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Review Article

IgE AND ITS RECEPTORS, A REVIEW

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Background

Immunoglobulin E was first detected as reaginic antibodies in allergic sera by Prausnitz in 1921.[1] He passively sensitized himself by injecting serum from his allergic colleague Küstner. This provided the first evidence that a serum factor was involved in the mediation of allergic reactions of the immediate type. Since then several investigators have studied the properties of reaginic antibodies. In 1967 an atypical myeloma protein (ND), lacking the antigenic determinants characteristic of the known immunoglobulin classes was identified.[2] At the same time evidence for a correlation between reaginic antibodies and ND protein was obtained by Stanworth et al,[3] demonstrating the specific blocking of the P-K reaction by ND protein. Simultaneously a reaginic antibody from a ragweed-sensitive individual's serum was purified and characterized by Ishizaka's group[4] and was subsequently shown following the exchange of antisera in 1968 to possess the same antigenic determinants as those of IgE ND. Consequently the protein was officially designated as immunoglobulin E or IgE.[5]

The IgE molecule

IgE has a molecular weight near 190000 daltons of which 12% is accounted for by carbohydrate and has a sedimentation coefficient of 7.92 S.[6] The molecule has a basic structure similar to other immunoglobulin classes, i.e. a four chain unit comprised of two light chains and two heavy chains (epsilon) linked together by disulfate bonds. The epsilon chains (IgE ND) consist of 547 amino acid residues as has been determined by conventional protein sequencing,[7] as well as gene sequencing analysis.[8] The IgE molecule contains one variable region and four constant homology regions (C_H1, C_H2, C_H3 and C_H4) with 15 cysteine residues, which all participate in the formation of disulfate bonds. Of the six carbohydrate side chains of the IgE molecule, one is located within the V-C region (Asn-145), two in the C_H1 (Asn-173 and Asn-219), one in the C_H2 (Asn-262) and two are located in the C_H3 region (Asn-371 and Asn-394).[9] Treatment of IgE with papain yields an intact Fc and two Fab fragments. IgE is susceptible to pepsin digestion, and treatment for 30 minutes to 4 hours produces a large fragment corresponding to F (ab')2 and containing the C_H1 homology region.[10]

Early observations on allergic sera revealed reaginic antibodies to be heat-sensitive.[11] Thus heating of the IgE molecule at 56°C for 30 minutes was found to abrogate its cytophilic activity. Since the antigen-binding property of heat-treated IgE remained unaffected, it was suggested that the heat-sensitive site is located within the constant region. Further work on Fc fragments has revealed that this loss of cytophilic activity upon heat treatment can be attributed to changes in either the C_H3 or C_H4 domains.[9] IgE is a minor component of serum protein. The normal serum IgE levels have been shown to range between 1.0-287 IU/ml (1 IU=2.3 ng).[12] The catabolic rate of IgE has been reported to be 2-3 days[13] whereas mast cell-bound IgE has been shown to have a half-life of 25 days.[14] It has been reported that IgE myeloma protein (PS) is incapable of activating the classical complement pathway, a finding which was earlier associated with reaginic antibodies[11] and later with aggregated IgE.[15] However, a new myeloma IgE (Des) has been reported to be

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capable of fixation and activation of the classical complement pathway.[16] IgE, unlike IgG, does not cross the placental barrier.[17]

The most important biological property of IgE is its ability to bind to tissue mast cells and basophils. In addition, it is now known that IgE binds to lymphocytes,[18] monocytes and macrophages,[19] eosinophils,[20] and platelets.[21] Apart from its ability to bind to cells, there are also several soluble proteins which are known to have an IgE binding property.[22,23]

The receptor with high affinity for IgE

On the surface membrane of mast cells and basophils a protein is expressed which binds exclusively to monomeric IgE with high affinity. It is the binding of IgE to this receptor and its interaction with specific allergen which triggers mast cell and basophil degranulation and the release of inflammatory mediators responsible for type I hypersensitivity. Most of the data on the structure of this receptor, also referred to as the high affinity receptor for IgE ($Fc_{\varepsilon}RI$), has been obtained from studies of a rat basophilic leukemia (RBL) cell line.

