O Receptor de Alta Afinidade para a IgE na Resposta Inflamatória Alérgica

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RESUMO

O receptor de alta afinidade para a imunoglobina E (FcεRI) foi classicamente descrito em mastócitos e basófilos. Recentemente, o FcεRI foi também detectado na superfície de monócitos e macrófagos, em células de Langerhans e outras células dendriticas que expressam o marcador CD1a, em eosinófilos e em certas linhas celulares T. Embora a ligação da IgE ao FcεRI por si mesma não active a célula que expressa o receptor, a interacção subsequente entre as moléculas de IgE ligadas a receptores e alergenos para os quais essas IgE sejam específicas, induz activação celular e síntese e/ou libertação de diferentes tipos de mediadores. Estes efeitos são reproduzidos quando se estimulam as células que expressam o FcεRI, com anticorpos anti-receptor. Embora os efeitos mais conhecidos da activação através do FcεRI sejam aqueles que se passam a nível do mastócito e do basófilo, com as suas consequências em tremos de fenómeno de hipersensibilidade de tipo I, outras células FcεRI--positivas sofrem igualmente fenómenos de activação, desgranulação e libertação de diferentes tipos de medidadores. O FcεRI, pelo menos em células como as células de Langerhans e em monócitos, pode igualmente servir para captar alergenos de uma forma extremamente eficiente, com subsequente apresentação a linfócitos T, no contexto de moléculas de classe II do complexo major de histocompatibilidade. Embora os efeitos ligados à activação através da forma membranar do FcεRI possam estar envolvidos no desencadear da resposta inflamatória alérgica, uma forma solúvel do FcεRI parece possuir propriedades anti-alérgicas, quer *in vivo* quer *in vitro*, o que poderá abrir novos campos de intervenção terapêutica na área de doenças alérgicas.

PALAVRAS-CHAVE: FcεRI; alta afinidade; solúvel; receptor para IgE; reacção alérgica tardia; mastócitos; eosinófilos; células de Langerhans; células T; pele; mucosa nasal; mucosa brônquica; atopia.

SUMMARY

The high affinity receptor for immunoglobulin E (FcεRI) was classicaly described on mast cells and basophils. Recently, FcεRI was also detected on the surface of monocytes and macrophases on Langerhans' and other CD1a-bearing dendritic cells, on eosinophils and on certain T cell lines. Although the binding of IgE to FcεRI does not activate the receptor-bearing cell, the subsequent interaction between receptor-bound specific IgE molecules and the relevant allergen induces cell activation and synthesis and/or secretion of different types of mediators. These effects can be reproduced by stimulating FcεRI-bearing cells with anti-receptor antibodies. Although the best known effects of FcεRI-mediated cell activation are those seen in the mast cell and basophil, and which eventually result in type I hypersensitivity, other FcεRI-positive cells also undergo activation, synthesis and degranulation of different types of mediators. FcεRI, at least in cells such as Langerhans cells and monocytes, can also be used for an extremely effective uptake and presentation of allergens in the context of class II major histocompatibility molecules. Although the effects due to triggering of the membrane form of FcεRI may be involved in the pathophysiology of the inflammatory allergic response, a soluble form of FcεRI seems capable of externing anti-allergic effects both in vivo ***and*** in vitro, ***which may have therapeutic prospects in allergic disease.***

KEY-WORDS: FcεRI; high affinity; soluble; IgE receptor; late-phase reaction; mast cells; eosinophils; Langerhans' cells; T cells; skin; nasal mucosa; bronchial mucosa; atopy.

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INTRODUCTION

This review describes the structure, cellular expression and functional aspects of the high affinity receptor for IgE (FcεRI). It also analyses the possible pathogenic implications of expression of FcεRI on cells other than mast cells and basophils and elaborates on the prospects of a therapeutic approach specifically targeted against this receptor in the context of clinical allergy.

