

IgE receptors

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IgE receptors are implicated as important components of the immunological pathway in allergic and inflammatory diseases. Recent investigations have begun to unravel the structure, signal transduction and function of IgE receptors from different cell types in rodent and human systems. Studies of the mechanisms involved might provide opportunities for therapeutic intervention strategies in the treatment of allergic and hypersensitivity reactions.

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Current Opinion in Immunology 2001, 13:721–726

0952-7915/01/\$ – see front matter

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Abbreviations

DC	dendritic cell
ER	endoplasmic reticulum
NGF	nerve growth factor
USF	upstream regulating factor

Introduction

IgE is known to play a role in allergic inflammatory processes such as anaphylaxis, allergic rhinitis, asthma and atopic dermatitis. As with other immunoglobulins, two distinct types of receptors have been demonstrated for IgE, namely the high-affinity IgE receptor (FcεRI) and the low-affinity IgE receptor (FcεRII).

In humans, the ‘classical’ tetrameric FcεRI (αβγ2) is constitutively expressed on effector cells of anaphylaxis (i.e. mast cells and basophils), whereas a trimeric form of FcεRI (αγ2) is variably expressed on antigen-presenting cells such as monocytes, Langerhans cells and peripheral blood dendritic cells (DCs) (Figure 1). Recently, FcεRI αβ- and γ-chain mRNA has been detected in neutrophils, eosinophils and human platelets; however, only limited information is available about the exact structure and surface expression of FcεRI on these cells. The α-chain of FcεRI is responsible for IgE binding, the β-chain increases stability and signaling capacity, and the dimer of the γ-chain, which is shared by other Fc receptor complexes, carries two immunoreceptor tyrosine-based activation motifs (‘ITAMs’) for downstream signal propagation.

Binding of polyvalent antigens by receptor-bound IgE causes receptor aggregation and triggers cellular activation. This leads to the release of inflammatory mediators and vasodilators from effector cells of the allergic reaction. Activation of eosinophils by FcεRI provides defense mechanisms against parasitic infection, whereas FcεRI on antigen-presenting cells can deliver IgE-bound antigen into MHC class II antigen-presentation pathways. IgE

antibodies also interact with FcεRII, which is involved in antigen presentation, cellular cytotoxicity and the regulation of IgE production.

Human FcεRII (known as CD23) is a Ca²⁺-dependent type C-lectin and exists in two forms: CD23a, which is constitutively expressed on B cells and is associated with endocytosis of IgE-coated particles; and CD23b, which is induced in particular by IL-4, is found also on non-B cells such as T cells, Langerhans cells, monocytes, macrophages, platelets and eosinophils, and mediates phagocytosis of soluble IgE complexes. CD23 at the cell surface is turned over to yield a series of soluble fragments (sCD23) of different molecular weights, which are formed in an autocatalytic process involving cleavage of membrane-bound CD23 by a matrix metalloprotease.

This review will provide an overview of new developments in IgE-receptor research within the past year.

FcεRI

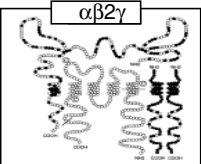
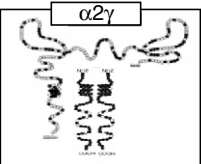
Regulation of FcεRI surface expression and interaction with IgE

The mechanisms underlying FcεRI assembly and surface expression are of considerable interest. Recently, it has been shown that overexpression of an upstream regulating factor (USF) capable of enhancing class I promotor activity, named the ‘rat USF2FL clone’, increases transcription of the human high-affinity IgE receptor α-chain through specific binding of the CAGCTG motif in the first intron. In contrast, overexpression of the CACGTG-binding isoforms USF2δ1 and USF2δ2 reduces the transcription of the FcεRIα gene, suggesting the presence of different roles of each variant [1].

Another relevant mechanism influencing the surface expression of FcεRI is the intracellular assembly of the α- and γ-chains of FcεRI, which leads to the masking of a retention signal and export of the receptor complex from the endoplasmic reticulum (ER) to the cell surface. Glucosidase trimming of terminal glucose residues seems to be a crucial step in the export of immature FcεRIα from the ER and represents a quality control mechanism for this event. The association of the α- and γ-chains of FcεRI is mandatory for their transfer into the Golgi compartment, where terminal glycosylation with complex sugars takes place [2*].