The chemical and molecular structure of this high affinity receptor for IgE has been extensively studied.[24-26] It appears that $Fc_{\varepsilon}RI$ contains four polypeptide chains: a single alpha chain, a single beta chain and two identical gamma chains linked by disulfate bonds. The alpha chain is a heavily glycosylated subunit of 50-60KDa, exposed on the outer surface of the cell and carrying the IgE binding site. Recently the cDNA for rat alpha chain has been isolated[26] and shown to possess two homologous domains (residue 65-102 and 148-182). There is a significant degree of homology (34%) between the alpha chain of $Fc_{\varepsilon}RI$ and the Fc gamma receptor.[27] The cDNA for the corresponding human alpha chain has been reported,[28,29] indicating an overall homology between human and rat sequences of 68% and 45% at the nucleotide and protein levels. Despite several attempts, the alpha chain has not been successfully expressed in transfected cells, and so it is believed that alpha chain expression requires also the beta or gamma subunits or both.[30] The beta chain is a single polypeptide with a 32 KDa molecular weight, which is closely related to the alpha chain.[30] It has been shown that the major part of the beta chain structure is embedded in the plasma membrane.[23] A cDNA for the beta subunit from a cDNA library derived from RBL cells has been identified.[26] It appeared that the beta chain contained 243 amino acids with no NH_2 terminal signal sequence. The gamma subunit consists of two identical polypeptides with a molecular weight of 7-9 KDa linked by disulfate bonds.[23]

The receptor with low affinity for IgE

The receptors for sites within the Fc part of all major immunoglobulin classes have been reported to be expressed on various hematopoietic cell lineages. The interaction of the Fc region of immunoglobulin with the Fc receptor provides an important communication between antibody molecules and their effector functions, such as phagocytosis, antibody-dependent cytotoxicity (ADCC), secretion of potent mediators and modulation of the immunoregulatory network. Because the Fc receptor provides these central functions of the immune response, the investigation of its structural relationship and functions can be crucial for the better understanding of the mechanism of immune responses. This may provide a means of designing therapeutic approaches for immunological disorders, such as allergy and autoimmunity.

Historically, Lawrence et al.[18] first reported that radiolabelled aggregated IgE binds to human lymphocytes and then Capron et al.[19] described an IgE-mediated defence against schistosomules by rat macrophages. These two important observations provided evidence for the existence of an IgE Fc receptor distinct from that expressed on basophils and mast cells.[24]

In later studies a close relationship between the expression of the Fc receptor for IgE on lymphocytes (now designated $Fc_{\varepsilon}RII$) and the synthesis of IgE was recognized. For instance, the expression of $Fc_{\varepsilon}RII$ for IgE on lymphocytes and monocytes in patients with atopic disorders is higher than in non-atopic subjects.[31] In the rat the proportion of $Fc_{\varepsilon}RII$ positive B-cells markedly increased after infection with the parasite *Nippostrongylus brasiliensis*[32] which is known to induce parasite-specific synthesis of IgE. The expression of the low affinity receptor for IgE has also been reported on eosinophils from hypereosinophilic patients, a condition in which total IgE levels are significantly increased.[21]

In the Second International Workshop on Leukocyte Antigens it was reported that a certain 45 KDa molecule B-cell differentiation marker (designated CD23) is identical to the low affinity receptor for IgE.[33] Since then, an extraordinary amount of research has been carried out to characterize the multi-functional properties of this receptor. Information has been obtained pertaining to the mechanism of B-cell growth and differentiation, regulation of IgE synthesis and mediatory functions from soluble fragments of this multi-functional receptor.

Molecular weight of $Fc_{\varepsilon}RII$/CD23

$Fc_{\varepsilon}RII$/CD23 is a single chain glycoprotein with a molecular weight of 45-47 on SDS-PAGE.[34]

The $Fc_{\varepsilon}RII$/CD23 on RPMI-8866 cells has been reported to be comprised of three components with apparent molecular weights of 65-95, 45, and 25-37 KDa.[35,36] They have shown that murine $Fc_{\varepsilon}RII$ comprises a major band of 49 KDa with predominant subcomponent fragments of 38 and 28 KDa.

