

Fc receptors as determinants of allergic reactions

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Activation of the high-affinity receptor for IgE (FcεRI) on allergic effector cells induces a multitude of positive signals via immunoreceptor tyrosine-based activation motifs, which leads to the rapid manifestation of allergic inflammatory reactions. As a counterbalance, the coaggregation of the IgG receptor FcγRIIB mediates inhibitory signals via immunoreceptor tyrosine-based inhibition motifs. Advances in the positive and negative regulation of Fc receptor expression and signaling have shed light on the role of Fc receptors in our immune system, indicating them to be bifunctional, inhibitory and activating structures. Based on these findings, exciting new therapeutic strategies have been developed, such as the use of chimeric fusion proteins, which concomitantly activate FcεRI and FcγRIIB. These new approaches successfully take advantage of the bivalent character of Fc receptors and pave the way for innovative strategies to modulate allergic immune reactions.

The nature of allergic reactions

Nasal itching, sneezing, rhinorrhea, wheezing, breathlessness or eruption of multiple hives immediately after allergen exposure are typical clinical symptoms of allergic diseases such as allergic asthma, allergic rhinoconjunctivitis, atopic eczema, urticaria, or food- or insect allergy. These diseases affect nearly a third of the population worldwide, with an increasing incidence [1,2]. Allergic reactions are defined as a hyperreactivity toward normally nonimmunogenic substances. Compared with the wide spectrum of allergens that can elicit an allergic reaction, the structural components and molecular mechanisms underlying allergic reactions are a uniform sequence of events. The first phase of an allergic reaction is the so-called sensitization phase, in which contact with allergens leads (depending partially on genetic predisposition) to the production of allergen-specific IgE and IgG molecules by B cells [3]. In the next step, the IgE molecules bind to IgE receptors on other cells, such as mast cells or basophils. Finally, clustering of allergens and crosslinking of IgE molecules bound to the high-affinity Fc receptor for IgE (FcεRI) on effector cells induces cell activation and the onset of the allergic immune response [4,5]. In parallel, inhibitory signals counter-regulate the activation signals, which supports the hypothesis that allergic diseases result

not only from excessive activation of cells, but also from a deficiency at the level of the suppressing molecules [6,7]. Consequently, the balance of positive and negative signals in this interplay might be a regulating strategy of physiological importance, and an increase in inhibitory signals might be what prevents healthy, nonallergic individuals from manifesting allergic diseases. Shifting the balance by enhancing the impact of inhibitory signals in allergic individuals is therefore a promising therapeutic option.

FcεRI is the main mediator of allergic reactions

FcεRI has a central role as the initial ‘docking station’, providing the starting signal for the allergic signal-transduction cascade. FcεRI can be subdivided into an IgE-binding section, represented by the FcεRIα subunit, and a signal-transducing section, represented by the β and γ subunits. Because binding of IgE to FcεRI is the prerequisite for the ignition of a complex cascade of events, the amount of FcεRI expressed on the surface of cells determines the quantity of allergen-specific IgE and thereby the quantity of allergens that gain access to effector cells to make an allergic reaction possible [8,9]. In the human and rodent immune systems, the tetrameric form of FcεRI is expressed on allergic effector cells, including mast cells and basophils, and consists of an α chain, a β chain and a γ-chain dimer. The trimeric FcεRI variant can be detected on human antigen-presenting cells (APCs) such as monocytes or dendritic cells and consists of an α chain and a γ-chain dimer but no β chain [10]. Structural factors influencing the expression of the FcεRI variants are complex and have been the subject of considerable interest in recent years.

A quality assurance process determines the fate of FcεRIα

The FcεRIα chain is heavily N-glycosylated in its extracellular section and is responsible for binding of the Fc portion of IgE to the receptor. The assembly of FcεRIα takes place in the endoplasmic reticulum (ER), which is the organelle responsible for the quality assurance of the assembly [11,12]. Here, the coordination of the initial core glycosylation and appropriate folding of the FcεRIα chain occurs [13]. Later on, the so-called immature variant of the FcεRIα chain is transported to the Golgi compartment, where terminal glycosylation and replacement of mannose-rich sugars with complex heterogeneous sugars

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occurs [12]. In the absence of the FcεRIβ and FcεRIγ chains, the FcεRIα chain is trapped in the ER as a result of its ER retention signal located in its cytoplasmic domain. Only the presence of the γ-chain subunits can mask the retention signal, and thereby enable the FcεRI complex to leave the ER and undergo full maturation, thus facilitating the surface expression of the complete complex [13] (Figure 1).

