

Mechanisms of IgE Inflammation

Lanny J. Rosenwasser

© Springer Science+Business Media, LLC 2011

Abstract The prevalence of diseases such as allergic asthma and rhinitis continues to increase in the United States, affecting millions of people. It is well-established that allergy contributes to the pathogenesis of most asthma, especially in children and young adults. Despite current therapy (eg, inhaled corticosteroids, anti-leukotrienes, and bronchodilators), patients with moderate to severe asthma remain symptomatic and experience frequent exacerbations of disease requiring oral corticosteroids, emergency department treatments, and hospitalizations. Allergic diseases are traditionally referred to as *immediate* or *type 1 hypersensitivity reactions*, with IgE as a critical factor. IgE is involved in allergic inflammation, especially in early-phase response, but it may also be involved in the late-phase allergic response. A direct correlation between serum IgE levels and asthma exists. As logarithm IgE values increase, asthma prevalence increases linearly, even in patients who are categorized as having nonallergic asthma. In addition, there is a significant, although low association in allergic rhinitis with IgE levels and positive skin test reactivity to pollens. 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, thereby reducing allergic inflammation. This review aims to provide an overview of the basic science of the IgE molecule and the clinical efficacy of anti-IgE therapy in allergic and asthmatic diseases.

Keywords IgE · Fc receptors · Inflammation

L. J. Rosenwasser (✉)
Allergy-Immunology Division, Children's Mercy Hospital,
University of Missouri-Kansas City School of Medicine,
2401 Gillham Road,
Kansas City, MO 64108, USA
e-mail: lrosenwasser@cmh.edu

Introduction

In 1967, Ishizaka and Ishizaka [1] described a new antibody isotype in the IgE molecule. Since its discovery, IgE has been shown to be important in allergic diseases, as well as in immune responses to parasitic infection [2–4]. The IgE molecule is composed of two light chains and two heavy chains. The overall structure is similar to that of other classes of antibodies, but it is distinguished by the sequence of the heavy chain constant region. As opposed to IgG, which contains three heavy chains, IgE contains four heavy chain constant domains (Cε1–Cε4) (Table 1) [5]. The additional domain Cε2 replaces the hinge region [6].

The allergen-binding site is located on the variable regions of the heavy and light chains. The Fc fragment of the IgE molecule can bind to two types of immunoglobulin Fc receptors: the high-affinity IgE receptor (FCεRI) and the low-affinity IgE receptor (FCεRII, or CD23). The binding site for both FCεRI and FCεRII is located in proximity to but on different parts of the Cε3 domain of the IgE molecule [5–9]. IgE molecules are mainly produced by plasma cells in the mucosa-associated lymphoid tissue [10]. Most of the IgE that is produced is bound by FCεRI expressed by mast cells and basophils [10]. In nonallergic individuals, the level of plasma IgE is 10,000- to 50,000-fold less than that of plasma IgG. Even in highly atopic individuals, the level of plasma IgE remains less than 1,000-fold that of plasma IgG [10].

The dimeric Fc fragment of the IgE antibody has full binding activity for FCεRI [11–13]. IgE antibody binds to FCεRI in the absence of antigen; thus, the receptor adopts antigenic specificity of the prevalent IgE repertoire [5]. Cross-linking of the receptor through antigen–antibody interaction leads to the initiation of a signal transduction cascade and downstream effects [14].

Table 1 IgE: a summary

One of 5 classes of immunoglobulin
Binds high-affinity IgE FcεRI receptors on mast cells and basophils, and antigen-presenting cells
Binds to CD23 or lower-affinity IgFc receptor on airway smooth muscle cells, antigen-presenting cells, and B cells
Triggers a release of inflammatory mediators, including cytokines and other autacoid molecules
Strong association between IgE and allergic diseases, including asthma
All IgE and eosinophilia in mammals are thymus dependent, and participation of CD4 ⁺ T-helper type 2 lymphocytes in IgE production is critical

Regulation of IgE Synthesis

The major regulatory step in IgE synthesis is the regulation of IgE class-switch recombination. A comprehensive review of this subject was recently completed [10]. Common to all isotype switching are the germline transcription of *CH* genes and the induction of activation-induced cytidine deaminase (AID) expression [10–15]. IgE class-switch recombination is accomplished through two pathways: the classical and alternative pathways [10]. The classical, or T-cell–dependent pathway of IgE synthesis involves the presence of interleukin (IL)-4, IL-13, or both during ligation of the CD40-CD40 ligand (CD154) that leads to the induction of Cε germline transcription and induction of AID.