Molecular structure of $Fc_{\varepsilon}RII$/CD23

The cDNAs encoding human $Fc_{\varepsilon}RII$/CD23 have been isolated and cloned from the RPMI-8866 cell line by three

groups of investigators.[39-41] It appears that Fc_εRII/CD23 is a molecule consisting of 321 amino acids, which is expressed with its N-terminal in the cytoplasm and its C-terminal outside the cell. This unusual transmembrane orientation has been reported for the chicken hepatic lectin[42] and the invariant chain of HLA-DR antigens.[43]

A new cDNA clone designated as Fc_εRIIb has been recently reported.[44] The extracellular and transmembrane regions of Fc_εRIIb are identical to that of Fc_εRII, which was previously reported and is now termed Fc_εRIIa. The nucleotide sequence derived from Fc_εRIIb cDNA differs from that derived from Fc_εRIIa cDNA only in its 5' terminal region. The sequence which corresponds to exon 1 and exon 2 of the Fc_εRIIa gene is missing from all Fc_εRIIb cDNA. Instead, a nucleotide sequence of 84 bp has been observed in the N-terminal region, resulting in the first seven amino acids of the N-terminal end of Fc_εRIIa being substituted with a different sequence of 6 amino acids in Fc_εRIIb.

Fc_εRII/CD23 binding site on IgE molecules

Considerable work has been carried out to define the sites on the IgE molecule that bind the high affinity receptors.[24] Similarly, attempts have been made to determine the low affinity receptor binding sites on IgE molecules.[45,46]

Recently, by synthesizing 10 different peptide sequences within the C_H2, C_H3 and C_H4 domains of human IgE and production of rabbit polyclonal anti-peptide antibodies we have been able to map the binding site of Fc_εRII/CD23 on the IgE molecule.[47] Our findings indicate that two sequences representative of residues 364-383 and 401-415 within the C_H3 domain, despite being linearly separated, could be involved in the binding of IgE to both membrane bound and soluble forms of Fc_εRII/CD23.

IgE low affinity receptor and homology with animal lectins

The lectins are generally considered to be nonenzymatic proteins which selectively bind to specific carbohydrate structures.[48] An increased body of evidence has demonstrated the existence of a large number of animal lectins. The C-type (Ca^{++}dependent) animal lectins as exemplified by the asialoglycoprotein receptor, are all structurally related, whilst the S-type (thiol-dependent) animal lectins form a distinct group.[49]

The amino acid sequence of human Fc_εRII/CD23 shows a significant homology with chicken hepatic lectin and asialoglycoprotein receptors.[39,40] Asialoglycoprotein receptors are cell surface proteins of hepatocytes having a specificity for galactosyl glycoproteins. A domain (amino acids 163-282) with 42 identical amino acids has been found within Fc_εRII and hepatic lectin.[41] The position of 6 out of 8 cysteine residues of Fc_εRII is comparable to that of 6 out of 7 cysteine residues of the asialoglycoprotein receptor, indicating that these proteins have similar secondary structures in their extracellular domains. In the extreme C-terminal end of the Fc_εRII/CD23 molecule, the reverse sequence of Arg-Gly-Asp (RGD) is present.[39] This sequence has been seen in a variety of molecules such as fibronectin, fibrinogen and collagen, indicating that Fc_εRII/CD23 may participate in cell-cell contact and cell adhesion.[49,51] It has been suggested that lectin-carbohydrate interactions mediate potentially significant adhesion events during lymphocyte migration.[52] The lectin homology domain and RGD sequence within Fc_εRII/CD23 need to be investigated in order to establish whether or not they participate in these physiological events.