The availability of mature FcεRIα differs between allergic and nonallergic individuals. The amount of the mature variant of FcεRIα is much higher in allergic individuals, especially in APCs, than in nonallergic individuals, in which the immature FcεRIα form predominates in the intracellular space of APCs [14]. Moreover, only APCs of allergic individuals display a high intracellular level of FcεRIγ, whereas FcεRIγ is nearly

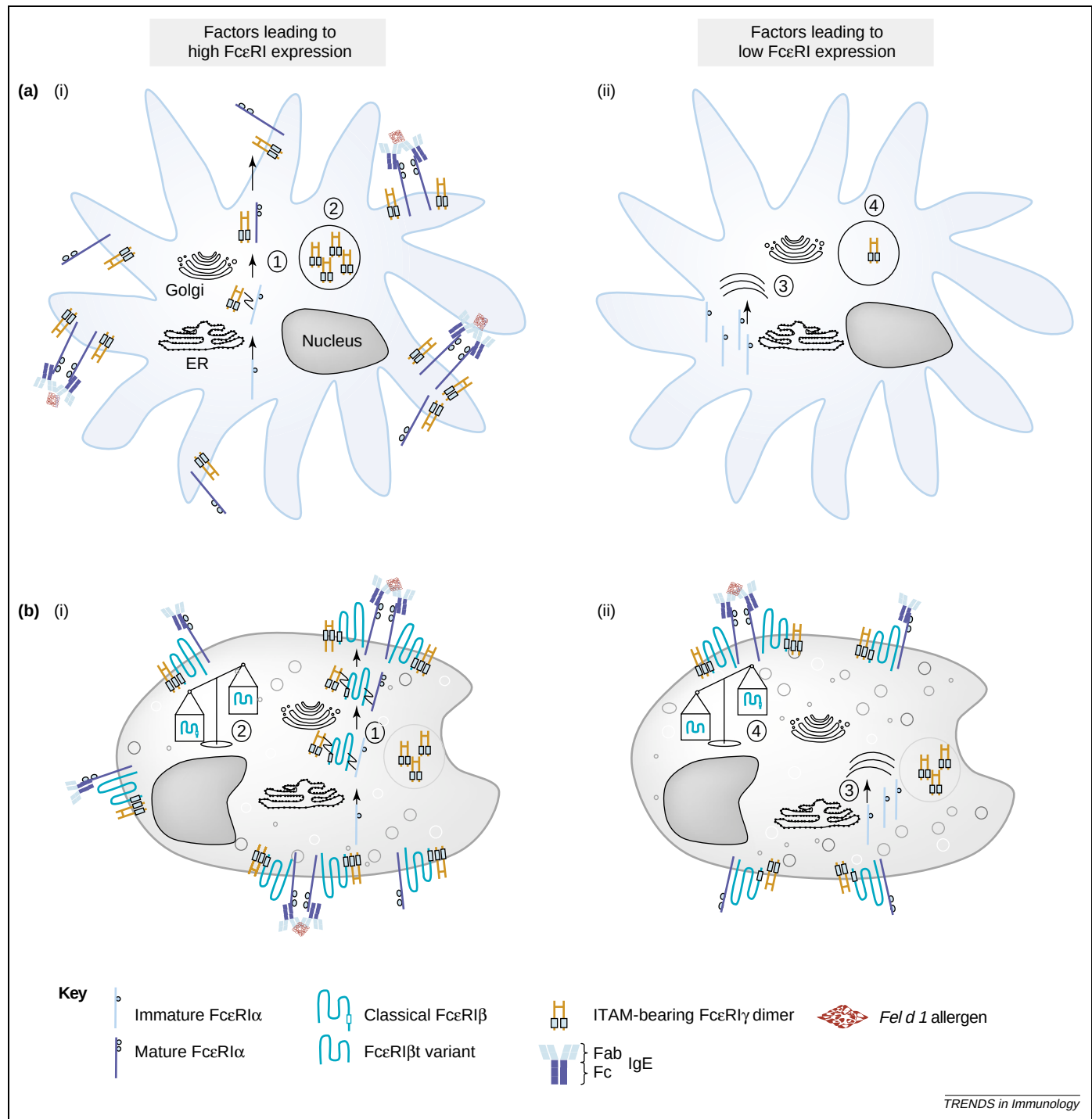


Figure 1. Mechanisms influencing the quality and quantity of the FcεRI subunits and FcεRI surface expression by (a) dendritic cells and monocytes and (b) mast cells and basophils. (a) In APCs, the balance between the immature and mature FcεRIα variant [(1) and (3)] determines the amount of trimeric FcεRI expressed on the cell surface. Furthermore, the size [high (2) or low (4)] of the FcεRIγ pool determines the amount of IgE-binding FcεRI expressed on the cell surface, in particular, because FcεRIβ is completely absent from these cells. (b) In mast cells and basophils, core glycosylation and initial folding of immature FcεRIα takes place in the ER. In the presence of the FcεRIβ and FcεRIγ subunits, FcεRIα is transported to the Golgi compartment, where terminal glycosylation take place (1); otherwise, immature FcεRI is trapped in the ER (3). Predominance of classical FcεRIβ favors FcεRI surface expression (2), whereas the FcεRIβt variant counteracts FcεRI surface expression of tetrameric FcεRI by effector cells (4).

