Review

Eosinophilic esophagitis is characterized by a non-IgE-mediated food hypersensitivity

Review initiated by the EAACI Eosinophilic Esophagitis Interest Group

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Abbreviations used in this article: ACD, allergic contact dermatitis; AD, atopic dermatitis; APT, atopy patch test; DHR, drug hypersensitivity reaction; EoE, eosinophilic esophagitis; FPIES, food protein-induced enterocolitis; GERD, gastro-esophageal reflux disease; GI, gastrointestinal; Ig, immunoglobulin; IBD, inflammatory bowel disease; OAS, oral allergy syndrome; PPI-REE, proton pump inhibitor-responsive esophageal eosinophilia; SFED, six food elimination diet; SPT, skin prick test; TCR, T cell receptor; TNF, tumor necrosis factor.

Abstract

Eosinophilic esophagitis (EoE) is a chronic disease characterized clinically by symptoms of esophageal dysfunction and histologically by eosinophil-predominant inflammation. EoE is frequently associated with concomitant atopic diseases and immunoglobulin E (IgE) sensitization to food allergens in children as well as to aeroallergens and cross-reactive plant allergen components in adults. Patients with EoE respond well to elemental and empirical food elimination diets. Recent research has, however, indicated that the pathogenesis of EoE is distinct from IgE-mediated food allergy. In this review, we discuss the individual roles of epithelial barrier defects, dysregulated innate and adaptive immune responses, and of microbiota in the pathogenesis of EoE. Although food has been recognized as a trigger factor of EoE, the mechanism by which it initiates or facilitates eosinophilic inflammation appears to be largely independent of IgE and needs to be further investigated. Understanding the pathogenic role of food in EoE is a prerequisite for the development of specific diagnostic tools and targeted therapeutic procedures.

Current definition of EoE

As a consequence of intense research in the field of esophageal eosinophilia, our understanding of eosinophilic esophagitis (EoE) has developed from strict clinic-pathologic criteria leading towards a conceptual definition which includes pathogenic aspects (1-3). According to current recommendations, EoE represents a chronic, immune/antigen-mediated esophageal disease characterized clinically by symptoms of esophageal dysfunction and histologically by eosinophil-predominant inflammation (2). EoE has been recognized as having a spectrum of clinical signs and symptoms, endoscopic findings as well as pathologic features. However, the term "immune/antigen-mediated" does not address the question where EoE should be positioned in the wide range between autoimmune and allergic diseases. In addition, there are likely subgroups of patients who do not meet this strict definition; for example, some have less than 15 eosinophils per high power field (hpf), but otherwise fulfill the criteria of EoE (2).

The two most common causes of eosinophilia in the esophagus, normally devoid of eosinophils in healthy humans, are gastroesophageal reflux (GERD) and EoE (2). However, yet another form of esophageal eosinophilia has recently emerged having clinical manifestations and histological features indistinguishable from EoE, but distinct from GERD, apart from the fact that it is responsive to high-dose of PPI whereas EoE is histologically refractory to PPI. Hence, it is called PPI-responsive esophageal eosinophilia (PPI-REE) (4,5). Patients with PPI-REE frequently exhibit environmental and/or food allergen sensitizations like patients with EoE, whereas the atopy rate in patients with GERD is similar to that of the general population. Moreover, the inflammatory markers of PPI-REE are more similar to those of EoE than of GERD: positive for factors involved in eosinophil chemotaxis (eotaxin 3, CCL26), barrier integrity (desmoglein 1, DSG1), tissue remodeling (periostin, POSTN), and mast cell specific activity (carboxypeptidase A, CPA3) (4). The molecular signature typical of PPI-REE and EoE could be reversed by PPI therapy only in PPI-REE (4), suggesting the molecular signature is either a sign of disease or marker of eosinophilic inflammation. Mechanisms proposed to explain the PPI response include an acid-independent, anti-inflammatory action of PPIs on the one hand, or a PPI-induced restoration of esophageal barrier function on the other (6). In summary,

it is possible that PPI-REE and EoE are the consequence of the same underlying immunologic mechanism, but additional research is required to confirm this concept.