In contrast, the alternative pathway does not require T-cell interaction but does require the presence of IL-4. For example, corticosteroids can induce IgE synthesis in the presence of IL-4 by upregulating CD40 ligand expression on the T and B cells [16, 17]. A second pathway to induce class-switching to IgE exists when B-cell–activating factor belonging to the tumor necrosis factor family and proliferation-inducing ligand expressed on monocytes and dendritic cells (DCs) bind to their respective receptors on B cells in the presence of IL-4 [18]. In addition, Epstein-Barr virus can nonspecifically induce IgE class-switching, which is likely due to CD40 mimicry by virus-encoded latent membrane protein 1 [10, 19]. A regulatory protein in the classical complement pathway, C4-binding protein has been shown to mimic the CD40 ligand [20]. In the presence of IL-4, the interaction between this molecule and CD40 will induce transcription of germline Cε and expression of AID, thereby causing class-switching to IgE [10, 20].

IgE class-switching is negatively regulated by several mechanisms. Cytokines such as interferon-γ and IL-21 inhibit development of T-helper type 2 (Th2) cells, the suppression of Cε germline transcription, or both [10]. Various B-cell surface

receptors (B-cell receptor, CD45, cytotoxic T-lymphocyte antigen 4, and CD23) inhibit IgE class-switching through different mechanisms, such as altering the signal transduction cascade that leads to IgE class-switch recombination [10]. Several transcription factors, such as B-cell lymphoma 6 and inhibitor of DNA binding 2, can also inhibit IgE class-switching. B-cell lymphoma 6 competitively inhibits signal transducer and activator of transcription 6 binding, thus repressing IL-4-induced Cε germline transcripts by skewing the cytokine profile to a Th1-type cytokine.

FCεRI

FCεRI belongs to an antigen receptor superfamily that includes the B-cell receptor, T-cell receptor, and several IgE Fc receptor isotypes (Table 2) [5]. As the name implies, the high-affinity IgE receptor binds with a high affinity to the IgE molecule, with an equilibrium dissociation constant or binding affinity of 10^{-9} to 10^{-10} M [5]. FCεRI consists of four transmembrane polypeptides with the composition αβγ2 [6]. This tetramer structure is expressed only on mast cells and basophils. An alternate form on αβγ2 trimer [14] is expressed on a variety of other hematopoietic cell lines, including eosinophils [21], DCs, activated macrophages, and Langerhans cells [22–25].

The extracellular portion of the α chain binds to the Cε3 of the IgE molecule [5, 14]. The β and γ chains are required for receptor transmembrane insertion and intracellular signal transduction [14]. Although the α subunit is highly N-glycosylated, glycosylation is not necessary for the IgE binding [26]. The extracellular region of the α chain contains two immunoglobulin domains, D1 and D2 [14]. The crystal structures of the Fc fragment of human IgE bound to FcγRIα are positioned at an acute angle to one another, forming a convex surface at the top of the molecule, and a marked cleft is enclosed by the two globular immunoglobulin domains. Through the discovery of the crystal structure, it was revealed that one receptor binds one dimeric IgE-Fc molecule asymmetrically through interactions at two sites [27]. This is important because the interaction of one receptor with the IgE-Fc blocks the binding of a second receptor [14].

Two interaction sites exist for the IgE-Fc on the receptor surface, which explains how a 1:1 complex between antibody and receptor is formed [5, 28]. Of the two Cε3

Table 2 High-affinity IgE Fc receptor

FCεRI is composed of 4 chains: α, β, and 2 γ
Mast cells and basophils are effectors for immediate hypersensitivity reaction and express the fuse FCεRI
FCεRI is αβ2 or antigen-presenting cell

receptors, one is formed by the C-C' loop in the receptor D2 domain, and the second is involved in the four solvent-exposed tryptophans (D1–D2 interface) [5, 14].

