

The Role of the High-Affinity IgE Receptor, FcεRI, in Eosinophilic Gastrointestinal Diseases

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KEYWORDS

- Fc-reception • Food allergy • Th2 mucosa
- Gastrointestinal inflammation

Primary eosinophilic gastrointestinal disorders (EGIDs) are a heterogeneous group of diseases that include eosinophilic esophagitis (EoE), eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic enteritis, and eosinophilic colitis. The unifying hallmark and diagnostic marker of EGIDs is an eosinophil-rich inflammatory infiltrate of the gastrointestinal mucosa, in the absence of known causes for eosinophilia. The etiology of EGIDs is not yet fully understood. The pathogenesis, however, seems to involve a complex interplay of genetic predisposition, exposure to food and environmental allergens, and IgE-mediated activation of the immune system.^{1–4} Accumulating evidence relates EGIDs to the group of immune disorders, such as IgE-mediated allergy, mediated by T helper type 2 cells. This article describes a possible role of IgE-mediated immune-activation via the high-affinity receptor for IgE, FcεRI, in the pathogenesis of primary EGIDs.

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EOSINOPHILIC GASTROINTESTINAL DISORDERS AS IgE-MEDIATED ALLERGIC DISEASES?—PROS AND CONS

Several lines of evidence support the concept of EGIDs as some form of allergic disorder. A majority of patients with EGIDs have concomitant IgE-mediated allergies to food and aeroallergens, making a possible causal relation between EGIDs, especially EoE, and IgE-mediated allergies a pertinent subject of discussion. EoE has been increasingly confused with erosive esophagitis in the adult gastrointestinal (GI) world. A growing body of data shows a strong association with allergic sensitizations and atopic illnesses. Positive skin-prick tests to common environmental and food allergens are seen in up to 79% of children with EoE.⁵ In a recent case series of 23 adults with EoE, 82% had serum IgE specific for one or more food allergens, and 78% had allergic diseases, mainly allergic rhinitis.⁶ Atopic disorders in general seem to be more prevalent in patients with EoE compared with the total population. In an Australian cohort of 45 children with EoE, 55.56% also had atopic eczema, 66.67% had asthma, and 93.33% had allergic rhinitis.⁷ A study in adults previously diagnosed with EoE revealed that 68% had a present or past history of allergic illnesses, rhinitis being the most common, and 77% had sensitizations to aeroallergens.⁸ Food allergens in particular have been shown to be causally linked with EoE. For most patients, elimination of foods based on allergy testing or an elemental diet abolished symptoms and reversed histologic pathologies.^{9–11} The sensitization spectrum to food allergens in children with EoE is comparable to that for the general pediatric population, with milk, egg, soy, peanut, and wheat being most common.^{5,12} As is typical in a “classic” allergy, the sensitization pattern in adult EoE patients seems to shift toward dietary allergens cross-reactive with aeroallergens, such as carrot, tomato, and wheat.^{6,8} While classic IgE-mediated anaphylaxis is generally rare in EGIDs patients, a single study reported a history of anaphylaxis in 24% of children with EoE, a rate 100 times that of the general population.⁷

Further evidence of a close pathophysiological link between “classic” IgE-mediated allergic disorders and EGIDs is the finding that allergic inflammation of the respiratory system during allergen season is accompanied by eosinophil infiltration of the gastrointestinal mucosa. Eosinophilic inflammation of the esophageal mucosa¹³ and duodenal mucosa¹⁴ has been found in patients with respiratory tract allergy during the pollen season. Some EoE patients even experience a seasonal variation in symptoms and esophageal inflammation, depending on the environmental allergen burden.¹⁵ In children newly diagnosed with EoE, the intensity of esophageal eosinophilia was higher in the summer than during the winter months, further emphasizing a role of seasonal environmental allergens in the pathogenesis of EoE.¹⁶

Most strikingly, EGIDs patients have been shown to benefit from IgE-targeted therapy. In nine adult patients with eosinophilic gastroenteritis and a history of atopy, treatment with anti-IgE antibodies (omalizumab) significantly decreased symptom scores, serum IgE levels, and allergen skin test wheal and erythema responses. Absolute blood eosinophil counts as well as tissue eosinophilia in the duodenum and the gastric antrum also declined.¹⁷