Already early reports on EoE mentioned concomitant allergic diseases and elevated total serum immunoglobulin E (IgE) levels in about 70% of the patients (7,8). After receiving elemental formulas, children with esophageal eosinophilia not responding to pharmacological and/or surgical anti-reflux therapy, showed marked improvements (9). This observation suggested that EoE could represent an allergic disease in which food proteins play an important role. However, further research revealed that EoE seems not to be simply an IgE-mediated food allergy. What, then, are the underlying causes of EoE and what role might food and/or other antigens play in the pathogenesis? In this review initiated by the EAACI Eosinophilic Esophagitis Interest Group, we will discuss recently published work on EoE in the context of an immune/antigen-mediated disease.

EoE-associated IgE-sensitization to food and aeroallergens
EoE is associated with elevated total IgE levels as well as IgE-sensitization to food and aeroallergens (10). In a pediatric EoE cohort, sensitizations to food and environmental allergens have been observed in 75% and 79%, respectively (11). Skin prick testing in children with EoE revealed increasing reactivity with inhalant allergen with age, while the reactivity to foods decreased (12). Children with EoE were mainly sensitized to milk, eggs, soy, wheat/rye, beef and peanuts (13). In adult EoE patients, specific IgEs to food and inhalant allergen components have been detected in 91% (14). These patients were mainly sensitized to pollens, in particular cross-reactive plant allergen components such as profilins and pathogenesis-related (PR)10 proteins (14). Noteworthy is the observation of local immunoglobulin class switching and production of IgE in the esophageal mucosa of pediatric EoE patients (15). Considering all these findings, EoE was initially suspected of being an IgE-mediated allergy to food and cross-reactive plant allergens.

On the other hand, clinical trials of targeted food elimination diets, as well as of IgE blocking, failed to show an IgE-mediated mechanism. Measuring specific IgE levels and/or skin prick testing were not sufficient to clearly identify causative food allergens (13,14,16,17). Moreover, elimination diets based solely on IgE-sensitization to food allergens as determined by skin prick tests (SPT) and/or specific IgE determinations could

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not improve EoE in a significant number of patients (16,18,19). The positive predictive values for causative food identified by SPT ranged from 26% to 96%, with an average of 47% (16). Based on the assumption that IgE plays a key role in pathogenesis, a therapy with an anti-IgE antibody for 12 weeks in pediatric and adult EoE patients was initiated in a non-placebo controlled study resulting in a remission rate of only 33% despite an effective reduction of IgE levels observed in the esophageal tissue (20). In a double-blind placebo-controlled study anti-IgE treatment was not better than placebo in inducing EoE remission (21). Taken together, recent clinical and research data lead us to conclude that EoE, while often associated with IgE sensitization, is not simply an IgE-mediated food allergy.

EoE exhibits features of a Th2 predominant inflammation

The inflammation of EoE is predominantly eosinophilic, but is also characterized by increased numbers of T cells and mast cells infiltrating the esophageal mucosa, as well as high expression levels of IL-5 and TNF-α (Figure 1) (22). Transcriptome analysis of EoE tissue showed a distinct Th2 pattern with significantly elevated mRNA levels of eotaxin-3, IL-5, IL-5 receptor α-chain and IL-13 (23,24). In experimental models, both eotaxin and IL-5 were essential for eosinophil recruitment, accumulation and activation in the esophagus as well as for epithelial hyperplasia and remodeling (25-28). Moreover, IL-13 can induce eotaxin-3 production by esophageal epithelial cells (29). In addition to the Th2 cytokines, EoE patients show elevated blood levels of IL-1α, IL-6 and IL-8, but lower levels of IL-12, IL-17 and CD40L as compared with healthy controls, while the gene expression of receptors for IL-1, IL-9 and IL-17 is also upregulated in EoE lesions (23,24).

Treatment with corticosteroids resulted in a reduced expression of eotaxin-3, IL-5 and IL-13 and was followed by a decrease of eosinophil numbers in the esophagus of EoE patients (29). Although reducing eosinophil inflammation in the esophagus, blocking IL-5 or IL-13 with therapeutic antibodies has yet to be proven to be clinically useful, although trends have been seen in preliminary studies (30,31). In summary, Th2 immune responses are a striking feature and most likely contribute to the pathogenesis of EoE, but are not the sole players as pro-inflammatory cytokines are also expressed that may regulate additional responses.

