

The Immunoglobulin E Receptor: Expression and Regulation

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The interaction of immunoglobulin E (IgE) and its receptors is critical for the manifestation of allergic disease. Currently, IgE receptors include the high-affinity FcεRI and the low-affinity FcεRII. FcεRI is a tetrameric or trimeric complex, and each has distinct expression patterns and unique functional consequences. In general, serum levels of IgE regulate FcεRI expression, and novel therapies that lower the concentration of IgE have provided insights into the contribution of this receptor in allergic disease. Newer therapies targeting FcεRI-signaling elements and the low-affinity IgE receptor, FcεRII (CD23), are being developed.

Introduction

Immunoglobulin E (IgE) antibody is a critical “gatekeeper” of the human allergic response [1]. Its presence was first theorized in 1921 when Heinz Kustner, at the time a fish-allergic medical assistant, injected his serum into Otto Prausnitz and transferred his allergic sensitivity [2]. It was not until almost 50 years later that two groups characterized the essential serum component as IgE antibody [3,4]. This vital discovery radically altered the existing paradigm of allergic disease and has been guiding research and clinical therapy ever since.

The specificity of IgE antibodies for one of a broad array of allergens serves as the basis for diagnosing allergic disease. Through skin and radioallergosorbent testing (RAST), clinical allergists use these IgE-specific reactions every day to identify and manage individuals with atopic illnesses. Although the interaction of IgE to its specific allergen is certainly important, the relationships between IgE and its receptors are also critical for understanding the allergic response.

Two main receptor subtypes that bind free IgE have been identified. The high-affinity IgE receptor (FcεRI) was originally thought only to be found on basophils and mast cells [5]. More recent evidence, however, suggests that it is found on monocytes, eosinophils, peripheral blood dendritic cells

(DCs), and Langerhans' cells in the skin [6••]. A low-affinity receptor, FcεRI I (CD23), has also been identified on a variety of hematopoietic cells, including B lymphocytes.

In this article, we focus on the regulation of the high-affinity IgE receptor, FcεRI, and examine its expression and function on specific cell types. We also discuss the impact of omalizumab, a monoclonal antibody that binds free IgE, in understanding the role of FcεRI in allergic disease pathophysiology. Finally, we look ahead to emerging therapeutics targeted at IgE and its receptors.

FcεRI Levels and Regulation of Expression Regulation of FcεRI expression by serum IgE levels

Although IgE was identified in the late 1960s, the identification of FcεRI and the regulation of its surface expression came much later. In a study of 26 allergic subjects, Malveaux *et al.* [7] found that the number of FcεRI receptors per basophil ranged from 6000 to 600,000 and that this closely correlated with the levels of IgE in the serum. They postulated that basophil FcεRI receptor numbers in individuals with allergic disease are modulated by the concentration of free IgE in the serum.

Nearly two decades later, Sihra *et al.* [8] expanded these findings by exploring the relationship between free IgE and FcεRI receptor levels for cell types other than the basophil. Subjects with allergic disease (rhinitis, asthma, or atopic dermatitis) were compared with nonatopic controls for cell surface FcεRI on basophils, monocytes, and eosinophils. They found that FcεRI expression in basophils was 500 times greater than that in monocytes, whereas eosinophil FcεRI expression was not detected in most subjects. In the few patients in whom eosinophil surface FcεRI expression was detected, the number of receptors per eosinophil was at least 1000-fold less than that for basophils. Furthermore, positive correlations were found between serum IgE and FcεRI on monocytes and basophils, but not eosinophils.

More recent work has confirmed the relationship between serum IgE and FcεRI levels on basophils across a broad range of diseases [9]. Blood basophils were obtained from nonallergic subjects and subjects with allergic asthma, atopic dermatitis, hypereosinophilic syndromes, hyper-IgE syndrome, helminth infestation, and IgE myeloma. A significant positive relationship between serum IgE and basophil FcεRI receptor density suggested that the effects of serum IgE on FcεRI expression exist

independent of an atopic state. However, the absence of a similar relationship for monocytes indicates that other cofactors found exclusively in allergic disease are needed to modulate FcεRI surface expression on monocytes.

