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Review

Expression and function of an IgE-binding animal lectin (ϵ BP) in mast cells

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Abstract: ϵ BP (IgE-binding protein) is a 31,000 M_r protein originally identified in rat basophilic leukemia (RBL) cells. The protein is composed of two domains with the amino-terminal domain containing a highly conserved repetitive sequence and the carboxyl-terminal domain containing consensus sequences shared by other β -galactoside-binding soluble lectins. The protein has wide tissue distribution, is found on cell surfaces and in extracellular milieu. By combined efforts from several research groups including ours a multifunctional nature of this lectin began to emerge. This review emphasizes the following characteristics of ϵ BP: (i) ϵ BP is secreted by cells such as macrophages; (ii) like many other lectins, ϵ BP functions at least bivalently; (iii) ϵ BP has specificity for distinct oligosaccharide structures that have a terminal galactose not masked by sialic acids; and (iv) in addition to binding IgE, ϵ BP binds to surfaces of various cell types via lectin-carbohydrate interaction. Importantly, ϵ BP binds to the IgE receptor on mast cells. We propose that ϵ BP can function as a modulatory protein on various cells by cross-linking critical cell surface glycoproteins. The proposed action of ϵ BP on mast cells is presented as a model.

Key words: Glycobiology; Animal lectin; ϵ -BP; IgE; Mast cell

Introduction

Glycobiology has emerged as an exciting new frontier in biological sciences with animal lectins playing a prominent role. This review focuses on an animal lectin that was identified in our laboratory via its IgE-binding property, hence the name IgE-binding protein (ϵ BP). The same protein has also been studied by a number of other laboratories and various functions have been proposed. In this review, we will briefly describe the historical aspects and biochemical properties of ϵ BP and then summarize evidence for the

extracellular localization and multivalent property of ϵ BP. Information will then be presented that supports our view of how this lectin may function as an extracellular protein by recognition of critical cell surface glycoproteins, culminating with a model depicting ϵ BP as a broad-spectrum modulatory protein. It is important to recognize at the outset that the function of this protein is not limited to mast cells and its IgE-binding property is merely one of a spectrum of functions of this protein.

Historical Aspects

A few years ago we discovered an IgE-binding protein (ϵ BP) of Mr 31,000 in rat basophilic

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leukemia cells (Liu and Orida, 1984; Liu et al., 1985). Cloning and sequencing of cDNA revealed a novel sequence with several interesting structural features (described in section III) (Liu et al., 1985; Albrandt et al., 1987; Liu, 1990). Subsequently, another group of researchers cloned cDNA coding for a mouse carbohydrate-binding protein, CBP35, and sequence comparison revealed that it is highly homologous to rat ϵ BP (Jia and Wang, 1988). In a collaborative effort, we showed that ϵ BP, like CBP35 has an intrinsic galactose-binding activity and that ϵ BP and CBP35 are rat and mouse protein homologues, respectively (Laing et al., 1989). It then became clear that the same lectin has also been studied by several other groups and designated variously as metastasis-associated lectin (L-34) (Raz et al., 1989) and lung lectins (HL-29 or RL-29) (Sparrow et al., 1987; Leffler and Barondes, 1986). More recently, the Mac-2 antigen, a murine macrophage cell-surface protein, has been shown to be homologue of ϵ BP (Cherayil et al., 1989). There has been an exponential growth in our knowledge of this animal lectin and its multifunctional nature. Although we continue to use the term ϵ BP, we expect that a name will soon be designated by consensus for this multifunctional lectin.

Biochemical Properties of ϵ BP

As mentioned, ϵ BP has been studied (with different designations) by several research groups. Protein sequences of this lectin from various species have been established, either from DNA cloning or direct protein sequencing.

ϵ BP contains two domains

(Fig. 1) One characteristic feature of ϵ BP is that it has a two-domain structure. The carboxyl-terminal domain contains both hydrophobic and hydrophilic regions typical of globular proteins. In contrast, the distinct amino-terminal domain is composed of a highly conserved sequence of nine amino acids, Tyr-Pro-Gly-Pro/Gln-

