–77. https://doi.org/10.1016/j.mucimm.2023.06.001
59 Nguyen N, Fernando SD, Biette KA, Hammer JA, Capocelli KE, Kitzenberg DA, et al. TGF-β1 alters esophageal epithelial barrier function by attenuation of claudin-7 in eosinophilic esophagitis. Mucosal Immunol. 2018;11(2):415–26. https://doi.org/10.1038/mi.2017.72
60 Rothenberg ME, Spergel JM, Sherrill JD, Annaiah K, Martin LJ, Cianferoni A, et al. Common variants at 5q22 associate with pediatric eosinophilic esophagitis. Nat Genet. 2010;42(4):289–91. https://doi.org/10.1038/ng.547
61 Noti M, Wojno ED, Kim BS, Siracusa MC, Giacomin PR, Nair MG, et al. Thymic stromal lymphopoietin-elicited basophil responses promote eosinophilic esophagitis. Nat Med. 2013;19(8):1005–13. https://doi.org/10.1038/nm.3281
62 Hammad H, Lambrecht BN. Barrier epithelial cells and the control of type 2 immunity. Immunity. 2015;43(1):29–40. https://doi.org/10.1016/j.immuni.2015.07.007
63 Marwaha AK, Laxer R, Liang M, Muise AM, Eiwegger T, Immune Dysregulation G. A chromosomal duplication encompassing interleukin-33 causes a novel hyper ige phenotype characterized by eosinophilic esophagitis and generalized autoimmunity. Gastroenterology. 2022;163(2):510–3.e3. https://doi.org/10.1053/j.gastro.2022.04.026
64 Masuda MY, Pyon GC, Luo H, LeSuer WE, Putikova A, Dao A, et al. Epithelial overexpression of il-33 induces eosinophilic esophagitis dependent on il-13. J Allergy Clin Immunol. 2024;153(5):1355–68. https://doi.org/10.1016/j.jaci.2024.01.017
65 Masterson JC, Biette KA, Hammer JA, Nguyen N, Capocelli KE, Saeedi BJ, et al. Epithelial HIF-1α/claudin-1 axis regulates barrier dysfunction in eosinophilic esophagitis. J Clin Investig. 2019;129(8):3224–35. https://doi.org/10.1172/JCI126744
66 Davis BP, Stucke EM, Khorki ME, Litosh VA, Rymer JK, Rochman M, et al. Eosinophilic esophagitis-linked calpain 14 is an il-13-induced protease that mediates esophageal epithelial barrier impairment. JCI Insight. 2016;1(4):e86355. https://doi.org/10.1172/jci.insight.86355
67 Kottyan LC, Davis BP, Sherrill JD, Liu K, Rochman M, Kaufman K, et al. Genome-wide association analysis of eosinophilic esophagitis provides insight into the tissue specificity of this allergic disease. Nat Genet. 2014;46(8):895–900. https://doi.org/10.1038/ng.3033
68 Azouz NP, Ynga-Durand MA, Caldwell JM, Jain A, Rochman M, Fischesser DM, et al. The antiprotease spink7 serves as an inhibitory checkpoint for esophageal epithelial inflammatory responses. Sci Transl Med. 2018;10(444):eaap9736. https://doi.org/10.1126/scitranslmed.aap9736
69 Azouz NP, Klingler AM, Pathre P, Besse JA, Baruch-Morgenstern NB, Ballaban AY, et al. Functional role of kallikrein 5 and proteinase-activated receptor 2 in eosinophilic esophagitis. Sci Transl Med. 2020;12(545):eaaz7773. https://doi.org/10.1126/scitranslmed.aaz7773

70 Brusilovsky M, Rochman M, Shoda T, Kotliar M, Caldwell JM, Mack LE, et al. Vitamin d receptor and stat6 interactome governs oesophageal epithelial barrier responses to il-13 signalling. Gut. 2023;72(5):834–45. https://doi.org/10.1136/gutjnl-2022-327276
71 Kleuskens MTA, Haasnoot ML, Herpers BM, Ampting M, Bredenoord AJ, Garssen J, et al. Butyrate and propionate restore interleukin 13-compromised esophageal epithelial barrier function. Allergy. 2022;77(5):1510–21. https://doi.org/10.1111/all.15069
72 Smith SA, Ogawa SA, Chau L, Whelan KA, Hamilton KE, Chen J, et al. Mitochondrial dysfunction in inflammatory bowel disease alters intestinal epithelial metabolism of hepatic acylcarnitines. J Clin Investig. 2021;131(1):e133371. https://doi.org/10.1172/JCI133371
