

IgE and FcεRI Regulation

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Abstract

The high-affinity immunoglobulin (Ig)E receptor, FcεRI, regulates the action of mast cells and basophils and therefore, regulates the expression of atopic disease. There have been several recent observations that demonstrate new behaviors for this receptor. The control of FcεRI expression, control of cell function by FcεRI, and expression of FcεRI on other cell types are important new areas of understanding currently being explored.

Index Entries

IgE; FcεRI regulation; mast cells, basophils, dendritic cells, signal transduction, atopy.

Introduction

A central feature of allergic reactions is the aggregation of the high-affinity immunoglobulin (Ig)E receptor, FcεRI, to initiate a change in the behavior of the cell expressing the receptor. Presently, it is apparent that not only do mast cells and basophils express this receptor on their cell surface but that Langerhans' cells (1), monocytes (or a subset of monocytes; ref. 2), and cells derived from monocytes (such as dendritic cells [3]) also express this receptor. There are additional controversial reports that the receptor is also expressed on eosinophils (4–6), neutrophils (7), and platelets (8), but this biology is not yet as well defined. For example, our own evidence indicates the presence of the FcεRIα subunit inside of eosinophils, but

there is no measurable cell surface expression (6). There may be conditions allowing surface expression (9,10), but this possibility requires further exploration and/or confirmation. Despite these unsettled issues, it is now clear that numerous cell types can express this receptor, thus broadening the biology that revolves around IgE antibody.

It is also clear that the presence of monomeric IgE antibody alters the expression of FcεRI. Studies by Malveaux and Lichtenstein (11) in 1978 noted a correlation between cell surface FcεRI densities on peripheral blood basophils and the titer of serum IgE. A similar result was obtained more recently in a study examining a wider range of diseases with elevated serum IgE (12). Studies in the laboratory of Chaviva Isersky (13) in the mid-1980s noted

that inclusion of IgE in cultures of rat basophilic leukemia (RBL) cells increased expression of FcεRI. This observation was not extended to nontumor cells for several years, possibly because there were other observations of FcεRI processing that distinguished RBL cells from normal human basophils and mast cells. Nevertheless, the possibility remained that IgE modulated FcεRI expression, and this was more directly addressed by studies in the early and mid-1990s, both in human basophils and mast cells and murine mast cells (14–17). The observation that the presence of IgE could upregulate expression of FcεRI and that its absence could downregulate expression has important implications for both the biology of atopy and therapeutic approaches attempting to control this disease constellation.

Regulation of FcεRI Expression

FcεRI is a receptor that can be composed of three subunits, designated α , β , and γ . When all three components are present, the stoichiometry of expression is one α -, one β -, and two disulfide-linked γ -subunits. The α -chain is responsible for binding IgE, and the X-ray crystal structure of the combined IgE and receptor extracellular domain has been resolved to 3.5 Å (18). IgE binds to the receptor asymmetrically; there are two primary contact sites between FcεRI α and the Ce2–Ce3 domains of IgE whereby FcεRI α binds to each of the Ce3 chains of IgE at different sites (18,19). This type of binding precludes more than one IgE binding to one FcεRI α . The large area of contact and the amino acid residues involved leads to a very high-affinity interaction. Additionally, Ce3 of IgE must change conformation during binding to optimize contact (18,20,21). There is currently no known function for the cytoplasmic tail of the α -subunit.

Both the β - and γ -chains contain immunoreceptor tyrosine activation motifs (ITAMs) that mediate interaction with closely associated kinases; the receptor subunits have no enzymatic activity.

