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Coordinated action of IgE and a B-cell-stimulatory factor on the CD23 receptor molecule up-regulates B-lymphocyte growth

(Epstein–Barr virus transformation/interleukins/lymphokines)

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ABSTRACT **The CD23 (BLAST-2) antigen, recently identified as the low-affinity IgE receptor of B lymphocytes, has also been implicated as the focus for growth-promoting signals delivered to activated B cells by a low molecular weight B-cell growth factor (BCGF). Here we show that IgE and BCGF can coordinate B-lymphocyte growth through their opposing effects on the CD23 molecule. While the activation of purified quiescent B cells with phorbol 12-myristate 13-acetate led to the induction of 45-kDa CD23 at the surface membrane, the inclusion of IgE increased CD23 expression by a factor of ≈5. The addition of BCGF resulted in the rapid release of a 35-kDa form of CD23 from the cell surface. This shed molecule is associated with autocrine growth factor activity. Substantially more of this material was generated by BCGF acting on cells that had been stimulated in the presence of IgE. The combined effects of IgE and BCGF on DNA synthesis in activated B cells were more than additive. IgE similarly augmented the stimulatory capacity of a CD23 antibody that mimics the biological actions of BCGF. Binding of the anti-receptor antibody to its 45-kDa target at the B-cell surface also prompted the release of the 35-kDa soluble species. These results demonstrate a pleiotropy in the CD23 molecule with regard to both ligand binding and the subsequent behavior of the receptor. The ability of this single receptor to orchestrate a B-lymphocyte response through a variety of ligands and its role in normal and transformed autocrine growth are discussed.**

The recent availability of purified and cloned gene products has allowed a rapid advance in elucidating the molecular and biological properties of soluble mediators that direct B-lymphocyte growth. An unexpected feature of these predominantly T-cell-derived factors is their broad tissue specificity (1–4). Even among B lymphocytes themselves, pleiotropy in a single factor can be observed both in terms of the activation states where cells are responsive and the biological sequelae to the interactions between cell and lymphokine (1, 5). These observations suggest that control of B-lymphocyte physiology might be dictated by the detailed interplay of several cytokines, with homeostasis being maintained through a finely regulated expression of one or more key receptor molecules. Surface structures possessing a guiding role for B lymphocytes equivalent to that of the interleukin 2 (IL-2) receptor on T cells (6) have remained elusive. Recently, however, using monoclonal antibodies as probes, a number of research groups have defined molecules that may serve to coordinate B lymphocytes in their response to the multitude of activities that would be generated following stimulation of the immune system (7–9). For one of these molecules, designated CD23, the biological information delivered to the cells by a presumed agonistic antibody is indistinguishable from the effects of a 12-kDa T-cell-derived B-cell growth factor (BCGF) (10). This material represents a lymphokine that appears to be distinct from interleukins 4 and 5 (11, 12).

While the growth-regulating properties of CD23 were being described (10, 13), two groups isolated genomic clones for the B-lymphocyte IgE receptor (14, 15) and one showed that the expressed 45-kDa product was equivalent to the CD23 molecule (16). This IgE receptor is shared by some monocytes, hypodense eosinophils, and a subpopulation of platelets (17–19). Fragments have been identified as IgE-binding factors (20), whereas a more general role has been suggested by the observation that such material, when released from virally transformed B-lymphoblastoid cells, possesses autocrine growth factor activity (21), possibly identical to the 25- to 30-kDa B-cell-derived BCGF originally described by J.G. and coworkers (22) and more recently by other groups (23, 24).

In this report we describe the induction of intact and shed forms of CD23 during activations of normal B lymphocytes and the coordination of these events by IgE, BCGF, and an anti-receptor antibody. The subsequent outcome on B-cell stimulation indicates that the CD23 molecule is pivotal to the control of B-lymphocyte physiology.

MATERIALS AND METHODS

Materials. $Na^{125}I$ (carrier-free) and [*methyl*-^{3}H]thymidine (25 Ci/mmol; 1 Ci = 37 GBq) were obtained from Amersham. Protein A-Sepharose CL-4B and Sepharose CL-4B were from Pharmacia (Uppsala, Sweden). Rabbit antiserum to mouse immunoglobulins was obtained from Dakopats (Copenhagen); prestained molecular weight standards for $NaDodSO_4$/PAGE, lactoperoxidase from bovine milk, phenylmethanesulfonyl fluoride, benzamidine hydrochloride, ε-aminocaproic acid, iodoacetamide, leupeptin, pepstatin, and soybean trypsin inhibitor were obtained from Sigma. Low molecular weight BCGF was obtained semipurified from Cellular Products (Buffalo, NY). Recombinant IL-2 was purchased from Genzyme (Norwalk, CT).