73 Wheeler JC, Vanoni S, Zeng C, Waggoner L, Yang Y, Wu D, et al. 17β-Estradiol protects the esophageal epithelium from IL-13-induced barrier dysfunction and remodeling. J Allergy Clin Immunol. 2019;143(6):2131–46. https://doi.org/10.1016/j.jaci.2018.10.070
74 Straumann A, Conus S, Grzonka P, Kita H, Kephart G, Bussmann C, et al. Anti-interleukin-5 antibody treatment (mepolizumab) in active eosinophilic oesophagitis: a randomised, placebo-controlled, double-blind trial. Gut. 2010;59(1):21–30. https://doi.org/10.1136/gut.2009.178558
75 Appanna R, Gargano D, Caputo A, De Bartolomeis F, Ricciardi L, Santonicola A, et al. Changes in mucosal igg4(+)- and il-10(+)-cell frequencies in adults with eosinophilic esophagitis on a two-food elimination diet. Clin Immunol. 2023;257:109853. https://doi.org/10.1016/j.clim.2023.109853
76 Löhr JM, Vujasinovic M, Rosendahl J, Stone JH, Beuers U. Igg4-related diseases of the digestive tract. Nat Rev Gastroenterol Hepatol. 2022;19(3):185–97. https://doi.org/10.1038/s41575-021-00529-y
77 Schuyler AJ, Wilson JM, Tripathi A, Commins SP, Ogbogu PU, Kruzsewski PG, et al. Specific igg(4) antibodies to cow's milk proteins in pediatric patients with eosinophilic esophagitis. J Allergy Clin Immunol. 2018;142(1):139–48.e12. https://doi.org/10.1016/j.jaci.2018.02.049
78 Rispens T, Huijbers MG. The unique properties of igg4 and its roles in health and disease. Nat Rev Immunol. 2023;23(11):763–78. https://doi.org/10.1038/s41577-023-00871-z
79 Blanchard C, Wang N, Stringer KF, Mishra A, Fulkerson PC, Abonia JP, et al. Eotaxin-3 and a uniquely conserved gene-expression profile in eosinophilic esophagitis. J Clin Investig. 2006;116(2):536–47. https://doi.org/10.1172/JCI26679
80 Nhu QM, Chiao H, Moawad FJ, Bao F, Konijeti GG. The anti-α4β7 integrin therapeutic antibody for inflammatory bowel disease, vedolizumab, ameliorates eosinophilic esophagitis: a novel clinical observation. Am J Gastroenterol. 2018;113(8):1261–3. https://doi.org/10.1038/s41395-018-0145-1
81 Morgan DM, Ruiter B, Smith NP, Tu AA, Monian B, Stone BE, et al. Clonally expanded, gpr15-expressing pathogenic effector t(h)2 cells are associated with eosinophilic esophagitis. Sci Immunol. 2021;6(62):eabi5586. https://doi.org/10.1126/sciimmunol.abi5586
82 Link VM, Subramanian P, Cheung F, Han KL, Stacy A, Chi L, et al. Differential peripheral immune signatures elicited by vegan versus ketogenic diets in humans. Nat Med. 2024;30(2):560–72. https://doi.org/10.1038/s41591-023-02761-2
83 Durairaj J, Waterhouse AM, Mets T, Brodiazhenko T, Abdullah M, Studer G, et al. Uncovering new families and folds in the natural protein universe. Nature. 2023;622(7983):646–53. https://doi.org/10.1038/s41586-023-06622-3
84 Rieder F, Nonevski I, Ma J, Ouyang Z, West G, Protheroe C, et al. T-helper 2 cytokines, transforming growth factor beta1, and eosinophil products induce fibrogenesis and alter muscle motility in patients with eosinophilic esophagitis. Gastroenterology. 2014;146:1266–77. e1–9. https://doi.org/10.1053/j.gastro.2014.01.051
85 Muir AB, Dods K, Henry SJ, Benitez AJ, Lee D, Whelan KA, et al. Eosinophilic esophagitis-associated chemical and mechanical microenvironment shapes esophageal fibroblast behavior. J Pediatr Gastroenterol Nutr. 2016;63(2):200–9. https://doi.org/10.1097/MPG.0000000000001100
