

The Role of Immunoglobulin E and Immune Inflammation: Implications in Allergic Rhinitis

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Current Allergy and Asthma Reports 2005, 5:252–258
Current Science Inc. ISSN 1529-7322
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Immunoglobulin E (IgE) plays a critical role in the allergic inflammatory process in diseases such as allergic rhinitis. Cross-linking IgE bound to its receptor on cells by multivalent allergens initiates a chain of events resulting in allergic immune responses. Mast cells and basophils are involved in the early, immediate response, which is marked by cellular degranulation and the release of proinflammatory mediators, including histamine. Antigen-presenting cells are also activated by allergen-loaded IgE, resulting in immunomodulation of T-cell responses. The IgE molecule binds to two types of receptors, the high-affinity (FcεRI) and low-affinity (FcεRII or CD23) receptors, that have differing properties important in mediating allergen-induced responses. New therapies targeting the IgE molecule reduce allergen-stimulated immune responses and improve the clinical symptoms in subjects with allergic rhinitis. Understanding the role of the IgE molecule is necessary to appreciate the development and use of novel therapies targeting its actions.

Introduction

Immunoglobulin E (IgE) is a critical factor in the allergic inflammatory process in diseases such as allergic rhinitis. Binding of allergens to IgE located on the cell surfaces of mast cells and basophils activates the release of proinflammatory mediators and cytokines important in eliciting an allergic response. The involvement of IgE is especially pronounced in the early phase response, but it is also involved in late-phase allergic responses. IgE binds to two types of receptors, the high-affinity (FcεRI) receptor, expressed on mast cells, and basophils, and antigen-presenting cells (APCs), the low-affinity (FcεRII or CD23) receptor, expressed on airway smooth muscle cells and several hematopoietic cells including monocytes, macrophages, dendritic cells (DCs), lymphocytes, and eosinophils.

Recent advances in our understanding of the role of IgE in allergic inflammation have led to the development of a monoclonal antibody to IgE that reduces IgE levels and, therefore, reduces allergic inflammation. The clinical applications of targeting the IgE molecule or its receptors may have profound effects on the way allergic rhinitis is treated in the future.

The Immunoglobulin E Molecule

The IgE molecule is one of the five immunoglobulins within the humoral immune system that were first identified in 1967 by Ishizaka and Ishizaka [1]. The overall structure of IgE is similar to the other classes of antibodies consisting of a heterotetramer of two heavy and two light chains with variable and constant regions, but it differs by its sequence of ε-heavy chain constant regions. As opposed to IgG, which contains three heavy chains, IgE contains four heavy-chain constant domains (Cε1–Cε4) [2•]. The plasma levels of IgE compared with the other classes of immunoglobulins are the lowest. In nonallergic individuals, the plasma level of IgE is 10,000-fold to 50,000-fold less than that of plasma IgG (IgE, 50–300 ng/mL versus IgG, 10 mg/mL) [3,4••]. However, half of the IgE molecules are in the tissues (respiratory mucosa, gastrointestinal tract, and skin) bound to cells, in particular, mast cells, which accounts for its important role in immediate hypersensitivity reactions and allergic inflammation.

The allergen-binding site on the IgE molecule is located on the variable regions of the heavy and light chains (antigen-binding fragment [Fab]). The IgE molecule (constant region fragment [Fc]) binds to two types of receptors, the high-affinity IgE receptor (FcεRI) and the low-affinity IgE receptor (FcεRII or CD23). The affinity for IgE of the high-affinity IgE receptor is 10^9 M^{-1} and that of the low affinity IgE receptor is 10^8 M^{-1} for IgE-antigen complexes, and 10^7 M^{-1} for IgE alone [5••]. In addition to IgE binding with high affinity to the FcεRI receptor, the IgE molecule has a very slow dissociation rate off the FcεRI receptor that helps explain its long half-life [3]. The binding site for both the high- and low-affinity IgE receptors are located on the Cε3 domain of the IgE molecule [6•,7,8] (Fig. 1).