In rodents, all three components must be expressed for placement of the receptor on the cell surface (22,23), whereas in humans the receptor can be expressed in the absence of FcεRI β (22). It seems likely that this ability to express FcεRI, even the absence of FcεRI β , explains the ability of non-mast cell/basophils in humans to express FcεRI as the $\alpha\gamma 2$ species. In transgenic mice expressing human subunits, monocytes and Langerhans' cells are able to express the human FcεRI $\alpha\gamma 2$ (24). However, it should be noted that, from one perspective, this situation is not much different than that observed in rodents, where all three subunits are needed for surface expression. In humans, the cells that do not express FcεRI β (for reasons not yet fully understood) also only express very low densities of FcεRI, up to 100-fold less receptor than basophils. For example, it is not uncommon to observe 500,000 FcεRI on circulating basophils of atopics and a maximum of 5000 receptors (and sometimes considerably less) on their monocytes. Because the expression of the receptors on monocytes and dendritic cells is also influenced by circulating IgE (this form of regulating receptor expression seems intact [2,25–28]), it is possible that the absence of FcεRI β restricts the cell's ability to load its cell surface with high densities of FcεRI. Studies with transfected cell lines demonstrate that co-expression of FcεRI β leads to lines that express higher densities of FcεRI, although these studies do not suggest such a marked difference in expression levels in cells expressing $\alpha\gamma 2$ vs $\alpha\beta\gamma 2$. Notably, the stable transfectants with the heterotrimer $\alpha\gamma 2$ expressed only three- to sixfold lower densities of surface FcεRI than stable transfectants expressing the heterotetramer $\alpha\beta\gamma 2$ (29). There are additional implications for differential FcεRI β expression (30), and these are examined further later. However, it seems likely that there are at least two conditions with a strong influence on the expression of FcεRI: expression of FcεRI β and the local concentration of IgE antibody. Modulation of receptor expression can also follow

exposure of mast cells to interleukin (IL)-4 (but not basophils; refs. 17, 31, and 32), although the extent to which this mechanism is direct or indirect through effects on maturation or phenotype plasticity is not clear.

Gene Regulation

The genomic organization of the subunits of FcεRI is well described, but the *cis*- and *trans*-acting factors regulating the promoters of these genes are poorly understood. Figure 1 shows the available evidence for genomic structure. Notably, the expression of the receptor coincides (at least within the temporal discrimination currently examined in cell culture studies) with the expression of other proteins associated with mast cell maturation (at least those proteins associated with identifiable mast cells; ref. 33). Therefore, it seems likely that some of the *trans*-acting factors, such as GATA-1 or 2 (which have been associated with upregulation of other mast cell-associated genes), may play a role in turning on expression of this receptor (34,35). Because FcεRIβ appears to play an important role in the expression and activity of this receptor, the regulation of its expression attracts special attention.

Notably, the gene for FcεRIβ is located in humans in the region of 11q13, a region that has been associated in various studies with many aspects of atopic disease (36); this region also contains a variety of related four-transmembrane-spanning proteins now identified as MS4A, with FcεRIβ designated as MS4A2. More recently, polymorphisms of the *FcεRIβ* gene have been associated with atopy (37,38), total IgE levels (39), asthma (40), bronchial hyperresponsiveness (41), allergic rhinitis (42), and atopic dermatitis (43). In particular, three polymorphisms in the coding region, I181L, V183L, and E237G, show linkage with atopy; however, to date, efforts to find a change in the behavior of FcεRIβ with these changes incorporated have not revealed significant differences from the canonical FcεRIβ (44). The question remains regarding whether there are

other functions of FcεRIβ affected by these polymorphisms. Several single-nucleotide polymorphisms (SNPs) have also been identified in an extended region of the *FcεRIβ* gene. A total of 38 sequence variants were identified from a population of 12 individuals: 35 were SNPs, 2 were simple dinucleotide repeats, and 1 a three-base deletion (45). The authors of this study predict that this survey captured (with 99% probability) alleles with a frequency greater than 0.1. Surprisingly, this survey did not detect the I181L and V183L polymorphisms, although it did detect the E237G variant.

Of the 38 polymorphisms, only the E237G variant is found in the coding region. Other than the E237G variant, none of these polymorphisms has been tested for modifications in the regulation of its expression. A more recent study found an association between expression of the E237G variant and expression of FcεRI on circulating basophils (46). However, for reasons still unclear, this SNP is also associated with a higher IgE level, which may account for the higher receptor expression. More interestingly, the same study found that two other SNPs in the promoter of the *FcεRIβ* gene were tightly linked to the E237G SNP and that these polymorphisms did lead to more promoter activity by unknown mechanisms.