86 Cho JY, Doshi A, Rosenthal P, Beppu A, Miller M, Aceves S, et al. Smad3-deficient mice have reduced esophageal fibrosis and angiogenesis in a model of egg-induced eosinophilic esophagitis. J Pediatr Gastroenterol Nutr. 2014;59(1):10–6. https://doi.org/10.1097/MPG.0000000000000343
87 Beppu LY, Anilkumar AA, Newbury RO, Dohil R, Broide DH, Aceves SS. Tgf-beta1-induced phospholamban expression alters esophageal smooth muscle cell contraction in patients with eosinophilic esophagitis. J Allergy Clin Immunol. 2014;134:1100–7 e4. https://doi.org/10.1016/j.jaci.2014.04.004
88 Kasagi Y, Dods K, Wang JX, Chandramouleeswaran PM, Benitez AJ, Gambanga F, et al. Fibrostenotic eosinophilic esophagitis might reflect epithelial lysyl oxidase induction by fibroblast-derived TNF-α. J Allergy Clin Immunol. 2019;144(1):171–82. https://doi.org/10.1016/j.jaci.2018.10.067
89 Schoepfer AM, Safroneeva E, Bussmann C, Kuchen T, Portmann S, Simon HU, et al. Delay in diagnosis of eosinophilic esophagitis increases risk for stricture formation in a time-dependent manner. Gastroenterology. 2013;145(6):1230–6.e62. https://doi.org/10.1053/j.gastro.2013.08.015
90 Klochkova A, Fuller AD, Miller R, Karami AL, Panchani SR, Natarajan S, et al. A role for age-associated alterations in esophageal epithelium in eosinophilic esophagitis-associated fibrosis. Front Allergy. 2022;3:983412. https://doi.org/10.3389/falgy.2022.983412
91 Macpherson AJ, McCoy KD. Standardised animal models of host microbial mutualism. Mucosal Immunol. 2015;8(3):476–86. https://doi.org/10.1038/mi.2014.113
92 Akei HS, Mishra A, Blanchard C, Rothenberg ME. Epicutaneous antigen exposure primes for experimental eosinophilic esophagitis in mice. Gastroenterology. 2005;129(3):985–94. https://doi.org/10.1053/j.gastro.2005.06.027
93 Rajavelu P, Rayapudi M, Moffitt M, Mishra A, Mishra A. Significance of para-esophageal lymph nodes in food or aeroallergen-induced inkt cell-mediated experimental eosinophilic esophagitis. Am J Physiol Gastrointest Liver Physiol. 2012;302(7):G645–654. https://doi.org/10.1152/ajpgi.00223.2011
94 Niranjan R, Rayapudi M, Mishra A, Dutt P, Dynda S, Mishra A. Pathogenesis of allergen-induced eosinophilic esophagitis is independent of interleukin (il)-13. Immunol Cell Biol. 2013;91(6):408–15. https://doi.org/10.1038/icb.2013.21
95 Zuo L, Fulkerson PC, Finkelman FD, Mingler M, Fischetti CA, Blanchard C, et al. Il-13 induces esophageal remodeling and gene expression by an eosinophil-independent, il-13r alpha 2-inhibited pathway. J Immunol. 2010;185(1):660–9. https://doi.org/10.4049/jimmunol.1000471
96 Masterson JC, McNamee EN, Hosford L, Capocelli KE, Ruybal J, Fillon SA, et al. Local hypersensitivity reaction in transgenic mice with squamous epithelial il-5 overexpression provides a novel model of eosinophilic oesophagitis. Gut. 2014;63(1):43–53. https://doi.org/10.1136/gutjnl-2012-303631
97 Li D, Wei Y, Wang J, Wang B. Animal models of eosinophilic esophagitis, review and perspectives. Anim Model Exp Med. 2024;7(2):127–35. https://doi.org/10.1002/ame2.12391
98 Pilat JM, Jacobse J, Buendia MA, Choksi YA. Animal models of eosinophilic esophagitis. J Leukoc Biol. 2024;116(2):349–56. https://doi.org/10.1093/jleuko/qiae043
99 Mishra A, Hogan SP, Brandt EB, Rothenberg ME. An etiological role for aeroallergens and eosinophils in experimental esophagitis. J Clin Investig. 2001;107(1):83–90. https://doi.org/10.1172/JCI10224
100 Mishra A, Rothenberg ME. Intratracheal il-13 induces eosinophilic esophagitis by an il-5, eotaxin-1, and stat6-dependent mechanism. Gastroenterology. 2003;125(5):1419–27. https://doi.org/10.1016/j.gastro.2003.07.007