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Lessons learnt from hypersensitivity reactions of the skin

EoE shares many similarities with dermatoses that are due to T cell responses of the skin independent of IgE. Therefore, it appears logical to consider antigen-triggered T cell-mediated mechanisms for the pathogenesis of EoE (Figure 1).

T cell responses in allergic contact dermatitis

In allergic contact dermatitis (ACD), chemical allergens penetrate into the skin where they form complexes or bind covalently to proteins of immune and structural cells in the skin and, thus, may induce innate immune responses as well as generate T cell epitopes (32). Contact allergens, e.g. nickel, are recognized by pattern recognition receptors (PRR) resulting in the production of pro-inflammatory cytokines such as IL-1 and IL-18. This irritant effect of contact allergens is essential for the subsequent activation of the adaptive immune system leading to a Tc1/Th1 and Tc17/Th17 effector/memory T cell response (33). Contact hypersensitivity is dependent on T cell-mediated cytotoxicity via FAS/FASL and perforin pathways (34). In ACD, Th1/Th17 cells may amplify the cytotoxic cascade as they increase T cell–keratinocyte adhesiveness and promote ICAM-1–dependent non-antigen-specific keratinocyte killing by T lymphocytes (35). However, there is little evidence for an IL-17-mediated process in EoE (36).

T cells in drug hypersensitivity

While immediate allergic drug hypersensitivity reactions (DHR) are mediated by specific IgE bound to mast cells and basophils, delayed (non-immediate) allergic DHR are T cell-mediated. Analogous to haptens, drugs are presented either covalently bound to peptides in the binding grove of MHC molecules on antigen-presenting cells or complexed to amino acids in MHC molecules and TCR (37). Recently, a concept for the pharmacological interaction of drugs with immune receptor (p-i concept) has been proposed, suggesting a non-covalent binding enabling a direct interaction with immunological receptors such as MHC and TCR (38,39). Thus, the antigen might bind either to the MHC complex, thereby modifying the structure that is recognized by the TCR leading to a specific T cell activation or directly to a specific TCR requiring additional MHC interaction for full T cell activation

(38). In cutaneous reactions, drug-specific cytotoxic T cells have been demonstrated that can contribute to tissue damage via perforin/granzyme B or FAS/FASL mechanisms (40,41). In DRESS, an oligoclonal expansion of activated CD8+ T cells directed against viral antigens derived from *Herpes* viruses, whose replication is enhanced by the culprit drug, has been observed in the skin and visceral organs (42).

Food-specific T cell responses in the skin

Over 80% of patients with atopic dermatitis (AD) have increased IgEs to foods and inhalant allergens in the peripheral blood (43). However, the positive predictive value of IgE specific to food allergens is low (44). Interestingly, in 45% of patients reacting upon food allergen challenge, eczematous reactions with or without prior immediate reactions have been observed, suggesting the occurrence of late, most likely T cell-mediated reactions against foods (44). Indeed, in patients with food-triggered AD exacerbations, relevant food allergen specific T cells have been detected in the peripheral blood as well as the skin (45,46). Moreover, positive atopy patch test (APT) reactions to inhalant and food allergens can be detected in the absence of corresponding IgE-responses (47). Although widely used, the APT has limited value in the diagnosis of food allergy in EoE (16) perhaps owing to the fact that here the skin and not the esophagus is tested. Upon food allergen, but not nonspecific stimulation, peripheral blood mononuclear cells from EoE patients with or without allergen-specific IgE produce significant amounts of IL-5 (48). In peanut-allergic children, skin- and gut-homing T cells expressing Th2 and Th9 genes as well as IL-9 and IL-5 production by distinct T helper cell populations have been reported (49).

To date, the presence of food allergen-specific T cells in EoE has not been demonstrated. Furthermore, it remains uncertain when and where the sensitization to food allergens occurs. In adult EoE patients, airway allergy precedes EoE (50). Recent data suggest that an epicutaneous sensitization with ovalbumin may result in an antigen-induced gastrointestinal food allergy via the TSLP-basophil axis or in an IL-17-mediated response depending on the animal model (51,52). Furthermore, filaggrin mutations as risk factors for eczema, the atopic march and peanut allergy have been reported,

indicating that an impaired epithelial barrier function may predispose to allergen sensitization and atopy (53,54).