Recent evidence supports the regulation of FcεRIα by free IgE in mast cells and basophils. The density of basophil surface IgE and FcεRIα expression correlates with serum levels of IgE regardless of the disease state [3*]. *In vitro*, IgE incubation leads to a functional upregulation of FcεRI surface expression on human basophils, with a variable magnitude of the responsiveness to antigenic challenge,

Figure 1

Subunit composition	Species	Cell type	Associated cell function
	Human Rodent Canine	Mast cells	Cell activation and degranulation
		Basophils	
	Human	Monocytes	Antigen presentation
		Blood DCs	Modulation of cell differentiation
		Langerhans cells	
?	Human	Neutrophils	Allergic disease
		Eosinophils	Defense against parasitic infections
		Platelets	Inflammation

Current Opinion in Immunology

An overview of the FcεRI subtypes expressed by different cells and species, and their associated cell functions. As the question mark indicates, the exact surface structure of FcεRI on human neutrophils, eosinophils and platelets is still not completely elucidated; it is the subject of controversy and has been discussed by different research groups.

indicating that not all components of the signal transduction pathway are upregulated in a balanced manner [4•].

The structural interaction of the Fc fragment of IgE with the FcεRI α-chain is a key initial event of the allergic response and has been investigated by several research groups. Analysis of the crystal structure at high resolution revealed that each Cε3 domain of IgE binds a distinct binding site of FcεRIα in an asymmetrical manner and suggested a kinetic scheme for IgE binding. Inhibitors of one of these sites might accelerate the dissociation of receptor-bound IgE, and might prove useful in the treatment of acute allergic reactions in which dissociation of IgE from mast cells would be helpful [5•,6•,7].

The recent work of Borkowski *et al.* demonstrates that FcεRI upregulation is a result of the stabilization of the receptor at the cell surface, the use of a pre-formed receptor pool and a continued basal level of protein synthesis (see Update).

The role of the FcεRI β-chain

The β-chain of FcεRI can enhance FcεRI maturation and assembly processes, leading to an increase in surface expression and an amplification of signal transduction capacity within the cells [8,9]. Despite their genetic linkage with atopy, polymorphisms of the β-chain do not affect this signal amplification function, and instead may be related to functions of the β-chain that are not as yet defined [10•]. Research on the interaction of the FcεRI β- and γ-chains has shown that only the γ-chains are aggregated after sub-optimal stimulation of FcεRI by multivalent antigens; in

contrast, optimal degranulation of mast cells and basophils causes distinct aggregation of β- and γ-chains, which do not co-aggregate but mostly form homogenous aggregates [11].

Functional aspects of FcεRI on effector cells

Mast cells

Aggregation of FcεRI might orchestrate the allergic reactions in different ways [12]. It was shown previously that the level of nerve growth factor (NGF) is increased in serum from humans with allergic diseases and asthma [13]. There is some evidence that NGF may be specifically released by stimuli that cause an allergic reaction: mast cells have been shown to release significantly high levels of NGF in response to both IgE and specific antigen stimulation through the FcεRI [14].

Another interesting finding in the past year has been the low levels of FcεRI mRNA in mast cells derived from umbilical cord blood compared with the levels in mast cells derived from adult peripheral blood [15•]. These data suggest that IgE-mediated reactions during early infancy may be restricted through selective inhibition of FcεRIα transcription at progenitor stages [15•].

Asai *et al.* and Kalesnikoff *et al.* have recently provided evidence that mast cell survival and growth are promoted by monomeric IgE binding to its high-affinity receptor (see Update). The ability of IgE to enhance mast cell survival and FcεRI expression may contribute to amplified allergic reactions.

Basophils

In about 10% of human donors, basophils do not release histamine in response to FcεRI crosslinking. Despite normal

FcεRI expression, these 'non-releaser basophils' also fail to form membrane ruffles, to upregulate VLA-4-mediated adhesion to target cells, and to produce IL-4. Protein levels of Syk, a tyrosine kinase that is essential for proximal FcεRI signal transduction, are undetectable even though levels of Syk mRNA are normal in these cells [16,17]. Understanding the underlying mechanisms of the reversible suppression of Syk protein expression in non-releaser basophils and the replication of this property in patients with allergic inflammation could be a tool to limit symptomatic diseases.

Neutrophils

Although the role of neutrophils in the pathogenesis of asthma has not been defined clearly, these cells have been found in the human bronchial wall of allergic and non-allergic subjects. Recently, both mRNA and the cell-surface expression of FcεRI were identified in neutrophils from asthmatic subjects; furthermore, engagement of the FcεRI was shown to induce the release of IL-8 [18•]. This observation provides a potential mechanism by which these cells may contribute to the manifestation of allergic disorders.

Eosinophils

Kabaya *et al.* showed that human eosinophils, and mouse eosinophils transgenic for human high-affinity IgE receptors, express low levels of the high-affinity IgE receptor and release IL-10 upon receptor activation; thus they contribute to the regulation of the immune response and its effector mechanisms in this way (see Update).

