

The human IgE network

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IgE and its receptors are believed to have evolved as a mechanism to protect mammals against parasites. But other and intrinsically innocuous antigens can subvert this system to provoke an allergic response. For human populations in industrialized countries, allergy and asthma now represent a far greater threat than parasitic infection, and the main impetus for current studies of the IgE system is the hope of understanding and intervening in the aetiology of allergic diseases.

IMMUNOGLOBULIN E (IgE) occurs only in mammals and is one of five classes of antibody recognized in man. Its role in defence against parasites was first established by work on the cell-mediated killing of schistosomes *in vitro*^{1,2}, as well as by epidemiological studies in areas of endemic schistosomiasis and other parasitic diseases^{3,4}. IgE-secreting B cells are abundant in the skin, lungs and gut, the main sites of parasitic invasion. IgE elicits a range of cellular responses to antigens, culminating in anatomical and physiological changes which exclude parasites from the body. These include inflammation, itching, coughing, lacrimation, bronchoconstriction, mucus secretion, vomiting and diarrhoea, all common symptoms in allergic disorders.

Allergy is generally caused by the overproduction of IgE in response to common environmental antigens, such as those present in pollen, foods, house dust mites, animal danders, fungal spores and insect venoms. Predisposition to allergy, however, appears to result from an interaction between genetic and environmental factors. The most common allergic diseases are asthma, allergic rhinitis (hay fever), atopic dermatitis and food allergies, but the most dangerous is anaphylactic shock, usually provoked by insect stings or parenteral medication. Allergy in one form or another afflicts more than 20 per cent of the population, and the alarming increase in its prevalence, morbidity and mortality over the past decade has led to its designation as the "number one environmental disease"^{5,6}.

Existing drugs offer partial relief of symptoms in some of these conditions, but there is a clear need for more effective treatments. Recent advances in our understanding of the structure, function and synthesis of IgE and its receptors now promise new approaches to the design of therapies for allergy.

Changing perspectives in the IgE system

IgE constitutes a minuscule fraction of the total antibody in human serum (50–300 ng ml⁻¹, as compared with 10 mg ml⁻¹ of IgG) and is therefore of little help in neutralizing antigens. However, its action is powerfully amplified by the activities of the receptors to which it binds. The 'high-affinity' receptor on skin mast cells and blood basophils, FcεRI (receptor for the Fc region of the ε-chain of IgE), is responsible for immediate hypersensitivity reactions; when a multivalent allergen associates with FcεRI-bound IgE, it crosslinks receptor molecules on the cell membrane. This triggers degranulation of the cell, rapid release of stored mediators, notably histamine, and the synthesis and secretion of cytokines that attract and activate inflammatory cells⁷. Although FcεRI has recently been discovered on Langerhans cells^{8,9}, eosinophils^{10,12} and activated monocytes (G. Stingl, personal communication), its biological functions in these cell types have not been identified, except that in eosinophils it can mediate IgE-dependent killing of schistosomes *in vitro*^{10,12}.

Activation of inflammatory cells by the products of mast-cell degranulation induces a 'low-affinity' IgE receptor, FcεRII, also known as CD23. This receptor was previously thought to be responsible for the IgE-dependent cytotoxic activities of inflammatory cells, and it does indeed mediate the phagocytosis of immune complexes by monocytes *in vitro*^{10,11}. The recent observation that FcεRI as well as FcεRII is expressed on eosinophils^{12,102}, monocytes and Langerhans cells^{8,9,13}, however, raises the question of which receptor mediates which effector function of IgE.

The role of FcεRII in the humoral immune response has only recently come to light (see refs 14–16 for reviews). On the surface of B cells, it plays a part in IgE-dependent antigen presentation to T cells and in adhesion of B cells to each other. It is also expressed copiously on follicular dendritic cells (FDC) and may thus be involved in the homing of B cells to the germinal centres of secondary follicles in the lymph nodes and spleen. Soluble fragments of FcεRII (sFcεRII) stimulate the growth and differentiation of the precursors of plasma cells, T cells and basophils, thereby initiating both humoral and cell-mediated immune responses. Although FcεRII is C-type lectin, it does not bind to the carbohydrate component of IgE; the inference that this part of the molecule must recognize something else has recently

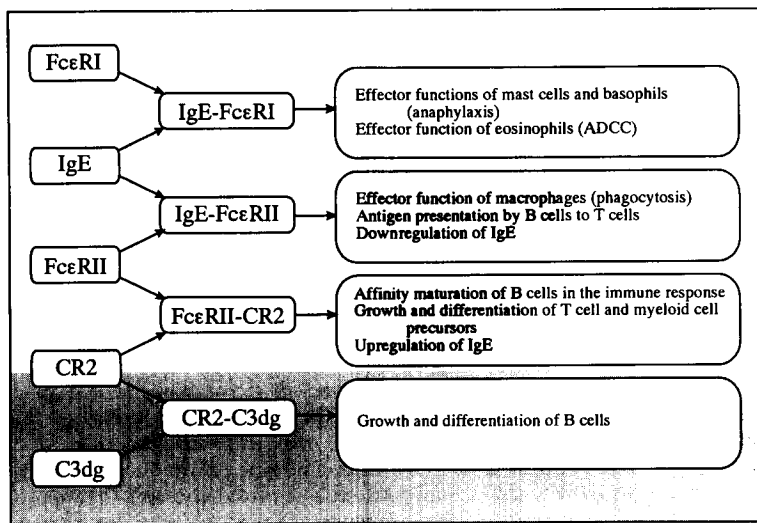


FIG. 1 Principal components of the IgE network. IgE, FcεRII and CR2 each have two or more natural ligands, and the physiological functions of the different complexes, and the cells in which these occur, are listed. The shaded area represents the overlap of the IgE antibody and complement systems; C3dg is one of the active fragments of the complement component C3.

been borne out with the discovery that it binds to CR2 (complement receptor 2)¹⁷. This protein, also called CD21, was already known to be a receptor for fragments of complement component C3 and the Epstein-Barr virus (EBV). It appears to mediate two important cytokine activities ascribed to FcεRII, the upregulation of IgE synthesis¹⁷ and the rescue of germinal centre B cells from apoptosis¹⁸. IgE itself also closes a negative feedback loop by switching off its own synthesis, through interaction with FcεRII.

These observations can now be interpreted in terms of a system of interacting proteins which we call the IgE network; Fig. 1 presents the principal components of this network and summarizes the physiological functions triggered by their interactions.