There is a recently identified splice variant of FcεRIβ that may influence the cell surface expression of FcεRI (47). This splice variant, designated β_T, includes the fifth intron of the *FcεRIβ* gene, and because this intron contains a stop codon, a truncated version of FcεRIβ is generated as a protein. Recent studies using stable and transient transfectants of Fcε β and FcεRIβ_T indicate that the normal chaperone functions of FcεRIβ are disrupted by the presence of FcεRIβ_T. In the current model of FcεRI synthesis, FcεRIα contains an endoplasmic reticulum (ER) retention sequence modulated by the presence of either FcεRIβ or FcεRIα in humans. This allows FcεRI to progress to the Golgi for further glycosylation and migration to the plasma membrane. When FcεRIβ_T

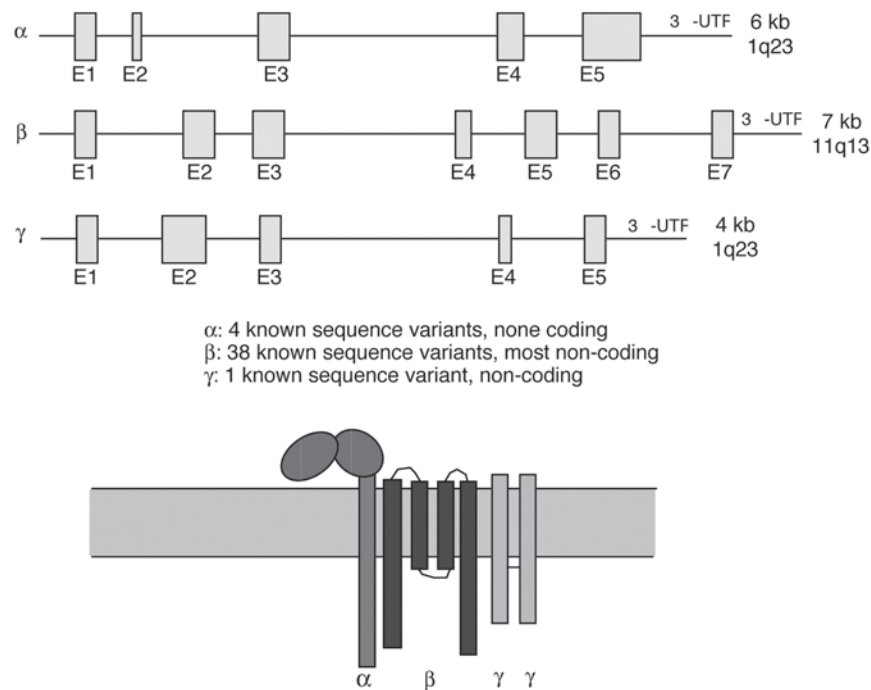


Fig. 1. Schematic of the genomic structure of the three subunits of the high-affinity IgE receptor.

associates with Fc ϵ RI α in the ER, it apparently does not mask this retention signal, and the complex becomes targeted for destruction, resulting in suppression of Fc ϵ RI expression at the cell surface. Transcripts for Fc ϵ RI β_T have been detected in cultured human mast cells and circulating basophils, although a detailed analysis of its presence in the general population (or in patients with atopic diseases) and its influence on expression levels of Fc ϵ RI have not been conducted.