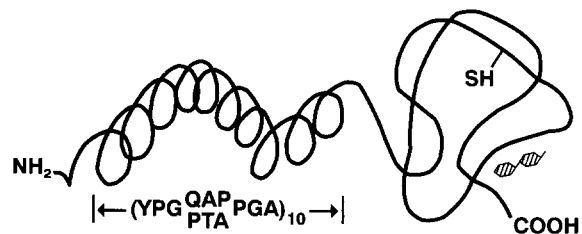


Fig. 1. A model for ϵ BP structure. A two-domain structure of ϵ BP is depicted. The amino-terminal domain, which consists of tandem repeats of nine amino acids (Tyr-Pro-Gly-Gln/Pro-Ala/Thr-Pro/Ala-Pro-Gly-Ala), is presented as a hypothetical helical structure with many turns. The carboxyl-terminal domain is viewed as a typical globular structure. A single cysteine residue in the carboxyl-terminal domain is shown (SH). A pair of solid hexagons indicates the putative carbohydrate-binding site of ϵ BP.

Ala/Thr-Pro/Ala-Pro-Gly-Ala, repeated ten times (Albrandt et al., 1987). This sequence has significant similarity with collagen, although it lacks the repetitive Gly-X-Y sequence characteristic of collagen and essential for its triple helical structure. The repeats also bear similarity to the repetitive sequences found in elastin. The cDNA coding for human ϵ BP, Mac-2 and L-29 have recently been cloned (Robertson et al., 1990; Cherayil et al., 1990; Oda et al., 1991). Comparing the deduced sequence of human ϵ BP with that of rat and mouse ϵ BP revealed that the two-domain structure and protein sequence of this lectin are highly conserved.

ϵ BP is a soluble lectin containing an S-type carbohydrate-recognition domain

Animal lectins have been classified according to the type of carbohydrate-recognition domains (CRD) they contain (Drickamer, 1988). One is C-type (calcium-dependent), a notable example being the cell adhesion proteins, selectins (LEC-CAM) (Springer and Lasky, 1991). The other type is S-type with the classical example being the 14 kDa soluble galactose-binding lectins. The carboxyl-terminal domain of ϵ BP shares significant sequence similarity with the 14 kDa lectins (Liu, 1990) and thus ϵ BP is a new example of an S-type lectin. Genes for S-type lectins also are

similarly organized. We have recently cloned ϵ BP genomic DNA and determined that the carboxyl-terminal domain is encoded by three exons (Gritzmacher et al., 1992). These three exons correspond well in size and share sequence homology with the three exons coding for 14 kDa S-type lectins (Gitt and Barondes, 1991; Ohyama and Kasai, 1988).

ϵ BP is functional in the absence of reducing agents

It is well established that the activity of 14 kDa S-lectin is dependent on reducing agents ((Tracey et al., 1992) and references therein). For this reason, this type of lectin has been designated as thiol-dependent, or S-type (Drickamer, 1988). The carbohydrate-binding function of CBP35 has also been described as dependent on reducing agents (Roff and Wang, 1983). However, in our earlier work, ϵ BP was purified in the absence of reducing agents. Therefore, we questioned the thiol-dependency of this subtype of lectins. To clarify the difference between ϵ BP and CBP35, we compared the thiol dependency of ϵ BP from mouse, rat and human cell lines. We found that ϵ BP was isolated in comparable amounts, regardless of whether the cells were lysed in the presence or absence of reducing agents (Frigeri et al., 1990). Furthermore, purified ϵ BP was subjected to extensive dialysis in the presence or absence of 2-mercaptoethanol (2-ME) followed by assessment of IgE-binding activity. Essentially equivalent activity was found for ϵ BP irrespective of whether 2-ME was present (Frigeri et al., 1990). We thus concluded that ϵ BP is functionally stable in the absence of reducing agents. Therefore, it is advisable that S-type designates the soluble nature of the lectins rather than thiol-dependency.

Other protein characteristics

In addition to the above characteristics, part of the carboxy-terminal domain sequence of ϵ BP shares significant sequence similarity with a region of macrophage/lymphocyte IgG receptor (Albrandt et al., 1987). Further sequence analysis revealed that the protein does not contain a

classical signal sequence or a membrane-spanning region. Both mouse and rat sequences do not contain potential N-linked glycosylation sites (Albrandt et al., 1987; Jia and Wang, 1988). However, there is one potential N-linked site within the amino-terminal portion of the human sequence (Robertson et al., 1990); although it is unknown if this site is utilized.