While evidence in support of pathogenetic implications of IgE-mediated allergies for EoE is accumulating, limited data are available for primary eosinophilic gastritis, enteritis, and gastroenteritis. Some investigators report atopy and increased serum IgE-levels to food proteins in a majority of their EoE patients and resolution of symptoms upon elimination of the causal allergen or elemental diet.⁴ In eosinophilic colitis, IgE does not seem to play a role, and radioallergosorbent and skin-prick tests are characteristically negative.^{4,18}

IgE-mediated mechanisms play a role in up to 79% of EoE patients and a considerable subgroup of patients with other EGIDs, but such mechanisms are likely only one component in the complex pathophysiology of EGIDs.^{4,12} In contrast, a substantial group of patients with EGIDs are not atopic.^{4,12} They show no measurable allergen-specific serum IgE, have negative skin-prick tests, and no symptoms temporally related to allergen exposure. Still, many patients without elevated specific serum IgE respond to elimination of certain foods or an elemental diet. In these patients, T cell-mediated mechanisms, consistent with the delayed-type food hypersensitivity, have been suggested by several studies. Peripheral blood T cells from patients with allergic eosinophilic gastroenteritis have been described to be of the T helper type 2 (Th-2) phenotype.¹⁹ Beyer and colleagues²⁰ reported a Th-2 skew in milk-specific T cell lines from the duodenal lamina propria of children with and without milk-specific IgE who had been diagnosed with eosinophilic gastroenteritis. Blood lymphocytes of positively challenged children with milk- and soy-protein induced enterocolitis proliferated upon in vitro stimulation with soy, cow's milk, and egg white.²¹ In a murine model, induction of experimental EoE was accompanied by an increase in B- and T-lymphocyte subpopulations in the esophagus, and mice lacking adaptive immunity or deficient in T cells were protected from disease.²² In the absence of measurable serum IgE, a proposal has emerged that a local population of IgE-producing B cells or cell-bound IgE in resident mucosal immune cells may play a role. However, such a population has not yet been identified in EGID patients.

In summary, clinical and experimental data suggest that IgE sensitizations and atopic illnesses are highly associated with EGIDs, but whether they are causally linked or just concomitant disorders is not clear yet. Nevertheless, because the majority of patients feature IgE sensitizations and allergy to food and environmental allergens, local IgE-mediated mechanisms are highly likely to play a role. Available data suggest that EGIDs are positioned between purely IgE-mediated, immediate-type allergies and cellular-mediated delayed-type Th-2 responses. Based on these pieces of evidence, we hypothesize that the high-affinity IgE receptor, FcεRI, plays a role in the pathogenesis of EGIDs.

THE HIGH-AFFINITY RECEPTOR FOR IgE, FcεRI

FcεRI is one of the key molecules in the pathophysiology of allergic reactions.^{23–25} As a multimeric cell surface receptor, FcεRI shares with other immune recognition receptors the overall structure of a ligand-binding immunoglobulin domain-containing protein (α -chain) associated with signaling subunits that regulate cellular activation (β - and γ -chains) (Fig. 1).^{24,26,27} FcεRI binds its ligand, the Fc part of IgE, monovalently via its α -chain. IgE binding per se does not lead to activation of immune cells. The extremely stable IgE-receptor complex on the surface of peripheral blood and tissue cells should rather be pictured as a loaded gun waiting for contact with IgE-specific antigens, which trigger the allergic cascade.