GENERAL CONSIDERATIONS

The presence of specific receptors for immunoglobulin E (IgE) on several cell types provides a mechanism for coupling antigen-antibody interactions with cellular effector responses. There are at least three types of receptors that specifically bind IgE with different affinities[1]. The high affinity IgE receptor (FcεRI) is capable of binding the Fc region of monomeric IgE with an affinity at least two orders of magnitude greater than the two other receptor types[2]. The binding of IgE by FcεRI present on the cell membrane does not activate the receptor-bearing cell but, in appropriately sensitized individuals, the interaction of FcεRI-bound IgE with the relevant antigen elicits a response that varies according to the cell type. In mast cells and basophils, for instance, the response principally consists of dreganulation and release of pre-formed mediators and cytokines[2,5], and *de novo* formation of substances relevant to the acute phase of allergic reactions[2]. In cells such as Langerhans cells and monocytes/ /macrophages, the presence of FcεRI could significantly enhance their role as antigen-presenting cells[6,7], as well as their mediator release[8]. Finally, novel approaches to targeting the FcεRI suggested by murine studies[9,10], may have therapeutic possibilities in allergic diseases.

STRUCTURAL AND GENOMIC ASPECTS

FcεRI is a tetrameric complex consisting of one α-chain and two γ-chains, associated by non-covalent interactions[11]. The α-, β- and γ-chains have one, four and one membrane-spanning regions, respectively (Fig. 1). The binding site for IgE is located on the α-chain[12,16], but the β- and γ-chains are necessary for signal transduction through FcεRI. Studies with co-transfection of α- and γ-chains have suggested that in the human, the α- and γ-chains may be sufficient for the expression and function of FcεRI on the cell surface[17]. Complementary DNA clones coding for the human α-[18,19] and γ-[17] chains have been isolated. Recently, great interest was raised by the observation that the β-chain of the FcεRI was located on chromosome 11q13 and was in close linkage with a putative gene for atopy[20]. In addition, a substitution in one aminoacid in the β-chain has also been shown to be associated with high total serum IgE levels[21].

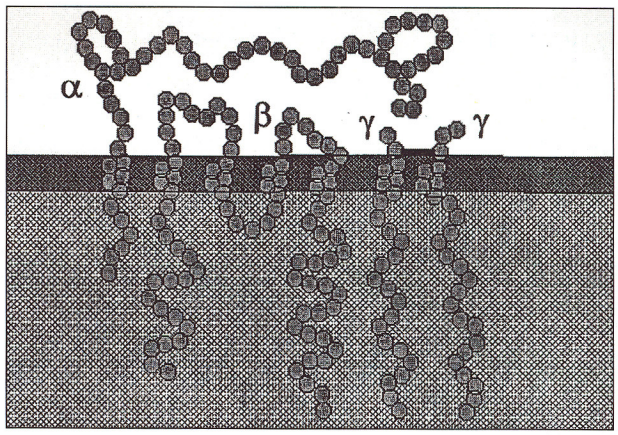

Fig. 1 - Estrutura do receptor de alta afinidade para a IgE (FcεRI), composto por uma cadeia α, que contém o local de ligação para a fracção Fc da IgE; uma cadeia β, e um homodímero de cadeias γ. As cadeias β e γ são necessárias para a transdução de sinal.

Each receptor molecule binds one IgE molecule[22,24], and several studies have shown, at least in mast cells and basophils, that for efficient cell activation and mediator release, a minimum of two receptors must be cross-linked by allergen[25,26]. This may not be the case in other cell types, particularly in terms of allergen uptake and presentation.

A recombinant, soluble form of FcεRI, basically composed of the α-chain on its own or of constructs of the α-chain and the Fc portion of IgG, can bind IgE *in vitro* with affinity similar to that of the membrane form[27,28]. This has led several groups to express the recombinant form of soluble form of FcεRI in several systems in order to study both the stoichiometry of IgE binding to the α-chain[25,26,29], and the effects of soluble FcεRI on IgE production by B cells[30] and in type I hypersensitivity reactions in animal models[10].