Mechanisms of serum IgE effects on FcεRI

It is currently thought that serum IgE mediates its effects on FcεRI expression by stabilization of FcεRI turnover rather than by increasing production of the receptor subunits. Several groups of investigators have independently confirmed this hypothesis [10–12]. Using human basophils, MacGlashan *et al.* [10] demonstrated that removal of IgE from occupied FcεRI receptors led to accelerated loss of the unoccupied receptors from the basophil surface, but no such loss was noted in occupied receptors. They also demonstrated that FcεRI synthesis rates did not change in the presence or absence of free IgE. A second study by Kubo *et al.* [11] used brefeldin A, a chemical that prevents transport of new FcεRI molecules to the cell surface. By incubating peritoneal and bone marrow-derived mouse mast cells in brefeldin A, they demonstrated that FcεRI receptor levels on the surface of mast cells drop dramatically in the absence of free IgE in culture but remained stable if IgE was present.

FcεRI Structure and Cellular Expression

Structure and subunit function

FcεRI on basophils and mast cells is found as a tetrameric complex consisting of one IgE-binding α chain, one β chain, and two disulfide-linked γ chains [13]. A trimeric form of the FcεRI is variably expressed on human monocytes, Langerhans' cells, and peripheral blood DCs. The trimer is composed of one α subunit and 2 γ subunits [13]. In murine models, this optional expression of the FcεRIβ subunit has not been observed [14].

In both receptor forms, the α subunit is the specific component of FcεRI that binds to the c3 domain of IgE (Fig. 1). Expression of the α subunit is upregulated by interleukin (IL)-4 in mast cells, monocytes, and eosinophils [15].

In contrast, the β subunit functions as an amplifier of downstream events after initial FcεRI activation [16] and also amplifies FcεRI cell surface expression [17]. This latter function may account for the large differences in surface receptor density between cells that contain the β subunit (basophils) and those that do not (antigen-presenting cells [APCs] such as monocytes) [17]. Human basophil β subunit expression is upregulated by IL-3 [18] and as a consequence of in vivo allergen challenge [19].

Lastly, the γ chain dimers are also concerned with signal transduction and are required to permit surface α display [13]. In trimeric receptor-bearing cells, regulation of γ expression may influence the level of surface FcεRI receptor detected [20]. Factors controlling γ expression are as yet unidentified.

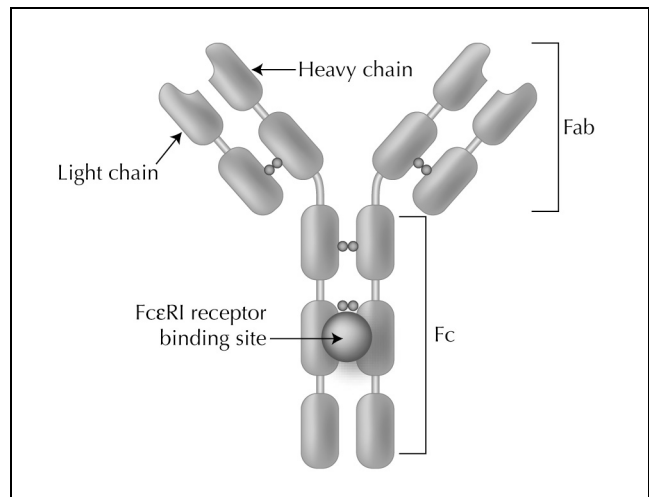


Figure 1. Structure of immunoglobulin E. Omalizumab binds to FcεRI binding site. FcεRI—high-affinity IgE receptor.

Tetrameric FcεRI receptor complex: basophils and mast cells

It is well-accepted that cross-linking of the tetrameric FcεRI complexes on mast cells and basophils leads to cellular activation, resulting in degranulation, synthesis of lipid mediators, and release of inflammatory cytokines leading to the recruitment of leukocytes that augment and propagate the allergic response [5].