Some of the dynamics of Fc ϵ RI β expression have been studied. One question that arises when considering the ability of Fc ϵ RI to be expressed with or without Fc ϵ RI β is whether the ratio of Fc ϵ RI β to Fc ϵ RI α is constant among cells that can express the tetrameric form of Fc ϵ RI (i.e., basophils or mast cells). Because the most accessible cell is the basophil, this cell was examined for the above ratio using donors with known differences in cell surface Fc ϵ RI density. Surprisingly, this ratio was considerably variable, ranging nearly 100-fold (48). Figure 2 shows the relationship between the ratio and total cell surface Fc ϵ RI; greater ratios were

associated with greater Fc ϵ RI density, and if the data is taken at face value, the relationship appears to saturate (these data have not been "adjusted" to account for differences in total serum IgE concentration). The same studies found that IL-3 can upregulate the steady state expression of messenger RNA (mRNA) for Fc ϵ RI β , and unpublished studies suggest that IL-3 does not alter mRNA degradation; therefore, the change in steady state is likely the result of increased transcription. Fc ϵ RI β protein also increases in culture with IL-3. Only a few studies of promoter regulation have been performed. A study of the murine Fc ϵ RI β promoter suggests a role for GATA-1 (which may be sensitive to the presence of IL-3; ref. 49), and a study of the human promoter concluded that OCT-1 *cis*-acting elements have a role in Fc ϵ RI β gene transcription (50).

In one study of SNPs in the Fc ϵ RI α gene, only three SNPs were identified; none were in the coding region, but all were located in the 5' flanking region (51). One SNP was found to have an association with serum total IgE levels in an asthmatic population. A second study has

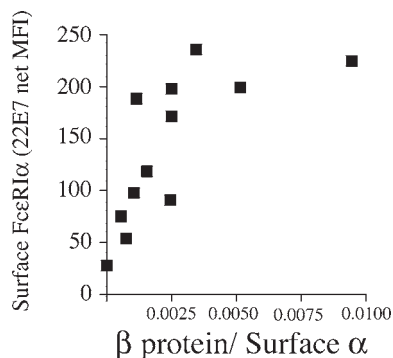


Fig. 2. Relationship between the ratio of FcεRIβ to FcεRIα and cell surface expression of FcεRI on peripheral blood basophils.

identified a SNP in the promoter of the FcεRIα gene (52). This SNP appears to increase transcription frequency by adding an additional GATA-1 site to the promoter, and in a Japanese population, allergic donors were more likely to be homozygous for the "T" variant that confers higher transcription rates.

The γ-subunit of FcεRI is shared among several immunoreceptors, including FcεRI, FcγRIα, and FcγRIIIα. This shared status raises the interesting possibility that competition for this common resource among Fc receptors present in the same cell may influence their expression (53). The FcεRIγ gene is located on human chromosome 1q23, and it is a member of the T-cell receptor-ζ family of signaling molecules. As shown in Fig. 1, this gene appears to have five exons, with the leader sequence of the protein occurring in exon 1, the very short extracellular domain starting within exon 2, and the critical ITAM spanning exons 4 and 5. Although Genbank appears to include several possible sequence variants for the coding region of this gene, these variants may be sequencing artifacts because a recent study failed to find the various mutations in a screen of 146 different donors (54). Only one polymorphism was found in one donor, and it coded for a valine to methionine mutation in a noncoding region. Although this is a relatively small gene, the absence of SNPs in the coding region is surprising (the average gene having one SNP per

kilobase pair). A search of the broader population may turn up additional polymorphisms.

Similarly to the β-subunit, the γ-subunit has two potential roles: regulating the expression of the α-subunits by protecting them from premature shunting into a degradative pathway in the ER and providing the cell surface receptor with all important ITAMs. Each γ-subunit has one ITAM, therefore FcεRI has at least two ITAMs (if the receptor is heterotrimeric) and three ITAMs (if the receptor is heterotetrameric). The γ ITAMs are known to provide a docking site for syk SH2 domains (for which there are two in tandem that can bind to both γ ITAMs). These ITAMs are critical for the function of the receptor (55,56).