CELLULAR EXPRESSION AND FUNCTION

FcεRI can be expressed by different cell types. Although traditionally described on mast cells and basophils[31,32], the high affinity receptor has more recently been detected on monocytes[34], Langerhans cells[35,36], eosinophils[37] and certain T cell lines[38]. We have recently shown the presence of increased numbers of FcεRI-bearing cells in bronchial biopsies from patients with asthma (atopic and non-atopic) and from non asthmatic, atopic patients[39], and after allergen challenge in the skin[40] (Fig. 2) and nose[41] of atopic patients. Very little is known about the possibility of modulation of expression of FcεRI on the cell surface by citokines or other mediators, except for the upregulation that was shown to occur in mast cell and T cell lines, after incubation with IL-9[38].

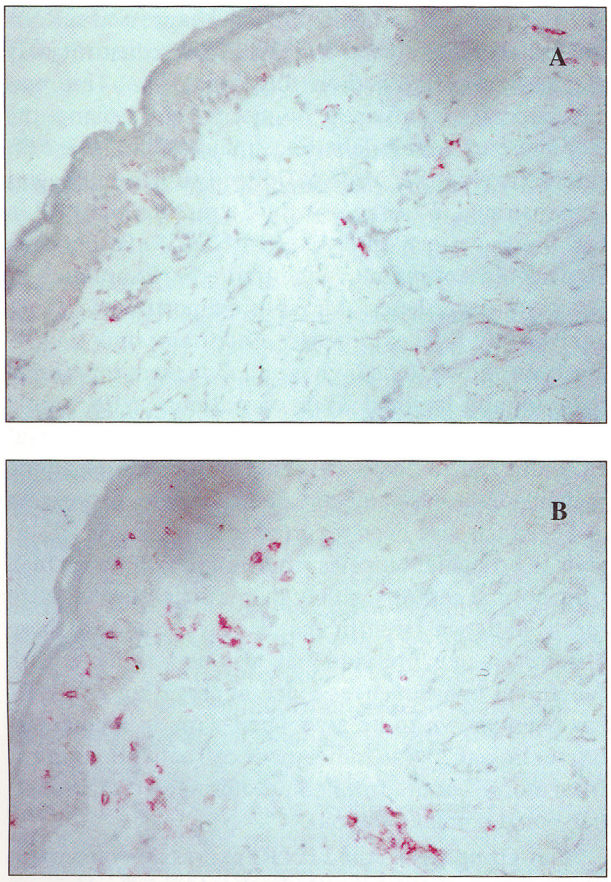

Fig. 2 - Células positivas (a vermelho; ICC) para a cadeia α do FcεRI 24 horas após injecção intradérmica de diluente controlo (A) ou alergeno (B)

Mast cells and basophils

It has been known for some time that both mast cells and basophils bind IgE through at least two types of receptors, with different affinities[31,33]. One of the receptors on murine mast cells was shown to bind IgE with high affinity, due to a slow dissociation of the bound IgE[31]. These results were subsequently confirmed with human basophils[42]. Aggregation of at least two receptor molecules is necessary for efficient signal transduction and cell activation of mast cells and basophils[25,26], although antibodies directed against epitopes on the FcεRI α-chain have the same effect, in the absence of IgE[43,45]. In both mast cells and basophils, activation through FcεRI ultimately results in the release of newly synthesized and pre-formed mediators. Striking morphological changes can be observed within minutes and culminate in degranulation[46]. In addition, mast cells and basophils have also been shown to synthesize and release different cytokines (e.g., GM--CSF, IL-3 TNFα) after prolonged cross-linking of FcεRI[3,4,47].