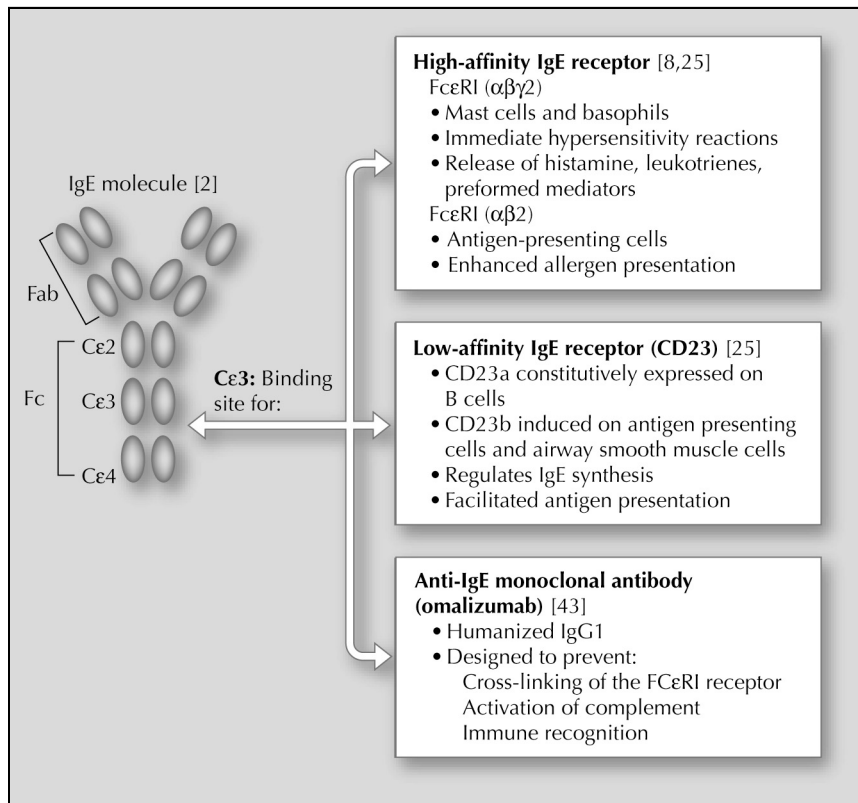


Figure 1. The high- and low-affinity IgE receptor in addition to the anti-IgE monoclonal antibody (omalizumab) bind to the Cε3 domain of the IgE molecule. The allergen/antigen binding site fragment (Fab) and the constant region fragment (Fc) are indicated. Important functions of the high- and low-affinity IgE receptors and anti-IgE molecule are summarized.

Regulation of Immunoglobulin E Synthesis

The major regulatory step in IgE synthesis is the control of IgE class switch recombination [4••]. For B cells to switch from synthesis of IgM to other immunoglobulin isotypes, such as IgE, germline gene transcription of C_H genes, class switch recombination, and B-cell differentiation into Ig-secreting plasma cells need to occur [3]. Important to inducing IgE synthesis in B cells are the cytokines, interleukin (IL)-4 and IL-13. Of these cytokines, IL-4 is thought to be the most critical stimulus for IgE synthesis. Both IL-4 and IL-13 activate germline ε transcription and class switching in B cells through the signaling molecule, signal transducer and activator of transcription (STAT)-6. The second signal that needs to occur for successful class switch to IgE to proceed is ligation of CD40 on B cells with CD154 (CD40 ligand) on T cells. This pathway is referred to as the classic or T cell-dependent pathway of IgE synthesis [4••].

Alternative pathways exist that do not require T-cell interaction, but do require the presence of IL-4. For example, in the presence of IL-4, corticosteroids can upregulate CD154 expression on T cells and induce IgE synthesis [9,10]. Additionally, IgE class switching can be induced in the presence of IL-4 when the B cell-activating factor belonging to the tumor necrosis factor family (BAFF) and a proliferation-inducing ligand (APRIL) expressed on monocytes and DCs bind to their respective receptors on B cells [11]. Also, a regulatory protein in the classic complement pathway, C4 binding protein (C4BP), can mimic CD154 and induce transcription of germline Cε and expression of

activation-induced cytidine deaminase (AID) expression, resulting in class switch to IgE [12]. Moreover, Epstein-Barr virus (EBV) can nonspecifically induce IgE class switching by mimicking CD40 by its virus-encoded latent membrane protein 1 (LMP1) [4••].