Existence of ϵ BP in Extracellular Media

Both the 31 kDa (i.e., ϵ BP) and 14 kDa S-lectins do not contain a classical signal sequence. Nevertheless, the possible extracellular functions of this class of lectins have been discussed (Barondes, 1984). Barondes and coworkers have studied soluble animal lectins extensively and have provided evidence for extracellular functions of certain S-type lectins. Some of these lectins are initially concentrated inside the cells, but are eventually exported (Barondes, 1984). Interestingly, the externalization of this sub-type of lectins appears to be regulated by cell differentiation or tissue development (Cooper and Barondes, 1990).

We have also analyzed the sub-cellular localization of ϵ BP in the cells. Using two different approaches with the aid of anti-peptide antibodies specific for ϵ BP, we concluded that ϵ BP is primarily a cytoplasmic protein and only a small portion of total cellular ϵ BP is associated with cellular membranes (Gritzmacher et al., 1988). A similar conclusion was reached in studies of CBP35; although the lectin was also noted to be present in the nucleus (Moutsatsos et al., 1986). In the above studies with anti-peptide antibodies, we also demonstrated a distinct but low-level surface expression of ϵ BP (Gritzmacher et al., 1988). With high-affinity rabbit polyclonal antibodies generated against recombinant ϵ BP, we subsequently quantitated cell surface ϵ BP levels on various mast cell and macrophage lines (Frigeri and Liu, 1992). The expression of ϵ BP on the cell surface of mast cells and macrophages was thus definitively established.

Since ϵ BP does not contain any recognizable

transmembrane segment, it was at first not clear how the protein was expressed on the cell surface. We subsequently demonstrated that ϵ BP is displayed on cell surfaces in a manner that is elutable by lactose, most likely through attachment to cell surface glycoconjugates (Frigeri and Liu, 1992). We also showed that the putative ϵ BP-binding sites are present in comparable amounts on the surfaces of various mast cell and macrophage lines as demonstrated by using radiolabeled ϵ BP (Frigeri and Liu, 1992).

In addition to the results described above, we demonstrated that the level of surface ϵ BP on RBL cells increases when the cells are activated by IgE immune complexes (Frigeri and Liu, 1992). By pulse-chase analysis, Mac-2 has been recently shown to be secreted by activated macrophages (Cherayil et al., 1989). We have also detected ϵ BP in the peritoneal lavage fluid from thioglycollate-stimulated mice but not in untreated mice (Frigeri, L.G., unpublished observation). Taken together, the findings suggest the interesting possibility that ϵ BP functions in the extracellular environments.

Multivalent Property of ϵ BP

Like many other lectins ϵ BP behaves at least bivalently, as best demonstrated by its ability to agglutinate erythrocytes (Frigeri et al., 1990). With the production of large amounts of human recombinant ϵ BP (Hsu et al., 1992), we were able to analyze in detail the basis of the multivalency. First, we obtained a fragment of ϵ BP that contains only the carboxyl-terminal half of ϵ BP (designated as ϵ BP-C). By equilibrium dialysis, we determined that both ϵ BP and ϵ BP-C contain only one lactose-binding site (Hsu et al., 1992). However, ϵ BP-C differs from ϵ BP in that the former does not cause hemagglutination.

Subsequently, when analyzing ϵ BP binding to solid-phase IgE, we obtained an important clue for the basis of the multivalency. ^{125} I-labeled ϵ BP was exposed to IgE coated on microtiter plates in the presence of various concentrations of ϵ BP

and ϵ BP-C. As expected, ϵ BP-C inhibited the binding effectively in a dose-dependent fashion. In significant contrast, increasing ϵ BP concentrations enhanced the binding of ^{125} I- ϵ BP to IgE, reflecting cooperative binding (Hsu et al., 1992). The results were interpreted as an indication that ϵ BP self-associates and that this property is dependent on the amino-terminal portion of ϵ BP.

We then probed for the existence of oligomers of ϵ BP by a chemical crosslinking study (Hsu et al., 1992), an approach widely used in assessment of protein self-association. Higher molecular weight species appeared in appreciable amounts when ϵ BP (50 μ g/ml, 1.9 μ M) was treated with 1,5-difluoro-2,4-dinitrobenzene (DFDNB). Even higher quantities of the high molecular weight species were observed using ϵ BP at 150 μ g/ml (5.7 μ M). The apparent Mr values of these species corresponded to those predicted for ϵ BP oligomers ranging from dimers to hexamers. These species resulted from chemical crosslinking, since they were not detected in the sample of ϵ BP at 150 μ g/ml incubated in the absence of DFDNB. A striking contrast was obtained when equivalent molar concentrations of ϵ BP-C were similarly treated. In this instance, although a species apparently corresponding to a dimer was detected when ϵ BP-C was present at 30 and 90 μ g/ml (1.9 and 5.7 μ M, respectively), significantly less of the higher molecular weight species were formed. Densitometric analyses of autoradiographs provided quantitative data supporting a higher degree of crosslinking of ϵ BP (64%) as compared to ϵ BP-C (27%) (Hsu et al., 1992).