Using double immunocytochemistry (ICC), we characterized expression of the FcεRI α-chain on mast cells present in sections from the nasal and bronchial mucosa and the skin of atopic and non-atopic patients[39,41]. Although in the bronchial mucosa there was a trend for expression of FcεRI being greater on mast cells from atopic than from non-atopic subjects, this did not reach significance. In general, therefore, 85% and 97% of mast cells were FcεRI$^+$ in the bronchial and nasal mucosa, respectively. In the skin, 90% and 95% of mast cells were FcεRI$^+$ before and after allergen challenge, respectively. Conversely, mast cells accounted for most of FcεRI$^+$ cells in the nose, lung and skin (63%, 70% and 50%, respectively). These results show that, at least when surface expression of FcεRI is analysed with ICC, expression of this receptor on mast cells is heterogeneous. In the skin, the phenotype of almost 10% of FcεRI$^+$ cells observed after allergen challenge could not be identified. We believe that these were basophils.

FcεRI α-chain expression on basophils from atopic patients and non-atopic controls was also studied by our group using dual-colour flow cytometry[48]. Expression was significantly higher in atopic than in non-atopic subjects, and correlated with the levels of total serum IgE.

Monocytes/macrophages

IgE-dependent activation of monocytes may potentially have a crucial role in allergic tissue inflammation in view of the capacity to induce mediator release and to take part in antigen uptake and presentation. Human peripheral blood monocytes[49] and rat alveolar macrophages[50] were shown to release mediators such as LTC_4 after binding IgE. Although monocytes also express the low affinity IgE receptor (CD23)[51] and the IgE-binding protein εBP[33], which are preferentially involved in the binding of IgE-antigen complexes, FcεRI is apparently the most important IgE receptor for monomeric IgE. This is supported by experiments showing that blocking antibodies against the α-chain of FcεRI (15-1 mAb), but not blocking antibodies against CD23 were able to prevent almost completely the binding of allergen-specific monomeric IgE to surface receptors on peripheral blood monocytes from atopic subsjects[7]. From a functional point of view, subsequent cross-linking of FcεRI-bound monomeric IgE by specific allergen may induce activation and/or degranulation of monocytes and/or macrophages, as indirectly suggested by anti-FcεRI antibody-mediated sustained cytosolic Ca^{2+} increase in peripheral blood monocytes from atopic subjects[34]. Furthermore, a recent report has shown that triggering of FcεRI with monoclonal antibodies also induces release of prostaglandin E2[8].

Expression of FcεRI on the membrane of monocytes and macrophages may also be crucial for antigen uptake and presentation to T cells as demonstrated in monocyte--enriched peripheral blood mononuclear cells

(ME-PBMC)[7]. In these experiments, ME-PBMC were shown to present allergen to T cell clones in a highly efficient way if allergen were targeted to FcεRI. Importantly, this ability was almost completely abrogated when competitive anti-FcεRI (but not anti--CD23) mAb were added to *in vitro* cultures.

Our group has studied the expression of the FcεRI α-chain on monocytes in bronchial[39], cutaneous[40] and nasal[41] biopsies. Baseline (bronchial) and post allergen--challenge (nasal and skin) biopsies consistently showed the presence of high numbers of FcεRI α-chain$^+$ monocytes/macrophages in the cellular infiltrate, ranging between 25% of total macrophages in the nasal and bronchial mucosae and 45% in the skin. Conversely, FcεRI α-chain$^+$ monocytes/macrophages comprised about 20%, 35% and 40% of total FcεRI α-chain$^+$ cells in the cellular infiltrate in the nose, lung and skin, respectively. The results suggest the presence of two subsets of macrophages (FcεRI$^+$ and FcεRI$^-$) and may explain why a previous report could not find expression of FcεRI α-chain on factor XIIIa$^+$ macrophages in the skin of patients with atopic dermatitis[52].