In contrast, IgE class switching can be turned off or negatively regulated by several mechanisms. Most prominent is through inhibiting the development of type 2 helper T cells (Th2) and suppression of Cε germline transcription by the cytokines, interferon-γ (IFN-γ) and IL-21 [4••]. Interfering with the signal transduction cascade through various B-cell surface receptors such as the B-cell receptor (BCR), CD45, CTLA-4, and CD23 can also lead to inhibition of IgE class switching. Because STAT6 is the important signaling molecule for activating transcription of germline Cε messenger RNA, inhibiting this molecule inhibits IgE class switching. The transcription factor B-cell lymphoma (BCL6) competitively inhibits STAT-6 [13].

The High-Affinity Immunoglobulin E Receptor

The high-affinity IgE receptor, FcεRI, belongs to an antigen-receptor superfamily that includes the B-cell receptor (BCR), T-cell receptor (TCR), and several IgG Fc receptor isotypes [6•]. The FcεRI exists in two forms as either a heterotetramer (αβγ2) on mast cells and basophils [2•], or as a heterotrimer (αβ2) [14] on monocytes, Langerhans cells, eosinophils, and DCs [15]. Activation of the heterotet-

ramer Fc ϵ RI ($\alpha\beta\gamma 2$) on the surface of mast cells and basophils occurs through allergens cross-linking IgE receptor-bound molecules. This interaction results in the immediate hypersensitivity reaction characterized by mast cell degranulation, the release of preformed mediators (histamine), and synthesis of leukotrienes, cytokines (such as IL-4), and chemokines [3]. The heterotrimer Fc ϵ RI ($\alpha\gamma 2$) is also activated by allergen and results in the release of proinflammatory cytokines and enhanced allergen presentation [15] (Fig. 1). The binding of a multivalent allergen permits the Fc ϵ RI to aggregate with other receptors and initiate cell activation. In the absence of a multivalent antigen, activation of the Fc ϵ RI is inhibited by the heavily N-glycosylated alpha chains [3,16].

Unique to the expression of the Fc ϵ RI receptor on mast cells and basophils is the presence of the β chain. The β chain contains distinct immunoreceptor tyrosine-based activation motifs (ITAMs) in its cytoplasmic tail that result in differential binding affinities of protein tyrosine kinases (PTKs) [3]. Lyn, a protein tyrosine kinase belonging to the src kinase family, preferentially binds to the β chain ITAM. In comparison, the src kinase, Syk, binds to both the β and γ chains but has higher affinity for the γ chain common to both forms of the Fc ϵ RI [3]. The β chain can enhance maturation and assembly of the high-affinity IgE receptor, thus leading to an increase in cell surface expression and enhanced signal transduction within the cells [17].

Through the discovery of the crystal structure of the Fc ϵ RI, it was found that one receptor binds one dimeric IgE molecule asymmetrically through interactions at two sites [18]. The importance of the one IgE molecule binding to one Fc ϵ RI is probably twofold. The 1:1 interaction blocks the binding of a second receptor [14]; and, the binding of one IgE molecule to one receptor likely prevents the cross-linking of receptors and, thus, prevents premature cell activation in the absence of an antigen or allergen [3].

Expression of the Fc ϵ RI receptor on the surfaces of mast cells, basophils, and DCs correlates with the concentration of IgE such that a reduction in IgE level results in decreased surface expression of the Fc ϵ RI [19–22]. This has clinical application in the treatment of allergic diseases and is discussed later. IgE can regulate Fc ϵ RI expression by a number of mechanisms. Binding of IgE to Fc ϵ RI stabilizes the expression of the high-affinity IgE receptor at the cell surface and prevents its internalization and degradation. In addition, IgE uses a preformed pool of receptors comprising recycled and recently synthesized receptors [23].