The IgE molecule

Prausnitz and Küstner¹⁰³ first demonstrated the presence of a factor in the blood of allergic subjects which, when transferred to the skin of non-allergic individuals, rendered them sensitive to allergens. This substance was identified as a cytophilic antibody by the Ishizakas¹⁰⁴, but its concentration was below the threshold of detection by protein assay. It could, however, be separated from the known immunoglobulins, IgM, IgG and IgA, and was named IgE from the erythema that the allergens provoke in sensitive skin¹⁹. The first tangible evidence that IgE existed came from a rare myeloma, and the protein from this cell line afforded a standard for the measurement of IgE concentrations in blood, as well as material for the first structural studies. The cells were also the source of messenger RNA for cloning the ε-chain cDNA, the starting point for some of the later structural studies of IgE (reviewed in ref. 20).

The protein sequence revealed that IgE shares the overall structure of other classes of antibody, but is distinguished from them by the sequence of its (ε) heavy-chain constant region. Like the μ-chain of IgM, this consists of four constant domains (Cε1–Cε4), one more than in IgG, IgA or IgD. The additional domain (Cε2) replaces the hinge region of the other antibody classes (Fig. 2). The two C-terminal domains of IgE (Cε3 and Cε4) are highly homologous to those of IgG, and can be modelled on the basis of the crystal structure of human IgG Fc (Fig. 2; refs 21, 22).

Limited proteolysis of IgE yields an Fc fragment (Cε2–Cε4) that can still bind FcεRI and FcεRII but isolated Cε2 and Cε4 domains cannot. Synthesis of recombinant peptides in *Escherichia coli* or mammalian cells, and the exchange of domains between rodent and human IgE have provided direct evidence that the FcεRI binding site is located in Cε3, and it is now clear that the first twelve amino acids of Cε3 are necessary for binding (see refs 20, 23 for reviews), although other residues in Cε3 or Cε4 can perturb the interaction^{24,25}. The solvent-accessible part of this dodecapeptide sequence occupies a position near the central axis of the Cε3 domain pair in the predicted structure of IgE (Fig. 2). Although monomeric recombinant peptides are recognized by FcεRI, only one of the two sites appears to be accessible in the native IgE molecule.

The binding site for FcεRII has been mapped to Cε3 by similar means^{24,26}, but deletion of the first twelve amino acids of the domain does not eliminate binding, and it must therefore be distinct from the FcεRI site. More precise mapping is needed, but antibody blocking and peptide inhibition experiments²⁶ already indicate that the site is near the glycosylated residue Asn 371 (Fig. 2). If so, the two FcεRII binding sites in IgE are as far as possible from each other and from the central axis of the molecule. The receptor binds only to disulphide-linked ε-chain fragment dimers, and is probably itself at least a dimer able to bind both sites on IgE at once (compare Fig. 6a). Both FcεRI and FcεRII bind to IgE peptides synthesized in *E. coli*^{20,26}, indicating that the carbohydrate components of IgE (Fig. 2) are not required for either interaction. (A soluble S-type lectin that can bind to the carbohydrate components, known as Mac-2 or εBP, has recently been found on human neutrophils²⁷; it may thus

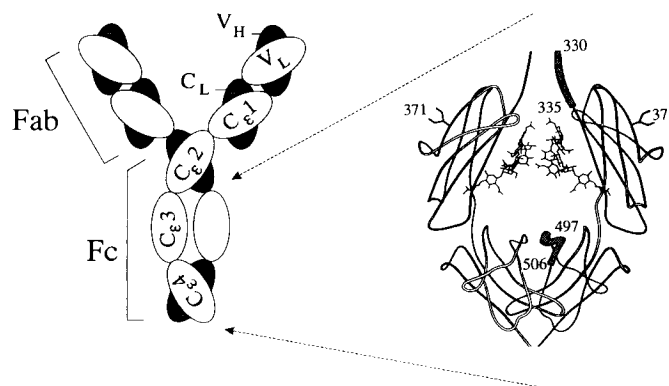


FIG. 2 The structure of human IgE. The IgE molecule consists of two identical light (L) chains (κ or λ) and two identical ϵ heavy (H) chains, folded into domains as shown on the left. Also indicated are the two antigen-binding fragments (Fab), and the constant (C) region fragment (Fc) in which the receptor binding sites are located. In each Fab, a disulphide bridge links CL to Cε1, and in Fc, two bridges link the Cε2 domains of the ε-chains. On the right, the predicted fold of the polypeptide chain within the Cε3 and Cε4 domains is shown, together with the complex-type oligosaccharide chains that are N-linked to Asn 394 and lie between the Cε3 domains. This glycosylation site is conserved in other immunoglobulin classes; a second ε-specific glycosylation site at Asn 371 is also indicated schematically. The structure of these domains has been modelled^{21,22} on the homologous crystal structure of IgG Fc. A segment of the ε-chain sequence (residues 330–335) that has been implicated in FcεRI binding is highlighted. This region, at the N-terminal end of the Cε3 domain (and shown for only one ε-chain), is expected to be accessible, although its conformation is uncertain and may not be as extended as shown here. The region indicated in Cε4 (residues 497–506) corresponds to the peptide that has been proposed as a vaccine for the treatment of allergy (see text, and ref. 87).

play a part in parasitic infections and/or allergy¹⁰⁵, but will not be discussed further here as little is known about its structure at present.)

One striking feature of IgE that has only recently become apparent is that, in contrast to IgG, it is bent. Resonance energy transfer between fluorophores attached to different parts of the chain reveals that the distance between the N- and C-termini of the IgE molecule in solution is no more than 7 nm, compared with the 17.5 nm implied by a planar structure²⁸. The shape of IgE does not appear to change when it binds to FcεRI, and distances between the two fluorophores and others dispersed in the membrane indicate that the Fc region of a receptor-bound IgE molecule lies parallel to the membrane surface²⁸. The discovery that IgE is bent (as shown in Figs 4 and 6a) profoundly alters our view of its interactions with FcεRI and FcεRII, providing a new framework for the interpretation of existing experimental data.

The high-affinity receptor FcεRI

The rat basophilic leukaemia (RBL) cell line was the first source of FcεRI, and of information about its interaction with rodent IgE and the way in which it activated cells. No comparable human cell line exists even today, although the genes for the human receptor have been expressed in non-basophilic human cell lines and in the RBL cell line^{29–31} to allow studies of the interaction with human IgE (see refs 32, 33 for reviews).