Using dual-colour flow cytometry, expression of FcεRI α-chain was studied by our group on peripheral blood monocytes from atopic patients and non-atopic controls[48]. Although average FcεRI α-chain expression on monocytes was one hundred-fold less (as determined by specific mean fluorescence of binding of the FcεRI α-chain mAb) than in basophils, the receptor was detected in about 28% of total monocytes. In addition, the percentage of FcεRI$^+$ monocytes was greater in atopic than in non-atopic subjects. A previous report had only detected the receptor on monocytes from atopic individuals[34] but recent evidence of significant expression of FcεRI on monocytes from non-atopic individuals has been obtained under certain culture conditions[53]. Membrane expression of FcεRI may last longer on monocytes from atopic subjects than on those from non-atopic subjects because of the stabilizing effects of IgE upon binding to the receptor and this may explain differences in detectable expression of FcεRI on monocytes between the two groups of subjects[53]. Interestingly, our study showed a positive correlation between FcεRI expression on peripheral blood monocytes and total serum IgE[48].

CD1a$^+$ Langerhans' and dendritic cells

CD1a+ Langerhans cells (LC) are very potent antigen-presenting cells[54,55]. LC were initially shown by immunocytochemistry to express membrane IgE molecules in patients with atopic dermatitis[56], particularly in lesional, inflamed cutaneous areas[57]. Expression of membrane IgE was later also detected on LC from normal skin[58]. As in monocytes, IgE binding was first demonstrated to be mediated by CD23[59,60] and the IgE-binding protein εBP[61]. Subsequent experiments showed that purified epidermal LC expressed mRNA for the FcεRI α- and γ-chains and constitutively expressed FcεRI on their membrane[35,36]. This was subsequently confirmed on dermal LC, using the technique of double-labelling immunofluorescence[52]. Interestingly, the high affinity IgE receptor was demonstrated to be the principal structure involved in IgE binding since antibodies to CD23, εBP or even FcγR could not inhibit such binding[62]. Expression of FcεRI is nevertheless variable on purified LC[63], as analysed by flow cytometry[64], and, more importantly, has been shown to be higher on LC present in lesional than in non-lesional skin of patients with atopic dermatitis[35]. In addition, FcεRI expression on CD1a$^+$ LC and dendritic cells is higher in the skin of atopic than in non-atopic subjects[35]. Furthermore, expression of FcεRI has also been reported to be higher on CD1a$^+$ cells in bronchial biopsies from atopic asthmatics than from normal controls, although this difference failed to reach statistical significance[65]. Nevertheless, these differences in expression may also be associated with functional consequences since aggregation of FcεRI has been shown to be associated with an increase in intracellular Ca^{2+} (an indicator of cell activation) in LC from atopic but not from non-atopic subjects (Strobel, personnal communication).

Our group has studied FcεRI expression on dermal CD1a$^+$ LC or LC-like cells in the dermis[40]. Using a polyclonal antibody (997) to the FcεRI α-chain, we detected the high affinity receptor on dermal CD1a$^+$ LC in baseline biopsies from the skin of atopic patients. Although FcεRI$^+$ dermal LC comprised only about 3% of the total number of FcεRI$^+$ cells in the dermis, about 94% of dermal LC were FcεRI$^+$. Allergen challenge was not associated with significant increases in the percentage of FcεRI$^+$ LC. Most dermal FcεRI$^+$ LC were located in perivascular units, where T cells, amongst other cell types, can also be observed. This location would facilitate interactions between LC and T cells and possibly contribute to subsequent local presentation of antigens by LC to T cells. It is indeed knwon that dermal CD1a$^+$ LC or LC-like cells are potent antigen--presenting cells for T cells[54,55]. More importantly, allergens may be preferentially uptaken and presented to T cells by IgE-bearing LC, as demonstrated in LC isolated from patients with atopic dermatitis of which only the IgE-bearing LC were shown to present allergen to T cells[6].

