Inhibition of IgE-receptor interactions

Brian J Sutton, Rebecca L Beavil and Andrew J Beavil

The Randall Centre for Molecular Mechanisms of Cell Function, King’s College London, London, UK

Immunoglobulin E plays a central role in allergic disease and, as our understanding of the network of interactions between IgE and its receptors improves, new opportunities for therapeutic intervention emerge. IgE binding to its ‘high-affinity’ receptor, FceRI, first identified on mast cells and now known to be expressed on a variety of other cell types, is the best characterised interaction, and has attracted most attention. The ‘low affinity’ receptor, FcεRII/CD23, first found on B-cells, appears to be part of a more complex network that has yet to be fully elucidated. Two recent advances concerning the IgE-FceRI interaction are noteworthy. The first is the development of a monoclonal anti-IgE antibody, now in advanced clinical trials, which inhibits this interaction and certainly proves the viability of this approach. The second is the publication of the crystal structure of the complex between IgE and FcεRI, which opens the way for the first structure-based design of small molecule inhibitors.

The interactions between immunoglobulin E (IgE) and its cellular receptors have been studied over many years with the aim not only of understanding the molecular mechanisms underlying the allergic response, but also of identifying molecular targets for therapeutic intervention. The first receptor to be identified, termed FceRI by virtue of the fact that it binds to the Fc region of IgE, was found on mast cells and basophils. IgE binds to cells bearing this receptor with such a high affinity (Kₐ ~ 10⁻¹⁰ M⁻¹), that they are permanently coated with IgE, and thus sensitised for rapid activation when challenged with allergen. This activation, triggered by aggregation of as few as two receptor molecules by multivalent allergen, leads to release of molecules that promote an immediate inflammatory response. A second receptor was later discovered on B-cells, termed FcεRII and also identified as CD23 (the name that will be used in this review), to which IgE binds with lower affinity (Kₐ ~ 10⁻⁷ M⁻¹). This interaction is involved in both IgE regulation and allergen presentation by B-cells, but understanding the functional roles of CD23 is further complicated by the fact that it exists both as a cell surface molecule and in a soluble form generated by cleavage from the cell surface; furthermore, it exists in both monomeric and oligomeric states, as will be discussed in more detail below (see Sutton & Gould¹ for a review).
These two receptors, FcεRI and CD23 are very different in their molecular structure. FcεRI belongs to the immunoglobulin superfamily and is highly homologous in sequence and structure to the IgG Fc receptors, while CD23 is a member of the C-type lectin superfamily (which includes clearance proteins such as the asialoglycoprotein receptor). Despite the fact that CD23 is a lectin-like molecule and IgE is a glycoprotein, binding does not occur through the carbohydrate component of IgE, and the search for another ligand for CD23 led to the discovery of the interaction with another B-cell surface molecule, CD21 or CR2 (complement receptor 2)\(^2\). This extended the network of IgE interactions to the complement system. The more recent discovery of interactions between CD23 and the complement receptors CR3 (CD11b/CD18) and CR4 (CD11c/CD18), which are members of the integrin superfamily and also implicated in inflammatory mechanisms\(^3\), extends the IgE network yet further. The early characterisation of these interactions, and the appreciation of this extended network have been

![Fig. 1 Positive feedback between allergen uptake, mediated by both FcεRI and CD23 on antigen presenting cells (APC), and activation of effector cells such as mast cells and basophils, bearing FcεRI. Both activated effector cells and T-cells can provide necessary signals (IL-4 and CD40L) for induction of heavy-chain switching to IgE in B-cells. CD23 on B-cells (see Fig. 3) further contributes to the differentiation of committed B-cells into IgE-secreting B-cells.](image-url)
reviewed elsewhere\textsuperscript{1-4}. Here, we shall concentrate solely on the receptors FcεRI and CD23 and their interactions with IgE, since only these are understood in sufficient detail at present to allow consideration of intervention at the molecular level.