FcεRI Activation

Cross-linking of FcεRI with multivalent antigen is critical in triggering cellular events, which include the release of mediators (histamine, newly synthesized leukotrienes, and IL-4) [5, 10, 14]. Whereas other receptor types (hormone or cytokine receptors) dimerize and signal after binding a well-defined ligand, these Fc receptor types act as adaptors between highly variable antigen-binding sites and the intracellular signal transduction machinery [5]. Flexible linkers between the antibody Fab and Fc arms appear necessary to accommodate the variable structures of Gab-antigen complexes and the need to cross-link two or more receptors to initiate signaling [5, 14, 29, 30]. Therefore, multivalent antigens can promote co-localization of receptors but cannot form specific contacts that dimerize Fc receptors [5]. However, it remains unclear whether co-localization leads to specific signaling structure or simply to membrane re-localization of the complex [5].

The FcεRI α chains do not aggregate in the absence of antigen, probably because of extensive glycosylation [14]. This glycosylation at the surfaces of the α chain presents premature aggregation and permits interaction with the synthetic machinery [14, 31]. However, binding of multivalent antigen overcomes the intrinsic resistance of the α chains to interaction [14].

Activation of the trimeric FcεRI on the other leukocytes, such as monocytes, may also contribute to the pathogenesis of allergic diseases [32]. For example, activation of the antiapoptotic ligands Bcl-2 and Bcl-xL also protects from CD95 fast-mediated apoptosis [32]. In addition, IL-10 production occurs after cross-linking FcεRI alters monocyte differentiation toward a macrophage species and away from a DC phenotype [33]. Also, activation of FcεRI in atopic donors with high expression of FcεRI leads to the downstream activation of the proinflammatory transcription factor nuclear factor-κB [34].

Regulation of FcεRI Expression

Early observations predicted that the FcεRI expression on the surface of mast cells and basophils correlated with IgE concentrations such that a reduction in IgE level was predicted to decrease surface expression of FcεRI [35–37]. This has been found to be true in clinical trials in which reduction in serum IgE levels led to a reduction in FcεRI on circulating basophils [38]. IgE can upregulate FcεRI

expression via several mechanisms. IgE binding stabilizes the receptor of the cell surface, which prevents receptor internalization and degradation. In addition, IgE uses a preformed pool of receptors comprising recycled and recently synthesized receptors [39].

FcεRII (CD23)

CD23 is an intriguing molecule with diverse functions. Although the name implies low-affinity binding, it displays only 1 logarithm difference in binding compared with the high-affinity IgE receptor, with an equilibrium dissociation constant or binding affinity of 10^8 M^{-1} for IgE antigen and 10^7 M^{-1} for IgE alone (Table 3) [40]. Unlike other Fc receptors that are structurally classified in the immunoglobulin-like superfamily, CD23 is a C-type lectin, type 2 transmembrane protein with an intracytoplasmic C terminus [40]. CD23 binds to the Cε3 domain of IgE, which is close to but differs from the FcεRI binding site [7].

CD23 is expressed as two different forms: CD23a and CD23b. CD23a is expressed constitutively on B cells, and CD23b is found on several cells, such as monocytes, eosinophils, DCs, Langerhans cells, and platelets [25]. Besides binding to IgE, CD23 is known to bind to other ligands, including CD21 and the adhesion molecules CD11b and CD11c, which helps to explain its wide variety of functions [41, 42]. CD23 may be cleaved by proteases to the soluble CD23 form, which is proinflammatory [43]. Ligation of IgE to CD23 on B cells leads to an array of functions, including B-cell differentiation, apoptosis, and regulation of IgE synthesis [41]. In contrast, soluble CD23 can upregulate IgE synthesis through various mechanisms. Soluble CD23 competes with membrane CD23 in binding to IgE. By preventing IgE membrane CD23 from binding the inhibitory IgE synthesis, signals are turned off, thereby allowing increased production of IgE. In addition, triggering CD21 by binding soluble CD23 increases IL-4-induced IgE production, upregulating Cε germline transcripts. However, triggering CD21 alone in the absence of an IL-4 signal does not increase Cε germline transcripts [44].