Eosinophils

Eosinophils can bind IgE with low affinity through receptors such as FcεRII/CD23[66] and Mac2/ε-binding protein[67]. More recently, Soussi Gouni *et al*[37] showed that FcεRI was also expressed on peripheral blood eosinophils from patients with hypereosinophilic syndromes and on eosinophils present in the skin of

patients with atopic dermatitis and bullous pemphigoid. Using Northern blotting and RT-PCR techniques, these authors demonstrated that isolated eosinophils expressed mRNA for the α, β and γ chains of FcεRI. Furthermore, using flow cytometry and ICC with the competitive monoclonal antibody (mAb) 15-1 to the α-chain of FcεRI, these authors were able to detect eosinophils positive for the receptor in peripheral blood and the skin. Finally, using the mAb 15-1 in two sets of experiments, a dose-dependent inhibition of monomeric IgE binding was observed in cultured eosinophils, and eosinophil degranulation as indicated by the release of eosinophil peroxidase was detected when 15-1 was added to the cultures. Our group studied the expression of FcεRI on eosinophils in atopic and non-atopic patients[48]. Dual colour flow--cytometry showed that peripheral blood eosinophils from both atopic and non-atopic donors express FcεRI on the cell membrane although at very low levels, as compared to basophils or monocytes. Furthermore, there was a significantly greater expression (p=0.004) of FcεRI on eosinophils from atopic donors than on those from non-atopic donors.

We also used the technique of ICC to study the expression of FcεRI on eosinophils present in biopsies taken from the nasal mucosa of patients with allergic rhinits, from the bronchial mucosa of patients with allergic asthma and from the skin of atopic patients[39,41]. Expression of FcεRI was detected on eosinophils in the three types of biopsies. In general, there was a wide inter-patient variability of expression of the receptor on eosinophils, particularly in the nose and lung. Furthermore, although the percentage of FcεRI$^+$ cells that were eosinophils was relatively low both in the nose and in the lung (median, range = 6%, 0 - 35% and 4%, 0 - 14%, respectively), about 20% (10 - 45%) of FcεRI$^+$ cells were eosinophils after allergen challenge in the skin. Conversely, 15%, 5% and 26% eosinophils were FcεRI$^+$ in the nose, lung and skin, respectively. These results confirm other studies performed in atopic dermatitis[68] and show that eosinophils are capable of expressing at least the α-chain of FcεRI, although there is great variability of expression between different tissues. Amongst other reasons, the use of high doses of allergen injected intradermally, as opposed to the relatively lower doses used for allergen challenge in the nose and natural exposure in the lung, may account for the differences observed in FcεRI expression observed between tissues.

It is still debatable whether eosinophils can indeed express the complete FcεRI receptor on their membrane. Although messenger RNA for the β- and γ-chains was detected by some authors in eosinophils purified from the peripheral blood of patients with hyper-eosinophilia[37], others have only been able to detect mRNA for the α-, but not for the β- or γ-chains in peripheral blood eosinophils isolated from atopic subjects (Bjerke *et al*, personnal communication). Further, Bjerke *et al* could not detect expression of the α- or γ-chain protein on the membrane of eosinophils and the α-chain was only observed within eosinophil granules, using electron microscopy. Our own results, in contrast, show that eosinophils isolated from the peripheral blood of atopic patients (asthma, rhinitis or atopic dermatitis) express the α-chain on their membrane, albeit at low levels. Since the membrane expression of the α-chain depends on the presence of the γ-chain[17], this suggests that eosinophils may be able, under certain circumstances, to express the functional receptor, consisting of both chains, on their surface. Clearly, the possibility of expressing the full receptor on eosinophils may have different implications. We have found a positive correlation between the numbers of FcεRI$^+$ (α-chain) eosinophils and the size of the cutaneous late phase reaction 24 h after allergen injection ($r = 0.89$; $p = 0.02$; Spearman's test). If eosinophils can express the full receptor on their membrane, triggering of FcεRI may induce mediator release[37] and be involved in IgE-mediated antigen presentation, since eosinophils can also act as antigen--presenting cells[69]. In this case, our positive correlation would suggest that the magnitude of the late phase reaction may, at least in part, depend on mediators released by activated FcεRI$^+$ eosinophils. On the other hand, if eosinophils can only express the α-chain in their granules, and eventually release it as a soluble form of FcεRI, then FcεRI$^+$ eosinophils may to a certain extent be involved in the downregulation of the magnitude of the late phase reaction, since soluble FcεRI has been shown in an animal model to downregulate type I hypersensitivity reactions[10,70].