IgE-Dependent Regulation

The addition of IgE to a culture of purified human basophils results in the upregulation of cell surface FcεRI. The upregulation is caused by the interaction of IgE with the receptor itself and not with accessory cells or other receptors that may bind IgE (57). There is an unexpected concentration dependence for upregulation; the EC₅₀ for upregulation is approx 250 ng/mL (approx 1 nM) of IgE, which is 30- to 100-fold higher than the anticipated concentration for 50% occupancy of the receptor (58). When cell surface receptor increases, so too does the total FcεRIα content of the cell. Similarly, removal of IgE results in loss of both cell surface receptor and total cellular FcεRIα (58). These results suggest that there is no major preformed store of receptor that shuttles from inside to the outside of the cell (or vice versa). The model that best fits this and other observations on the behavior of the system regarding IgE is one in which FcεRIα is constitutively synthesized and IgE controls the loss of receptor from the cell surface once it appears on the surface of the cell (59). The mechanism of loss remains unknown, but IgE clearly protects the receptor from loss (60). If endogenously present IgE is removed from the cell by a treatment with a slightly acidic buffer, then the receptor is lost, with a

half-life of approx 24 h (reloading these treated cells with IgE completely prevents loss; ref. 59). No changes in the steady state concentration of mRNA for FcεRIα, FcεRIβ, or FcεRIγ have been observed to follow culture with IgE, nor is the synthetic rate of FcεRIα altered by the presence of IgE (59). The unexpected EC50 for upregulation results from the slow forward rate constant of IgE binding to the receptor. This is logical, because the receptor is only protected from loss if IgE is bound, and higher concentrations of IgE are needed to compensate for the relatively slow forward binding constant of the reaction (as the newly formed receptor appears on the cell surface). There is a familiarity to this situation. CD23 (FcεRII) expression also depends on IgE (61–63). For this receptor, IgE protects its loss by a proteolytic mechanism. However, for FcεRI, drugs that inhibit the proteases cleaving CD23 do not inhibit loss of FcεRI in the absence of IgE (59).

A second unexpected outcome of in vitro studies of IgE interaction with the receptor is that the dissociation constant is considerably slower than estimates based on transfected cell lines. The in vitro studies suggest that 10 d are required for 50% dissociation, even if an IgE trap is included in the culture (such as Xolair/E25 or Tanox's Hu901) (58). This result suggests that the affinity of IgE for FcεRI in a natural setting is quite high (more like 10¹¹). The consequence of this higher affinity is that dissociation of IgE from cells in vivo may take many weeks, a point discussed in further detail later.

The studies of IgE-dependent regulation of FcεRI expression provided the first indication that monomeric IgE could provide a signal to the receptor (it should be noted that dimeric IgE actually results in suppression of upregulation). Although the "signal" for IgE-mediated retention of FcεRI may be the passive presence of bound IgE, the possibility of monomeric IgE signaling through the receptor led to various studies in which monomeric IgE had a wide variety of effects on mast cell function. The ini-

tial studies of this phenomenon noted various signaling steps activated by IgE (enriched for monomeric species by high-performance liquid chromatography). Indeed, with the exception of degranulation and arachidonic acid metabolite release, there was little distinction between monomeric IgE-induced activation and aggregation of FcεRI with antigen (64).

Because of the long history of studies that began with sensitization of the cells with antigen-specific IgE, these results were confusing. The EC50 for the activation of signaling by putatively monomeric IgE is quite high (approx 1 μg/mL). The data suggested a radical rethinking of the consequences of IgE binding to its receptor. However, there now appears to be something subtler operating in these in vitro conditions that may or may not have application in vivo. The key experiment revealing this subtlety derives from the nature of the IgE used to demonstrate the effect. To date, the IgE that most readily demonstrates strong signaling is a mouse monoclonal IgE that is specific for conjugated dinitrophenyl haptens. Inclusion of monovalent hapten with the IgE prevents the signaling induced by the putatively monomeric IgE, suggesting that the antigen binding portion of the monomeric IgE interacts with its ligand to induce a reaction similar to aggregation. The nature of this interaction remains unclear, but it appears that not all monomeric IgE molecules can induce this kind of signaling. Kawakami and colleagues (65) labeled IgE species as highly cytokinergic (HC) or poorly cytokinergic (PC). There remains considerable debate regarding the frequency of HC IgEs, but this problem has not been examined in the context of natural systems. The antidinitrophenyl (anti-DNP) IgE that most readily induces overt signaling is commercially available as SPE-7. The ligand binding site of SPE-7 has been shown to bind to three possibly very different ligands (66). The hypothesis has been proposed that SPE-7 represents a type of IgE that may interact weakly with some extracellular structure—not necessarily DNP-like—inducing a