Expression of Fc_εRII/CD23 on B-cells

Most of the early data on the expression of the low affinity receptor for IgE on hematopoietic cells has been obtained by use of a rosette assay, in which ox erythrocytes sensitized with myeloma IgE have been used for determination of the percentage of Fc_εRII positive cells.[53] Using this method, the percentage of Fc_εRII/CD23 expressed on lymphocytes of normal donors has been observed to be 4.3%. By employing monoclonal antibodies directed against Fc_εRII/CD23,[34] it has been demonstrated that this molecule is expressed on most CD20 (a pan B-cell marker) positive B-cells within the peripheral blood, and to a lesser extent on tonsillar B-cells, but not on CD20 positive bone marrow B-cells. Fc_εRII/CD23 is not expressed on resting mantle zone B-cells in secondary lymphoid tissue, whereas most germinal center B-cells and follicular dendritic cells, both in germinal centers and tonsillar crypts, expressed this molecule.[54,55] Most EBV-transformed B-cell lines strongly express Fc_εRII/CD23,[56,57] whereas the majority of Burkitt's lymphoma cell lines were either negative or only weakly expressed this receptor.[58] Most of the B-cells derived from chronic lymphocytic leukemia (B-CLL) patients,[59,60] and approximately one-third of B-cells from non-Hodgkin lymphoma patients express Fc_εRII/CD23.[61]

Induction of Fc_εRII/CD23 on human B-cells

Fc_εRII/CD23 is not only weakly expressed on resting B-cells, but upon stimulation by antigens,[62] mitogens,[63,64] or soluble protein derived from T-cells,[64-66] the expression of the molecule on these cells is up-regulated. As the B-cell is driven to a further stage of maturation, becoming a plasma cell producing immunoglobulin, the cell membrane positivity for the receptor is lost. Up-regulation of Fc_εRII/CD23 in the early stage of B-cell activation has been of particular interest to several investigators. In this respect, the inducibility of the receptor on different hematopoietic cell lineages, as well as the ability of different lymphokines and mitogen to stimulate the induction of this receptor have been extensively studied. Early investigations indicated that the proportion of Fc_εRII/CD23 bearing cells amongst normal rat lymphocytes[67]

and mouse macrophages and lymphocytes,[68] increases in the presence of rat and mouse IgE respectively. It has been shown that pokeweed mitogen (PWM) significantly increases the expression of $Fc_{\varepsilon}RII$/CD23 on peripheral blood mononuclear cells.[63] Addition of IgE and conditioned media from PHA-activated mononuclear cells has been shown to induce the expression of this receptor.[44] Similar findings have been found as a result of using a combination of phorbol ester and IgE in a culture of resting B-cells.[69] It has been recently found that soluble IgE, in complex with specific antigen, substantially increases the expression of $Fc_{\varepsilon}RII$/CD23 and HLA class II antigens[62] which are physically[70] and functionally[52,71] associated on the membrane of human B-cells. As mentioned above, the role of soluble T-cell derived factor in relation to the modulation of the cell surface membrane has been studied. It has been reported that recombinant human interleukin 4 (IL-4) specifically enhances the expression of $Fc_{\varepsilon}RII$/CD23 on human B-cells, whereas other T-cell derived lymphokines such as IL-2, IL-1, IFN-γ, GM-CSF, and low molecular B-cell growth factor (BCGF) were found to be inactive in this respect.[58] It has been seen that IL-4 induction of expression of $Fc_{\varepsilon}RII$/CD23 on the cell membrane correlates with the level of induction of specific mRNA.[39] Induction of $Fc_{\varepsilon}RII$/CD23 on normal peripheral monocytes and a monocytic cell line has also been studied. $Fc_{\varepsilon}RII$/CD23 can be up-regulated on peripheral monocytes by recombinant IL-4, but not by other lymphokines.[72]

It appears that IL-4 induced expression of this receptor on B-cells, but not on monocytes, is down-regulated by IFN-γ, suggesting a different pathway for expression of $Fc_{\varepsilon}RII$/CD23 on B-cells and monocytes. This observation, in parallel with that of Yokota et al.[44] that $Fc_{\varepsilon}RIIa$ is constitutively but specifically expressed only in B-cells whereas $Fc_{\varepsilon}RIIb$ is expressed in a variety of cells following stimulation by IL-4, explores the heterogeneity in regulation of expression, as well as biological function, depending on the cell type expressing either of these classes of receptor.