T cell lines

Messenger RNA for the FcεRI α- and γ-chains has been detected by Northern blot and RT-PCR analyses in murine T cell lines, cultured in the presence of IL-9[38]. Furthermore, these T cell lines could also bind IgE in a CD23-independent way, when incubated with IL-9. Indeed, although these T cell lines constitutively expressed CD23, which can bind IgE with low affinity, binding of IgE was only detected after incubation with IL-9, which induced expression of FcεRI without affecting expression of CD23. FcεRI , thus far, has not been detected on peripheral blood T cells from atopic patients[48], or on CD3$^+$ T cells present in the cutaneous LPR[40,52] or in the bronchial mucosa[39]. At the moment, although it may be possible that under certain circumstances, some T cells may express FcεRI, this awaits confirmation and the relevance of such expression still has to determined.

Atopy-related IgE and FcεRI expression

The observation of a relationship between the number of receptor-bound IgE on purified human basophils and the level of myeloma IgE added to the culture medium first suggested that IgE-binding receptors on these cells were not saturated although the possibility that a direct effect of IgE in terms of induction of receptor expression could not be excluded[71]. Such a relationship was later confirmed in basophils isolated from atopic and non-atopic subjects, in which receptor--bound IgE correlated with the total serum IgE concentration[72], and reproduced in basophils cultured with IgE-rich serum[73]. These experiments suggested that the number of receptors on basophils was modulated by the serum IgE concentration, although the possibility of genetic association or modulation by similar regulatory factors between serum IgE and the number of IgE receptors could not be excluded.

The first indication that expression of FcεRI itself correlated with serum IgE levels was given by a murine model of *Nippostrongylus brasiliensis* infection, in which changes in expression of FcεRI on mast cells showed a highly significant correlation with infection--induced changes in serum IgE[74]. Using flow cytometry, our group was the first to describe a strong correlation between total serum IgE levels and the number of FcεRI receptors on basophils and monocytes from atopic and non-atopic patients[48]. Furthermore, the level of receptor occupancy on these cell types also correlated with the level of total IgE. An association between total serum IgE and the numbers of FcεRI--bearing cells was also observed in bronchial biopsies from asthmatic patients[39].

Another line of research produced interesting observations which provided, at least theoretically, a possible explanation for the association observed between total serum IgE and expression of FcεRI. These observations consisted of the demonstration of the localization of the gene for the β-chain of the FcεRI on chromosome 11q13, in close linkage with a putative gene for atopy[20]. This would suggest that altered expression of the β-chain (and, eventually, FcεRI) might be associated with the high IgE status of atopy. Interestingly, a common variant of the β-chain (leucine substituted for isoleucine at position 181 in the fourth transmembrane domain) was then demonstrated amongst unrelated nuclear families with allergic asthmatic probands, and shown to be associated with high total serum IgE levels[21].

The relevance of the findings concerning the β-chain of FcεRI and the putative atopy gene need further clarification and assessment of their relevance. Indeed, several groups have failed to detect linkage between the putative atopy gene and a marker on chromosome 11q[75,79]. In addition, as mentioned before, expression of FceRI in humans does not require the β-chain. The possibility still remains, however, that expression of the β-chain may somehow modulate expression of the other FcεRI component chains. Altered expression of the β-chain might therefore be expected, at least in theory, to have consequences in expression of the complete receptor. At present, the relevance of the observations regarding the genetics of the FcεRI β-chain still has to be ascertained.