From these results, we proposed the following model: **ϵ BP forms dimers or oligomers through non-covalent inter-molecular association involving the amino-terminal domain.** The amino-terminal domain is composed of proline/glycine-rich tandem repeats. It is possible that this domain forms a unique tertiary structure that is predisposed to intermolecular association. Moreover, the self-association constant for ϵ BP must be low, since we have not detected stable ϵ BP dimers or oligomers without using chemical

crosslinkers. However, protein self association may be facilitated as ϵ BP binds to multivalent ligands, resulting in highly stable complexes (Figure 2). Recently, positive cooperativity in binding of L-29 (identical to ϵ BP) to laminin was reported (Massa et al., 1993). Consistent with our model, the requirement of the amino-terminal domain for the observed positive cooperativity was also noted. However, these authors showed that there was no difference in sensitivity to lactose inhibition for binding of L-29 to laminin at high and low concentrations of L-29. Thus, the situation may be more complex than the model proposed in Fig. 2 and further experimentations are necessary to clarify the mechanisms of self-association of ϵ BP.

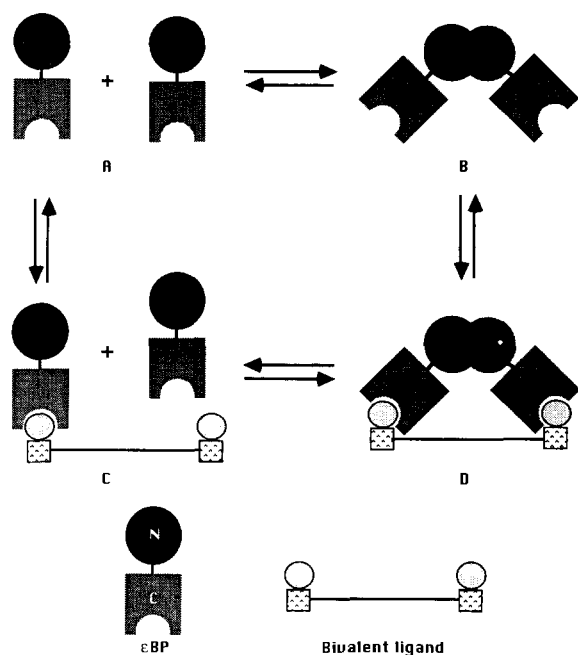


Fig. 2. Model of ϵ BP self-association resulting in a dimer with a much higher avidity than the monomer for a bivalent ligand. A schematic diagram illustrating noncovalent homodimerization of ϵ BP. Our model depicts that (i) monomeric ϵ BP is favored in solution (A) and (ii) ϵ BP has a tendency for self association involving the amino-terminal domain (A- $\rightarrow$ -B). When ϵ BP encounters a bivalent ligand monovalent interaction occurs (A- $\rightarrow$ -C) and then the second molecule can bind to the ligand much more tightly due to protein-protein interaction (C- $\rightarrow$ -D).

Another possible mechanism to account for ϵ BP bivalency needs to be considered. ϵ BP contains a single cysteine residue in the carboxyl-terminal domain and thus theoretically can dimerize by forming an intermolecular disulfide bridge, producing a bivalent molecule. It has recently been reported that disulfide-linked dimers of CBP35 (identical to ϵ BP) exist (Woo et al., 1991). However, we believe that the presence of such a species alone does not explain the multivalency of ϵ BP, considering that ϵ BP possesses hemagglutination activity in the presence of reducing agents. Nevertheless, the observation of disulfide-linked ϵ BP dimer is significant and how the dimer may contribute to the function of ϵ BP should be addressed. It is possible that non-covalent self association and covalent dimerization occur in conjunction, resulting in more stable oligomeric structures with a concomitant higher avidity for multivalent ligands.