hybrid form of aggregate on the cell surface. There is evidence from studies by Daeron and his colleagues (67) in the early 1980s that aggregation of FcεRI with cell surface structures leads to signaling and mediator release. Furthermore, studies by McConnell in the mid 1980s demonstrated that even transiently associating receptors whose densities were quite high could induce signaling (68–70).

More recently, Metzger and associates (71) showed that signaling dynamics may follow a process called “kinetic proofreading” (the ability of a signal to progress through the entire cascade, dependent on the transience of the first signal, which in this case is aggregation) but that certain steps can escape kinetic proofreading. In experimental studies of this escape mechanism, a more transient signal could induce cytokine/chemokine release. Together, this information leads to the hypothesis that IgE interacting weakly with cell surface structures may generate weak signals that drive only certain aspects of cell function. The studies by Kawakami and associates (72) suggest that at least one such process is survival of mast cells.

Because even IgE-induced survival requires the same early signaling components as normal aggregation-induced secretion (73), it appears possible that transiently weak signals are driving survival. If this viewpoint is correct, then the central issues regard how often one finds antigen-specific IgE that can engage in this behavior and the requirements necessary for the effects to occur (IgE concentration and the density of unoccupied FcεRI)? It should be noted that it is unlikely that IgE protects loss of FcεRI through a similar mechanism. Treatment of human basophils with an inhibitor of src-family kinases—which should completely inhibit the initiation of normal signaling—does not inhibit the protection afforded by IgE bound to receptor. Using mast cells derived from mice not expressing syk kinase, monomeric IgE continues to result in upregulation of FcεRI, whereas its effects on survival are blocked (73).

One prediction of a model in which IgE does not influence the synthesis of FcεRI (but only protects its loss once expressed) is the existence of a steady state, reached even in the absence of IgE (59). This is found in experimental studies, and it appears that the natural steady state is somewhere between 5000 and 10,000 receptors per cell (58,59,74). At concentrations of IgE that allow the lowest steady state to occur, the occupancy of the receptor is quite low. For example, at 5 ng/mL of IgE, receptor occupancy is less than 20%. As demonstrated later, even this level of occupancy (and low density) might be sufficient for partial function of the cell.

The *in vitro* studies of IgE dissociation from human basophils suggest slow dissociation, with a half-life of approx 10 d. Recent studies of changes in mast cell receptor densities following treatment of patients with anti-IgE antibody (omalizumab) suggest a long half-life as well (75). Although it is possible that conditions in the skin of patients (where the biopsies for mast cell receptor density were taken) do not allow a rapid loss of IgE from the mast cell, the results are compatible with the *in vitro* data. Conversely, the apparent rapid loss of receptor (and IgE) on circulating basophils in the same patients (74) appears to contradict the *in vitro* studies. However, one explanation for the discrepancy relates to the rapid turnover of basophils in circulation (76). When considering how anti-IgE antibody acts on the system and making some assumptions about the life span of circulating basophils, the data become consistent with what is known about IgE dissociation times. Indeed, this analysis also leads to the conclusion that the apparent loss of IgE and receptor from circulating basophils is, counter-intuitively, a measure of the rate that receptors are loaded onto basophils during maturation and the length of time that basophils mature—that is, from the time they begin expressing receptor to their appearance and disappearance from peripheral blood. Parenthetically, if this analysis is correct, then basophils in the

bone marrow synthesize receptors faster than observed *in vitro*.