absent from the APCs of nonallergic individuals [14]. Taken together, a crucial balance between the immature and the mature FcεRIα subunit determines whether or not IgE surface binding is facilitated.

The FcεRIβ – an amplifier with opposing functions

The FcεRIβ chain is an amplifier of FcεRI surface expression and signal transduction [15,16]. The FcεRIβ chain augments the processing of nascent FcεRIα chain and FcεRIα- or β-chain association and accelerates – in the same way as a chaperone – the intracellular trafficking of the FcεRIα chain to the cell surface. Although FcεRIβ contains an immunoreceptor tyrosine-based activation motif (ITAM), this does not itself induce signal transduction but rather amplifies the signal-transduction cascade induced by the ITAM of FcεRIγ. In summary, the amplification of the signal transduction by the FcεRIβ chain is achieved by enhanced phosphorylation of FcεRIγ and recruitment and association of tyrosine kinase signaling molecules, such as Syk or Lyn with FcεRIβ.

In a recent study, an alternative, truncated splice variant of FcεRIβ (FcεRIβt) was discovered in effector cells; this variant lacks the ITAM and acts as a negative regulator of FcεRI expression [17]. FcεRIβt has a short half-life and is rapidly degraded after it has been recognized by the proteasome quality control process in the ER. FcεRIβt associates only with the immature FcεRIα chain, and not with the properly folded mature FcεRIα chain or the FcεRIγ chain. FcεRIβ and FcεRIβt variants are coexpressed in cells and compete with each other. A predominance of the classical full-length FcεRIβ chain results in strong FcεRI surface expression and efficient signal transduction, whereas predominance of the truncated FcεRIβt chain has a negative effect on FcεRIβ function and results in lower FcεRI surface expression and weak signal transduction (Figure 1b). In this way, a crucial balance between the two FcεRIβ variants might control not only the surface expression of FcεRI, but also the efficacy of its signal transduction.

FcεRIγ – a limiting but decisive factor

The γ-chain dimer is a common feature not only of the FcεRI variants, but also of other FcR complexes, and it belongs to the ζ-chain protein family. The FcεRIγ chain is a disulfide-linked γ2 homodimer, and each γ-chain has a short extracellular section, a transmembrane region containing 21 residues and a cytoplasmic domain, which contains one ITAM per chain. In human APCs, FcεRIγ is the limiting factor for surface expression of the whole FcεRI complex. A low intracellular pool of FcεRIγ detectable in the APCs of individuals without allergic diseases correlates with the accumulation of immature FcεRIα in the ER. By contrast, intracellular FcεRIγ is present in high amounts in individuals with allergic diseases. This might enable immature FcεRIα to leave the ER and to acquire full maturity upon terminal glycosylation in the Golgi compartment, thus leading to expression on the cell surface of the complete trimeric FcεRI complex with high IgE-binding capacity [14] (Figure 1a). For signal transduction, FcεRIγ and its ITAMs are of crucial importance in both FcεRI variants [18,19].

Together, the signal-transduction mechanisms associated with FcεRI activation (Figure 2) lead to the subsequent release of histamine and other preformed mediators of allergic inflammation, as well as to synthesis of lipid mediators and cytokines by effector cells [4,20,21]. In APCs, FcεRI is pivotal in the uptake of allergens within the skin of patients with allergic diseases such as atopic eczema. Here, FcεRI-bearing APCs present the processed allergens to T cells. This process is followed by T cell priming [22], and might also be involved in determining the T helper cell profile [22]. Allergen challenge of APCs induces the release of chemotactic signals and proinflammatory mediators, such as tumor necrosis factor-α and monocyte chemotactic protein 1 (MCP-1) [23]. This might contribute to the characteristic allergic inflammatory reactions and flare-up of eczematous skin lesions in atopic eczema [22].