**Functional diversity of FcεRI and CD23**

FcεRI is now known to be expressed on a variety of cells in addition to mast cells and basophils. It has been found on Langerhans cells and dendritic cells where it is involved in antigen presentation, on eosinophils where it plays a role in defence against parasitic infection, and also monocytes (see Kinet\textsuperscript{5} for a review). CD23 is also expressed on a variety of cells that include antigen-presenting cells\textsuperscript{6}. Thus blocking of IgE-receptor interactions may have functional consequences at different stages of the allergic response, and inhibition of IgE-dependent uptake of allergen, for example, would clearly be desirable. Figure 1 schematically indicates the involvement of both receptors in allergen uptake and presentation to T-cells by antigen-presenting cells (APC), and the involvement of FcεRI in allergen-induced activation of mast cells. Both activated T-cells and effector cells can then provide the necessary signals (IL-4 and CD40-L) for switching B-cells to IgE synthesis, which in turn promotes sensitisation of both effector cells and APC in positive feedback, perpetuating the allergic state\textsuperscript{7}.

The binding of IgE to FcεRI, and to CD23 on the cell surface is depicted schematically in Figure 2. The IgE molecule has a bent structure (as discussed in the following section) and interacts with the second Ig-like extracellular domain of the FcεRI α-chain through its Ce3 domains, as revealed in a crystal structure of the complex\textsuperscript{8}. In contrast, the IgE-binding lectin domains of CD23 are connected to the membrane by a triple-stranded α-helical ‘stalk’ region, and the interaction, again with the Ce3 domains of IgE, involves two ‘heads’\textsuperscript{7}. However, the structure of the CD23 head has yet to be determined (although it has been modelled on the structures of other C-type lectins), and the details of its binding to Ce3 are not known. The interactions shown in Figure 2 represent those involved in the presentation of allergen-IgE complexes by these two receptors, and also in the case of FcεRI, the sensitisation of mast cells and basophils by IgE for allergen-induced activation. Membrane-bound CD23 (mCD23) also delivers a down-regulatory signal for IgE synthesis by B-cells when engaged by IgE-allergen complexes (see Gould et al\textsuperscript{7} for a review), and anti-CD23 antibodies have been investigated for their therapeutic potential\textsuperscript{9-11}. Their mechanism of action is still debated, but one of these anti-CD23 antibodies, now in clinical trials, is thought to function by co-ligating mCD23 with the IgG receptor FcγRII/CD32 on the same cell through its Fc region\textsuperscript{11}.
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CD23 also exists in a soluble form (sCD23), cleaved in the stalk region by an endogenous, membrane-bound metalloprotease\(^ \text{12} \). It is this sCD23 that acts as a B-cell growth factor up-regulating the production of IgE, though only when it is trimeric, not when monomeric\(^ \text{13} \). Since sCD23 binds to both IgE, including membrane-bound IgE (mIgE), and CD21\(^ \text{2} \), it has been proposed that trimeric sCD23 may promote IgE synthesis by cross-linking mIgE and CD21 on B-cells committed to IgE synthesis\(^ \text{1,7} \). This is shown schematically in Figure 3, which also identifies potential points for intervention. Soluble fragments of these molecules such as monomeric CD23 heads\(^ \text{13} \), sCD21 domains\(^ \text{14} \) or antibodies to these molecules\(^ \text{9-11} \), are potential inhibitors of such events at the B-cell surface, as are inhibitors of the endogenous metalloprotease(s) that cleave CD23 from the cell surface\(^ \text{15} \). Der \textit{p1}, the major house dust mite allergen and a cysteine protease, also cleaves mCD23 (and CD25, the IL-2 receptor), and in this way may promote IgE synthesis by simultaneously removing the down-regulatory signal (\textit{via} mCD23) and promoting the up-regulatory signal (\textit{via} sCD23)\(^ \text{16} \). Inhibitors of Der \textit{p1} are being developed as a means to combat house dust mite allergy.
Fig. 3 Schematic representation of the cross-linking of mIgE and mCD21 by trimeric sCD23 at the surface of a B cell committed to IgE synthesis. Inhibition of either interaction, (indicated by X) may suppress IgE production. In mIgE, the additional domains linking the Ce4 domains to the membrane are shown; in mCD21, glycosylation sites on the domains of CD21 are indicated.

While all of these lines of research are actively being pursued in the quest for a means to down-regulate IgE production via CD23, they are at a relatively early stage and will not be considered further here. We now turn to the IgE molecule itself and its interaction with FceRI, for it is here that the most promising developments have occurred recently.