The Low-Affinity Immunoglobulin E Receptor (Fc ϵ RII or CD23)

The low-affinity IgE receptor, Fc ϵ RII or CD23, differs from all the other antibody receptors that belong to the immunoglobulin-like superfamily. Instead, CD23 is a single chain, C-type lectin, type 2 transmembrane protein of 45 kDa [5••]. CD23 exists in two different forms, CD23a and

CD23b, which differ by six to seven amino acids. CD23a is constitutively expressed on B cells, whereas CD23b is induced by IL-4 and expressed on several cell types, including airway smooth muscle cells [24], and hematopoietic cells, such as B and T cells, Langerhans cells, monocytes, DCs, macrophages, platelets, neutrophils, and eosinophils [25•]. Another difference in the CD23 molecule is that besides binding to IgE, CD23 binds to other ligands, such as complement receptor 2 (CD21), and the adhesion molecules, CD11b and CD11c, which may explain the wide variety of its functions [26,27].

The expression of CD23 is greatly increased on monocytes and lung alveolar macrophages, circulating B lymphocytes, and airway smooth muscle cells from allergic subjects [24,28–30]. CD23 is upregulated *in vitro* by binding to its ligand, IgE [31], or by cytokine stimulation, primarily IL-4 [29]. Activating CD23 on APCs such as monocytes/macrophages can promote the generation of pro-inflammatory cytokines, including IL-1 β , IL-6, and tumor necrosis factor-alpha (TNF- α) [29,32,33]. Membrane CD23 receptor can be cleaved to a soluble receptor (sCD23) that has further inflammatory properties likely through its ligation to the adhesion molecules, CD11b and CD11c [34].

Triggering of the CD23 receptor by IgE on B cells not only enhances antigen presentation [35], but increases synthesis of IgE [31]. In addition, binding of sCD23 to CD21 increases IL-4-induced IgE production by upregulating C ϵ germline transcripts [36]. In contrast, cross-linking the CD23 receptor inhibits IgE synthesis [37]. Recently, a primate, anti-CD23 monoclonal antibody, IDEC-152 (IDEC Pharmaceuticals, San Diego, CA), resulted in a significant decrease in IgE concentrations in a dose-dependent manner in asthma subjects treated with a single dose [38].

Antigen Presenting Cells and Immunoglobulin E

Antigen presenting cells, including monocytes, macrophages, DCs, and Langerhans cells, are important in IgE-mediated allergic responses. Both the Fc ϵ RI and Fc ϵ RII (CD23) receptors are expressed on these APCs and are important in facilitating allergen presentation to allergen-specific T cells [25•]. As discussed, the Fc ϵ RI receptor exists as a trimeric complex ($\alpha\gamma 2$) on these cells [15]. Multivalent allergens activate the Fc ϵ RI receptor on APCs, initiating a cascade of events [25•]. IgE bound to the Fc ϵ RI recognizes specific allergen, leading to internalization via endocytosis [15,39]. Allergen is subsequently processed into specialized endosomal major histocompatibility (MHC) class II compartment (MIIC)-like organelles of DCs. Cathepsin S-dependent ligand peptide loading occurs with the newly synthesized MHC class II molecule for the presentation of Fc ϵ RI-targeted agents [25•].

Facilitated antigen presentation is also greatly enhanced through the low-affinity IgE receptor, CD23

[35]. The efficiency of the antigen presentation by the CD23 receptor may be explained in part by its close association on the cell surface with the MHC class II antigen, human leukocyte antigen (HLA)-DR. CD23 co-localizes intracellularly with HLA-DR, and its association may help stabilize specific APC-T-cell interactions and, thereby, contribute to T-cell activation [40].