Epithelial barrier and innate immune responses in EoE

There is increasing evidence that EoE is associated with a dysfunction at the epithelial barrier followed by an eosinophilic inflammation similar to AD which is concomitant in over half of EoE patients (Figure 1). In esophageal epithelial cells, the expression of epidermal differentiation complex (EDC) genes, e.g. filaggrin, SPRR3 and keratins, is downregulated in response to IL-13 and in active EoE, where it could be only partially normalized upon therapy (55,56). Desmoglein (DSG)-1, an intercellular adhesion molecule responsible for epithelial integrity and barrier function was one of the most strongly downregulated genes in EoE (29). A downregulation of DSG-1 gene, e.g. by IL-13, was shown to result in the separation of epithelial cells (spongiosis) followed by impaired barrier function as well as by periostin induction further potentiating inflammation (57). Ultrastructural analysis revealed a significantly decreased number of desmosomes per cell in EoE biopsies as compared to healthy controls, which was reversible after treatment (58). Furthermore, the expression of filaggrin and the tight junction proteins zonula occludens (ZO)-3 and claudin-1 is decreased in EoE, correlating with spongiosis (59). Consistent with this finding, mutations in filaggrin are over-represented in EoE patients (55) and homozygous mutations of DSG1 cause a severe atopy syndrome which includes EoE (60).

In stratified epithelia, the activity of proteases is tightly regulated by protease inhibitors. The loss of inhibition results in cleavage of desmosomal proteins and loss of barrier integrity, facilitating the penetration of allergens and microbes as well as the subsequent generation of danger signals and protease activated receptor (PAR)-2 activation (61). In active EoE, a significantly decreased expression of the protease inhibitor LEKTI has been observed (36).

TSLP that is produced by epithelial cells in response to PAR-2, toll-like receptor (TLR) stimulation or mechanical injury, strongly induces Th2 immune responses by stimulating dendritic cells, T cells, eosinophils, mast cells and basophils (62). Upon stimulation with TSLP, eosinophils that bear the TSLP receptor on their surface generate

extracellular DNA traps associated with granule proteins that are able to kill bacteria (63). Interestingly, the expression of TSLP is increased in EoE and correlates with the number of eosinophils generating eosinophil extracellular traps (36). Genetic variants of TSLP and its receptor have been associated with an increased susceptibility to EoE overall, and in males, respectively (64,65). Furthermore, the gene of esophageal selective calpain (CAPN) 14, a member of the calpain protease family involved in the cleavage of inflammatory mediators such as IL-33, was upregulated in active EoE, while the calpain inhibitor CAST was downregulated (66). In line with these findings, genetic variants in the CAPN 14 gene locus are linked with EoE susceptibility (67) and increased expression of innate cytokines including IL-33 by epithelial cells has been detected in EoE (36).

Immense efforts have been undertaken to identify the role of the microbiota in the immune system, in particular in association with immune-mediated diseases. Microbiota research aims at elucidating their role in initiating and perpetuating inflammation and, conversely, the effect of diseases and treatment procedures on the microbiota. Compared to healthy controls, the bacterial load of the esophagus is increased in EoE patients regardless of treatment and disease activity, with a relative abundance of gram-negative bacteria in active EoE (68,69). Recently, IgE-sensitization to *Candida albicans* has been reported in pediatric and adult EoE patients (14,70). Whether an esophageal colonization with *Candida albicans* and later sensitization is owing to EoE inflammation or corticosteroid therapy remains to be investigated. Furthermore, any potential role of IgE specific for *Candida albicans* in the pathogenesis of EoE is uncertain.

Taken together, recent research suggests that impaired epithelial barrier function plays a major role in initiating and perpetuating EoE inflammation as it facilitates the penetration of allergens and microbes and generates danger signals leading to an activation of epithelial cells as well as innate and adaptive immune cells with subsequent chemokine and cytokine production resulting in Th2 immune responses. There is evidence of a dysbiosis of microbiota in EoE, however, the consequences in terms of microbial-triggered eosinophilic inflammation and the particular role of diet on the microbiome in the esophagus remain to be investigated.