More recently, occupancy of FcεRI by IgE has also been shown to prolong mast cell survival [21,22]. Asai *et al.* [21] demonstrated that monomeric IgE, which would not cross-link FcεRI and, therefore, not lead to downstream activation, prevented apoptosis of mouse mast cells in growth-factor-suppressed culture conditions. This suggests that elevated serum IgE levels in atopic individuals may lead to elevated basophil and mast cell numbers, thereby increasing the severity of the clinical allergic response. However, there is limited evidence in human allergic subjects to support that elevations in IgE levels yield increased numbers of these cells (see later).

Trimeric FcεRI receptor complex: antigen presenting cells

In APCs such as monocytes, DCs, and Langerhans' cells, the trimeric FcεRI receptor complex is thought to facilitate antigen presentation to CD4⁺ lymphocytes [23]. FcεRI-mediated allergen uptake by APCs is up to 1000 times more efficient than allergen uptake by any other route [23], suggesting that the threshold dose of allergen exposure necessary to initiate APC presentation or activation of T cells may be lowered in vivo. Other functions have also been ascribed to FcεRI on these different cell types. For example, Katoh *et al.* [24] demonstrated that activation of FcεRI by cross-linking prevented apoptosis of monocytes and enhanced expression of anti-apoptotic molecules such as bcl-2 and bcl-xL.

Dendritic cells in lung mucosal tissue have been found to express FcεRI in both asthmatic and control subjects

[25]. Asthmatic patients had a greater number of DCs and a higher proportion of DC-expressing FcεRI than controls. A more recent study [26] examined peripheral blood DCs in individuals with and without asthma. Unlike the previous study [25], they found no difference in FcεRI-receptor density between the two groups. However, the peripheral blood DCs of asthmatic subjects had higher levels of receptor occupancy and bound IgE more efficiently in vitro than control subjects. This implies that selective recruitment of peripheral blood DCs to sites of allergic inflammation may be related to the binding affinity of FcεRI for IgE.

The Langerhans' cell is an APC that resides in the dermis and functions as a sentinel of the cutaneous immune system. Semper *et al.* [27] examined intracellular α subunit expression and cell surface FcεRI expression in subjects with currently active or with a history of atopic dermatitis, asthma, and allergic rhinitis as well as nonallergic controls. The intracellular α subunit was found in all subjects, regardless of atopic status. However, only subjects with currently active atopic dermatitis, asthma, or allergic rhinitis expressed cell surface FcεRI. This indicates that the presence of ongoing allergic inflammation is required for expression of the receptor complex, perhaps through differential expression of the FcεRIγ subunit [20]. Furthermore, local allergic disease, such as asthma, can lead to systemic change in skin-based FcεRI expression.

Eosinophils

There is a great deal of controversy as to whether human eosinophils express FcεRI on their cell surfaces. Rajakulasingam *et al.* [28] demonstrated that FcεRI⁺ cells and eosinophils increased after segmental bronchial challenge with *Dermatophagoides pteronyssinus*. Colocalization studies indicated that the number of FcεRI⁺ cells that were eosinophils jumped from 4% to 85% to 95% after challenge. However, this and other similar studies used immunohistochemistry and were, therefore, unable to discriminate between intracellular and cell-surface FcεRI expression. Subsequently, Seminario *et al.* [29] found large intracellular FcεRIα subunit pools in eosinophils of allergic subjects and only detected surface FcεRI in 1 of 26 individuals studied. Similarly, Kita *et al.* [30] were unable to detect FcεRI on circulating eosinophils. Only after in vitro sensitization with IgE did they detect a very small amount of surface expression of FcεRI on the eosinophil, and this was only 0.5% of the expression seen on basophils.

The function of FcεRI on human eosinophils is also debated. An earlier study by Gounni *et al.* [31] suggested that FcεRI may enhance immune defense against parasites. Specifically, they demonstrated that FcεRI is expressed on eosinophils from hypereosinophilic patients, is involved in eosinophil degranulation, and participates in eosinophil-mediated cytotoxicity against *Schistosoma mansoni*. In contrast, in the study by Kita *et al.* [30], no such eosinophil effector functions were activated via cross-linking the surface FcεRI.