IgE increases FcεRI surface expression

A positive correlation between serum IgE levels and the IgE-binding capacity of human basophils was shown even before FcεRI had been characterized [21]. Several groups confirmed that binding of IgE to FcεRI regulates the expression of FcεRI on mast cells and basophils both *in vivo* and *in vitro* [24–28]. Importantly, in many of these studies, this upregulation was shown to be accompanied by increased FcεRI-dependent effector functions. In one of these studies [24], IgE-mediated upregulation of mouse mast cell FcεRI expression was shown to have an early phase that was insensitive to the protein synthesis inhibitor cycloheximide, followed by a late phase that was sensitive to cycloheximide. In more recent studies, this upregulation was shown to be a complex process involving stabilization of the receptor on the cell surface and utilization of a preformed receptor pool derived from recycled and recently synthesized receptors [29]. This study [29] also showed that, although a basal level of FcεRI protein synthesis is required for IgE-mediated upregulation to occur, there is no indication of increased protein synthesis. Monomeric IgE also induces trimeric FcεRI upregulation on dendritic cells by a comparable mechanism, thus enhancing the IgE-dependent antigen-presenting function of these cells [14].

FcγRIIB puts the brakes on allergic reactions

Once the complete FcεRI complex is expressed at the cell surface, the flow of the signal-transduction cascade is triggered when an allergen binds and crosslinks specific IgE molecules on the cell surface. However, a couple of mechanisms have evolved to curtail and prevent allergic activation, even at its earliest time point of initiation [30]. Integral to these mechanisms is FcγRII, which is a member of the IgG receptor family and preferentially binds IgG complexes [31]. FcγRII has both activating and inhibitory elements and, as an immunological switch, can convey the 'off' and the 'on' signals of allergic reactions [32]. Inhibitory FcγRIIB is co-expressed with activating FcγRIIA in a large variety of cells, but FcγRIIA is absent from mast cells or basophils [33] (Table 1). The forms FcγRIIB1 and FcγRIIB2 in humans result from alternative splicing and differ only in the region encoded by the intracytoplasmic exon. When