The IgE molecule as a target

The Fc region of the IgE molecule, which contains binding sites for both FceRI and CD23, consists of a disulphide-linked dimer of two polypeptide chains each folded into the Ce2, Ce3 and Ce4 domains – a total of six domains. The Ce2 domains have no counterpart in IgG, which instead has a flexible ‘hinge’ region linking the antigen-binding Fab regions to the (four-domain) receptor-binding Fc region. This replacement of a flexible hinge with a pair of disulphide-linked folded domains leads to a very different structure for IgE, compared with the flexible Y-shaped IgG
molecule. Spectroscopic studies have shown that IgE adopts a compact, bent structure both in solution and when bound to FcεRI\textsuperscript{17}, as shown schematically in Figure 2A. Furthermore, X-ray scattering studies have shown that IgE Fc is bent, between the Ce2 and Ce3 domains\textsuperscript{18}. Thus although IgE Fc consists of two identical chains, it has an asymmetric structure, with a ‘concave’ face and a ‘convex’ face. This asymmetry, and the topology of its binding to FcεRI α-chain domains, clearly shows why a single IgE molecule cannot simultaneously bind to two receptors – a necessity since such an event could lead to receptor aggregation and mast cell activation in the absence of allergen. In fact we now know that receptor binding also causes a conformational change in the Fc that precludes binding to a second receptor molecule\textsuperscript{8}. With regard to the design and development of inhibitors of receptor binding, both the asymmetry and the conformational change turn out to be critical aspects of the IgE structure.

The first attempts to inhibit IgE binding to FcεRI involved synthesising short peptides from the IgE Fc region, and the earliest of these was a pentapeptide from the linker region between Ce2 and Ce3 identified by sequence comparison of IgE with IgG, IgA and IgM\textsuperscript{19}. Although doubt was subsequently cast upon the inhibitory properties of this peptide\textsuperscript{20}, larger peptides including this segment were found to be inhibitory\textsuperscript{21,22}, and mutagenesis studies confirmed the importance of this region of the Fc\textsuperscript{23}. The crystal structure of the complex\textsuperscript{8} finally confirmed the key role of this N-terminal region of the Ce3 domains. However, competition of such a high affinity interaction with short peptides is clearly always going to be difficult, and the alternative of blocking with antibodies to IgE has long been considered a promising strategy.

Therapeutically useful antibodies to IgE must have the property of blocking IgE binding to the receptor, but clearly must not bind to receptor-bound IgE since this could lead to cross-linking of IgE/receptor complexes and cell activation. The asymmetric structure of receptor-bound IgE (Fig. 2A), and the conformational change in the Fc upon receptor binding, explains why a subset of anti-IgE antibodies directed to the receptor binding site may indeed have this property. However, soluble IgE is not the only target. mlgE is expressed on the surface of B-cells committed to IgE synthesis, and targeting mlgE could lead to the elimination of these B-cells and the suppression of IgE levels. Indeed, early studies with an anti-IgE established that the molecule must be bivalent in order to be effective\textsuperscript{24}, implying that cross-linking of mlgE was occurring, and even earlier studies in mice with anti-IgE demonstrated long-term inhibition of IgE synthesis\textsuperscript{25,26}. Since mlgE has an additional region of polypeptide chain linking the Ce4 domains to the membrane that is not present in secreted IgE (see Fig. 3), this unique structural feature can be used to target antibodies specifically to mlgE\textsuperscript{27}. 
Two distinct strategies have been employed to generate anti-IgE antibodies. One is to use a vaccine approach, raising the antibodies in a natural response to a short peptide or larger fragments of IgE Fc (e.g. Cε2–Cε3), but this will not be discussed further here. The other approach is to engineer a humanised monoclonal anti-IgE molecule for therapeutic application and, while a number of groups have pursued this route (e.g. Corne et al.), by far the most advanced is the humanised monoclonal IgG antibody rhuMab-E25 from Genentech Inc. This antibody has specificity for the receptor-binding region of IgE Fc, but cannot bind to receptor-bound IgE and thus cannot trigger mast cell or basophil degranulation. Its half-life in serum is approximately 14 days, much longer than that of free IgE, which is approximately 2 days, and its affinity for IgE is extremely high, 1.5 x 10^10 M^-1. However, even this affinity is only just high enough to enable it to compete and block soluble IgE binding to FceRI. Since the rate of dissociation of IgE from cell surface FceRI is extremely slow (k_d ~ 10^-5 s^-1; i.e. 20 h for half of the IgE molecules to dissociate from the surface), and perhaps only 1% of receptors on a mast cell need to be occupied by IgE for allergen-induced triggering to occur, this mechanism alone is unlikely to account for the dramatic efficacy reported for this antibody. In human trials, with a single dose administered every one or two weeks (monthly in later trials), circulating IgE levels fell to less than 1% of their original value, strongly indicative of a direct effect upon the IgE-secreting B-cells. The precise molecular mechanism for this phenomenon has not been elucidated, but direct binding to B-cells has been demonstrated. It may involve cross-linking of mlgE on the B cell, but inhibition of other B cell surface interactions required for proliferation, such as those depicted in Figure 3, or disruption of interactions between mlgE and the Ig-α and Ig-β chains of the B cell receptor that are required for signalling, could certainly also be effected by rhuMab-E25. As discussed in the following section, however, suppression of IgE synthesis by a soluble receptor fragment, sFceRIα, has been shown to be due to a direct interaction with mlgE, as this molecule is monovalent, cross-linking of mlgE is clearly not the only possibility.