Signal transduction

So far, signaling events initiated by FcεRI have been explored mostly in rat basophilic leukemia cell lines bearing tetrameric FcεRI and are currently not understood fully [19••]. The crosslinking of FcεRI and IgE on mast cells triggers mitogen-activated protein (MAP) kinase activation and cytokine gene expression. Recently, an alternative pathway triggered by FcεRI cross-linking, in which Jun N-terminal kinase (JNK) activation and cytokine production is regulated in part by the signaling complex MEKK2–MEKK5–ERK5, has been described [20•,21•]. Inhibition of this latter pathway blocks activation of the TNF-α promoter [21•,22•].

Another interesting recent finding concerns ubiquitination, which leads to the degradation of proteins by proteasomes and acts as a sorting signal to internalize proteins destined to the endosomal/lysosomal pathway. The presence of ubiquitinated FcεRI in clustered rafts upon receptor aggregation has been reported and is likely to be an important parameter regulating the IgE-triggered signaling that occurs in rafts [22•]. In view of these data, it has been proposed that the functionally important interaction of the tyrosine kinase Lyn with crosslinked IgE–FcεRI [23•] might be caused by their mutual co-association with lipid rafts [24,25].

By contrast, it has been suggested that FcεRI and Lyn interact through protein–protein interactions that neither depend on their post-translational modification of the kinase with lipid

moieties nor result exclusively from their colocalization in specialized membrane domains. In addition, it has been shown that detergent-resistant microdomains offer no refuge for proteins phosphorylated by FcεRI [26•,27•]. Procedures routinely used to isolate the detergent-resistant microdomains dissociate FcεRI and artificially accentuate the distribution of phosphorylated chains in the microdomains [26•,27•].

SH2-mediated membrane translocation is essential for Syk to be activated by FcεRI and mediate downstream events that lead to histamine release [28•]. Besides the tyrosine kinases, which are already known to play a role in the FcεRI signal transduction, the linker for activation of T cells ('LAT') has been shown to participate in this mechanism for the first time [29]. Another new aspect in this field of research is the HRS-binding protein, which is thought to be involved in trafficking during endo- and exocytosis and is assumed to play a regulatory role in the FcεRI-triggered secretory response of rat mast cells [30].

In addition, during the past year several studies have provided important new insights into new mechanisms that influence FcεRI-associated signal transduction. Sphingosine kinase seems to act as a permissive factor for stimulating FcεRI in mast cells [31], whereas acute lowering of cholesterol results in an increased release of secretory components in FcεRI-activated cells [32]. Finally, the phosphoinositide-3-OH kinase might have a role in initiating an antigen-mediated Ca²⁺-entry mechanism in effector cells [33].

Recently published data from Saito *et al.* provide evidence that the Dos/Gab family scaffolds regulate the PI(3)K pathway *in vivo* and the associated signalling molecules may be new targets for developing drugs to treat allergy (see Update).

The role of FcεRI on antigen-presenting cells

Monocytes

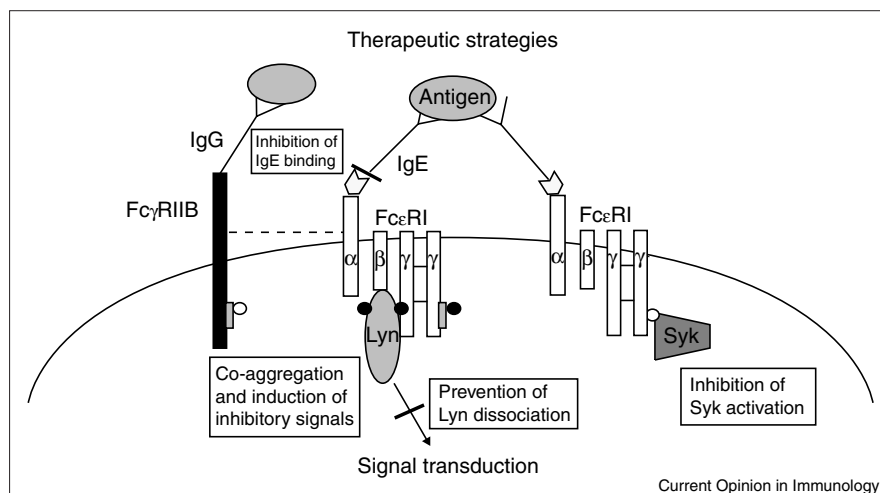
For blood monocytes, two different mechanisms modulating the expression of FcεRIα have been identified: addition of IL-4 and IL-13 significantly enhances surface expression of FcεRIα; and this expression is significantly inhibited by glucocorticoids [34]. Cells of the human monocytic parental cell line THP1 display surface FcεRI in response to IL-4 or receptor ligands such as IgE [35]; thus, regulation of FcεRI on human monocytic cells might be studied on the basis of this model system, which is suited to address issues of FcεRI modulation in the context of allergic diseases.