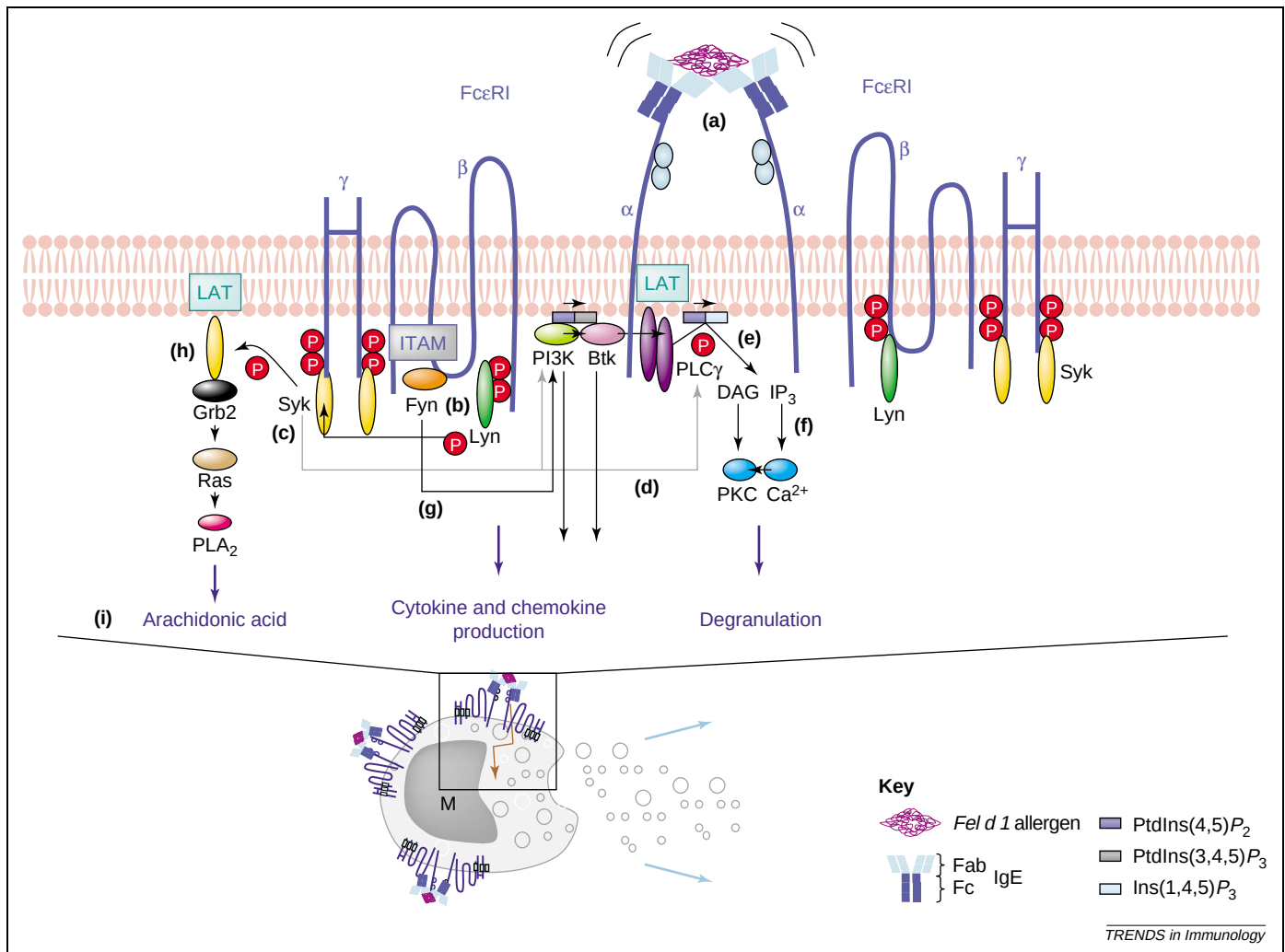


Figure 2. The signal-transduction cascade induced after FcεRI aggregation. (a) Allergen challenge and crosslinking of IgE molecules bound to FcεRI (blue) induces a sequence of phosphate transfer events, which themselves support the activation of newly recruited signaling proteins. (b) FcεRI crosslinking activates Lyn, which phosphorylates the ITAM of the FcεRIβ and FcεRIγ subunits. (c) FcεRI aggregation induces the recruitment of the tyrosine kinase Syk, which phosphorylates linker for activation of T cells (LAT). (d) This enables recruitment of phospholipase Cγ (PLCγ) via its SH2 domain. (e) PLCγ hydrolyzes membrane-bound phosphatidylinositol (4,5)-bisphosphate (PtdIns(4,5)P₂) to inositol (1,4,5)-trisphosphate [Ins(1,4,5)P₃] and diacylglycerol (DAG), which (f) interfere with the mobilization of calcium ions, protein tyrosine phosphorylation reactions and recruitment of SHIP-1 and SHIP-2 lipid phosphatases to downstream of tyrosine kinase (Dok) family proteins (not shown) and thus to protein kinase C (PKC) activity. (g) FcεRI engagement activates Fyn, which binds via additional Fyn molecules to the SH2 domain of phosphatidylinositol 3-kinase (PI3K) subunits, ultimately leading to phosphorylation of PtdIns(4,5)P₂ to PtdIns(3,4,5)P₃ by the catalytic subunit of PI3K and recruitment of Bruton's tyrosine kinase (Btk). (h) LAT also recruits adaptor molecules such as growth factor receptor-bound protein 2 (Grb2), which, via the Ras-mitogen-activated protein kinase cascade, leads to phospholipase A₂ (PLA₂) activation and ultimately to the synthesis and release of lipid mediators derived from arachidonic acid. (i) Together, these mechanisms induce the subsequent release and exocytosis of histamine (degranulation) and other mediators of allergic inflammation by effector cells (such as arachidonic acid, cytokines and chemokines [4,20,21,62]).

co-aggregated with FcεRI, FcγRIIB inhibits mast cell activation. Inhibitory receptors such as FcγRIIB typically have an immunoreceptor tyrosine-based inhibition motif (ITIM) as a counterpart to the ITAM. An ITIM is a 13 amino acid sequence that is crucial for the allergic dampening function of FcγRIIB [34]. After FcεRI–FcγRIIB coaggregation on effector cells, FcγRIIB becomes phosphorylated

and recruits the Src homology 2 (SH2) domain-containing inositol 5-phosphatases SHIP1 and SHIP2, which contribute to the inhibition [22,35]. As a consequence of a complex cascade of events, the initial signaling mechanisms are inhibited and release of allergy mediators from effector cells is diminished or completely suppressed (Figure 3).

Table 1. Distribution of FcεRI, FcεRII, FcγRIIA and FcγRIIB in different cell types^a

Type of Fc receptor	Affinity for Ig	Cellular distribution	Refs
FcεRI	> 10 ¹⁰ M ⁻¹ to IgE	Mast cells; basophils; eosinophils; dendritic cell subtypes	[10,53]
FcεRII (CD23)	< 10 ⁶ M ⁻¹ to IgE	Platelets; B cells; macrophages; dendritic cell subtypes	[33,61]
FcγRIIA (CD32A)	< 10 ⁷ M ⁻¹ to IgG3 > IgG1, IgG2	Neutrophils; eosinophils; macrophages; platelets; dendritic cell subtypes	[33,61]
FcγRIIB (CD32B)	>> IgG4 < 10 ⁷ M ⁻¹ to IgG3 > IgG1 > IgG4 > IgG2	B-cells (FcγRIIB1, FcγRIIB2); mast cells (FcγRIIB2); basophils (FcγRIIB2); neutrophils (FcγRIIB2); eosinophils (FcγRIIB2); macrophages (FcγRIIB2); dendritic cell subtypes (FcγRIIB2)	[33,61]

^aAn overview of the distribution of the high-affinity receptor for IgE (FcεRI) and the low-affinity receptor for IgE [FcεRII (CD23)] in addition to the IgG receptors FcγRIIA and FcγRIIB on human cells and their affinity to immunoglobulins (Ig).