A further beneficial effect of lowering the concentration of free IgE is that the cell-surface expression of FceRI is down-regulated. This has been observed on a range of FceRI-expressing cells, and shown directly for basophils following rhuMab-E25 administration. The fact that this is a direct result of interaction between IgE and the receptor has also been demonstrated. The reduction in circulating IgE, and consequent lowering of FceRI expression, constitute a most effective negative feedback effect.

Figure 4 summarises the activities of rhuMab-E25 discussed so far, and also illustrates a further site of action at the level of antigen.
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Fig. 4 Potential effects of an anti-IgE therapeutic agent. From the left: sequestering free IgE; interaction with mIgE (shown with Ig-α and β chains) on B-cells, either cross-linking mIgE or disrupting interactions required for signalling to suppress IgE synthesis; inhibition of IgE binding to FceRI on mast cells, basophils or antigen presenting cells; inhibition of IgE binding to CD23 on antigen presenting cells. (After Fig. 1 in Chang33.)

presentation. Both FceRI38,39 and CD236 have been implicated in this process, and since the binding sites for both receptors are known to overlap in the Cε3 domain, simultaneous inhibition of both interactions is feasible. Not only may IgE-dependent allergen presentation be inhibited in this way, but it has also been proposed that the IgE-anti-IgE complexes may serve a beneficial role. Their relatively long half-life of approximately 14 days may enable them to mop up free allergen and clear it from the system via IgG-dependent mechanisms33. It has even been suggested that this short-term shift towards a non-IgE-dependent response may lead to longer-term alteration in the response of patients undergoing anti-IgE therapy33.

The future for this therapeutic antibody, which has already completed Phase III clinical trials for allergic rhinitis and asthma, is therefore very promising. Administration is i.v., must be repeated regularly and may be costly, but it will certainly have application to the more severe allergic conditions. However, if prolonged treatment causes a permanent shift in the patient's response to allergen, away from IgE-mediated mechanisms, then this is a very exciting prospect indeed.

Receptor-based inhibitors

The crystal structure of the extracellular domains of FcεRIα (see Fig. 5A) was solved in 199840, but earlier molecular modelling of the two Ig-like
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Fig. 5 Schematic representations of the structures of: (A) the FcεRI α-chain domains; (B) the complex between IgE Fc Ce3–Ce4 domains and FceRIα; (C) the uncomplexed IgE Fc Ce3–Ce4. The locations of two inhibitory peptides, and the binding site of detergent molecules found in the crystal structure of the complex, are shown. N denotes the N-termini of the two Ce3 domains.