Function of $Fc_{\varepsilon}RII$/CD23

A variety of biological functions have been described for $Fc_{\varepsilon}RII$/CD23, mostly on the basis of which cell type expresses it. They include growth promoting activity for B-cells, autostimulatory activity for established B-cell lines and B-cell differentiation activity to regulate production of specific immunoglobulin isotypes. Also, IgE-mediated effector functions of eosinophils and platelets,[21] inhibition of monocyte migration[52] and induction of fever[73] have been attributed to this receptor.

B-cell growth activity of $Fc_{\varepsilon}RII$/CD23

It has been shown that $Fc_{\varepsilon}RII$/CD23 is expressed only on mature sIgM and IgD positive B-cells, and inducibility of this molecule is also restricted only to the stage in which B-cells bear this phenotype.[34,65] Gordon and his associates[74] first reported that certain monoclonal antibodies directed against $Fc_{\varepsilon}RII$/CD23 can mimic the effects of a T-cell derived B-cell growth factor (BCGF) on phorbol ester activated tonsillar B-cells. Similar activity has been reported using other monoclonal antibodies against this receptor in tonsillar B-cells.[75,78] The contribution of IgE has also been investigated,[69] indicating that human IgE can augment the stimulatory activity observed by both BCGF and monoclonal antibody. It has also been reported that $Fc_{\varepsilon}RII$/CD23 is a prerequisite for transformation of B-cells by Epstein Barr virus (EBV). An isolated $Fc_{\varepsilon}RII$/CD23 negative B-cell population failed to become an immortalized cell line following infection by EBV.[54] Most EBV-transformed B-cell lines release the soluble fragments of $Fc_{\varepsilon}RII$/CD23 into the culture supernatants. Autostimulatory activity of this soluble protein on resting tonsillar B-cells activated by TPA has also been reported.[79] Delespesse et al.[80] showed that the response of B-cells to anti-IgM and IL-4 can be blocked by human IgE, or monoclonal antibodies specific for different fragments of sCD23 have been produced[36] which are capable of suppressing the autonomous growth and proliferation of a panel of EBV-immortalized B-cell lines in a dose-dependent manner. It is of particular interest that only monoclonal antibody directed against a 32-35 KDa fragment of sCD23 was found to affect the growth and proliferation of B-cell lines, while the MAb detecting a 25 KDa fragment was revealed to be inactive. It is worth mentioning that a similar pattern of activity has been seen when resting tonsillar high density B-cells were activated by mitogen and IL-4.[77] More importantly, it has been recently shown that recombinant soluble CD23 in association with IL-1α rescue the germinal center cells undergoing the apoptosis process.[81,82] These results indicate that $Fc_{\varepsilon}RII$/CD23, or its fragments, may play a crucial role in B-cell growth and proliferation.

Role of soluble $Fc_{\varepsilon}RII$/CD23 in regulation of IgE synthesis

The regulation of IgE synthesis has been studied in rodents.[22] Various studies have shown that supernatants of T-cell clones activated by PHA can enhance the production of IgE synthesis,[83] or supernatants of a T-cell line activated by parasite antigens can augment IgE synthesis by normal unstimulated B-cells.[84] These observations indicate that, following activation of T lymphocytes, a specific factor with IgE binding capacity, derived from an EBV-transformed B-cell line, can enhance the synthesis of IgE in B-cells from atopic individuals.[85] Coffman et al.[86] demonstrated that murine IL-4 induces IgE production by murine splenic B-cells activated with lipopolysaccharide (LPS). These observations, and the finding that IL-4 can specifically induce the expression[87] and enhance shedding of the receptor,[88,89] prompted several investigators to study the role of IL-4 and soluble $Fc_{\varepsilon}RII$/CD23 in regulation of IgE synthesis.