Activation of the immune system via FcεRI is dependent on multivalent crosslinking of FcεRI α -bound specific IgE. FcεRI α , however, only contains the IgE-binding site. Signaling events are initiated via immunoreceptor tyrosine-based activation motifs of the signaling subunits, the β - and γ -chains. A rather uncommon feature of FcεRI is that this receptor complex is expressed in different isoforms in a manner dependent on cell type and species. FcεRI can be expressed either as a tetrameric or a trimeric isoform. Tetrameric FcεRI, composed of the ligand-binding α -chain, one β -chain, and a pair of disulphide-linked γ -subunits (FcεRI $\alpha\beta\gamma_2$), is found on the surface of immune-effector cells, such as basophils and mast cells in rodents and humans (see Fig. 1). In

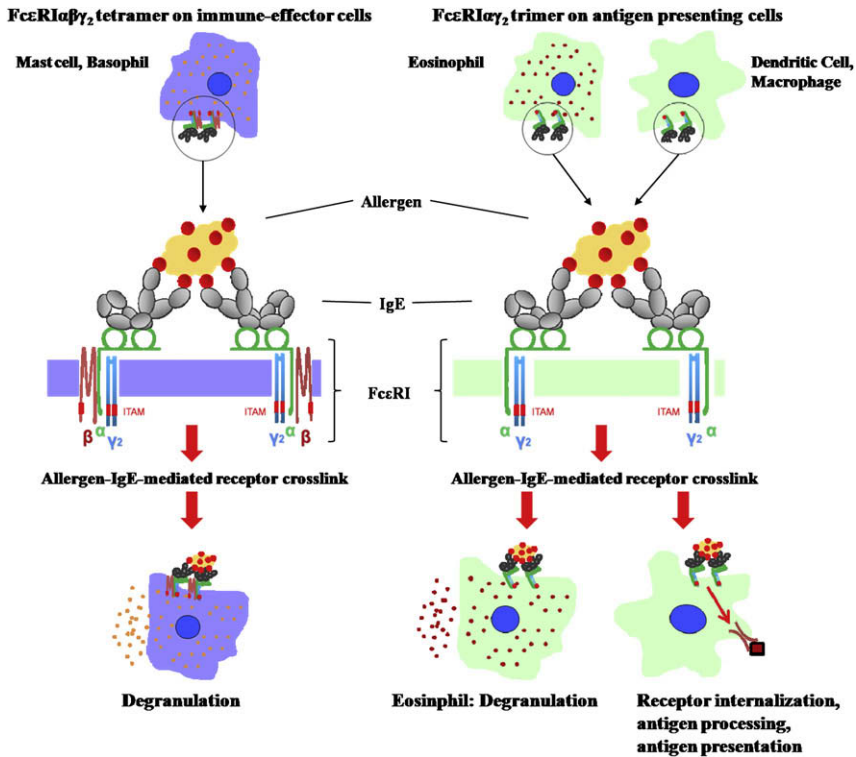


Fig. 1. IgE-FcεRI-mediated activation of cells of the immune system. Human FcεRI is expressed on mast cells and basophils in its tetrameric isoform (FcεRIαβγ₂) (*left panel*). Eosinophils, dendritic cells, and macrophages express the trimeric isoform of the receptor (FcεRIαγ₂) (*right panel*). Allergens activate immune cells by crosslinking FcεRI complexes loaded with specific IgE. The IgE-binding α-chain associates with the signaling subunits, β and γ. Each immunoreceptor tyrosine-based activation motif (ITAM) of the signaling subunits uses phosphotyrosin-based activation to induce degranulation of mast cells, basophils, and eosinophils. Dendritic cells and macrophages internalize allergen-IgE complexes after FcεRI crosslinking and shuttle them toward antigen presentation to elicit T helper cell responses.

the absence of β-transcripts, humans express a trimeric version of FcεRI on many cells of the innate and adaptive immune systems, including eosinophils and antigen-presenting cells (APCs).