FcεRI consists of four transmembrane polypeptides with the composition $\alpha\beta\gamma_2$, and although it is the α-chain that binds IgE, the β- and γ-chains are required for insertion of the α-chain into the membrane and for signal transduction. The extracellular portion of the α-chain contains two domains characteristic of the immunoglobulin superfamily (Fig. 3); it thus resembles the FcγR, FcαR, and poly-Ig receptors, which contain two or more extracellular immunoglobulin-like domains³². The extracellular

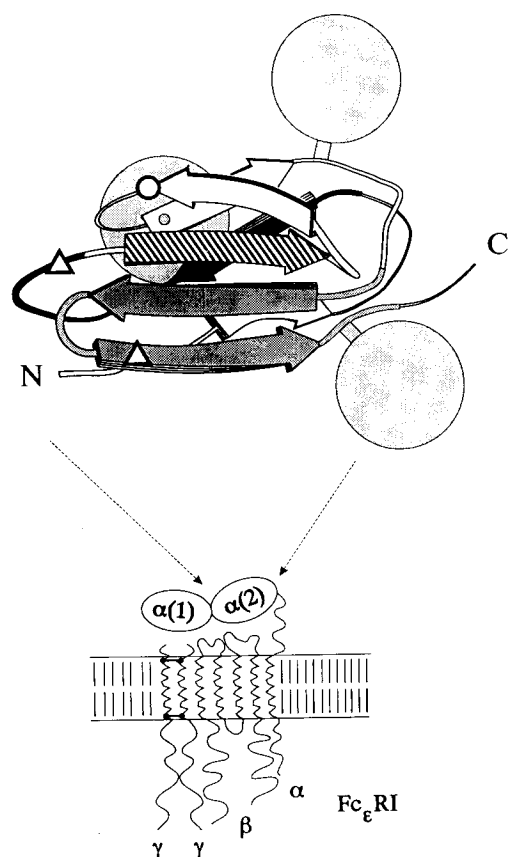


FIG. 3 Predicted structure of Fc ϵ RI α -chain. Top, predicted fold of the polypeptide chain within the second of the two immunoglobulin-like extracellular domains, $\alpha(2)$, modelled on homologous regions of known immunoglobulin superfamily domain structures, in particular CD2 (ref. 100). Strands of β -sheet are represented by arrows; the single intradomain disulphide bridge is not shown. Bottom, schematic representation of the IgE binding α -chain, β - and two disulphide-linked γ -chains of Fc ϵ RI. In the model of the $\alpha(2)$ domain, three segments are highlighted: black, peptide bound by an antibody that inhibits IgE-Fc ϵ RI interaction³⁸; cross-hatched, sequence of 7 residues conserved between the rat and human sequences and proposed as part of the IgE binding site¹⁰¹; stippled, segment corresponding to the homologous sequence of Fc γ RII that confers IgG binding when transplanted into Fc ϵ RI (refs 36, 37). Allelic variants of Fc γ RII have also been identified that affect IgG binding, and the homologous locations of these residues are indicated on the model: circle, residue 131; triangles, residues 116 and 161 (reviewed in ref. 36). The three glycosylation sites in $\alpha(2)$ are represented by the large shaded circles, which nevertheless underestimate the volumes occupied by complex-type N-linked oligosaccharide chains. The locations of all of these features are consistent with homologous Ig-binding regions in Fc ϵ RI and Fc γ RII that comprise residues of the four-stranded face of the domain, and adjacent loops.

region of Fc ϵ RI α -chain most closely resembles that of Fc γ RII (CD32) and Fc γ RIII (CD16), and indeed the latter has been shown to form a complex with the β - and γ -chains of Fc ϵ RI (refs 32, 34). Fc ϵ RI(α) is heavily N-glycosylated, but the carbohydrate component is not required for IgE binding¹⁰⁶.

The immunoglobulin-like domains of the receptor α -chain, although very similar to antibody V and C domains, form a recognizable subgroup within the immunoglobulin superfamily, which has been termed C2 (ref. 35). The atomic structure of these domains is still unknown, but their homology with known immunoglobulin-like domains allows them to be modelled with some assurance (Fig. 3). Studies of human Fc ϵ RI(α)-Fc γ RII (refs 36, 37) and interspecies Fc ϵ RI(α) chimaeras^{106,107} place the IgE binding region in the second domain ($\alpha(2)$ in Fig. 3), in accord with earlier conclusions based on the location of an epi-

tope recognized by an inhibitory antibody³⁸. A more precise definition of the site will require site-specific mutants, but mapping studies of the homologous interaction between Fc γ RII and IgG (Fig. 3) point to an exposed region of the four stranded face of the $\alpha(2)$ domain, and binding to this site would not be affected by the three putative glycosylation sites in the $\alpha(2)$ domain.

The interaction between IgE and Fc ϵ RI(α) may thus be envisaged as shown in Fig. 4. The IgE molecule binds with its convex surface facing the membrane²⁸. The receptor binding site, located in the N-terminal segment of C ϵ 3 that adjoins C ϵ 2 (Fig. 2), is thus accessible only on the same convex face; the second site will be occluded on the concave surface. This is consistent both with the presence of a single α -chain in the receptor, and its affinity for single ϵ -chains. It also explains why only one Fc ϵ RI α -chain can bind to IgE^{39,106}. The configuration of Fc ϵ RI(α) in the complex may depend on its interaction with IgE, as the kinetics of association have been taken to imply a conformational change upon IgE binding⁴⁰.

The low-affinity receptor Fc ϵ RII

Fc ϵ RII was independently characterized as a B-cell receptor for IgE, a marker for activated B cells (named CD23), and a marker for EBV-transformed B cells (named EBV-CS2). It was later found on various inflammatory cells (macrophages, eosinophils, platelets, natural killer (NK) cells), T cells, FDCs, Langerhans cells and epithelial cells of bone marrow and thymus^{14,15}, and is the only known antibody receptor that is not a member of the immunoglobulin superfamily. The C-type (calcium-dependent) lectin domain in its extracellular sequence places it in a family of proteins that includes the asialoglycoprotein receptor (ASGPR) and the adhesion proteins known as 'selectins'⁴¹. In common with the former, Fc ϵ RII has a cytoplasmic N-terminus and thus is classified as a type-II integral membrane protein.

This lectin domain is flanked on the C-terminal side by a sequence of unknown tertiary structure containing an inverse RGD (Arg-Gly-Asp) sequence which may act in cell adhesion¹². Although two ligands for Fc ϵ RII are already known, IgE and CR2, the presence of this adhesion motif implies that there may be a third, perhaps an integrin. On the N-terminal side the lectin domain is flanked by a sequence containing heptad hydrophobic repeats, which is predicted to form an α -helical coiled-coil 'stalk'⁴² and mediates trimer formation⁴³; this is followed by the