Similarities and differences between EoE and IBD

With inflammatory bowel diseases (IBD), such as Crohn's disease (CD) and ulcerative colitis (UC), the pathogenesis is determined by genetic factors, environmental and microbial factors together with an epithelial barrier dysfunction and subsequent innate and adaptive immune responses (71). The susceptibility to IBD is determined by genetic variants related to innate immunity, autophagy and phagocytosis in CD and to barrier function in UC (72). Due to an increased intestinal epithelial permeability, food antigens and microbes may activate pattern recognition receptors on epithelial cells resulting in a release of pro-inflammatory cytokines such as TNF-α, IL-1, IL-18 and IL-33 (Figure 1) (71). In contrast to EoE, predominantly Th1 cells and the IL-23/Th17 axis are activated in IBD (71). It has been hypothesized that due to a dysregulated innate intestinal immunity and barrier function, affecting both the diversity and composition of the microbiota, the immune response is initiated to eliminate invading antigens (e.g. microbes, food) and to restore epithelial barrier integrity, but may later turn into a chronic inflammation leading to the clinical manifestations of IBD (71,73).

Thus, the principal pathomechanisms of IBD seem congruent with those of EoE, although it is currently not clear which tissue-specific characteristics, including immune responses, environmental factors such as microbiota and food, as well as genetic predispositions favor a chronic Th1/Th17 inflammation as in IBD or a Th2 predominant inflammation as in EoE with corresponding clinical phenotypes. While both diseases have common mechanisms, the upstream events are likely to be different as EoE is associated with unique genetic susceptibility (TSLP and CAPN14) and atopy; whereas IBD is more related to innate immunity to microbial flora.

EoE is distinct from IgE-mediated food allergies

If one were to consider EoE as a kind of food allergy, how would its symptoms agree with the current concept of gastrointestinal (GI) allergies? A food allergy is defined as an abnormal immunologic response to a food substance occurring in a susceptible host and causing some type of GI inflammation. The vast majority of food allergies affecting the GI tract are characterized by a Th2 inflammation with predominant Th2 cytokine expression (that is IL-4, IL-13, and IL-5). Th2 inflammation can cause B cells to produce IgE

antibodies specific to certain foods or can lead to a chronic cellular inflammation frequently characterized by the presence of Th2 cell and eosinophils (74).

According to the immunological mechanism elicited, food allergies can be classified into: (a) IgE-mediated, which are immediate, short-lived reactions mediated by antibodies belonging to the IgE class, (b) cell-mediated, which usually have a delayed/chronic course, typically involving the GI tract and the cell component of the immune system responsible for inflammation, or (c) mixed, IgE- and cell-mediated (75). IgE-mediated reactions to foods are acute and highly reproducible. They are initiated by the cross linking of two or more allergen-specific IgE antibodies bound to their high-affinity receptor (FcεRI) expressed on mast cells and basophils as a result of a specific food allergen engagement. Such cross-linking determines the release of preformed mediators, in particular, histamine, that cause vasodilatation, angioedema, smooth muscle constriction, and increased mucus production (76).

Examples of typical IgE-mediated allergic reactions affecting the GI tract are the oral allergy syndrome (OAS) and the more severe GI food allergy, also known as "gastrointestinal anaphylaxis". When comparing IgE-mediated OAS and GI food allergies with EoE, the following differences become evident: EoE symptoms might be instant, but they are not transient, EoE inflammation is chronic, anaphylaxis is not a feature of EoE, and pollen-associated food allergens are not a typical trigger of EoE. It should be noted, however, that EoE patients can concurrently suffer from OAS and/or a GI food allergy.

Food protein-induced enterocolitis (FPIES), an increasingly recognized form of non-IgE mediated food hypersensitivity, is characterized by a delayed onset of vomiting with or without diarrhea, typically occurring in infants and toddlers from 2 to 6 h post-ingestion of the trigger food (77,78). FPIES is usually a transient disease which starts at 4 to 9 months of life or when solid foods are first introduced, and resolves by age 2 to 5 years (77). The foods most commonly involved in FPIES are milk, soy, rice, oats and eggs. IgEs specific to the trigger foods are usually not detectable (77,79). Although FPIES and EoE seem to share some clinical (symptoms, age of onset) and pathogenic (causative food triggers, increased TNF-α, epithelial barrier defects) features (80), other characteristics such as disease course, endoscopic and histologic findings discriminate FPIES from EoE.