The best-described regulator of FcεRI surface expression levels is the receptor's natural ligand, IgE. Binding of monomeric IgE to FcεRIα stabilizes the receptor at the cell surface as an IgE-FcεRI complex. This stabilization enhances surface expression of the receptor on immune-effector cells, as well as on APCs. The mechanism of this stabilization is not completely understood. Receptor surface stability seems to depend solely on the length of the stalk region of the FcεRIα chain.²⁸ In vivo, the cell surface density of FcεRI is thus tightly correlated with serum IgE levels. Allergic individuals show enhanced surface expression of the receptor on peripheral blood basophils, monocytes, and dendritic cells. Along the same line, treatment with anti-IgE monoclonal antibodies, such as omalizumab, not only decreases serum IgE but also FcεRI-surface expression on peripheral blood cells.^{29,30} Lower levels of surface FcεRI consecutively render immune cells less sensitive to allergen stimuli, as shown by

a significant increase in the allergen dose required for *in vitro* basophil activation following omalizumab therapy of eosinophilic gastroenteritis patients.¹⁷

With regards to EGIDs, it is important to stress that FcεRI expression on eosinophils also correlates with serum IgE concentrations.³¹ Furthermore, gene-expression profile analysis in EoE shows elevated levels of FcεRI.³² This review argues for a role of FcεRI-mediated immune activation in the gastrointestinal mucosa of EGID patients. Beyond the defined role of tetrameric FcεRI on mast cells and basophils in type I allergic reactions, we hypothesize that expression of trimeric FcεRI on human eosinophils and APCs is critically involved in the pathology of EGIDs.

IgE AND IgE-BINDING STRUCTURES IN THE GASTROINTESTINAL MUCOSA

The gastrointestinal immune system must balance its ability to respond to pathogens while remaining unresponsive to food and environmental antigens and the commensal microbiota.³³ Distortion of this delicate immune equilibrium in the gastrointestinal tract can result in a break of oral tolerance and precipitate inappropriate immune reactions,³⁴ including immediate hypersensitivity and EGIDs. The lines of defense against pathogens in the gastrointestinal tract include immunoglobulins, such as IgE. IgE antibodies are secreted into the gastrointestinal mucous by B cells of the lamina propria to immediately sense invading pathogens. In parallel with the falling numbers of parasite infections in industrialized countries, the specificity of the IgE repertoire has shifted from pathogens toward innocuous environmental antigens over the past century. This shift is reflected in the rising numbers of patients suffering from IgE-mediated allergies to airborne and food allergens.^{35–37}

Once an individual is sensitized to an allergen, allergen-specific IgE can be found in the serum, and is also secreted into various body fluids lining mucous membranes. Nasal fluid from children with respiratory allergies,¹⁴ bronchoalveolar lavage from asthmatics³⁸ and stool of food-allergic patients³⁹ contain allergen-specific IgE. Whether or not the saliva or stool of patients suffering from EGIDs also contains IgE remains to be analyzed.

IgE signals the presence of specific ligands at the mucosal surface to the mucosal immune system via IgE receptors. In addition to FcεRI, the high-affinity IgE receptor, humans express two other surface receptors for IgE in the gastrointestinal tract: the low-affinity IgE receptor, FcεRII or CD23, and galectin-3. Intestinal epithelial cells constitutively express the low-affinity IgE receptor CD23.^{40,41} So far, no data exist on the expression of FcεRI or galectin-3 on intestinal epithelial cells. FcεRI is, however, expressed on many immune-effector cells and APCs abundant in the mucosa throughout the gastrointestinal tract (see below). Here, we will focus on IgE-mediated FcεRI activation, which we believe to be critical in the pathology of EGIDs. Note that a detailed, comparative analysis of the nature and expression levels of IgE-binding structures in the gastrointestinal tract of healthy subjects and patients suffering from EGIDs is lacking so far. Detailed information on IgE-receptor expression in the gastrointestinal tracts of healthy subjects and diseased subjects will shed new light on mechanisms of IgE-mediated immune activation in EGIDs.