Signaling and Requirements for Function

The traditional view of immediate hypersensitivity is that there is first an immune response skewed in such a way that IgE antibody is generated; IgE binds to circulating basophils or tissue-bound mast cells or Langerhans' cells; and antigen re-enters the system sometime later and, by inducing aggregation of surface-bound specific IgE, initiates a signal in the IgE-bearing cells. For mast cells and basophils, one functional consequence is the secretion of various mediators. Some of these are preformed and stored in granules (e.g., histamine), and some mediators are newly formed, such as the leukotrienes or prostaglandins (mast cells). Histamine and arachidonic acid products like LTC₄ are released rapidly, but they are not released until later in the reaction; the cells also synthesize cytokines and chemokines.

Detailed studies of human basophils and less detailed studies of tissue mast cells indicate that only approx 2000 antigen-specific IgE molecules need be aggregated to result in 50% of the cells' maximal response (77,78). This sensitivity differs among individuals; notably, some individuals' basophils require less than 300 antigen-specific IgE molecules to reach the 50% response point (79). Because the typical atopic patient has 250,000 receptors, reducing the cellular response requires significant reductions in circulating IgE. Because receptor expression declines with decreases in free IgE, there is synergy in the reduction of cell surface IgE, but the synergy works in reverse with increases in IgE. Additionally, the minimum steady state achievable limits the effects of synergy at the low end of free IgE concentrations. In large part, only the occupancy of receptor continues to be reduced with further reductions in free IgE. The system responds to the total IgE con-

centration (i.e., these numbers apply when considering all IgE). However, for any given patient, antigen-specific IgE represents a fraction of the total IgE. If this fraction is low enough, then even modest reductions in total IgE may reduce cell function. Conversely, if antigen-specific IgE represents an appreciable fraction of the total IgE, it could be very difficult to achieve a reduction in the cell response. This possibility has not been directly examined, although preliminary data in a phase I trial of omalizumab (74) suggests that the ratio of antigen-specific IgE to total IgE is a predictor of the final suppression of the basophil response.

Phase I trials also demonstrated that at therapeutic doses of omalizumab, the basophil and mast cell responses were at a threshold. Slight reductions in omalizumab dose resulted in a near return to normal function. Figure 3 illustrates this result. Note that prior to the start of therapy, both IgE and FcεRI density on circulating basophils average approx 250,000 per basophil—that is, near total occupancy—with serum free IgE concentrations of approx 400 ng/mL (approx 2 nM). After 3 mo with circulating free IgE reduced to 4 ng/mL, receptor expression was reduced to approx 10,000 per cell, and IgE was reduced to less than 1500 per cell (i.e., <15% occupancy). Histamine release from isolated basophils stimulated with optimal or suboptimal concentrations of dust mite antigen was reduced an average of about 90%. At 6 mo, the dose of omalizumab was reduced by 3- to 20-fold, resulting in a 3-fold increase in serum free IgE and a 3-fold increase in receptor expression. Although the increase in receptor expression and loading with IgE was relatively subtle, there was a near complete return of antigen-induced histamine release to levels observed prior to treatment (80).

As noted earlier, one parameter of cellular responsiveness is sensitivity—that is, the number of antigen-specific IgE molecules per cell required for a half-maximal response. Knowledge of this parameter of cell function helps to explain what is needed for cells to respond. To

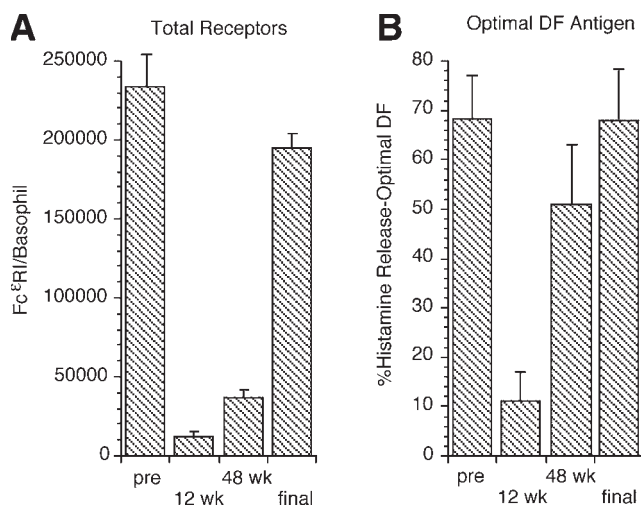


Fig. 3. Loss and recovery of antigen-induced histamine release from peripheral blood basophils during treatment with anti-IgE antibody relative to changes FcεRI expression.