Native purified fragments of $Fc_{\varepsilon}RII/CD23$ derived from RPMI-8866 were reported to enhance the synthesis of IgE by B-cells activated with IL-4.[88] Indirect evidence has been obtained for the involvement of $Fc_{\varepsilon}RII/CD23$, using monoclonal antibody directed against this molecule, indicating that IL-4 induced synthesis of IgE by PBMC can be suppressed in the presence of such antibody in B-cell cultures.[90] Similar results have been reported on the ability of IL-4 to enhance the production of IgE, and suppression of this IL-4 activity by monoclonal antibody against $Fc_{\varepsilon}RII/CD23$.[80] This observation that monoclonal antibody to $Fc_{\varepsilon}RII/CD23$ can suppress IL-4 induced IgE synthesis, strongly suggests that either $Fc_{\varepsilon}RII/CD23$ or its soluble forms are required for an IgE response.

The relationship between $Fc_{\varepsilon}RII/CD23$ and histamine releasing factors (HRFs)

The histamine releasing activity (HRA) of culture supernatants of human mononuclear cells was first reported by Thueson et al.[91] Similar activity has been reported within supernatants of PHA-activated mononuclear cells from asthmatic patients.[92] This leukocyte-derived HRA was further characterized by other investigators[93-95] and designated as histamine releasing factor (HRF). The production of HRF by activated T-cells,[96] alveolar macrophages,[93] monocytic cell line U937 and EBV-transformed B-cell line RPMI-8866[97] and platelets[98] has been reported. The relationship between HRF and IgE has been demonstrated by MacDonald et al.[99] Firstly, when IgE is removed from the surface membranes of basophils, HRF is no longer active; secondly, the activity is completely removed by passing the material containing HRF down an IgE-sepharose column, indicating the binding capacity of HRF for IgE. The molecular weight of HRF has been shown to be heterogenous; 30-50 KDa and 10-20KDa[94,100] bands have been revealed by SDS-PAGE. The relationship between soluble $Fc_{\varepsilon}RII/CD23$ and histamine releasing activity has recently been investigated.[101]

The IgE-affinity purified $sFc_{\varepsilon}RII/CD23$ derived from the culture supernatant of a lymphoblastoid cell line (RPMI-8866) has been shown to strongly trigger nasal polyp mast cells to release histamine in a dose-dependent manner.[101] By acid elution of IgE from the cell membrane it was clearly demonstrated that this effect is not orchestrated through an IgE mediated mechanism. More recently, our original suggestion has found more ground ever since it was demonstrated that recombinant soluble CD23 can trigger mast cells to release histamine via crosslinking of CD21 expressed on the mast cell membrane.[102] It has been reported that IgE is capable of protecting the membrane form of its low affinity receptor from becoming a target for proteolytic enzymes.[69] Moreover, it has been reported that a large amount of the soluble receptor is detected in sera from allergic patients in a complex with IgE.[103] Whether the formation of IgE-soluble receptor complexes can down-regulate the mechanism of mast cell triggering and histamine release by soluble $Fc_{\varepsilon}RII/CD23$ or not needs further investigation. Until the characterization of the molecular structure of the so-called HRF, its relationship with $sFc_{\varepsilon}RII/CD23$ despite the similarity in molecular size and cellular sources remains to be elucidated.

Prospect for future studies

IgE with its crucial role in allergic reactions, and its potential capability to bind to different types of membrane-associated receptors on various cells, has remained as a central focus and major target for research and immunological intervention. Several strategic approaches for these aims can be outlined, such as production of potent monoclonal antibody directed against specific sites on IgE molecules in order to prevent IgE from binding to its potential receptor on the cell surface. A similar approach may concern the design of IgE receptors (high and low affinity) in order to interfere with IgE cytophilic activity. Considering the role of CD23 and its active pharmacological soluble peptides in an IgE mediated response, several approaches such as the use of peptide and anti-peptide antibodies or cytokine antagonists are among the attractive strategies for those who are working in the field of designing an anti-allergic vaccine.

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