domains had provided a basis for the design of peptide inhibitors that incorporated amino-acids identified by mutagenesis to be critical for IgE binding. A peptide of 11 residues, constrained by a disulphide bridge between additional terminal cysteine residues to mimic the native conformation of the CC′ β-strands and intervening loop, inhibited IgE binding and mast cell degranulation in vitro. Subsequent analysis of the peptide by nuclear magnetic resonance spectroscopy showed that the β-structure had indeed formed, and the crystal structure of the IgE/FcεRIα complex now reveals that this region of the α(2) domain is
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critically involved. Another (linear) peptide from the adjacent BC loop region was found to inhibit IgE binding to FceRI\textsuperscript{82}, and it too can now be seen to include residues at the interface\textsuperscript{8}. However, even peptides constrained in structure to mimic a part of the IgE-Fc/FceRI\textalpha interface may not compete effectively with such a high affinity interaction, and more success has been obtained using larger fragments. The whole sFceRI\textalpha fragment has been investigated in several \textit{in vitro} and \textit{in vivo} animal model studies (see Sutton & Gould\textsuperscript{26} for a review), which showed that it could prevent IgE binding to mast cell receptors if administered before allergen challenge. Furthermore, a suppressive effect on IgE synthesis, as a result of binding of sFceRI\textalpha to mIgE, was demonstrated \textit{in vitro} with human B-cells\textsuperscript{36}. As mentioned above in relation to rhuMab-E25, the mechanism of this effect is not clear. sFceRI\textalpha is obviously monomeric, yet earlier studies with an anti-IgE concluded that a bivalent molecule was required for suppression, presumably to cross-link mIgE\textsuperscript{24}. A bivalent form of the soluble receptor, a fusion protein with IgG Fc in which two sFceRI\textalpha fragments replace the Fab arms of IgG, has been generated and shown to be effective in inhibition of mast cell degranulation \textit{in vitro} and the passive cutaneous anaphylaxis reaction in a rodent model\textsuperscript{43}. However, there have been no reports of the effect of this molecule upon IgE synthesis, or its mechanism of action, but it might be predicted to be more effective than sFceRI\textalpha.

FceRI\textalpha has been the subject of extensive mutagenesis studies to identify key residues in IgE binding, and it has proved possible to modestly enhance the affinity\textsuperscript{34,44-45}. Knowledge of the crystal structure of the complex\textsuperscript{8} now provides a basis for designing more effective mutations. Thus soluble receptor fragments in either monovalent or bivalent form might yet prove to be valuable therapeutic agents, with the ability not only to inhibit mast cell sensitisation, but also suppress IgE synthesis.

Ironically, a soluble form of the low affinity receptor, sCD23, has also been proposed as means to inhibit IgE binding to the high affinity receptor FceRI. A modified version of sCD23 with an isoleucine zipper motif (which promotes \alpha-helical trimer formation) fused to the stalk\textsuperscript{46}, displays greater stability as a trimer and higher affinity for IgE than natural sCD23 or mCD23, presumably through an avidity effect. The construct is 10,000-fold better at inhibiting IgE binding to mast cells than sCD23, and can, therefore, in principle compete with FceRI.

**The IgE-FceRI complex as a basis for inhibitor design**

A landmark in the study of IgE was the determination of the crystal structure of the complex between IgE Fc\textsubscript{3-4} (the Fc region consisting of the C\textepsilon\textsubscript{3} and C\textepsilon\textsubscript{4} domains), and the extracellular region of FceRI\textalpha\textsuperscript{8}.
This structure is represented in Figure 5B, which shows how the α(2) domain and linker region to α(1) of the receptor make contact with the N-terminal regions of both Ce3 domains of IgE. While the structure confirms many of the conclusions drawn from mutagenesis studies about the location and nature of the interface, it is also instructive to rationalise how mutations outside the binding interface, such as at the Ce3/Ce4 interface in IgE, exert an effect on binding. These allosteric effects provide clues to effective ways of inhibiting the interaction, as will be discussed below. It is fascinating to note the crucial involvement of the N-terminal linker region of Ce3 that includes precisely those residues proposed 25 years earlier by sequence comparisons, and that the CC' and BC loop peptides predicted to be important on the receptor, are indeed central to the interface.