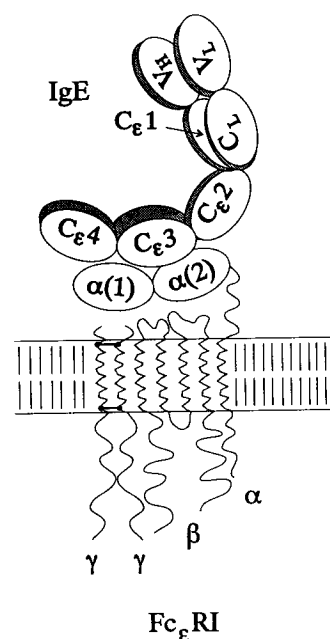
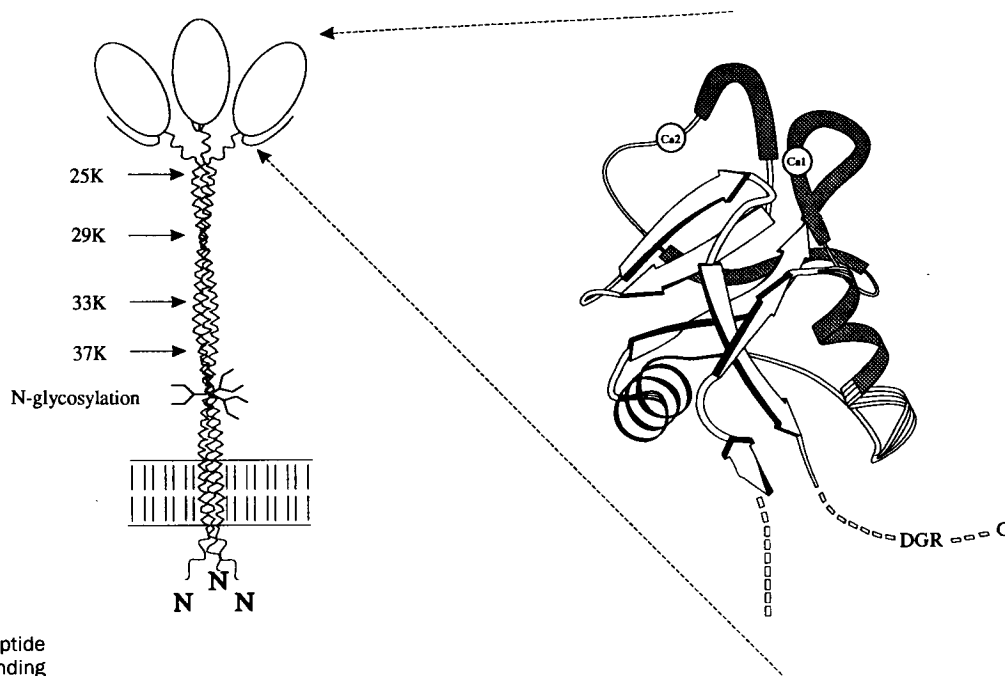


FIG. 4 Schematic representation of an IgE molecule bound to Fc ϵ RI. The IgE molecule adopts a bent conformation consistent with spectroscopic data²⁸, and the N-terminal region of the C ϵ 3 domain of IgE (compare Fig. 2) contacts the second domain of Fc ϵ RI α -chain (compare Fig. 3). The orientation of IgE relative to the membrane is also in accordance with experimental data²⁸.

FIG. 5 Schematic representation of human FcεRII, showing the triple α-helical coiled-coil stalk region (length ~15 nm), and the three heads that contain the C-type lectin homology regions. The single glycosylation site in each chain is shown schematically (not to scale) and the sites of proteolysis in the stalk region are indicated, together with the sizes of the soluble fragments released. The structure of the lectin-like head region shown on the right is based on the crystal structure of the homologous region of the mannose-binding protein⁴⁶. Of the two Ca²⁺-binding sites of MBP, only Ca2 is conserved in human FcεRII, although both appear to be conserved in mouse FcεRII. The four stippled segments of polypeptide chain are those implicated in IgE binding in studies with chimaeric proteins⁴⁷; the three loop segments form a contiguous surface region, the location of which is consistent with the Ca²⁺ dependence of IgE binding. The C-terminal extension to the lectin homology region that in human FcεRII



contains the reverse RGD sequence is indicated. (The four disulphide bridges within this region of human FcεRII are not shown.)

transmembrane sequence and a short cytoplasmic segment (Fig. 5). There are two forms of FcεRII, FcεRIIa and FcεRIIb, differing only in their 6/7 N-terminal amino acids¹⁵. They are derived from the same gene by the use of different promoters (a and b) controlling separate first exons, which are spliced to a common mRNA sequence. FcεRIIa is a developmentally regulated gene, expressed only in antigen-activated B cells before their differentiation into immunoglobulin-secreting plasma cells. FcεRIIb expression is inducible by interleukin-4 (IL-4) on all of the cell types mentioned so far.

The membrane form of FcεRII gives rise to soluble fragments (sFcεRII) by proteolysis. The initial cleavage, within the 'stalk' and close to both the cell membrane and the single site of N-glycosylation, releases a fragment of M_r 37,000 (37K) (Fig. 5). The nature of the proteases that cleave FcεRII *in vivo* is of considerable interest, as is the suggestion that the first to act may be, or require, sFcεRII itself¹⁵. The 37K fragment can be cleaved nearer the lectin domain to give fragments of 33, 29 and 25K containing the lectin domain and the C-terminal 'tail', and a 16K fragment lacking the tail (Fig. 5). It is remarkable that the fragments of different sizes appear to have quite different activities. All retain binding specificity for IgE, although the smaller fragments bind with lower affinity than the intact molecule. Only fragments of $M_r \geq 29K$ promote IgE synthesis, however, and indeed the 16K fragment inhibits this activity⁴⁴. The remaining cytokine activities are common to the intact molecule and all the fragments^{15,45}.

The recently determined crystal structure of the mannose-binding protein (MBP; ref. 46) makes it possible to model the structure of the lectin domain of FcεRII as shown in Fig. 5. The regions implicated in IgE binding⁴⁷ (shown stippled in Fig. 5) lie close to the Ca²⁺ binding site which is conserved in FcεRII (Ca2; Fig. 5) and forms part of the mannose-binding site in MBP⁴⁸, explaining why IgE binding is both Ca²⁺-dependent⁴⁹ and inhibited by fucose-1-phosphate¹⁵, even though binding to IgE does not involve carbohydrate²⁶. Fucose is implicated in the binding of FcεRII to CR2 (ref. 50), however, and if Ca2 indeed marks the carbohydrate binding site in FcεRII, the IgE- and CR2-binding sites must overlap (as implied by experimental data⁴⁵), so that IgE would compete with CR2 for binding to

FcεRII (see later). The model of FcεRII (Fig. 5) further predicts that the ligand-binding sites are remote from both the stalk and the Asp-Gly-Arg (DGR)-containing 'tail'.