101 Mestas J, Hughes CC. Of mice and not men: differences between mouse and human immunology. J Immunol. 2004;172(5):2731–8. https://doi.org/10.4049/jimmunol.172.5.2731
102 Zhang Y, Yang Y, Jiang M, Huang SX, Zhang W, Al Alam D, et al. 3d modeling of esophageal development using human psc-derived basal progenitors reveals a critical role for notch signaling. Cell Stem Cell. 2018;23(4):516–29.e5. https://doi.org/10.1016/j.stem.2018.08.009
103 Stein ML, Collins MH, Villanueva JM, Kushner JP, Putnam PE, Buckmeier BK, et al. Anti-il-5 (mepolizumab) therapy for eosinophilic esophagitis. J Allergy Clin Immunol. 2006;118(6):1312–9. https://doi.org/10.1016/j.jaci.2006.09.007
104 Spergel JM, Rothenberg ME, Collins MH, Furuta GT, Markowitz JE, Fuchs G 3rd, et al. Reslizumab in children and adolescents with eosinophilic esophagitis: results of a double-blind, randomized, placebo-controlled trial. J Allergy Clin Immunol. 2012;129(2):456–63, 463.e1-3. https://doi.org/10.1016/j.jaci.2011.11.044
105 Kuang FL, De Melo MS, Makiya M, Kumar S, Brown T, Wetzler L, et al. Benralizumab completely depletes gastrointestinal tissue eosinophils and improves symptoms in eosinophilic gastrointestinal disease. J Allergy Clin Immunol Pract. 2022;10(6):1598–605.e2. https://doi.org/10.1016/j.jaip.2022.02.037
106 Straumann A, Bussmann C, Conus S, Beglinger C, Simon HU. Anti-tnf-alpha (infliximab) therapy for severe adult eosinophilic esophagitis. J Allergy Clin Immunol. 2008;122(2):425–7. https://doi.org/10.1016/j.jaci.2008.06.012
107 Markowitz JE, Jobe L, Miller M, Frost C, Laney Z, Eke R. Safety and efficacy of reslizumab for children and adolescents with eosinophilic esophagitis treated for 9 years. J Pediatr Gastroenterol Nutr. 2018;66(6):893–7. https://doi.org/10.1097/MPG.0000000000001840
108 Kliewer KL, Murray-Petzold C, Collins MH, Abonia JP, Bolton SM, DiTommaso LA, et al. Benralizumab for eosinophilic gastritis: a single-site, randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Gastroenterol Hepatol. 2023;8(9):803–15. https://doi.org/10.1016/S2468-1253(23)00145-0
109 Kliewer KL, Gonsalves N, Dellon ES, Katzka DA, Abonia JP, Aceves SS, et al. One-food versus six-food elimination diet therapy for the treatment of eosinophilic oesophagitis: a multicentre, randomised, open-label trial. Lancet Gastroenterol Hepatol. 2023;8(5):408–21. https://doi.org/10.1016/S2468-1253(23)00012-2
110 Mayerhofer C, Kavallar AM, Aldrian D, Lindner AK, Müller T, Vogel GF. Efficacy of elimination diets in eosinophilic esophagitis: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2023;21(9):2197–210.e3. https://doi.org/10.1016/j.cgh.2023.01.019
111 Wechsler JB, Schwartz S, Arva NC, Kim KYA, Chen L, Makhija M, et al. A single-food milk elimination diet is effective for treatment of eosinophilic esophagitis in children. Clin Gastroenterol Hepatol. 2022;20(8):1748–56.e11. https://doi.org/10.1016/j.cgh.2021.03.049
112 Peterson KA, Byrne KR, Vinson LA, Ying J, Boynton KK, Fang JC, et al. Elemental diet induces histologic response in adult eosinophilic esophagitis. Am J Gastroenterol. 2013;108(5):759–66. https://doi.org/10.1038/ajg.2012.468
113 Warners MJ, Vlieg-Boerstra BJ, Verheij J, van Rhijn BD, Van Ampting MT, Harthoorn LF, et al. Elemental diet decreases inflammation and improves symptoms in adult eosinophilic oesophagitis patients. Aliment Pharmacol Ther. 2017;45(6):777–87. https://doi.org/10.1111/apt.13953