IgE TRANSPORT IN THE GASTROINTESTINAL TRACT

The common consensus is that CD23 acts as a transport receptor for IgE sampling in the gastrointestinal mucosa.^{42,43} IgE-mediated activation of the gastrointestinal immune system via CD23 has been studied in detail because intestinal epithelial cells constitutively express this receptor in mice as well as in humans.^{23,40} Intestinal epithelial cells use CD23 to mediate transepithelial crossing of intact IgE-allergen

complexes.^{44,45} Once these complexes bridge the barrier, they activate subepithelial mast cells and initiate immediate allergic responses in the gastrointestinal mucosa.³⁹ Besides transcytosis of IgE-antigen complexes, engagement of CD23 induces the release of IL-8 and CCL20 from intestinal epithelial cells.⁴⁶ These chemokines are capable of recruiting effector cells of late-phase allergic reactions and APCs. Strikingly, IL-8 is also one of the most important eosinophil chemoattractant cytokines.⁴⁷ The role of CD23 thus seems to extend to that of a pure transcytosis receptor at the gastrointestinal mucosal surface. CD23-triggered release of chemoattractants upon allergen exposure could contribute to the formation of the eosinophil-rich infiltrates characteristic of EGIDs.

While the role of CD23 in the gastrointestinal mucosa has been established, no reports on FcεRI expression on epithelial cells exist. It is therefore rather unlikely that FcεRI is a transcytosis receptor in intestinal epithelial cells. However, humans abundantly express FcεRI in the mucosa throughout the gastrointestinal tract on APCs, such as Langerhans cells and dendritic cells.^{48,49} In the oral mucosa, Langerhans cells constitutively express FcεRI in atopic and nonatopic patients.⁵⁰ Langerhans cells are also found in the esophageal epithelium.⁵¹ Humans constitutively express FcεRI in dendritic cells of the esophagus, the stomach, and the small intestine (Dehlink and colleagues, unpublished observation). Dendritic cells are not simply resident cells in the lamina propria of the gastrointestinal tract. They are able to open tight junctions of the epithelial cell barrier and send out projections into the intestinal lumen to monitor the antigenic environment of the gastrointestinal tract and sample noninvasive luminal bacteria.^{52,53} It is tempting to speculate that FcεRI on these dendritic cell protrusions functions as a transport receptor for IgE or IgE-antigen complexes into the lamina propria of the gastrointestinal tract in healthy or diseased subjects. This hypothesis remains to be investigated.

Transepithelial shuttling of IgE and IgE-antigen complexes is yet only one possible task of FcεRI on immune cells in the gastrointestinal mucosa. The extremely stable monovalent, high-affinity interaction of IgE with FcεRIα allows us to speculate about another trafficking mechanism. FcεRIα on blood cells could serve as a sponge for IgE anywhere in the organism and drag IgE from the periphery into mucosal tissues. This mechanism could be particularly important in EGIDs where lesions are typically described by high cell counts of eosinophils. These eosinophils could use surface FcεRI^{54,55} to enrich tissue IgE in the lamina propria of the gastrointestinal tract. Higher levels of tissue IgE would consequently lower the threshold for immune activation by specific allergens. In other allergic diseases, such as atopic dermatitis, high levels of IgE-occupied APCs have been described in eczematous skin.⁵⁶ An answer is urgently needed for the question of whether the same holds true for EGIDs.

ACTIVATION OF TETRAMERIC FcεRIαβγ₂ IN THE GASTROINTESTINAL MUCOSA—CONSEQUENCES FOR EOSINOPHILIC GASTROINTESTINAL DISORDERS

Tetrameric FcεRIαβγ₂ is a marker for mast cells and basophils (see **Fig. 1**), which are classic effector cells of immediate type (type I) allergic reactions. The binding of multivalent allergen to adjacent IgE-loaded FcεRI complexes on the cell surface leads to aggregation of neighboring receptors. Cross-linking of FcεRI initiates cell activation via immunoreceptor tyrosine-based activation motifs, which are present in one copy in the β-chain as well as in each of the γ-chains in FcεRIαβγ₂.^{48,57,58} In mast cells and basophils, this activation occurs within minutes after antigen contact and results in degranulation of preformed cytoplasmatic granules. Inflammatory mediators, such as histamine and serine proteases, are secreted into the extracellular space. This

results in the typical clinical manifestation of the early phase of allergic reactions, and causes the characteristic signs and symptoms of immediate-type hypersensitivity reactions, as in allergic rhinitis, asthma, IgE-mediated food allergies, or anaphylaxis.