The release of soluble fragments from membrane-bound FcεRII is inhibited by IgE⁵¹ and so IgE and IgE-antigen complexes repress IgE synthesis⁵². A possible mode of interaction between IgE and FcεRII is shown in Fig. 6a, with two lectin heads binding to the two sites on the IgE molecule, but it is clear from the relative dimensions of the two molecules that IgE cannot exert a direct steric effect upon the primary site of proteolysis (which releases the 37K fragment; Fig. 5). We have therefore suggested an allosteric mechanism⁵³ by which IgE binding stabilizes the coiled-coil stalk and protects it against proteolysis. This effect is mimicked by most monoclonal antibodies against FcεRII, but a small group of antibodies exert the opposite effect and promote IgE synthesis. This surprising observation, together with the fact that Fab fragments operate as effectively as the intact antibodies, cannot be explained in terms of receptor crosslinking, prompting consideration of an allosteric mechanism⁵⁴. We can now rationalize the effect of this second group of antibodies and Fab fragments in terms of a destabilization of the coiled-coil stalk and enhanced release of sFcεRII.

B-cell FcεRIIa has another function, as antigen-IgE-FcεRII complexes present antigen very effectively to T cells⁵⁵. Presentation entails internalization, degradation within a cytoplasmic compartment, and recycling of fragments to the cell surface. The role of FcεRII in endocytosis is thus similar to that of the homologous ASGPR in the degradation of glycoproteins by the liver. ASGPR is a trimer with a predicted structure resembling FcεRII (ref. 42); its activity depends upon its oligomeric character, which allows it to be crosslinked by multivalent ligands⁵⁶. By analogy, FcεRII's capacity for antigen presentation probably depends on its oligomeric structure too.

The trimeric structure of FcεRII may also account for the contrasting cytokine activities of the different soluble fragments. Only fragments larger than 25K, which retain part of the stalk, should remain as trimers. Such fragments would be able to crosslink membrane-bound IgE and CR2 on the B-cell surface, allowing IgE class selection by 37K and 29K (but not 25K)

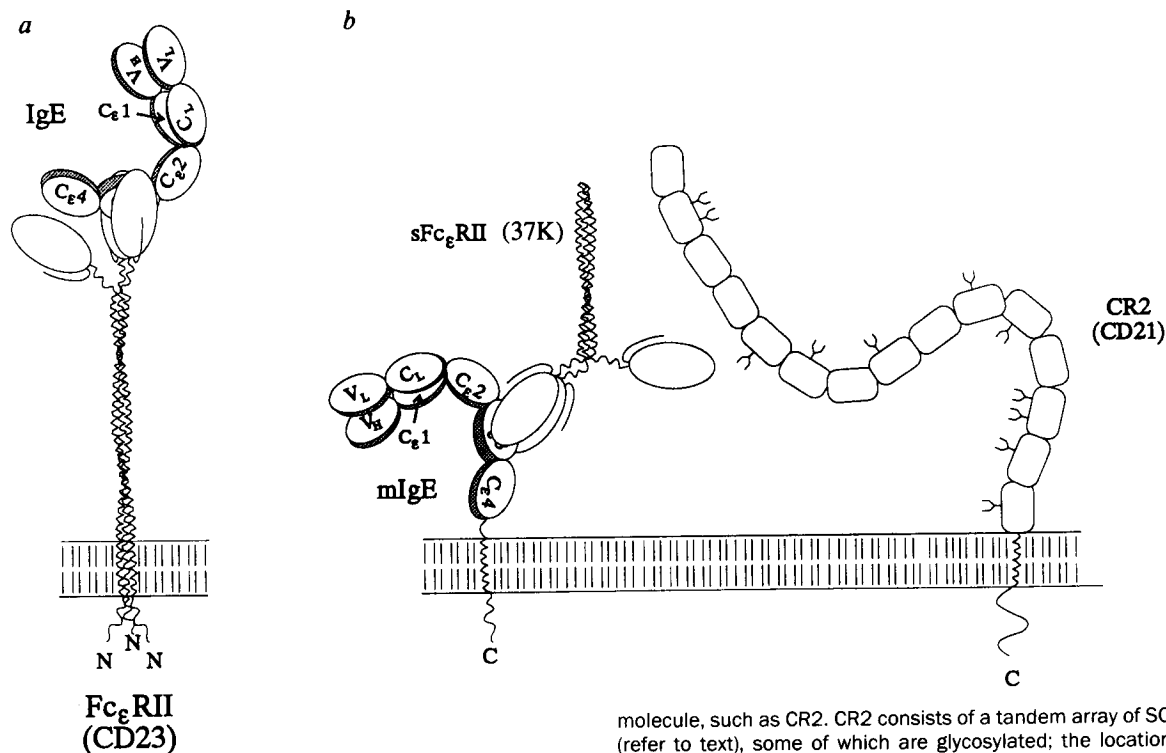


FIG. 6 Multiple interactions between IgE, FcεRII and CR2. *a*, The interaction between human FcεRII and IgE. Two lectin-like head regions of membrane-bound FcεRII combine with the two Cε3 domains of IgE. *b*, Interaction of trimeric 37K sFcεRII with membrane-bound IgE. The 'free' head may bind to another IgE molecule, or other cell surface

molecule, such as CR2. CR2 consists of a tandem array of SCR domains (refer to text), some of which are glycosylated; the locations of these sites are shown schematically. FcεRII may bind in the region of domain 5 (refer to text) and involve the recognition of carbohydrate. Crosslinking mIgE and CR2 (which forms a signal transduction complex with CD19; see text and Fig. 7) on the surface of a committed B cell may provide a mechanism for specific activation of IgE synthesis by FcεRII. (Molecules and cell membrane are drawn to scale.)

sFcεRII, as depicted in Fig. 6*b*. The transient nature of the fragments also suggests a mechanism for localizing their activity.

CR2 as counter-receptor for FcεRII

The discovery that CR2 is a counter-receptor for FcεRII resolved several questions at once, for it established that CR2 is the ligand for the inferred lectin function of FcεRII (refs 17,50), pointed to CR2 as the missing receptor required for cell signalling by FcεRII, and explained the link between FcεRII expression and B-cell transformation by EBV⁵⁷. Fragments iC3b, C3dg and C3d of the complement component C3, the EBV coat protein gp350/220 and α -interferon had previously been identified as ligands for CR2, and all of these molecules can deliver growth signals to B cells on binding (reviewed in ref. 58). CR2 was therefore thought to link the complement and antibody immune systems; it now appears to link the humoral and cellular arms of the latter as well.