Experience with omalizumab: Its lack of clinical efficacy in EoE

Omalizumab is an anti-IgE humanized monoclonal antibody that binds to the fragment crystallizable (Fc) region of the IgE molecule and thus prevents its binding to the high-affinity IgE receptor (Fc epsilon RI, FcεRI). In the only published prospective, randomized, double-blind, placebo-controlled study in 30 adult EoE patients (16 treated with omalizumab and 14 with placebo) omalizumab was given every 2-4 weeks for 16 weeks, based on weight and serum level of IgE. Before starting the treatment and at the end of the trial (16 weeks of treatment) symptoms evaluation, EGD and histological assessment of the eosinophil density (peak eos/hpf) in esophageal biopsies were performed. Patients treated with omalizumab had neither a significant improvement in symptoms nor a decrease of the eosinophil infiltration of the esophageal mucosa compared with placebo (21). This study confirmed anecdotal data from clinical cases reported in which omalizumab had been considered to improve IgE-mediated symptoms of food allergy, but not of EoE (81). Overall these data support the notion that EoE is not IgE-mediated. Clayton et al. speculated that IgG4 antibodies specific for a food allergen are blocking IgE responses (21). Indeed, in allergic diseases, an IgG4 response follows an IgE-mediated response and does block IgE-mediated mast cell activation (21). In EoE, extracellular granular deposits of IgG4 and abundant IgG4-containing plasma cells in the tissue, as well as increased serum levels of IgG4 reactive with specific foods have been observed, suggesting that in adults, EoE might be an IgG4- and IgE-associated disease and perhaps the balance between the two antibodies could be a key determinant (21). However, B cell-deficient mice also develop typical EoE, suggesting that antibodies may simply be non-pathogenic (82). Moreover, the anti-food IgG4 levels did not correlate with the age and duration of disease symptoms (21). Further studies will be necessary to really understand the pathogenic role of IgG4 in EoE.

EoE is characterized by a non-IgE-mediated food hypersensitivity
Since the first description of a series of clinical cases of EoE, food allergies have appeared to play a major role in causing a severe esophageal eosinophilia that resolved

on elemental diet, but not on aggressive GERD treatment, including Nissen fundoplication (6). In view of this, food allergens have been identified as triggers of EoE in most children and adults (6,16,82,83).

Thus, food as a trigger of EoE fulfills Koch's postulates since addition or subtraction of foods can cause disease or eliminate disease in EoE in nearly all patients. The most effective treatment in patients with EoE is an elemental diet that induces histological and clinical resolution in over 95% of pediatric and adult patients (83-86). Noteworthy is that IBD may also resolve upon elemental diet (87) with a mechanism that involves both bowel rest and a change in microbiome. So far, the explanation for remission of EoE on an elemental diet has always been linked to the avoidance of food allergens, rather than bowel rest/change in microbiome, but this possibility needs to be investigated further. This presumption was supported by the fact that elimination diets based on removal of the six most common food allergens (SFED-six food elimination diet) (82) or of the foods to which patients were sensitized (targeted elimination diets) have been shown to induce and maintain EoE remission in 72% and 45% of EoE patients, respectively (16,88). According to biopsy confirmation, the most common food proteins causing EoE are milk, followed by wheat, eggs, beef, soy and legumes, and chicken (16,83,89,90). Interestingly, peanuts, tree nuts, fish and shellfish are rare as causes for EoE despite being common causes of IgE-mediated reactions in adults.

The evidence that EoE is generally non-IgE-mediated is based on both clinical and research findings:

(1) Despite the fact that the majority of patients with EoE have specific IgEs to food allergens and/or aeroallergens, the detection of specific IgEs for food allergens, either by SPT or specific sera IgE (sIgE), has not proven successful for the identification of causative foods in EoE (84,85). Indeed, removal of SPT or sIgE positive foods is not superior to SFED (2,16,17,83,91). Moreover, it has been reported that the introduction of skin test negative foods into the diet sometimes induces clinical disease (6,16).