Recognition of Specific Glycoproteins by ϵ BP

Having established the existence of ϵ BP in the extracellular space and demonstrated the binding of ϵ BP to various cells, we were interested in identifying specific ligands recognized by ϵ BP beyond IgE. The identity of specific cell surface glycoproteins with the capacity to bind ϵ BP was seen as a crucial step in further defining the biological role of this lectin. We surface labeled RBL cells by radioiodination and affinity purified labeled protein using immobilized ϵ BP. Only three major protein bands were detected by SDS-PAGE (Frigeri et al., 1993). Significantly, when other cell lines were analyzed in the same manner, simple patterns were also seen. For example, ϵ BP was found to recognize primarily only one cell surface protein on human umbilical cord vein endothelial cells (Frigeri, LG, unpublished observation). The finding of a limited number of proteins that bind to ϵ BP in the different cell types examined indicated a high selectivity of glycoprotein recognition by ϵ BP.

Important insights to the function of ϵ BP were

gained by our finding that ϵ BP binds the high affinity IgE receptor (Fc ϵ RI) (Frigeri et al., 1993). From the analysis of ϵ BP-reactive glycoproteins on RBL cells mentioned above, we suspected that one of the proteins might be the α subunit of Fc ϵ RI, migrating as a broad band with M_r 50,000. We then subjected the ϵ BP-purified glycoproteins to affinity purification with IgE-Sepharose 4B and found that this M_r 50,000 protein did indeed bind IgE. To further prove that the detected species was Fc ϵ RI α , ϵ BP-purified glycoproteins were immunoprecipitated with two monoclonal antibodies specific for Fc ϵ RI (one against the α and the other against the β subunit). With each antibody, the M_r 50,000 species was precipitated, while the negative control IgG monoclonal antibody did not react with the protein. In addition, when Fc ϵ RI that was purified by using IgE affinity chromatography was mixed with ϵ BP-Sepharose 4B, we found a major portion of the purified receptor bound to ϵ BP. These results clearly established that ϵ BP recognizes Fc ϵ RI. Finally, the binding of ϵ BP to Fc ϵ RI on intact RBL cells was also demonstrated by chemical cross-linking experiments (Frigeri et al., 1993).

The finding of a limited number of glycoprotein species recognized by ϵ BP is not surprising. Recently, Rosenberg et al. reported that Mac-2 (identical to ϵ BP) binds two glycoproteins from human colon adenocarcinoma cell lines (Rosenberg et al., 1991), a result that is consistent with the restricted recognition of glycoproteins by this type of lectin. Carbohydrate specificity of RL-29 and HL-29, rat and human lung lectins, respectively (identical to rat and human ϵ BP), have been extensively studied (Leffler and Barondes, 1986; Sparrow et al., 1987). Although S-type lectins are generally referred to as galactoside-binding lectins, they exhibit selectivity for distinct oligosaccharide structures. Thus, the relative affinity of various saccharides for RL-29 is Gal(1) < Gal β 1-3GalNAc(7) < Gal β 1-4Glc(100) < Gal β 1-3GlcNAc(270) < Gal β 1-4GlcNAc(700) < GalNAc α 1-3(Fuc α 1 $\rightarrow$ 2)Gal β 1-4Glc(2500) (the numbers in parenthesis refer to the relative

activity of the saccharides) (Leffler and Barondes, 1986). Of physiological interest is the fact that this type of lectin appears to preferentially bind blood group A antigen.

Broad-Spectrum Modulatory Function of ϵ BP

Based on the various experimental data presented above, it is evident that ϵ BP is secreted by cells, such as macrophages, and binds selectively to some cell surface glycoproteins. It is conceivable that secreted ϵ BP has wide-ranging effects on a variety of cell types by binding to cell surface glycoconjugates. Since ϵ BP is expressed by various cells and is potentially secreted by these cells, it could thus exert its function in either an autocrine or paracrine fashion. The effect is expected to be broad because each cell type may have a different set of ϵ BP-reactive glycoconjugates linked to a spectrum of cellular functions. Since ϵ BP functions at least bivalently, it has the potential to link two glycoproteins that share oligosaccharide chains recognized by ϵ BP on any cell type. In this way, ϵ BP may modulate the functions associated with these glycoproteins.

The proposed activity of ϵ BP can be illustrated by using the effect of ϵ BP on mast cells as a model.