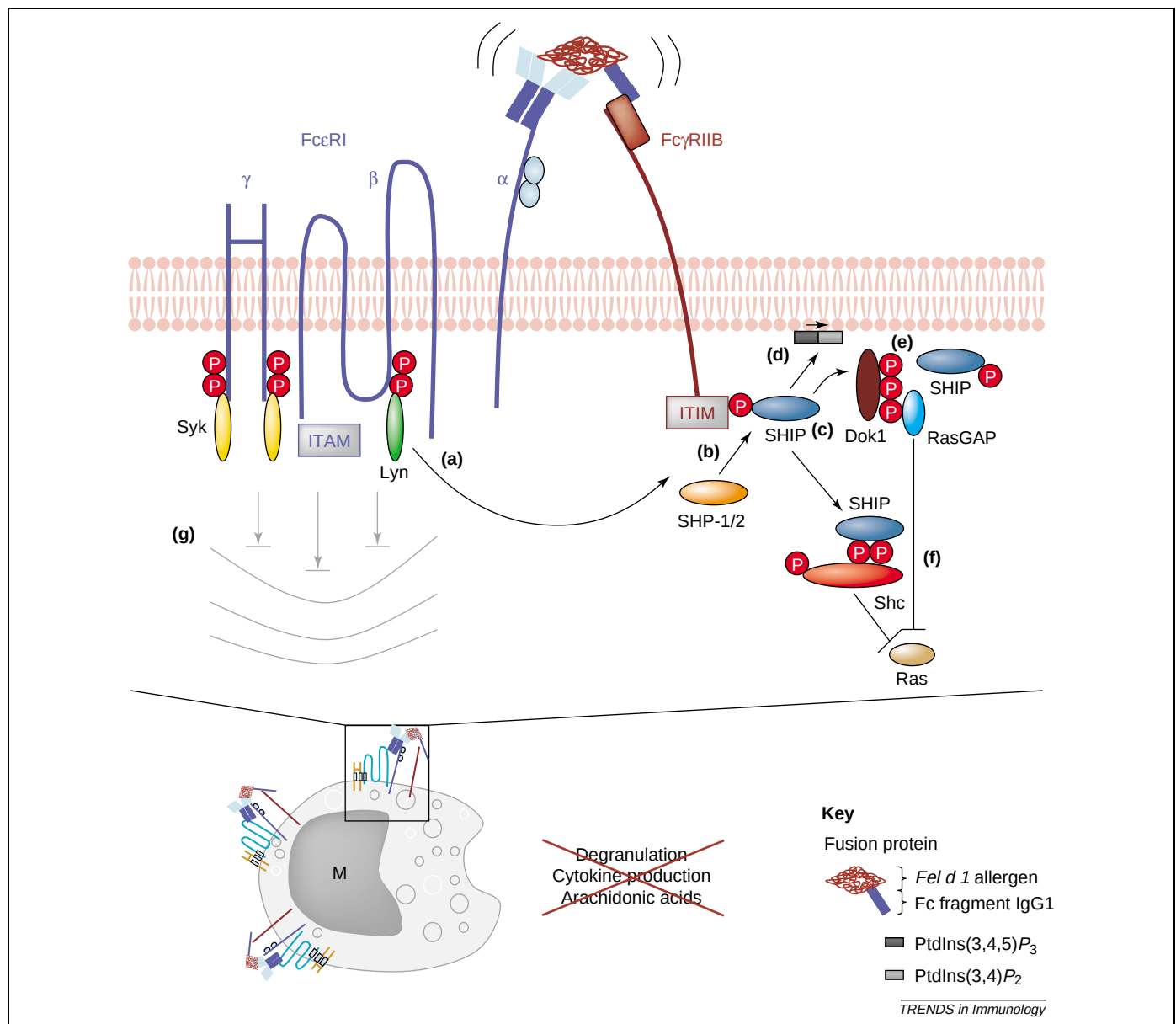


Figure 3. The cascade of signal-transduction events after FcεRI–FcγRIIB coaggregation. (a) FcεRI–FcγRIIB coaggregation induces Lyn, which phosphorylates the ITIM of FcγRIIB, and (b) the recruitment of SH2-domain-containing protein tyrosine phosphatase-1 and -2 (SHP-1 and -2). (c) The recruitment of SHP mediates the inhibition of Ras activation. (d) SHP accelerates the hydrolysis of PtdIns(2,3,4)P₃ to PtdIns(3,4)P₂ and inhibits the membrane recruitment and activation of Btk and PLCγ (not shown). (f) FcγRIIB-recruited SHP is tyrosine phosphorylated, binds to Dok and Src homology collagen (Shc) and inhibits Ras activation. (g) Together, these mechanisms lead to the inhibition of mediator release from effector cells [4,21,34,35,63]. Abbreviations: Ras-GAP, Ras GTPase-activating protein. Curved lines in (g) represent inhibition of the membrane recruitment and activation of Btk and PLCγ.

Therapeutic principles

Catching the primary mediators of allergic reactions with anti-IgE or anti-IgE-receptor antibody treatment

Nipping allergic reactions in the bud, while achieving a long-lasting effect, is the major aim of approaches targeting IgE molecules. Such approaches prevent the earliest steps of allergic reactions by reducing the occurrence of IgE–FcεRI receptor interactions. Treatment with anti-IgE antibodies results in a significant reduction of free IgE molecules in the sera of allergic individuals. As a secondary phenomenon, the number of IgE receptors (FcεRI), which sense and correlate with serum IgE levels, expressed on the cell surface of immunocompetent cells is concomitantly reduced with decreasing serum IgE levels. This reduces the probability of IgE binding and IgE–

allergen contact [36]. As mentioned above, binding of monomeric IgE alone stabilizes FcεRI on the cell surface and also enhances mast cell survival [21,37–39]. The advantage of this strategy is that any type of IgE molecule, regardless of its specificity, can be targeted. The disadvantage is that, although the efficacy of nonanaphylactic, humanized anti-IgE antibodies in patients with asthma or peanut allergy [40–42] has been proven in different clinical studies, this treatment regimen will most probably be used as a concomitant therapy and not as a single treatment or as a single therapeutic option for acute allergic reactions.