Recently we showed that receptor ligation of FcεRI at the beginning of the culture of human monocytes from atopic donors prevents the generation of monocyte-derived DCs, mainly owing to a marked increase in the production of IL-10. These data imply a novel pivotal function of FcεRI in modulating the differentiation of monocytes and DCs [36•].

Cells of mucosal tissue

Recent results have indicated that IgE and FcεRI may have a role in the control of bacterial pathogenicity and

Figure 2



Therapeutic strategies for allergic diseases that focus on the FcεRI signaling pathway. One direct way to block the FcεRI signaling is to interfere with IgE binding to its receptor. A second possibility is to inhibit the signaling events that occur downstream of FcεRI. This might be achieved, as shown here, by preventing the dissociation of Lyn from the phosphorylated receptor chains or by inhibiting the activation of Syk. A third strategy in this context is the recruitment of inhibitory FcγRII receptors to FcεRI.

intestinal inflammation. In transgenic mice expressing a humanized FcεRI, levels of colonic IL-4 are higher, the composition of the fecal flora is modified and bacterial translocation towards mesenteric lymph nodes is increased [37•]. These data suggest that FcεRI might even contribute to the development of intestinal inflammation.

FcεRII

The role of FcεRII in allergic diseases and inflammatory processes has been studied extensively, and its implication in IgE synthesis and IgE-mediated immune and inflammatory functions has been reviewed recently [38]. FcεRII and the newly described genes DC-SIGN and DC-SIGNR are encoded within a 105-kb region of 19p13, and their close linkage and similar gene structure might suggest that they have arisen through duplication of an ancestral gene [39].

Investigations in allergic rats revealed that enhanced intestinal transepithelial antigen transport is mediated by IgE and FcεRII [40•]. Blocking the binding of IgE to its receptor inhibits the transepithelial antigen transport and the hypersensitivity reaction, and might be a model for treatment strategies for allergic food reactions.

Regulation of the expression of CD23 on monocytes and monocytic cell lines has been studied in depth. Culture with cytochalasin E and substances activating the 5-lipoxygenase pathway can significantly upregulate the expression/release of FcεRII [41,42]. Another cell type that has been investigated in the context of FcεRII is the eosinophil: IgE binding on eosinophil surface receptors of atopic subjects results in the activation of these cells, suggesting that FcεRII has a pivotal role in this mechanism [43]. In atopic and non-atopic subjects, stimulation of FcεRII induces functional changes in eosinophils that are characterized by increased eosinophil migration associated with enhanced expression of the adhesion molecules LFA-1 (late-function antigen 1) and Mac-1.

Conclusions and future directions

Significant progress has been made in elucidating the role and regulation of IgE receptors on different cell types and IgE–receptor-mediated signals in immunological pathways. Over the past decade, work has focused in particular on determining the mechanisms that control and modulate allergic and inflammatory hypersensitivity reactions, with the aim of developing novel therapeutic strategies (Figure 2). Interfering with the binding of IgE to FcεRI and FcεRII is considered to be a straightforward strategy for specifically preventing IgE-mediated allergic reactions. Recombinant and synthetic peptides comprising structural elements of human IgE or human FcεRI have been investigated as competitive inhibitors of the IgE–FcεRI interaction. As a practical application, mimotope peptides coupled to carrier protein might be used to develop a peptide-based anti-allergy vaccine to induce anti-IgE antibodies — similar to the current approach that uses humanized nonanaphylactogenic anti-IgE monoclonal antibodies as a passive vaccine [44–47].

New routes to control allergic responses focus on inhibiting the earliest steps of the signal transduction cascade. This might be achieved by sequestering the FcεRIα-associated protein tyrosine kinase Lyn, eliminating or inactivating the protein tyrosine kinase Syk, or establishing an inhibitory cross-talk between FcεRIα and FcγRII that limits the FcεRI-mediated activation of Syk [48,49,50•]. Co-aggregation of FcγRII and FcεRI inhibits histamine release, IL-4 production and Ca²⁺ mobilization of basophils; on the basis of these data, analyzing the negative regulation of FcεRI signaling by FcγRII co-stimulation [44,49,51•,52,53•,54] in human basophils might give new insights into the development of future therapeutic strategies for allergic diseases.

Update

Recently it was shown by Borkowski *et al.* [55] that IgE binding to the α-chain is the minimal requirement for the

induction of FcεRI upregulation. The regulation of mast cell survival by IgE has been investigated and discussed by Asai *et al.* [56] and Kalesnikoff *et al.* [57]. Kabaya *et al.* [58] demonstrated that human eosinophils, and mouse eosinophils transgenic for human high-affinity IgE-receptors, are able to secrete IL-10 upon FcεRI-engagement. Finally, recent biochemical analyses by Saito *et al.* [59] have revealed that signaling pathways that are dependent on PI(3)K, a critical component of FcεRI signalling, are defective in Gab2^{-/-} mast cells.

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