The binding interface is extensive, and dominated by hydrophobic residues on the receptor, but intriguingly in the crystal structure, immediately adjacent to the interface, molecules of detergent from the crystallisation medium are seen to bind. One of these molecules interacts with amino-acid residues from one of the Ce3 domains, and seems to mimic the interaction occurring between the receptor and the same amino-acids on the other Ce3 domain. The authors suggest that the structure of this molecule could be extended in such a way as to disrupt the interaction; in effect it provides a lead compound for the design of a small molecule inhibitor.

Another lead towards designing an inhibitor comes from the discovery that the binding of receptor to the Ce3 domains involves a substantial conformational change in the IgE Fc. The structure of the free Fce3-4 fragment was also determined (see Fig. 5C) and, when compared with the structure of the Fce3-4 in the complex, a change in the angle of the Ce3 domains relative to the Ce4 domains was seen. In Figure 5, comparison of B and C clearly shows how both Ce3 domains ‘open up’ to accommodate the receptor. This change involves relative movement of amino-acids at the Ce3/Ce4 interface region (indicated in Fig. 5B,C), and thus explains why amino-acid substitutions in this region have been found to affect receptor binding. If this conformational change can be prevented, perhaps by designing a molecule to bind to the Ce3/Ce4 interface, receptor binding could be blocked by this ‘allosteric’ mechanism. The targeting of molecules to the homologous interdomain region of IgG has already been the subject of a detailed analysis. Comparison of the structure of the free receptor molecule with that of the complex, reveals that there is also conformational change in the C'-β-strand of the receptor upon binding. Clearly, there is induced fit of both partners upon interaction, a surprise for such a high affinity interaction (since conformational change incurs an energy cost), but an aspect that can perhaps be exploited in inhibitor design. Over the years,
a number of small molecules have been reported to inhibit IgE binding to FcεRI, including oligonucleotides and tetracyclic aromatic compounds; it would be instructive now to investigate whether they bind directly to the interface or act allosterically.

Finally, it must be remembered that two IgE Fc domains are missing from the crystal structure of the complex. The expected location of the Ce2 domains may be inferred from the positions of the N-terminal residues of Ce3 (indicated in Fig. 5B), and clearly there may even be direct interaction between Ce2 and FcεR1α. Although it has been shown that the presence or absence of the Ce2 domains does not appreciably affect the overall affinity of the interaction, the kinetics are substantially affected, such that both on-rate and off-rate are slower when they are present. In fact, the Ce2 domains have the effect of slowing the dissociation rate 20-fold (compared with Fcε3-4), thus contributing significantly to the long half-life of bound IgE and its ability to sensitise mast cells and basophils. It may, therefore, be possible, by targeting Ce2, to promote dissociation of IgE from the receptor. Since the bound detergent molecules in the crystal structure of the complex may occupy some of the space required by the Ce2 domains, they may provide a lead here too. Targeting what may be a relatively weak interaction to affect the dissociation kinetics, rather than attempting to block a high affinity interaction, may be a more tractable proposition.

**Conclusion**

The extensive network of interactions between IgE, its receptors and their counter-receptors offers numerous opportunities for molecular intervention. Few of these are sufficiently well understood at present, but the most studied and best characterised interaction of all is that between IgE and FcεRI, and we may shortly see a truly novel therapeutic agent for allergy that inhibits this interaction, the anti-IgE antibody, in clinical use. As a large protein molecule, it may suffer from limitations in the mode of administration and high cost, but it proves the feasibility of the approach and looks very promising indeed. The precise molecular details of the IgE/FcεRI interaction have also been revealed by X-ray crystallography, providing for the first time a firm structural basis for rational design of small molecule inhibitors. The emerging picture of a flexible IgE molecule undergoing conformational change upon receptor binding, suggests ways of allosterically inhibiting the interaction that had not been anticipated. The exploitation of these new structural data is for the future, but in principle small molecules can be produced more cheaply, may be delivered in a variety of ways, and may thus find application to a wider range of allergic conditions. Understanding of CD23 and its interactions lags behind that of FcεRI, and precise
structural data are still lacking, but it clearly plays a role in the regulation of IgE levels, and its interactions with IgE and CD21 may in due course provide new targets for therapeutic intervention.

Acknowledgements

The authors wish to acknowledge the support of the MRC, BBSRC, Wellcome Trust and National Asthma Campaign (UK) for their work in this field.

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