CR2 is a highly glycosylated membrane protein found on B-cells, FDCs and some T cells and basophils. Its extracellular region comprises 15 or 16 homologous units in tandem, each made up of 60–75 residues, with the compact fold of the short consensus repeat (SCR; ref. 59). This produces an extended flexible structure some 40 nm long⁶⁰, as shown in Fig. 6*b*, which also indicates the potential N-glycosylation sites. Several species of CR2 can be separated electrophoretically, only one of which is recognized by FcεRII (ref. 17); these may differ solely in their glycosylation. Differential glycosylation of CD21 is also of interest in relation to the recently reported ability of CD23 to induce degranulation of basophils by the crosslinking of CD21 (ref. 112). The binding sites for C3 fragments and EBV have been mapped with monoclonal antibodies to the two N-terminal domains^{61,62} and do not involve carbohydrate. By contrast, FcεRII binding is inhibited by carbohydrate⁵⁰ and by monoclonal antibodies¹⁷ with epitopes that overlap in domain 5 (refs 18, 61). The valency of the ligand is important for both the C3

fragments and EBV gp350/220, because B-cell proliferation is promoted by multivalent but inhibited by univalent ligands^{63,64}. It remains to be seen whether the stimulatory and inhibitory activities of different sFcεRII fragments can be rationalized in the same way.

sFcεRII can trigger CR2 on B-cells and enhance IgE synthesis (ref. 17; see also Fig. 6*b*), but the two molecules may elsewhere engage in adhesive interactions. FcεRII expression on the surface of B cells induces the homotypic adhesion of B cells, and sFcεRII inhibits the migration of monocytes (reviewed in ref. 16). In this case, the role of FcεRII is reminiscent of that of another group of C-type lectins, the selectins⁴¹. Most recently, the FcεRII-CR2 interaction has been implicated in the rescue of germinal-centre B-cells from apoptosis¹⁸; it thus participates in perhaps the most fundamental event in the immune response, the clonal amplification of B-cells selected by antigen. The possible contribution of the FcεRII-CR2 pair to this process is depicted in Fig. 7. Immune complexes held by FDCs can interact with membrane IgM (mIgM) on the surface of B cells, but this interaction alone is insufficient to stimulate the B cells because both antigen concentration and affinity are too low. Co-ligation of the B-cell protein CD19 can bring the threshold for activation into the physiological range⁶⁵, and the activation of mIgM and CD19 is synergistic⁶⁶. A ligand for CD19 has been sought without success, but CD19 forms a membrane complex with CR2 (ref. 67) and FcεRII can therefore act as ligand for this complex. The presence of C3 fragments bound to the immune complex may also serve to crosslink the two membrane complexes (Fig. 7) contributing to the observed synergism.

The demonstration that CR2 mediates the cytokine activities of FcεRII offers a new perspective on the process of B-cell transformation by EBV. Not only does EBV use CR2 to gain entry, but once inside it expresses two proteins, EBNA-2 and LMP-1, which activate the proto-oncogene *bcl-2* (implicated in the mechanism of cell survival⁶⁸), as well as the genes for FcεRII

and CR2 (ref. 69). Although FcεRII expression is normally shut down in the terminally differentiated cell, gene activation by EBNA-2 and LMP-1 is permanent, and hence infected cells continue to express both growth factor (sFcεRII) and receptor (CR2) indefinitely. Incubation of germinal-centre B cells with sFcεRII and IL-1 *in vitro* leads to expression of *bcl-2* (ref. 70), and FcεRII may therefore mediate the upregulation of *bcl-2* by LMP-1. CR2 can also bind the anti-oncoprotein p53 in transformed cells⁷¹; FcεRII and CR2 are thus clearly implicated at several stages in the mechanism of transformation of B cells by EBV.

Receptor coupling to intracellular signalling

Each of the four proteins that we have discussed exists in one or more membrane-bound forms acting as signal receptors. Propagation of these signals depends on the interactions between the receptor and other membrane-bound and cytoplasmic proteins. These interactions are by no means as well defined as the complexes formed by the receptors with each other, but some essential sequence motifs, and the proteins that recognize them, have been identified.

Membrane-bound IgE is expressed on cells committed to IgE synthesis and serves as an antigen receptor. As with other membrane immunoglobulins, it forms a complex with two disulphide-linked heterodimeric proteins, made up of immunoglobulin α- and β-chains, which function in signal transduction (see ref. 72 for review; see mIgM in Fig. 7). The cytoplasmic sequences of Ig-α and Ig-β each contain a 26-amino-acid sequence motif, (D/E)X₇(D/E)X₂YX₂(L/I)X₇YX₂(L/I), referred to as the antigen-receptor homology-1 (ARH1) motif, which associates with tyrosine kinases of the *src* family and phosphatidylinositol 3-OH kinase (PtdIns-3 kinase)⁷³. Similarly, antigen signalling by the IgE–FcεRI complex is mediated not by the ligand-binding α-chains, but by the associated β- and γ-chains, which also contain the ARH1 motif and associate with *src*-like kinases⁷⁴. Phosphorylation of residues within these motifs and in the associated proteins occurs during the early steps of signal transduction and modulates these interactions.

The short cytoplasmic region of FcεRII does not contain an ARH1 motif, and the mechanism of signal transduction by this receptor is unknown (though a *src*-like tyrosine kinase has been found associated with FcεRII in a human NK-like cell line⁷⁵). The α form of FcεRII, however, does contain the sequence YSEI, an example of the tetrapeptide motif that acts as a signal for transport to endosomes via coated pits⁷⁶. Thus FcεRIIa, but not b (which lacks this motif), can function in antigen presentation; conversely, the dipeptide motif NP present in the cytoplasmic sequence of FcεRIIb, but not a, is required for this receptor to mediate phagocytosis in monocytes¹¹. As the sequence YX₂(L/I) occurs (twice) within the ARH1 motif, its presence in the β- and γ-chains of FcεRI may be responsible for internalization of this receptor also.

As mentioned above, CD19 forms a complex in the membrane with CR2, and its extensive cytoplasmic sequence contains two copies of the motif YX₂M, which has been characterized as a binding site for PtdIns-3 kinase^{77,108}; the two tyrosines are required for this association¹⁰⁸. Subsequent steps in signalling by this complex, and by the mIgM complex with which it exhibits synergy, have yet to be elucidated in detail, but the two pathways appear to be distinct⁶⁶.

Feedback control of IgE synthesis

Expression of IgE is controlled both by heavy-chain switching and by the selection of IgE-committed cells for survival and differentiation. The requirements for selective switching to IgE have been defined by studies of peripheral blood mononuclear cells *in vitro*^{14,15,78}, and three molecular signals appear to be involved. The first is IL-4, which directs recombination to the constant region of the ε-heavy chain. The other two are CD40