(2) Clinical trials and case series have shown that therapy with omalizumab is not effective in inducing remission of EoE (21,81).

(3) Oral immunotherapy, which has been used successfully in IgE-mediated food allergy, is associated with an increased risk of developing EoE (e.g. in 2 to 10% of treated patients) (92-94).

(4) Children who outgrow IgE-mediated food allergy and therefore are able to reintroduce these foods in their diet, can later develop EoE to the same food (95).

(5) In experimental models in which food allergens are able to induce an EoE-like disease, mice with depleted IgE and devoid of mast cells still could develop esophageal inflammation and consequent food impaction similar to the wild-type mice (96,97).

Confirmation of EoE diagnosis and the practical search for offending foods

EoE is a clinico-pathological diagnosis. However, EoE and GERD have a substantial overlap of clinical and of histological features. For instance, the presence of heartburn and marked esophageal eosinophilia might be fairly common in both entities (2). In order to solve this diagnostic conundrum, updated consensus recommendations for diagnosis and management of EoE advocate performing a PPI trial in patients having symptoms suggestive of EoE and esophageal eosinophilia (2). Accordingly, a diagnosis of GERD was recommended for those patients responding to PPI therapy, whereas patients whose symptoms and inflammation persist were regarded as having EoE (2). Unfortunately, this diagnostic PPI trial did not fulfil the expectation of differentiating EoE from GERD, but unexpectedly uncovered a third category of patients, called PPI-REE, presenting with symptoms of EoE, but responding to PPI (5). With the exception of the responsiveness to PPI, PPI-REE, and EoE have common clinical, endoscopic, histological and molecular features.

EoE is a chronic and progressive disease. If left untreated complications, such as food impaction, esophageal stricture, narrow-caliber esophagus, and esophageal perforation are common (98,99). Therefore, once the diagnosis is confirmed, it is important to treat the eosinophilic inflammation not only to control the presenting symptoms, but also to preserve the morphological and functional integrity of the esophagus (2,10,87,99). Beside medications, diets avoiding culprit foods are an important therapeutic option (100). Of note, before an elimination diet can be established, it is necessary to identify the triggering foods, ideally with the help of a dietitian specialized in

dealing with this disease. Currently culprit foods are identified by demonstrating histological and clinical remission of EoE after the establishment of an elimination diet. In practice, after avoidance and after re-introduction of any food category, the effect must be controlled endoscopically and histologically (82,83). Serial endoscopies are therefore required to figure out an individual elimination diet. This approach is time consuming, inconvenient for patients, expensive, and affects the quality of life (101). Therefore, there is a need to develop non-invasive methods for the identification of the offending foods. The determination of food-specific IgG4 in the serum is a method currently under evaluation. Further phenotyping patients based on their esophageal gene expression, using a 94 gene transcript profile, is promising to be helpful (102).

Conclusions

There is strong evidence that foods, most likely food-proteins, are triggers of EoE, since elimination of culprit food categories as well as protein-free elemental diets result in an improvement of histological and endoscopic signs as well as of symptoms. Furthermore, the observation that the eosinophilic inflammation and the Th2 inflammation pattern reappear rapidly after re-introduction of the culprit foods are strong arguments that EoE is likely a food-driven disorder with features of food allergy. However, the spectrum of clinical presentations of EoE, the results of IgE-based diagnostic procedures, as well as the lack of efficacy of anti-IgE treatment suggests that EoE cannot be regarded as an IgE-mediated food allergy.

The mechanism by which food elicits EoE is not yet understood. It seems likely that a cellular mechanism similar to contact allergy of the skin or drug hypersensitivity plays a role. IgG4 formed against foods has been suspected of playing a role in EoE, perhaps as a blocking antibody analogous to AD and IBD, an impairment of the epithelial barrier, alterations of the microbiota and subsequent chronic inflammation might be the underlying pathogenic factors for EoE. Given this scenario, food might interfere either as an irritant, modulator of the microbiota or as an antigen/allergen to initiate and perpetuate inflammation (Figure 1). The identification of offending foods by empirical elimination diets and controlled re-introduction of foods is inconvenient for patients, time-consuming, and in the clinical routine hardly applicable. Nevertheless, this procedure is currently the only

reliable method to identify food triggers in EoE patients. Elucidating the exact mechanism of how foods affect EoE would allow the development of novel diagnostic tests. For instance, the determination of food-specific markers including T cell responses to specific foods could possibly overcome the limitations of SPT, APT, and empirical diets. As in IBD and atopic diseases, EoE should be considered as a complex disease with a disordered interplay between the epithelial barrier, innate and adaptive immune responses together with the composition of the microbiota.