Fc ϵ RI-dependent activation of mast cells also induces the synthesis of proinflammatory cytokines, chemokines, and lipid mediators. These mediators are involved in the late-phase allergic response, which is seen several hours after the initial allergen contact. Late-phase reactions are characterized by the recruitment of inflammatory cells, such as neutrophils, eosinophils, APCs, lymphocytes, and macrophages, to the site of allergen encounter.^{59–61}

Tissue specimens of EoE patients, besides having elevated eosinophil levels, display characteristics of inflammatory lesions of type I allergy. Increased numbers of IgE-bearing cells and activated mucosal mast cells are found⁶² and the mucosa is heavily infiltrated by lymphocytes and APCs.⁶³ Although “classic” immediate hypersensitivity reactions and anaphylaxis to food or airborne allergens are rarely seen in EGID patients, the finding of increased activated mast cell counts in EoE lesions⁶² strengthens our hypothesis that Fc ϵ RI-mediated immune activation plays a role in the pathology of EGIDs. However, the immunologic mechanisms underlying EGIDs seem to be more subtle and multifarious.

ACTIVATION OF TRIMERIC Fc ϵ RI $\alpha\gamma_2$ IN THE GASTROINTESTINAL MUCOSA—CONSEQUENCES FOR EOSINOPHILIC GASTROINTESTINAL DISORDERS

Humans constitutively express the trimeric isoform, Fc ϵ RI $\alpha\gamma_2$, on professional APCs in the GI tract, like dendritic cells and Langerhans cells. These professional APCs have the unique ability to elicit primary immune responses toward foreign antigens. Such an event is required for the adaptive immune response that characterizes delayed type Th-2-mediated immune responses considered central in the pathogenesis of EGIDs. This type of immune activation requires that an exogenous antigen enter the cell where it is processed rapidly to generate antigenic peptides. These peptides are then presented on major histocompatibility complex class II molecules at the APC surface for recognition by T cells of the adaptive immune system. The expression of Fc ϵ RI $\alpha\gamma_2$ on APCs in the human gastrointestinal tract and possible consequences for IgE-mediated immune activation as observed in EGIDs are discussed below.

Dendritic cells in the gastrointestinal tract monitor the gastrointestinal lumen. As mentioned earlier, dendritic cells of the intestinal mucosa reach through the epithelial cell layer with periscopelike protrusions for direct access to the antigenic environment of the intestinal lumen.^{52,53} Phagocytosis and macropinocytosis are key features of dendritic cells that ensure efficient antigen uptake. In addition to fluid phase antigen uptake, resting dendritic cells can use surface receptors, like Fc ϵ RI $\alpha\gamma_2$, for uptake of antigen. Receptor-mediated antigen uptake is a mechanism that allows the elicitation of efficient immune responses toward minor amounts of antigen.^{64,65} Surrogate ligands that enter the dendritic cell through receptor-mediated uptake are presented to T cells 100- to 1000- fold more efficiently when compared with soluble antigen.^{48,65} This mechanism could explain the strong immune responses observed once sensitization to antigens and the production of antigen-specific IgE has occurred in a patient.

In their immature state, dendritic cells reside at sites of antigen exposure, such as the mucosal surfaces or the skin. These dendritic cells have a high capacity to endocytose and process exogenous antigens. Upon exposure to innate stimuli (eg, Toll-like receptor ligands), dendritic cells undergo a process of functional maturation that includes the termination of antigen uptake, the migration from the periphery to secondary lymphoid organs, the up-regulation of surface major histocompatibility complex

and costimulatory molecules, and the secretion of cytokines, such as IL-12. Mature dendritic cells are able to productively present previously captured antigenic material to naïve T cells. Cognate contact with CD4⁺ T cells in lymphoid organs leads to CD40 ligand (CD40L)–dependent activation of dendritic cells. The stimulation of regulatory T cells is also dependent on dendritic cells.^{64,65} Detailed insight into IgE-mediated antigen presentation events in the gastrointestinal tract and consequences for the gastrointestinal T-cell repertoire is thus critical to our understanding of how the gastrointestinal system balances immune responses.