FcεRI Signaling

We provide a brief description of the early events in FcεRI signaling for discussion of therapeutic targets later. Readers are directed to a recently published, comprehensive review on this topic [32].

Cross-linking of FcεRI receptor-bound IgE by allergen results in phosphorylation of the immunoreceptor tyrosine activation motifs (ITAM) found on the β and γ chains of the FcεRI complex by the tyrosine kinase Lyn. The phosphorylation of the ITAMs leads to increased association of Lyn kinase with the β chain and binding of the γ chain with a second tyrosine kinase, Syk.

The phosphorylation of Syk kinase and the γ chain result in an increase in Syk kinase catalytic activity. This results in the initiation of the downstream activation of several parallel pathways, including phospholipases, adaptor proteins, and mobilization of intracellular calcium stores (Fig. 2). As a consequence of these intracellular events, degranulation occurs, and results in the rapid release of preformed cytoplasmic granule mediators, such as histamine and neutral proteases. In addition, newly synthesized mediators, including prostaglandin D₂ (mast cells) and leukotriene C₄, D₄, and E₄ (mast cells and basophils) and cytokines, such as IL-4 (from basophils) and IL-13 (from basophils and mast cells), are also newly transcribed and released. It is notable that current allergic therapies target these released mediators, such as antihistamines and leukotriene receptor antagonists.

Lessons Learned from Modulating the FcεRI Receptor

New therapeutics that target specific functional molecules in humans are being rapidly created. Although these agents are demonstrating clinical benefit, they are also providing important insights into human disease pathophysiology. In the case of allergic diseases, omalizumab has provided researchers such an opportunity to study the significance of IgE and FcεRI modulation in humans.

Omalizumab

Omalizumab is a humanized κ IgG1 antibody that binds to free IgE at the FcεRIα subunit binding site on the c3 domain of the IgE molecule (Fig. 1). This prevents binding of IgE to its receptors, including FcεRI, on effector cells. By design, omalizumab is unable to bind surface-bound IgE because its epitope is buried within the IgE–FcεRI complex. This prevents cross-linking and activation of FcεRI complexes by omalizumab and, to date, no significant reports of anaphylaxis have been observed with this therapy [33]. Clinically, omalizumab has been shown to be effective in reducing asthma exacerbations in patients with moderate to severe allergic asthma and allergic rhinitis [34,35••]. These studies have also included investigations of the effects of omalizumab on a variety of immune cell types in individuals with allergic disease.