Interestingly, in our study involving bronchial biopsies from atopic asthmatic, atopic non-asthmatic, non-atopic asthmatic and non-atopic non-asthmatic subjects, we showed that atopy is characterized by elevated numbers of FcεRI-bearing cells irrespective of the patients' asthmatic status[39]. Furthermore, we also showed that non-atopic asthmatic also have increased numbers of FcεRI-bearing inflammatory cells in the bronchial mucosa, in the absence of known allergies, possibly suggesting a deregulation of local IgE synthesis. Overall, our study indicated that expression of FcεRI in the bronchial mucosa is necessary but not sufficient for asthma, although other factors are required for the development of asthma in predisposed individuals.

Therapeutic prospects

Therapeutic approaches involving FcεRI have involved both the membrane and the soluble form. In one study, the FcεRI α-gene was targeted and "knocked--out" in embryonic stem-cells, thereby generating FcεRI-deficient mice[9]. Although there were no changes in mast cell development, both passive cutaneous anaphylaxis (PCA) and systemic anaphylaxis were inhibited in the FcεRI-deficient mice, thus indicating that although FcεRI was not necessary for mast cell development, it was necessary for induction of IgE--mediated anaphylaxis. These findings were supported by a different study showing that intravenous injection of the soluble form of FcεRI into previously antigen--sensitised mice mostly suppressed IgE-dependent type I hypersensitivity on re-exposure to the antigen[10]. In another study, using Rhesus monkey and human lung parenchymal tissues that were passively sensitized with allergen, incubation with a soluble construct consisting of human FcεRI joined to a truncated IgG heavy chain (FcεRI-IgG) abolished subsequent allergen--induced parenchymal contraction and histamine release that was observed in lung tissue not incubated with FcεRI-IgG[70]. In a different report, *in vitro* addition of recombinant soluble FcεRI to cultures of purified human B cells inhibited IgE production through specific interaction with the membrane-bound form of IgE[30]. To what extent this phenomenon may be relevant to the effects observed *in vivo* is not known at present. In indirect support of a positive correlation between blockage of binding of specific serum IgE to membrane-

-bound FcεRI and an inhibition of type I hypersensitivity allergic-like phenomena, interesting results have been obtained *in vitro*, with IgE-producing cell lines derived from allergic patients before and after "rush" immunotherapy[80]. In this report, "rush" immunotherapy was associated with a significant decrease in the *in vitro* binding of specific IgE to FcεRI, in the presence of antigen. This direct effect of antigen on IgE binding to FcεRI may, at least in part, explain the rapidly beneficial effects frequently observed with this type of immunotherapy[81,82].

Interaction with the function of FcεRI may have beneficial therapeutic applications and may eventually be achieved by interfering with the surface expression of FcεRI, the binding function of the receptor, and/or blockage of receptor-mediated signal transduction. At present, the only known method of reducing surface expression of FcεRI is through targeting and "knocking--out" of the receptor α-chain gene. This will of course raise clinical issues in human subjects. Theoretically, downregulation of receptor expression on the cell surface might also be achieved through the administration of inhibitory mediators (possibly cytokines). As discussed previously, interference with the binding of IgE by FcεRI, through the use of recombinant competitive molecules, that may block of induce conformational changes on the receptor binding site, appears to be a promising possibility. At present, however, it is unclear whether modulation of FcεRI expression on cells other than mast cells and basophils is not detrimental in immunological terms. Finally, dissociation of receptor-ligand interactions on the α-chain from signal transduction pathways (dependent on β- and γ-chains) could also impair the ability of FcεRI-bearing cells to initiate immune responses. The specificity of such interaction would, however, need to be sought, since the mechanism of signal transduction associated with FcεRI is still relatively unknown.

In summary, the high affinity receptor for IgE has an important role in allergic inflammation and further knowledge of the mechanisms of its expression and function may allow a more effective therapeutic intervention in allergic diseases.

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