Table 3 Low-affinity IgE receptor

CD23a is constitutively expressed on B cells
CD23b is induced by cytokines on antigen-presenting cells and airway smooth muscle cell
CD23b on B cells regulates IgE synthesis and facilitates allergen presentation

IgE on Antigen-Presenting Cells

The two receptors for IgE, FcεRI and FcεRII (or CD23), are expressed on antigen-presenting cells (APCs) and are critical in facilitating allergen presentation to allergen-specific T cells [25]. The main role of FcεRI and APCs is antigen focusing. Multivalent allergens activate FcεRI-bound IgE on APCs, initiating a cascade of events [25]. FcεRI-bound IgE is internalized and processed efficiently into specialized, endorsed major histocompatibility complex (MHC)-II compartment-like organelles of DCs. Cathepsin S-dependent ligand peptide loading occurs with the newly synthesized MHC-II molecule for the presentation of FcεRI-targeted agents [25].

DCs are potent APCs that play a significant role in promoting T-cell responses to antigens/allergens. Classically, myeloid precursor DCs (pDC1s or CD11c⁺ cells) are high IL-12 producers that induce a Th1 response, whereas plasmacytoid DCs (pDC2s or CD123⁺ cells) are low IL-12 producers that induce a Th2 response [45, 46]. However, it is now known that a given DC subset has remarkable plasticity in directing different types of T-cell responses [45, 47].

With this background, clinical studies have shown evidence that the monoclonal anti-IgE antibody omalizumab affects DCs and therefore may be able to modulate T-cell responses in addition to downregulating FcεRI expression of both precursor DC (type 1 and type 2) subsets [38]. A decrease or normalization in DC1s in patients treated with omalizumab during a grass pollen season, but not in a birch pollen season, has been shown [48]. These findings may be explained by the fact that in the absence of proinflammatory cytokines and mediators, DC1s promote the differentiation of Th2 cells. Furthermore, DC1s derived from monocytes and cultured with granulocyte-macrophage colony-stimulating factor and IL-4 induce both Th1 and Th2 differentiation [45]. Thus, decreased omalizumab-induced IL-4 production by mast cells during the pollen season may cause the apparent reduction in the number of myeloid DCs [45]. Together, these findings imply that anti-IgE therapy may cause immunomodulation of T-cell responses and inhibit IgE-mediated type 1 hypersensitivity.

Monoclonal Anti-IgE Molecule

The most recent advance in the treatment of allergic diseases is the development of a monoclonal anti-IgE antibody, omalizumab (Xolair; Genentech/Novartis, South San Francisco, CA, and Tanox, Houston, TX). In the design of the anti-IgE monoclonal antibody, several issues were considered. First, the antibody should not bind to IgE that is bound to the FcεRI, which would lead to mast cell

degranulation by cross-linking the receptor. Second, the IgE-anti-IgE immune complex should be biologically inactive and unable to activate complement or deposit the tissue. Third, the antibody should not be immunogenic and elicit antibody production to the anti-IgE antibody itself. Finally, it should be bind to IgE regardless of the specificity of the IgE molecule.

Selective binding of IgE requires that the monoclonal antibody bind only to free IgE and not to IgE bound to FcεRI and FcεRII. By using homology scanning mutagenesis, a murine monoclonal antibody that binds to the Cε3 portion of IgE, called *MAE11*, was constructed [48]. The MAE11 did not cross-link the receptor, which would have led to multiple biologic responses, possibly caused by anaphylaxis-induced mast cell degranulation. Furthermore, this selective binding prevents circulating IgE from binding to FcεRI. The monoclonal antibody can bind to IgE, regardless of specificities.

Clinical use of nonhuman antibodies in humans poses fundamental problems. Nonhuman antibodies are immunogenic, rapidly cleared, and usually demonstrate only weak recruitment of effector functions. MAE11 was humanized with a human IgG₁ framework to overcome these obstacles. It was found that only five changes in human framework residues were required to provide comparable binding with that of MAE11. The humanized antibody rhuMAb-E25 contains about 5% nonhuman residues relocated at the complementary-determining regions.