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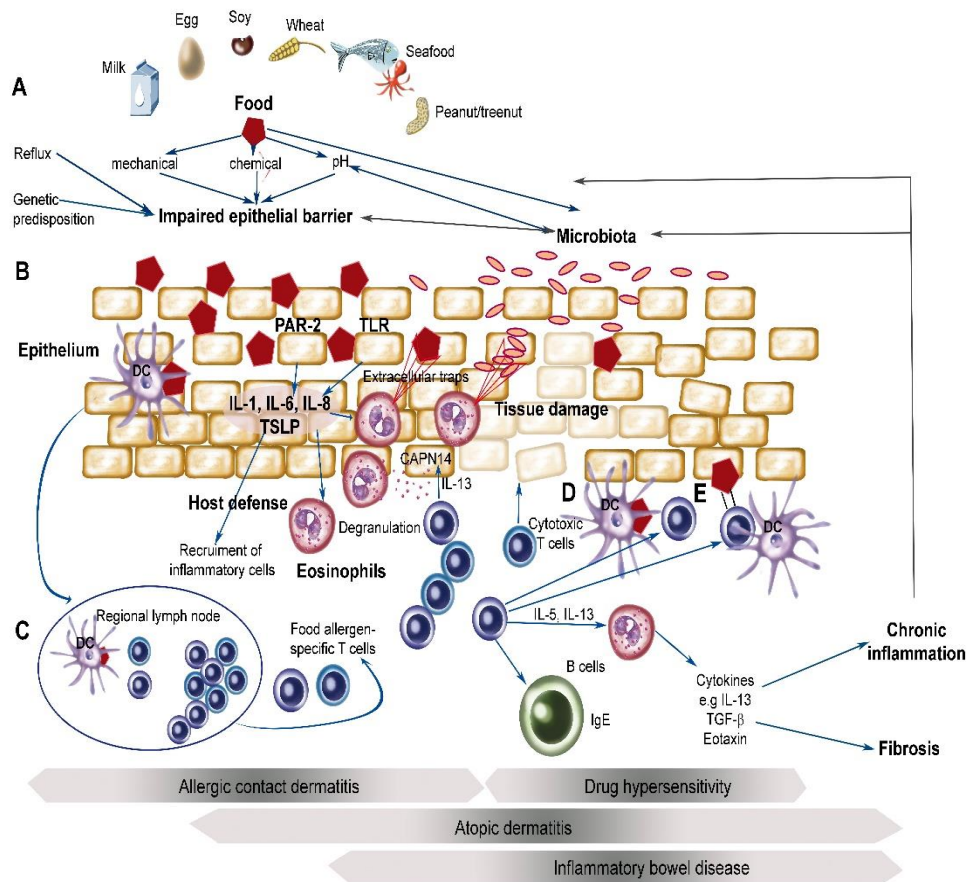
Figure 1 Food as a trigger in the pathogenesis of EoE. (A) In addition to the presence of a genetic predisposition or reflux disease, a food allergy would further disrupt the epithelial barrier and affect the microbiota. (B) Food allergens could then penetrate also in the skin, bind to pathogen-related receptors and activate epithelial cells to produce pro-inflammatory cytokines responsible for the recruitment and activation of inflammatory cells including eosinophils. (C) Antigen-presenting cells capturing food antigens, would migrate to the regional lymph nodes where they stimulate food-specific T cells. Food proteins may induce T cell responses either as a consequence of antigen presentation by dendritic cells (D) or directly (E) with subsequent eosinophil activation. By releasing toxic granule proteins and cytokines, eosinophils defend against invading pathogens, but cause tissue damage, stimulating fibrosis and perpetuating inflammation. The pathomechanisms of EoE overlapping with other diseases are indicated.