determine the average value of 2000 molecules per cell, human basophils were tested for histamine release. We have also examined other end points of secretion; a similar value applies to the secretion of LTC₄ and IL-4 (79,81). However, this may not be true for mast cells. Although human mast cells have not been examined for LTC₄ or cytokine secretion (but histamine release is similar to basophils), studies in cultured mouse mast cells suggest that cytokine release requires high densities of antigen-specific IgE (82). A similar parameter has not been developed for activation of other αγ2-FcεRI-bearing cells. For example, it is not known how much IgE must be bound to dendritic or Langerhans' cells to initiate substantial antigen presentation. Furthermore, the relationship between IgE concentration and expression of FcεRI on these cells is not well understood, although it is apparent that the relationship exists (2,25–27). Therefore, a prediction of how changes in IgE might alter the response of these cells cannot be made.

The consequences of reducing circulating IgE in humans—the reduction in basophil and mast cell secretion and, possibly, the reduction in function of dendritic and Langerhans'

cells—may regulate another important feedback loop. The cytokines secreted by basophils and mast cells are likely to regulate the allergic inflammatory status of their environment and are likely to regulate the immune response characteristics that lead to IgE synthesis. For example, there is mounting evidence that basophils are a primary source of IL-4 and IL-13 (83–86). In humans, it has not yet been possible to demonstrate IL-4 protein secretion from tissue mast cells or in cultured mast cells. However, this continues to be a controversial issue. Basophils secrete quantities similar to T-cells, and because the frequency of basophils (with their pan-specific IgE) is much greater than that of antigen-specific T-cells, basophils may generate most of the IL-4 present in tissues (at certain times). Recent studies in mice support a prominent role for basophils (87–90). Therefore, significant reductions in IL-4 and IL-13 secretion from basophils during a reduction in circulating IgE (e.g., with omalizumab) could have long-term consequences to the synthesis of IgE. Thus, the longer term feedback loop further favors a reduction in the atopic diathesis.

There is evidence that IgE synthesis occurs, in large part, in mucosal tissues (91–93). Indeed, there are examples of patients in whom serum IgE is unmeasurable but in whom IgE can be found in mucosal tissues. The feedback loop involving upregulation of FcεRI by IgE, upregulation of receptor (inducing greater IL-4 secretion, with antigen present), and IL-4 (inducing further B-cell switching for IgE synthesis) is an interesting possibility. One study suggests that although mast cells and basophils may express CD40L, only basophils can provide a full signal (IL-4 and CD40L) to local B-cells to drive the IgE switch (94). However, one might expect that this potentially strong positive feedback loop has some breaking mechanism. There are indications that aggregation of mIgE or CD23a on B-cells inhibits IgE generation (95,96). However, this negative feedback loop operates at IgE concentrations that are 100- to 1000-fold higher than the positive feedback loop noted

earlier. Therefore, the breaking action of this negative feedback loop occurs only at higher concentrations of IgE. Further regulation may come from the cytokines in these local environments that are also believed to regulate receptor expression.

Conclusion

There is rapidly expanding interest in the factors regulating expression of FcεRI. There remains considerable uncertainty regarding the importance of independent regulation of the FcεRIβ subunit or its splice variant β_T, both in terms of regulating expression and function of FcεRI. There is also only primitive understanding of the role of various polymorphisms in the subunit genes on the atopic phenotype. However, many efforts are being made to resolve these issues and to discover other factors that regulate expression of this receptor. To understand the variation in expression in atopy among patients, the role of this receptor on nonmast cell/basophils will be particularly important to elucidate. Of particular interest for understanding the variation in expression in atopy among patients, will be understanding the role of FcεRI on the function of cells that are not mast cells or basophils.

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