Trimeric FcεRI on primary human peripheral blood dendritic cells can, in principle, function as an antigen uptake receptor for major histocompatibility complex class II–mediated antigen presentation.⁶⁶ Thus, it is fair to assume that FcεRI may function the same way when expressed on dendritic cells located in the intestinal mucosa. FcεRI expression on mucosal dendritic cells and loading with IgE might result in “allergic sensitization” of patients with EGIDs. The inflammatory conditions in EGID patients might also allow non–professional APCs, such as macrophages and monocytes, to present allergen in a major histocompatibility complex class II–dependent fashion after FcεRI-mediated antigen uptake. Under inflammatory conditions, eosinophils can express major histocompatibility complex class II molecules and turn into non–professional APCs.^{67,68} It is thus tempting to speculate that antigen presentation by eosinophils contributes to the Th-2 phenotype of EGIDs. In EGIDs, APCs could engage the gastrointestinal immune system via IgE–FcεRI–dependent antigen presentation and that way initiate and sustain the self-perpetuating cycle that leads to chronic immune activation and aggravation of the disease.

IgE-INDEPENDENT ACTIVATION OF FcεRI IN THE GASTROINTESTINAL MUCOSA—IMPLICATIONS FOR EOSINOPHILIC GASTROINTESTINAL DISORDERS

Thus far, we described solely IgE-mediated FcεRI-activation events and their potential role in EGIDs. FcεRI-mediated immune activation can also occur in an IgE-independent manner. We therefore next want to discuss mechanisms of IgE-independent FcεRI activation with regards to EGIDs. Such mechanisms might be particularly relevant for the pathology of EGIDs in patients lacking elevated serum IgE levels or symptoms attributable to specific allergens. Two IgE-independent mechanisms of FcεRI-mediated immune activation have been described: (1) receptor crosslinking via galectin-3 and (2) receptor crosslinking via anti-FcεRIα IgG autoantibodies.

Galectin-3, formerly known as epsilon binding protein (εBP), is a β-galactose-containing oligosaccharide that binds to IgE, FcεRI, or both.^{23,69} Galectin-3 is commonly known as a marker for tumor progression,⁷⁰ but has also been shown to activate mast cells and basophils in the absence as well as in the presence of IgE.^{69,71} Whether galectin-3 is able to activate trimeric FcεRI as expressed by human APCs remains to be determined. In view of reports on elevated mast cell numbers in EGID patients,⁶² this oligosaccharide is an interesting candidate for modulating mast cell responses in the absence of IgE in EGID patients.

IgG autoantibodies with specificity for the alpha subunit of FcεRI (FcεRIα) are described to activate FcεRI-expressing cells by crosslinking the receptor via their Fab portion. In 30% of patients with chronic idiopathic urticaria, such antibodies are responsible for pseudoallergic reactions in absence of defined allergens.^{72–75} Recently, these autoantibodies were also described in patients with asthma.⁷⁶ It is possible that anti-FcεRIα autoantibodies play a role in EGIDs as well. In conclusion, this pathway of FcεRI activation allows for the novel speculation that autoimmune events may play a role in EGIDs in the absence of specific IgE sensitizations.

SUMMARY

We have discussed the possible contribution of the high-affinity IgE receptor, FcεRI, in the pathology of EGIDs. The hypothesis that FcεRI is indeed a critical structure in triggering eosinophilic inflammation in EGIDs is supported several ways. Numerous case reports and clinical studies have pointed out the strong association between EGIDs and atopic diseases. Gene expression profiling of EoE patients showed up-regulation of FcεRI. The inflammatory infiltrate in EGIDs is characterized by eosinophils, mast cells, and dendritic cells. Those cells abundantly express FcεRI. Most strikingly, anti-IgE therapy in patients with eosinophilic gastroenteritis improves symptoms and down-regulates FcεRI expression. It is therefore highly likely that FcεRI is critically involved in the pathology of EGIDs. However, there is still much ground to cover and primary data to collect. A better understanding of the role of FcεRI in IgE-mediated as well as IgE-independent immune activation will, we hope, point toward new therapeutic directions to combat EGIDs.

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