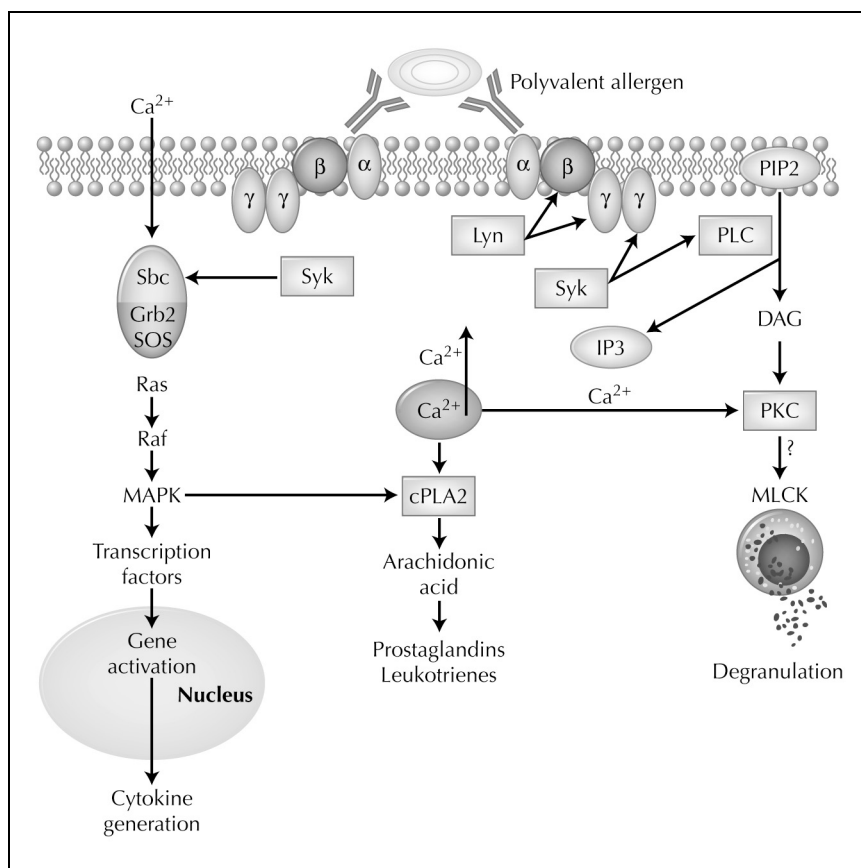


Figure 2. FcεRI receptor complex signaling on basophils. DAG—diacylglycerol; FcεRI—high-affinity IgE receptor; IP₃—inositol triphosphate; MAPK—mitogen-activated protein kinase (MAPK); MLCK—myosin light-chain kinase; PKC—protein kinase C.

Basophils

Years after Malveux theorized that basophil FcεRI receptor density is modulated by serum IgE levels, MacGlashan *et al.* [36•] provided direct evidence for this conclusion in early phase I studies with omalizumab. The treatment of 15 allergic subjects with the omalizumab antibody reduced free IgE levels to 1% of pretreatment levels. In parallel, this led to a marked downregulation of FcεRI receptors on basophils from an average of 220,000 receptors per basophils to 8300 receptors per basophil. As a functional consequence of this reduction, basophil allergen-induced histamine release was reduced 90%. It is important to note that no reduction in circulating basophil numbers were noted in subjects infused with omalizumab up to 1 year [37].

In a follow-up study, Saini *et al.* [37] demonstrated that as serum IgE levels rose following discontinuation of omalizumab, FcεRI expression on basophils also increased and rapidly restored basophil allergen-induced histamine release. Additionally they showed that FcεRI-depleted basophils taken from omalizumab-infused subjects rapidly increased FcεRI expression by in vitro exposure to IgE. Collectively, these observations firmly establish the regulatory relationship between free IgE and FcεRI expression on human basophils.

Mast cells

A more recent study [38•] compared the effects of omalizumab on skin mast cell FcεRI expression to that observed for

basophil FcεRI expression. Similar to basophils, skin mast cell numbers as enumerated in skin biopsies did not significantly change during the course of omalizumab-induced reductions in serum IgE. However, expression of skin mast FcεRI decreased substantially, but at a much slower rate (several weeks) than that observed for blood basophils in the same subject (1 week). This study [38•] also showed parallel reduction in allergen-induced skin-wheal response relative to FcεRI mast cell expression, indicating that the allergic response in humans is dictated by the density of FcεRI receptor complexes rather than the number of effector cells present. This finding is in contrast with previous murine work showing inhibition of apoptosis by monomeric IgE [21,22] and stresses the importance of studying human allergic mechanisms in vivo.

Dendritic cells

FcεRI expression on DCs is also decreased in the presence of omalizumab. DC subsets have been identified that promote Th1 (DC1) and Th2 (DC2) responses. Precursor DC cells (pDC) are an earlier DC developmental stage present in peripheral blood. Prussin *et al.* [39] identified pDC1 and pDC2 subsets in patients with seasonal allergic rhinitis who were enrolled in a placebo-controlled trial of omalizumab. They found that FcεRI expression was reduced by 53% in pDC1 and 83% in pDC2 after treatment with omalizumab. This decrease was highly correlated with serum IgE reduction and paralleled the changes seen in blood basophils.