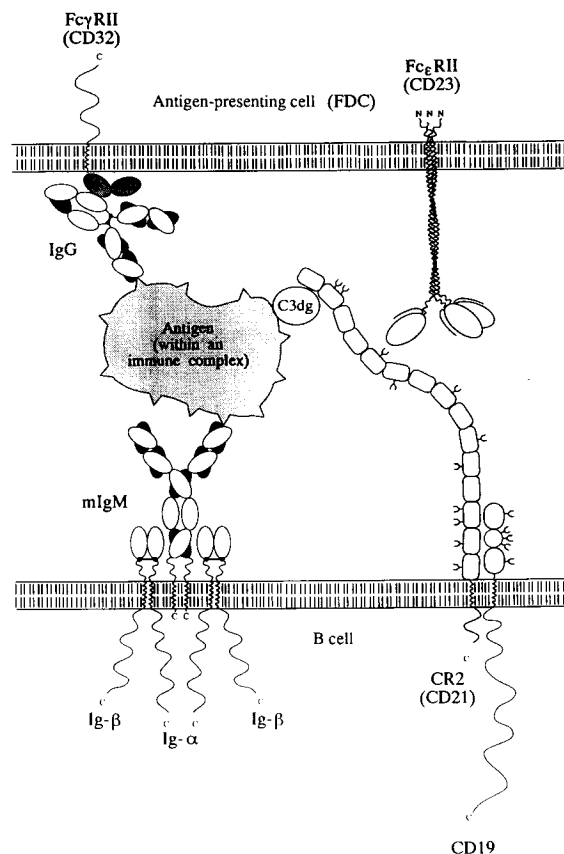
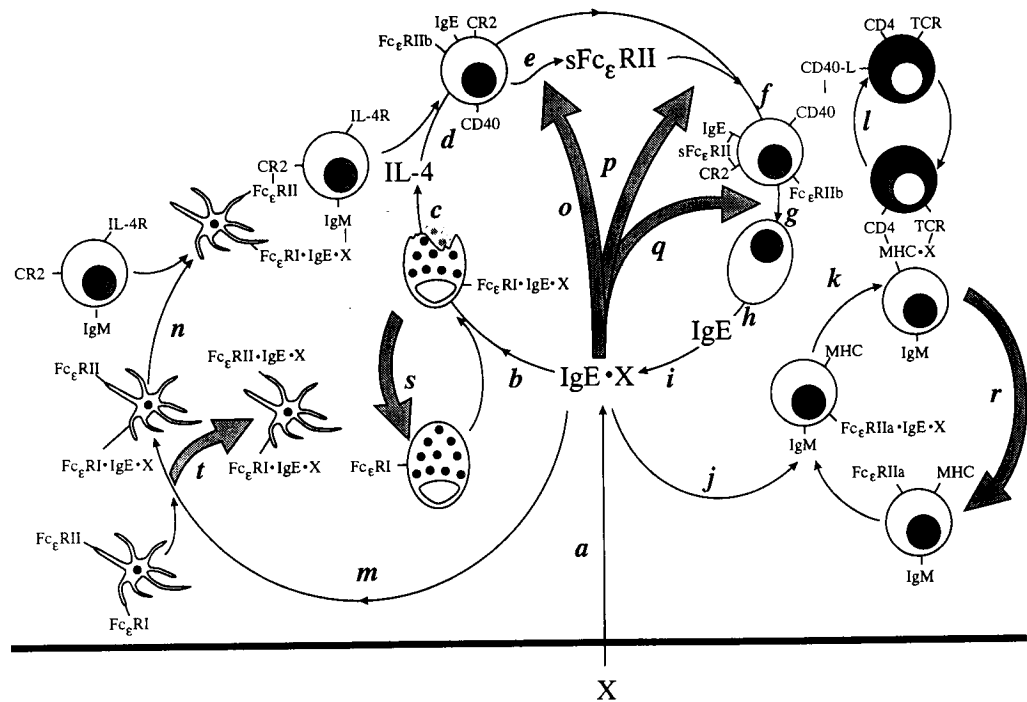


FIG. 7 Cell-cell interactions mediated by FcεRII and CR2. On the left, an IgG molecule attached to an antigen represents an immune complex that is bound to the surface of an antigen-presenting cell (such as a follicular dendritic cell, FDC) by means of an IgG Fc receptor (FcγRII is shown here). The immune complex is also bound to (and crosslinks) the B-cell antigen-receptor complex, which consists of mIgM and its associated disulphide-linked pairs of immunoglobulin α- and β-chains. These latter chains mediate signal transduction. On the right, FcεRII on the FDC interacts with CR2, which is in turn associated with CD19 in the B-cell membrane (and two other proteins, TAPA-1 and Leu-13; not shown). (CD19 consists of two extracellular Ig-like domains separated by a further truncated domain, and an extensive intracellular region.) The FcεRII–CR2 interaction promotes cell contact and delivers a signal to the B cell via CD19, which interacts synergistically with the signal transduced by mIgM and lowers the threshold for activation of B cells by immune complexes (see text). If complement activation also occurs, CR2 may interact with antigen-bound fragments of C3 (C3dg) in the immune complex, thereby enhancing the association between these two membrane complexes; the binding sites for C3dg (in domains 1–2) and FcεRII are distinct. A parallel mechanism might account for the presentation of IgE immune complexes by FcεRI on Langerhans cells which, like FDCs, also express FcεRII. The adhesion interaction between FcεRII and CR2 may also serve to enhance contact between other cells that express these molecules (B cells and T cells for example¹¹¹). Furthermore, the DGR-containing C-terminal extensions to each lectin domain of FcεRII may provide yet further opportunities for adhesive interactions or crosslinking of cell-surface molecules and generation of intracellular signals. (Molecules and cell membrane are drawn to scale.)

ligand (CD40-L) and FcεRII which induce the IgE-producing cells to become memory cells or plasmacytes respectively^{79,80}.

These choices are made, it is believed, in the germinal centres of secondary follicles in the lymph nodes and spleen; T cells are envisaged to be the source of IL-4 and to stimulate B cells through CD40-L, whereas FDCs are responsible for antigen presentation and the stimulation of B cells through FcεRII. It is now clear, however, that mast cells both secrete IL-4 (ref. 7) and express CD40-L, allowing them to perform the same activities in the skin, lungs and gut as do T cells⁸¹. IL-4 upregulates FcεRII on B cells and inflammatory cells, providing in turn a

FIG. 8 Feedback control of IgE synthesis. Positive signalling (thin arrows): *a*, Antigen X enters the system and forms a complex IgE.X; *b*, *j* and *m* are alternative fates for IgE.X at low concentrations of IgE. *b*, Binding of IgE.X to FcεRI on a mast cell. *c*, Secretion of IL-4 (and other inflammatory mediators that are not shown), activated by binding of IgE.X to FcεRI. *d*, Induction of FcεRIIb and CD40 expression, and class switching to IgE, in an antigen-activated B-cell by IL-4. *e*, Release of sFcεRII from the B cell itself or associated Langerhans cell. *f*, Binding of sFcεRII to CR2 and mIgE (Fig. 6b), promoting survival of the IgE-committed B cell. *g*, Differentiation of the cell into a plasmacyte, stimulated by the ligand of CD40 (CD40-L). *h*, Secretion of IgE. *i*, Binding of IgE to the antigen X. *j*, Binding of IgE.X to FcεRIIa on the surface of a B cell. *k*, Antigen presentation to a T-cell specific for the processed antigen X. *l*, Induced expression of CD40-L by the activated T-cell, and binding to CD40 on an IgE-committed B cell. Expression of CD40-L by mast cells (not shown) as well as T cells may obviate a strict requirement for the latter cells in the periphery. *m*, Binding of IgE.X to FcεRI on a Langerhans cell. *n*, Antigen presentation to a B cell involving the suggested co-ligation of FcεRI-IgM and FcεRII-CR2. Negative signalling (thick arrows): *o*, Inhibition of the cleavage of FcεRIIb



on the B cell (or Langerhans cell) by IgE.X. *p*, Inhibition of the binding of sFcεRII to CR2 on the B cell by IgE.X. *q*, Inhibition of the secretion of IgE, caused by IgE.X crosslinking of FcεRIIb on the B cell. *r*, Degradation of IgE in the course of antigen presentation, and *s*, after internalization by mast cells. *t*, Switching off the Langerhans cell by saturation of FcεRII at high IgE concentration.