Model 1: ϵ BP activates mast cells by bridging IgE receptors, receptor-bound IgE, or IgE and receptor. Because ϵ BP binds both IgE and Fc ϵ RI and because of its multivalent property, the following situations may be envisaged: (1) ϵ BP crosslinks two or more Fc ϵ RI; (2) ϵ BP crosslinks two or more receptor-bound IgE; and (3) ϵ BP bridges receptor bound IgE and Fc ϵ RI. Since it is well known that receptor aggregation is a necessary and sufficient signal for mast cell activation (Metzger et al., 1986), all of these above situations could lead to mast cell activation.

Model 2: ϵ BP modulates Fc ϵ RI-mediated mast cell activation through binding to Fc ϵ RI or IgE.

Another possible mode of action of ϵ BP is that it may have a modulatory effect on IgE receptor-mediated activation of mast cells. For example, it can be envisaged that by coupling two or more IgE receptor molecules, ϵ BP may augment receptor aggregation induced by IgE immune complexes (Fig. 3). In fact, we already have data supporting a potentiating activity of ϵ BP on

IgE-mediated serotonin release from RBL cells (Zuberi, R., Frigeri, L.G., and Liu, F.-T. unpublished results).

One interesting and unique feature that distinguishes ϵ BP from many other cytokines is the dynamic nature in its recognition of ligands. Specifically, the natural ligand of ϵ BP is a β -galactoside structure and the ligand binding is diminished when the galactose residue is derivatized with sialic acids (Leffler and Barondes, 1986). Therefore, the recognition of glycoprotein by ϵ BP is dependent on the presence of an appropriate galactose-containing structure and whether the galactose is capped by sialic acids. Recently, we provided an example of such differential recognition of glycoforms by ϵ BP. First, we noted that although human ϵ BP binds murine monoclonal IgE well, it binds poorly to a human myeloma IgE (Robertson et al., 1990). However, neuraminidase treatment of the myeloma IgE produced full binding activity for ϵ BP. We next investigated the degree of binding of ϵ BP to various polyclonal human IgE samples. We found that the level of IgE recognition by ϵ BP varied between samples containing comparable amounts of total IgE. Furthermore, for three of the four samples tested, a pronounced increase in binding to ϵ BP was found following neuraminidase treatment. The fourth sample, however, was unique in its high capacity of binding to ϵ BP with or without neuraminidase treatment (Robertson and Liu, 1991). We interpreted the data as an indication of the presence of different IgE glycoforms that vary in the extent of sialylation.

Therefore, we expect that the recognition of ϵ BP for various other glycoprotein ligands would also be dependent on their extent of sialylation. In this regard, it is important to note that the degree of sialylation is dependent on cell differentiation and activation. For example, there is a decrease in cell surface sialic acid upon maturation of myeloid cells (Lichtman and Weed, 1972). In addition, neutrophil activation has been related to desialylation occurring on the cell surface (Gallin, 1980). Recently, it has been shown that