This is notable because it suggests that omalizumab may reduce antigen presentation by FcεRI-bearing DCs. This, in turn, may prevent clonal expansion of naïve T cells into allergen-specific Th2 cells and also inhibit activation of Th2 lymphocytes to produce inflammatory cytokines. Omalizumab may potentially have an immunomodulatory effect on Th2 lymphocytes [39], and, clinically, it suggests that omalizumab may change the magnitude of the specific allergen response in human allergic disease.

Eosinophils

Eosinophils are recruited to the site of inflammation following initial allergen challenge by chemotactic mediators initiated by activated mast cells, basophils, and structural cells. Independent groups of investigators [40,41] have shown that eosinophil numbers are decreased in peripheral blood and mucosal tissue in allergic subjects treated with omalizumab compared with controls. This is most likely due to a diminished effector response of mast cells rather than a direct IgE-mediated effect on eosinophils.

Djukanovic *et al.* [41] found that omalizumab therapy resulted in decreased serum IgE, decreased FcεRI expression in airway mucosal biopsies, and decreased tissue and sputum eosinophils. Despite this, no change in airway hyperresponsiveness to methacholine was detected in omalizumab recipients. This last finding was surprising, given the significant cellular changes observed with omalizumab in allergic asthma. It implies that IgE FcεRI-dependent pathways may play a minimal role in mediating bronchial hyperresponsiveness.

Modulating the FcεRII Receptor

The low-affinity FcεRII receptor, also known as CD23, is found on a variety of hematopoietic cells and airway smooth muscle. FcεRII functions include presenting IgE-bound antigen to CD4⁺ lymphocytes [6••] and production of pro-inflammatory cytokines such as IL-1 and TNF-α by monocytes [42]. A novel IgG1 anti-CD23 antibody, IDEC-152, has been identified and shown to inhibit IgE B-cell synthesis in vitro [43].

Rosenwasser *et al.* [44] studied IDEC-152 in a placebo-controlled trial of 30 asthmatic subjects. Participants received a single IV infusion of the medication and were followed for 12 weeks afterward. A dose-dependent decrease in serum IgE was detected, although no clinical effects were observed. Minor side effects were noted, but no serious adverse events occurred in the treatment group.

Other Targets in the FcεRI Receptor Pathway Syk kinase inhibitors

Activation of Syk tyrosine kinase is one of the earliest signaling responses detected after cross-linking of FcεRI-receptor complexes with allergen. A recent preliminary report [45] examined the efficacy and safety of R926112, a Syk tyrosine

kinase small molecule inhibitor, in subjects with allergic rhinitis. Twenty subjects were enrolled in a double-blind, randomized, cross-over trial. One intranasal dose of R926112 was given, followed by nasal allergen challenge 15 minutes later. PGD₂ was significantly lower 5 minutes after challenge and showed a trend toward decrease at 10 minutes in the active treatment group compared with placebo. No difference, however, was seen in adverse events, clinical symptom scores, acoustic rhinometry, or concentration of histamine between the treatment groups. Although some clinical benefit of Syk inhibitors has been implied by work done in animal models [46,47], further studies must be performed to evaluate the effectiveness of these therapies in humans.

Conclusions

IgE and its receptors are crucial for the manifestation of allergic disease. The FcεRI-receptor complex is found as a tetrameric complex on basophils and mast cells, the effector cells of the initial allergic response. FcεRI expression is modulated by serum IgE, which stabilizes the receptor complex by preventing turnover. On APCs, FcεRI exists as a trimeric complex that facilitates the IgE-specific allergen response through antigen presentation to CD4⁺ lymphocytes.

Using omalizumab to decrease serum IgE and cell-surface FcεRI, researchers have studied the functional significance of the receptor complex in humans. In basophils and mast cells, FcεRI-receptor density, rather than total number of cells, dictates effector response. In DCs, reduction of FcεRI may potentially impact CD4⁺ lymphocyte responses.

Newer therapeutics directed at components of the FcεRI activation pathway as well as the FcεRII receptor are being developed. It is too early to tell if these compounds will prove useful in the treatment of allergic disease in humans. It remains vital, however, to realize their utility in further understanding the mechanisms of allergic disease.

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