Dendritic cells are professional APCs that play an important role in promoting responses to antigens. Myeloid precursor DCs (pDC1s or CD11c⁺ cells) are classically high producers of IL-12 and, therefore, induce Th1 responses. In contrast, plasmacytoid precursor DCs (pDC2s or CD123⁺ cells) are low producers of IL-12 and induce a Th2 response [41]. However, a given DC subset has remarkable plasticity in directing different types of T-cell responses [41]. The IgE molecule appears to be involved in DCs. The anti-IgE monoclonal antibody (mAb), omalizumab (discussed in detail later), rapidly reduces cell surface expression of the FcεRI receptor on both type 1 and type 2 precursor DC subsets [22]. In addition, a decrease or normalization in the number of DC1s in patients treated with the anti-IgE mAb therapy was reported to occur during a grass pollen season, but not in the birch pollen season [42]. Therefore, by affecting DC number and DC cell surface expression of the FcεRI receptor, the IgE molecule may be involved in regulating T-cell responses to antigen.

Clinical Implications

Given the role of the IgE molecule in the allergic inflammatory response, reducing its levels or inhibiting its actions could have a major impact on the treatment of allergic conditions. Possible approaches to regulate IgE synthesis include directly targeting the circulating free IgE molecule, blocking IgE transcription factors, inhibiting key cytokines (IL-4, IL-13), and targeting the IgE receptors. Omalizumab, a humanized, monoclonal antibody directed against IgE, has been developed and is currently approved for clinical use in moderate to severe persistent allergic asthma (Xolair, Genentech/Novartis, Basel, Switzerland). In addition, a primate, anti-CD23 monoclonal antibody (IDEC-152) has been developed and was recently demonstrated to be safe in humans [38].

The Monoclonal Anti-immunoglobulin E Antibody

Omalizumab is a humanized antibody (IgG1 framework) containing approximately 5% of non-human (murine) residues located at the complementarity-determining regions [43]. This antibody binds to the Cε3 domain on the IgE molecule and was designed to prevent cross-linking of the high-affinity IgE receptor, activation of complement, and immune recognition [43] (Fig. 1). Pre-clinical studies demonstrated that omalizumab-IgE immune com-

plexes were cleared in the serum compartment, and no specific tissue deposition was seen. Urinary excretion was the primary route of elimination that was mediated by interaction with FcγR. The overall clearance of the antibody-IgE immune complex was long, approximately 3 weeks [44,45]. Thus, total IgE levels (IgE complexes with omalizumab and free IgE) are elevated during treatment with omalizumab, even though the free-IgE concentrations are decreased. In multiple clinical trials using omalizumab, free-IgE levels are dramatically reduced by 88% to 99% to approximately 5 to 9 IU/mL.

Anti-immunoglobulin E and Clinical Studies

Clinical investigations using the anti-IgE antibody (omalizumab) in allergic subjects has provided further understanding into the role of IgE in allergic diseases such as allergic rhinitis. Several large, randomized, double-blind, placebo-controlled trials have assessed omalizumab therapy for the treatment of seasonal—ragweed-induced [46], birch-induced [47]—and perennial—dust mite-, dog-, or cat-induced—allergic rhinitis [48]. All of these studies found reduction in nasal symptom severity scores (sneezing; itchy, runny, and stuffy nose) and use of rescue antihistamines in addition to improvement in rhinitis-specific quality of life scores. The clinical results of these studies are summarized in Table 1. Furthermore, anti-IgE therapy was clinically evaluated in subjects receiving specific allergen immunotherapy for allergic rhinitis [49]. Findings from this study revealed that combination therapy (omalizumab plus specific immunotherapy) reduced nasal symptom load.

Substudies from these and other studies have been performed to examine the immune and inflammatory changes that occur with anti-IgE mAb therapy. In one such study [50], markers of allergic inflammation such as histamine release from basophils, blood eosinophil counts, and area of wheal reaction to allergen skin prick test were reduced with anti-IgE therapy compared with placebo. However, the only circulating mediator to significantly decrease was IL-13, although trends were observed for IL-5 and IL-8. No changes were detected for IL-6, IL-10, and soluble intracellular adhesion molecule. Other studies [51] have shown a reduction in the *in vitro* production of sulfidoleukotrienes from allergen-stimulated leukocytes in subjects receiving specific allergen immunotherapy and omalizumab compared with subjects receiving only specific allergen immunotherapy. However, no difference in urinary leukotriene E4 levels occurred [52].