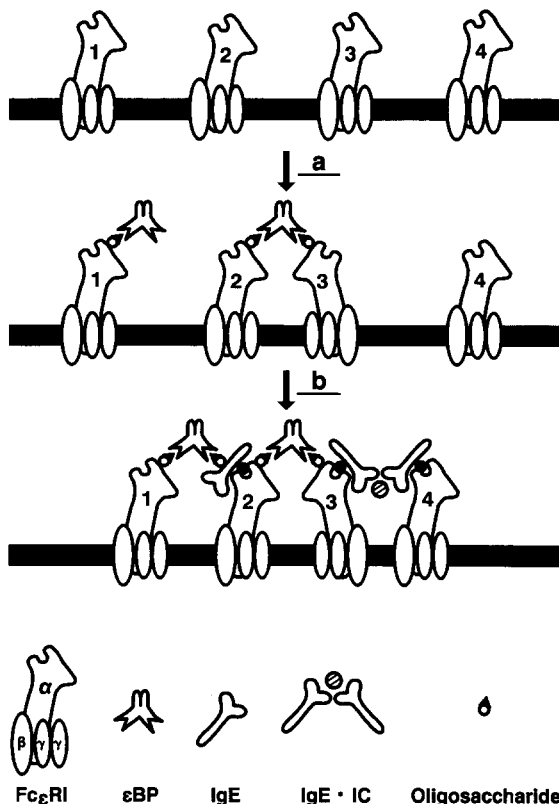


Fig. 3. Facilitation of IgE receptor aggregation by ϵ BP. This figure is a schematic drawing of the IgE receptor aggregation facilitated by ϵ BP. Step *a* depicts the exposure of mast cells to ϵ BP that results in coupling of two IgE receptor molecules (numbers 2 and 3) by ϵ BP. Step *b* depicts a subsequent exposure of the cells to IgE immune complexes (IgE-IC), that results in two other receptor molecules (numbers 1 and 4) being brought into proximity by IgE, because IgE bridges two receptor molecules directly (numbers 3 and 4) or via ϵ BP (numbers 1 and 2). For simplicity, the binding of ϵ BP to other glycoproteins and the bridging of two receptor-bound IgE by ϵ BP are not included in the diagram. The various structures are labeled at the bottom of the figure; the closed circle attached to IgE represents a peptide determinant recognized by the IgE receptor.

sialidase is mobilized from intracellular stores to the surface of neutrophils following neutrophil activation (Cross and Wright, 1991). The mobilized sialidase is then responsible for the activation-dependent desialylation of the neutrophil surface. Taking this information together, it appears that the degree of sialylation of cell surface glycoconjugates is a dynamic process. Therefore, we propose that: **recognition of cell surface glycoproteins by ϵ BP and the action of ϵ BP on various cells are functions of cell differentiation and activation.**

Conclusion

From the above analysis, it should be evident that ϵ BP is a multifunctional protein. The "multifunctionality" refers to two different aspects of ϵ BP. First, the structure of ϵ BP contains two separate domains with the amino-terminal repetitive sequence likely exhibiting a unique function that is distinct from the lectin function of the carboxyl-terminal domain. Second, ϵ BP is distributed widely and found in various tissues and subcellular compartments and is likely to display different functions in different environments. For example, it may have one function in the nucleus and totally different functions on the cell surface or in the extracellular fluid. The function on the cell surface may also vary depending on cell types. In fact, various functions proposed for S-type lectins include regulation of cell growth (Moutsatsos et al., 1987; Laing and Wang, 1988), neoplastic transformation and metastasis (Raz and Lotan, 1987; Raz et al., 1991) and cell adhesion (Woo et al., 1990). The multifunctional nature of soluble (S-type) animal lectins has been reviewed (Barondes, 1981; Harrison, 1991).

Several recent developments in our laboratory allowed us to expand further the multifunctional nature of ϵ BP. We found that ϵ BP binds to the surface of various cell types, including cells that normally do not express ϵ BP, for instance, lymphocytes and endothelial cells. We found that ϵ BP binding to these cells is a function of its

lectin property because the binding can be inhibited by lactose. Importantly, a limited number of glycoprotein species are recognized by ϵ BP on a given cell type.

Based on these new developments and other knowledge of ϵ BP summarized in this review, the following picture has emerged: (i) ϵ BP can bind to cell surface glycoproteins that possess specific oligosaccharide structures; (ii) because ϵ BP is released by certain cell types, it has the potential to target a wide range of cells by binding to their surface glycoproteins; and (iii) most importantly, because ϵ BP can function bivalently (or oligovalently), it can bridge two or more glycoproteins and possibly influence various functions of these cells. The actual biological function that is affected may be different for each cell type and may quite possibly depend on the specific function of the glycoprotein that serves as an ϵ BP ligand. It should also be mentioned that, in our view, ϵ BP resembles in many ways some cytokines. Specifically, it is produced by various different cell types and acts on a wide range of tissues. In this regard, it is significant that some of the interleukins, for example, IL-1 (Muchmore and Decker, 1987) and IL-2 (Sherblom et al., 1991), have been suggested to have lectin-like properties. The role of some S-type lectins in modulating cellular activity, by binding to critical cell surface glycoproteins, has been proposed before (Feizi and Childs, 1987) and may prove to be one of the general functions of soluble animal lectins.

In the case of mast cells, the modulatory function of ϵ BP appears evident. ϵ BP may be secreted by activated mast cells or macrophages. The secreted protein may either i) directly activate other neighboring mast cells through binding to receptor-bound IgE or IgE receptor; or ii) potentiate the activation of those mast cells mediated by other stimuli. In this way, ϵ BP may contribute to amplification of an inflammatory response. The discovery of a multifunctional lectin that binds IgE and IgE receptor thus adds a new dimension to allergy research. It also opens up new possibilities of modulation of the immediate hypersensitivity reaction.

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