local source of contact stimulation and of soluble growth factor. The co-expression of FcεRI and FcεRII in Langerhans cells^{8,9,13} may moreover imply that they could serve a function in the periphery analogous to that of FDCs in the germinal centres. These suggested interactions are summarized in Fig. 8.

Homeostasis also requires mechanisms that limit IgE production. Clearly IgE itself can exert negative-feedback control as its binding site on FcεRII overlaps with the site for CR2 (see above). IgE-antigen complexes are even more effective⁵² by reason of their higher affinity, and appear to act by blocking both the release of FcεRII (ref. 51) and the binding of sFcεRII to CR2. These feedback circuits will come into play only at IgE-antigen concentrations at which the sites on FcεRII are close to saturation. As Langerhans cells express both FcεRI and FcεRII, antigen presentation by these cells may be possible only when the former are occupied but the latter are free for interaction with CR2 (compare Fig. 7), thus being restricted to low IgE concentrations. In addition, IgE complexes can downregulate IgE synthesis by crosslinking FcεRII on B cells⁸² and the degradation of IgE in the course of antigen presentation mediated by FcεRII may also contribute to feedback control⁸³. All of these pathways for downregulation of IgE are represented in Fig. 8. The ability of FcεRII to promote germinal-centre B-cell survival, thymocyte maturation and myeloid cell differentiation through its interaction with CR2 suggests that it may also have a more general function in immunosuppression.

Prospects for new therapeutic strategies

The central position of IgE in the network of reactions leading to allergy commends it as a target for therapeutic intervention, whether at the level of its interaction with FcεRI, on the ensuing signalling pathways or the control of its biosynthesis.

Recombinant peptides comprising structural elements from IgE or FcεRI have been investigated as competitive inhibitors of the IgE-FcεRI interaction^{20,84,85}. The high affinity of IgE for

FcεRI ($K_a = 10^{10} \text{ M}^{-1}$) and its capacity to activate the mast cell at low receptor occupancy may limit the clinical value of these peptides⁸⁶; the design of new competitors with higher affinity, based on more detailed structural information or the random screening of peptide libraries, is a challenging option. An alternative approach is to restrict the accessibility of the binding sites in IgE or FcεRI by stabilizing an inactive conformation of one or the other. It may also be feasible to perturb the interaction of the FcεRI α -chain with its partner subunits, so that IgE binds without inducing signal transduction.

A search has been made for monoclonal antibodies that block binding of IgE to FcεRI without causing mast-cell degranulation^{86,109,110}. The success of such a strategy may depend on the bent structure of IgE, as any epitope involved in FcεRI binding would otherwise have an accessible counterpart on the other side of the molecule. The restricted accessibility of some epitopes may explain why certain anti-Fcε antibodies like soluble FcεRI(α) form only equimolar complexes with free IgE and none when it is bound to its receptor. Moreover, as shown schematically in Fig. 4, antibodies may be able to obstruct the IgE-receptor interaction even when their epitopes do not overlap the receptor binding site. It is even conceivable that by judicious choice of epitopes, a peptide might be found to serve as a vaccine that will generate antibodies that block binding; a candidate peptide has been suggested (Fig. 2; ref. 87). A more conservative approach would be to use univalent Fab or Fv fragments for passive immunization. The possibility of using monoclonal antibodies against receptor peptides in therapy is also being explored³⁸.

Too little is yet known about the signal transduction cascade in mast cells and basophils to allow speculation about how the downstream signalling processes might be interrupted. It is in this area, however, that empirical drug screening has had such notable success. Two fungal products, theophylline and cyclosporin A (CsA), have both been used in the treatment of asthma, the former for several decades, the latter only in recent clinical

trials⁸⁸. Theophylline was originally identified as an antagonist of mast-cell degranulation, but has serious side effects that result from its actions on other cell types. A derivative of theophylline, rolapram, has now been found to act preferentially on mast cells, and has been used to characterize a cyclic AMP phosphodiesterase isozyme, PDE-IV, which is the predominant form in the mast cells of allergic individuals and the target for the drug⁸⁹. Cyclosporin A was originally used to prevent the rejection of allografts. It binds proteins termed cyclophilins and may thus inhibit eosinophil chemotaxis⁹⁰, although other sites of action have been proposed⁹¹; another mode of action is suggested by the recent observation that the drug suppresses expression of CD40-L by mast cells⁸¹. The identification of target proteins for both rolapram and CsA may now allow the development of improved drugs on the basis of structural studies.

Knowledge of the reactions involved in the regulation of IgE synthesis (Fig. 8) may assist in designing drugs to intervene at this level. Monoclonal antibodies against either IL-4 (ref. 92) or the IL-4 receptor⁹³ eliminate expression of IgE in mice, as does inactivation of the IL-4 gene⁹⁴. Similarly, the interactions

between CD40 and CD40-L, and between FcεRII and CR2, can be blocked by soluble ligand fragments or antibodies *in vitro*, and may be exploited therapeutically if a concentration range can be found in which the more general immunosuppressive effects are tolerated^{95,96,111}.

A promising point of purchase is arguably the natural feedback loop by which IgE protects FcεRII against proteolysis. This could be enhanced by the use of a suitable IgE fragment, or by stabilizing the coiled-coil structure of FcεRII directly. Antisense RNA may in the future inhibit transcription of the IgE heavy chain⁹⁷, FcεRII (ref. 98) or FcεRI, but the problems associated with this technique *in vivo* remain to be solved. Chang *et al.* have investigated the use of monoclonal antibodies that crosslink FcγR and mIgE to downregulate IgE synthesis by committed cells⁹⁹. To avoid anaphylaxis caused by crosslinking IgE bound to FcεRI on mast cells, antibodies were raised against the sequence in mIgE that is missing from the secreted form. Antibodies such as these may be the first of a new generation of drugs for the treatment of allergy that are based on knowledge of protein structure. □

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