Further studies have examined changes occurring directly in the nose during anti-IgE treatment. As expected, nasal responses to specific allergen (mite) challenge were reduced during therapy with omalizumab [53], which correlated with a minimal, but statistically significant, reduction in the post-challenge increase in nasal lavage allergen-specific IgE. However, in this study, neither pre-

Table 1. Clinical results of randomized trials comparing the anti-IgE monoclonal antibody (omalizumab) to placebo for the treatment of seasonal and perennial allergic rhinitis

Results	Anti-IgE	Placebo	P value
Nasal symptom severity score (0–3 point scale)	0.84 0.7 1	1.2 0.98 1.4	0.001 [46] 0.001 [47] 0.001 [48]
Use of rescue medication (Average number of tablets per day)	0.12 0.59	0.21 1.37	0.005 [46] <0.001 [47]
Rhinitis quality of life scores (Percentage of subject with a ≥ 0.5 point improvement)*	44.10% 52%	30.60% 27%	<0.01 [46] 0.001 [48]
Overall efficacy of treatment (5 point scale, 5 is worsening of symptoms)	1.75	2.3	<0.001 [47]
Global treatment effectiveness (Percentage of subjects rating efficacy of treatment as good or excellent)	70.70% 59% 53%	40.80% 35% 34%	<0.001 [46] 0.001 [47] 0.001 [48]
Missed days of work, school, or both	0.1	0.4	0.005 [46]

Mean scores indicated.
 *Differences of ≥ 0.5 are interpreted as clinically meaningful [56].
 IgE—immunoglobulin E.

challenge nor post-challenge epsilon messenger RNA transcripts were affected by anti-IgE therapy within the nasal secretions. In other studies, biopsies taken from the nose during anti-IgE mAb therapy demonstrated decreased eosinophil-peroxidase positive cells and decreased IgE⁺ staining cells, compared with placebo [54]. The effects of the anti-IgE mAb plus specific immunotherapy resulted in decreased nasal tryptase levels in subjects, compared with those treated with placebo [55]. Taken together, all these studies suggest that reductions in circulating free IgE concentrations by anti-IgE therapy can have significant effect on the local environment in the nose. Thus, therapy targeting IgE may have clinical application in the treatment of allergic rhinitis.

Conclusions

The IgE molecule is an important immunoglobulin responsible for mediating allergic immune responses. IgE binds to mast cells and basophils through the heterotetramer ($\alpha\beta\gamma 2$), high-affinity IgE receptor, Fc ϵ RI. Allergens initiate a cascade of cellular events by cross-linking IgE molecules bound to the Fc ϵ RI receptor. These events are referred to as the immediate hypersensitivity allergic reaction and are characterized by cellular degranulation and release of preformed mediators (histamine) and synthesis of proinflammatory mediators, cytokines, and chemokines. The alternative form of the high-affinity IgE receptor, $\alpha\gamma 2$, is expressed on APCs, is involved in the release of proinflammatory mediators, and also enhances antigen presentation to T cells. The IgE molecule also binds to the low-affinity IgE receptor (Fc ϵ RII or CD23) expressed on the surface of airway smooth muscles cells, lymphocytes, and APCs, where it functions in IgE regulation and synthesis and facilitated antigen presentation. Both the high- and low-affinity IgE receptors bind to the IgE molecule at the

C ϵ 3 domain. A monoclonal antibody developed against the IgE molecule (omalizumab) also binds to the C ϵ 3 domain on the IgE molecule, and it significantly reduces free IgE levels. Omalizumab avoids immune recognition and does not cross-link the high-affinity IgE receptor or activate complement. Omalizumab reduces nasal symptoms and use of rescue medication, and demonstrates overall improvements in quality of life in subjects with seasonal and perennial allergic rhinitis. This therapy and other therapies aimed at regulating the IgE molecule and its receptors may have clinical significance in the future treatment of allergic rhinitis.

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