Other approaches target FcεRI itself, using chimeric proteins of human origin called FcεRI–Bak–Bax, which, after internalization by mast cells and basophils, induces

apoptosis of these cells [42]. The proapoptotic effect of the FcεRI–Bak chimeric protein is directly dependent on the surface level of FcεRI in the target cells, enabling the specific killing of FcεRI-expressing cells [42,43]. These proapoptotic chimeric anti-FcεRI proteins could possibly be used as a concomitant treatment of acute allergic diseases in the future.

Focusing on single elements of FcεRI signal transduction

The ability of inhibitory receptors to regulate IgE-mediated allergic reactions establishes them as potential targets for therapeutic intervention in the treatment of allergic diseases. Therefore, several treatment strategies are targeted at negative signaling molecules expressed on the surface of the cells involved or participating in the signal-transduction cascade [44]. Given the complexity of the downstream signaling cascade, the quest for a potential candidate for signal suppression is almost as challenging as finding a needle in a haystack.

However, one of the most promising approaches in this context is targeting the signal-transduction molecule Syk. This approach is based on the observation that a deficiency of the positive signaling molecule Syk downstream of FcεRI prevents basophils from degranulating after FcεRI crosslinking [45]. By contrast, a reduction in the negative signaling molecule SHIP induces a hyperdegranulation of basophils [46]. Small-molecule inhibitors have been used to block Syk and prevent mast cells from degranulation. A clinical study using the intranasally administered Syk kinase inhibitor R112 in patients with allergic rhinitis achieved a significant improvement of symptoms in the treatment group [47]. In animal models for asthma, the use of inhibitors of phosphatidylinositol 3-kinase and mitogen-activated protein kinases has been found to reduce anaphylactic contractions of the airways and airway hyper-responsiveness [48–50]. Furthermore, various tyrosine kinase inhibitors against Lyn, Syk, Lck, ZAP-70, Fyn, Btk and Itk have been investigated in animal models of asthma and found to be capable of blocking growth factor-induced hyperplasia of airway cells and antigen-induced cell activation; however, their efficacy now needs to be demonstrated in additional studies [48–50].