Tissue distribution and complex formation with IgE and rhuMAb-E25 after intravenous administration was studied in cynomolgus monkeys. No specific tissue deposition was observed. Pharmacokinetic analysis revealed that both rhuMAb-E25 and rhuMAb-E25 IgE immune complexes cleared the serum compartment, with urinary excretion as the primary route of elimination. Elimination of the immune complex is mediated by the interaction with FcγR. Immune complex clearance is slower than IgE level (IgE complexes with omalizumab), and total IgE is usually increased during omalizumab treatment, although free IgE levels decrease.

The largest immune complexes formed in vivo and in vitro are cyclic hexamers with a molecular weight of 1,000 kD. The size of the immune complex depends on the molar ratio of rhuMAb to IgE. At a 1:1 ratio, the cyclic hexamer formation was favored; at antibody or antigen excess, small heterotrimers were formed, with little detectable hexamer present at molar ratios of 3:1 or larger. There has been no significant association of rhuMAb-E25 or rhuMAb-E25 IgE immune complex with blood cells, and complement fixation is lacking. Omalizumab has been a mainstay in the treatment of moderate to severe asthma. It also has been considered for treatment of food allergy, allergic rhinitis, urticaria, and anaphylaxis.

Conclusions

The anti-IgE monoclonal antibody omalizumab represents a novel form of therapy in the treatment of allergic diseases. Statistically significant effects have been observed in the treatment of patients with both allergic upper and lower airway diseases. Omalizumab is a safe and efficacious therapy when used in the appropriate clinical settings. As clinical experience grows with the use of omalizumab, more will be learned about the mechanisms and effects of modulating IgE in vivo. At present, this form of therapy is best reserved for patients with a high risk of morbidity and mortality.

IgE is a critical factor in allergic inflammation. Binding of allergens to IgE located on the cell surface of mast cells and basophils activates the release of immediate mediators and eventually cytokines in the allergic response. IgE binds to two types of receptors. The first is a high-affinity FCεRI receptor expressed on mast cells; basophils; and APCs such as DCs, macrophages, and Langerhans cells. The lower-affinity receptor, FCεRII, or CD23, is expressed on airway smooth muscle cells; hematopoietic cells, including monocytes, macrophages, and DCs; eosinophils; and B lymphocytes. Recent information identified this pathway of allergen IgE receptor interactions on the different cell types involved in allergic responses in the lung, skin, and other organs as being critically important for the long-term allergic inflammation as the basis for these diseases. New therapeutic options directed at these IgE-dependent pathways is promising as long-term therapy for allergic and asthmatic disease.

Disclosure Dr. Rosenwasser has served as a consultant for Regeneron Pharmaceuticals and Sanofi-Aventis and has received grant support from Novartis.

References

- Ishizaka K, Ishizaka T. Identification of gamma E-antibodies as a carrier of reaginic activity. *J Immunol*. 1967;99:1187–98.
- Beasley R, Crane J, Lai CK, Pearce N. Prevalence and etiology of asthma. *J Allergy Clin Immunol*. 2000;105(suppl):S466–72.
- Burrows B, Martinez FD, Halonen M, Barbee RA, Cline MG. Association of asthma with serum IgE levels and skin-test reactivity to allergens. *N Engl J Med*. 1989;230:271–7.
- Sunyer J, Anto JM, Sabria J, et al. Relationship between serum IgE and airway responsiveness in adults with asthma. *J Allergy Clin Immunol*. 1995;95:699–706.
- Garman SC, Wurzburg BA, Trachevskaya SS, Kinet JP, Jardetzky TS. Structure of the FC fragment of human IgE bound to its high-affinity receptor FcεRI. *Nature*. 2000;406:259–66.
- Sutton BJ, Gould HJ. The human IgE network. *Nature*. 1993;366:421–8.
- Vercelli D, Helm B, Marsh P, et al. The B-cell binding site on human immunoglobulin E. *Nature*. 1989;338:649–51.
- Nissim A, Schwarzbaum S, Siraganian R, Eshhar Z. Fine specificity of the IgE interaction with the low and high affinity Fc receptor. *J Immunol*. 1993;150:1365–74.
- Presta L, Shields R, O'Connell L, et al. The binding site on human immunoglobulin E for its high affinity receptor. *J Biol Chem*. 1994;269:26368–73.
- Geha RS, Jabara HH, Brodeur SR. The regulation of immunoglobulin E class-switch recombination. *Nat Rev Immunol*. 2003;3:721–32.
- Basu M, Hakimi J, Dharm E, Kondas JA, Tsien WH, et al. Purification and characterization of human recombinant IgE-Fc fragments that bind to the human high affinity IgE receptor. *J Biol Chem*. 1993;268:13118–27.
- Keown MB, Ghirlando R, Young RJ, et al. Hydrodynamic studies of a complex between the Fc fragment of human IgE and soluble fragment of the Fc epsilon RI alpha chain. *Proc Natl Acad Sci USA*. 1995;92:1841–5.
- Keown MB, Ghirlando R, Mackay GA, Sutton BJ, Gould HJ. Basis of the 1:1 stoichiometry of the high-affinity IgE receptor Fc epsilon RI-IgE complex. *Eur Biophys J*. 1997;25:471–6.
- Turner K, Kinet JP. Signaling through the high-affinity IgE receptor Fc epsilon RI. *Nature*. 1999;402(suppl):B23–30.
- Chaudhuri J, Tian M, Khoury C, et al. Transcription-targeted DNA deamination by the AID antibody diversification enzyme. *Nature*. 2003;422:726–30.
- Jabara HH, Ahern DJ, Vercelli D, Geha RS. Hydrocortisone and IL-4 induce IgE isotype switching in human B cells. *J Immunol*. 1991;147:1557–60.
- Jabara HH, Brodeur SR, Geha RS. Glucocorticoids upregulate CD40 ligand expression and induce CD40L-dependent immunoglobulin isotype switching. *J Clin Invest*. 2001;107:371–8.
- Litinskiy MB, Nardelli B, Hilbert DM, et al. DCs induce CD40-independent immunoglobulin class switching through BlyS and APRIL. *Nat Immunol*. 2002;3:822–9.
- Brodeur SR, Angelini F, Bacharier LB, et al. C4b-binding protein (C4BP) activates B cells through CD40 receptor. *Immunity*. 2003;18:837–48.
- Gounni AS, Lamkhoui B, Delaporte E, et al. The high-affinity IgE receptor on eosinophils: from allergy to parasites or from parasites to allergy? *J Allergy Clin Immunol*. 1994;94:1214–6.
- Maurer D, Ebner C, Reninger B, Fiebigler F, et al. The high-affinity IgE receptor (Fc epsilon RI) mediates IgE-dependent allergen presentation. *J Immunol*. 1995;154:6285–90.
- Novak N, Kraft S, Bieber T. Unraveling the mission of FcεRI on antigen-presenting cells. *J Allergy Clin Immunol*. 2003;111:38–44.
- Robertson MW. Phage and Escherichia coli expression of the human high affinity immunoglobulin E receptor alpha-subunit ectodomain. Domain localization of the IgE-binding site. *J Biol Chem*. 1993;268:12736–43.
- Garman SC, Kinet JP, Jardetzky TS. Crystal structure of the human high-affinity IgE receptor. *Cell*. 1998;95:951–61.
- Keown MB, Henry AJ, Ghirlando R, Sutton BJ, Gould HJ. Thermodynamics of the interaction of human immunoglobulin E with its high-affinity receptor Fc epsilon RI. *Biochemistry*. 1998;37:8863–9.
- Metzger H. The receptor with high affinity for IgE. *Immunol Rev*. 1992;125:37–48.
- Kinet JP. The high-affinity IgE receptor (Fc epsilon RI): from physiology to pathology. *Annu Rev Immunol*. 1999;17:931–72.
- Letourner O, Schi S, Wille-Brown, Robertson MW, Kinet JP. Glycosylation of human truncated Fc epsilon RI alpha chain is necessary for efficient folding in the endoplasmic reticulum. *J Biol Chem*. 1995;270:8249–56.