Slamming on the brake – concomitant activation of inhibitory receptors

For the inhibition of FcεRI-mediated diseases, the coaggregation of FcεRI with FcγRII, and thereby the inhibition of FcεRI signaling, holds great potential for the treatment of allergic diseases. The first approach was undertaken nearly ten years ago using basophils preincubated with a monoclonal anti-FcγRII antibody and anti-mouse Ig antibodies [51]. Recently, a novel approach for achieving coaggregation made use of fusion proteins. One of these fusion proteins, which has been used successfully in *in vivo* and *in vitro* studies, is composed of a chimeric major cat allergen that recognizes IgE specific for the cat allergen *Felis domesticus* 1 (*Fel d* 1) bound to the surface of mast cells and basophils, linked to part of the constant (Fcγ) portion of a truncated human IgG, which coengages FcγRIIB [52]. The underlying

principle of this strategy has been proven with a precursor of the cat fusion protein termed GE2, which consists of a human IgG Fc fragment (Fcγ1) fused to a human IgE Fc fragment (Fcε). The great advantage of this principle is that the fusion protein can suppress allergen-mediated mast cell activation without undesirable simultaneous activation of the cells [53,54]. Coaggregation of FcεRI-bound IgE with FcγRIIB leads to the activation of ITIM and interruption of Syk signaling [55].

The efficacy of the fusion method has been demonstrated by the suppression of the IgE-mediated signal-transduction cascade of mast cells and basophils *in vitro* and suppression of the acute IgE-mediated allergic response in *Fel d* 1-sensitized mice *in vivo* [52,54]. The mechanism of inhibition is the result of modified calcium mobilization and modified tyrosine kinase phosphorylation, such as decreased phosphorylation of various intracellular substrates and increased phosphorylation of downstream of kinase-1 (Dok1), growth factor receptor-bound protein 2 and SHIP [55] (Figure 3).

Another approach, using a bispecific antibody composed of human Fab' fragment of IgE and human Fab' fragment of FcγRII for concomitant crosslinking of FcεRI and FcγRIIB, achieved similar results by inhibiting histamine release from human mast cells preincubated with the bispecific antibody following allergen challenge [56]. It is hoped that the principle of coaggregation of FcεRI and FcγRII, and the potential of IgG to counteract IgE, will lead to a gradually developing unresponsiveness to allergens.

The strategy of FcεRI–FcγRII coaggregation seems to be applicable not only to effector cells, but also to FcεRI-bearing APCs, which are of crucial importance in allergic skin diseases [57]. Coaggregation of FcγRII and the low-affinity receptor for IgE FcγRII (also known as CD23) in human B cells by chimeric fusion proteins inhibits germline transcription of the ε gene and IgE production *in vitro* [58]. The disadvantage of this strategy might be the occurrence of an undesired amplification of the allergic response – for example, as a result of unwanted coaggregation of activating FcγRIIA instead of FcγRIIB in cells coexpressing both receptor types. Therefore, the exact expression pattern of the different Fc receptor types on target cells should be studied.

It cannot be excluded that functional differences in FcγRIIB based on genetic polymorphisms of the FCGR2B gene region might alter the response and exclude a subgroup of patients from therapeutic options using FcεRI–FcγRII coaggregation [59]. Another caveat is that this option is limited to patients with single or only a few sensitizations, and might not be applicable to multi-sensitized patients. Increasing the rate of IgG receptor-mediated inhibitory signals is a mode of action that fusion proteins might share with classic immunotherapeutic strategies [60]. Immunotherapies that involve administration of increasing doses of allergens – for example, subcutaneously – result in the development of an allergen-specific IgG response within weeks. Newly formed allergen–IgG complexes are assumed thereby to inhibit further allergen-mediated effector cell activation via FcεRI–FcγRIIB coactivation.

The advantage of fusion proteins over classical immunotherapy is that the inhibitory effect is achieved immediately after administration of the fusion protein. This enables the fusion protein to serve as a short-term treatment. A further possible advantage is that *Fel d 1* allergens already bound to IgE might be displaced by the fusion protein, which might prevent the progression of the allergic cascade to anaphylactic shock.

Conclusion

The bivalent 'Janus' character of Fc receptors has a decisive role in the outcome of the allergic cascade and governs the potential of an allergen to elicit an allergic reaction. On the one hand, the quality and quantity of the FcεRI subunits FcεRIα, FcεRIβ and FcεRIγ determine the rate of allergen-effector-cell contact and the intensity of the FcεRI-mediated proallergic signals. On the other hand, the level of the protective IgG subtypes, in combination with the distribution of inhibitory FcγRIIB and other inhibitory molecules, determines whether activating proallergic or inhibiting antiallergic immune responses prevail. Given that the efficiency of the promoters of allergic reactions is partially genetically determined, the effects of the single pro- and anti-allergic components might be strikingly different in allergic versus nonallergic individuals. In addition to strategies aimed at directly blocking the initiation of the allergic cascade by FcεRI, physiological countermeasures such as FcγRIIB are emerging as one of the most promising approaches to target Fc receptors efficiently as determinants of allergic reactions.

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