29. Saini SS, MacGlashan d. How IgE upregulates the allergic response. *Curr Opin Immunol*. 2002;14:694–7.
30. Novak N, Bieber T, Katoh N. Engagement of Fc epsilon RI on human monocytes induces the production of IL-10 and prevents their differentiation in dendritic cells. *J Immunol*. 2001;167:797–804.
31. Kraft S, Katoh N, Novak N, Koch S, Bieber T. Unexpected functions of FcepsilonRI on antigen-presenting cells. *Int Arch Allergy Immunol*. 2001;124:35–7.
32. MacGlashan Jr DW, Bochner BS, Adelman DC, Jardieu PM, Togias A, Lichtenstein LM. Serum IgE level drives basophil and mast cells IgE receptor display. *Int Arch Allergy Immunol*. 1997;113:45–7.
33. MacGlashan Jr DW, Bochner BS, Adelman DC, et al. Down-regulation of Fc(epsilon)RI expression on human basophils during in vivo treatment of atopic patients with anti IgE antibody. *J Immunol*. 1994;158:1438–45.
34. Saini SS, MacGlashan Jr DW, Sterbinsky SA, et al. Down-regulation of human basophil IgE FC epsilon RI alpha surface densities and mediator release by anti-IgE infusions is reversible in vitro and in vivo. *U Immunol*. 1999;162:5624–30.
35. Prussin C, Griffith DE, Boesel KM, Lin H, Foster B, Casale TB. Omalizumab treatment downregulates dendritic cell FcepsilonRI expression. *J Allergy Clin Immunol*. 2003;112:1147–54.
36. Borkowski TA, Jouvin MH, Lin SY, Kinet JP. Minimal requirements for IgE-mediated regulation of surface Fc epsilon RI. *J Immunol*. 2001;167:1290–6.
37. Kijimoto-Ochiai S. CD23 (the low affinity IgE receptor) as a C-type lectin: a multidomain and multifunctional molecule. *Cell Mol Life Sci*. 2002;59:648–64.
38. Bonnefoy JY, Plater-Zyberk C, Leoanet-Henchoz S, et al. A new role for CD23 in inflammation. *Immunol Today*. 1996;17:418–20.
39. Aubry JP, Pochon S, Graber P, Jansen KU, Bonnefoy JY. CD21 is a ligand for CD23 and regulates IgE production. *Nature*. 1992;358:505–7.
40. Herbelin A, Elhadad S, Ouac F, de Groote D, Descamps-Latscha B. Soluble C23 potentiates interleukin-1 secretion of interleukin 6 and interleukin-1 receptor antagonist by human monocytes. *Eur J Immunol*. 1994;24:1869–73.
41. Henchoz S, Gauchat JF, Aubry JP, et al. Stimulation of human IgE production by a subset of anti-CD21 monoclonal antibodies: requirement of co-signal to modulate epsilon transcripts. *Immunology*. 1994;81:285–90.
42. Liu UJ, Kanzler H, Somelia V, Gillet M. Dendritic cell lineage, plasticity and cross-regulation. *Nat Immunol*. 2001;2:585–9.
43. Rissoan MC, Soumelis V, Kadowaki N, et al. Reciprocal control of T helper cell and dendritic cell differentiation. *Science*. 1999;283:1183–6.
44. Kalinski P, Hilkens CM, Wierenga EA, Kapsenberg ML. T-cell priming by type-1 and type-2 polarized dendritic cells: the concept of a third signal. *Immunol Today*. 1999;20:561–7.
45. Feuchtinger T, Bartz H, von Berg A, et al. Treatment with omalizumab normalizes the number of myeloid dendritic cells during the grass pollen season. *J Allergy Clin Immunol*. 2003;111:428–30.
46. Presta LG, Lahr SJ, Shields RI, et al. Humanization of an antibody directed against IgE. *J Immunol*. 1993;151:2623–32.
47. Shields RL, Whether WR, Zioncheck K, et al. Inhibition of allergic reactions with antibodies to IgE. *Int Arch Allergy Immunol*. 1995;107:308–12.
48. Fox JA, Hotaling TE, Struble C, Ruppel J, Bates DJ, Schoenhoff MB. Tissue distribution and complex formation with IgE of an anti-IgE antibody after intravenous administration in cynomolgus monkeys. *J Pharmacol Exp Ther*. 1996;279:1000–8.