Antisera and Immunoglobulins. EBVCS1, EBVCS4, and EBVCS5 antibodies were produced by hybridoma cell lines kindly provided by B. Sugden (McCardle Laboratory, Madison, WI). For immunoprecipitation studies, undiluted culture medium from these lines was used. Immunoglobulin fractions were prepared from hybridoma ascites fluid for use in functional assays and for biotinylation as previously described (13). Human myeloma IgE was a generous gift from D. R. Stanworth (University of Birmingham, Birmingham, U.K.).

Cells. The establishment, maintenance, and cloning of Epstein–Barr virus (EBV)-transformed lymphoblastoid cell lines have been described (22). B lymphocytes of high

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Abbreviations: BCGF, B-cell growth factor; IL-2, interleukin 2; FITC, fluorescein isothiocyanate; EBV, Epstein–Barr virus; PMA, phorbol 12-myristate 13-acetate; NP-40, Nonidet P-40.

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buoyant density were prepared from human tonsillar tissue by negative selections and on Percoll (Pharmacia, Uppsala) gradients exactly as described by Walker *et al.* (25).

Cell Cycle Analysis and Immunofluorescence. Incorporation of [^{3}H]thymidine into B cells was determined as described (25). Cytofluorometric analysis of the cell cycle was performed using propidium iodide staining and the method of Krishan (26). Cells were stained by indirect immunofluorescence using a mixture of monoclonal antibodies EBVCS1, -4, and -5 as first-stage reagent and developing either with fluorescein isothiocyanate (FITC)-labeled sheep IgG anti-mouse immunoglobulins in the second stage or with FITC-avidin when biotin-labeled EBVCS antibodies were used in the initial step. The intensities and distributions of fluorescent staining were assessed on a FACS IV (Becton Dickinson, Mountain View, CA) flow cytometer.

Radioimmunoprecipitation. Cell surface proteins were radioiodinated by the lactoperoxidase H_2O_2 method of Marchalonis *et al.* (27) with modifications. Cells (50–100 × 10^6) were washed three times with phosphate-buffered saline (PBS: 0.15 M NaCl/1.5 mM KH_2PO_4/9 mM Na_2HPO_4, pH 7.2) and were resuspended in 1 ml of PBS. To this was added 0.5–1 mCi of ^{125}I, followed by 100 μl of lactoperoxidase (5 mg/ml) and 50 μl of H_2O_2 (0.03% in PBS). The mixture was gently agitated and then was left at room temperature for 3 min, after which another 100 μl of lactoperoxidase and 50 μl of H_2O_2 were added, followed by a third 3-min incubation with 50 μl of peroxidase and 50 μl of H_2O_2. The cells were then washed three times in PBS containing 5 mM KI and aliquoted for further incubation or solubilization. For further incubation a portion of these washed cells was suspended in RPMI 1640 medium with 2% fetal bovine serum and incubated for 4 hr. The cells were then centrifuged and washed as before while the conditioned medium was concentrated 100- to 200-fold in a Minicon B15 concentrator (Amicon). The concentrate was then centrifuged and precleared along with the solubilized cell-derived samples. The washed cells were solubilized with 0.5% Nonidet P-40 (NP-40) in PBS (pH 7.2) containing 1 mM phenylmethanesulfonyl fluoride, 10 mM benzamidine hydrochloride, 50 mM ε-aminocaproic acid, 20 mM iodoacetamide, leupeptin at 10 μg/ml, pepstatin at 1 μg/ml, and soybean trypsin inhibitor at 100 μg/ml. The lysate was clarified by centrifugation at 100,000 × *g* for 30 min. All procedures were conducted at 4°C. The extract (200–300 μl) was precleared by the addition of 50 μl of Sepharose CL-4B gel followed by brief centrifugation in a bench centrifuge. Then 25–50 μl of EBVCS5 culture supernatant was added to the cleared lysate and left at 4°C overnight. A secondary antibody (rabbit anti-mouse immunoglobulins) was used to coat protein A-Sepharose beads (50 μl of antibody was added to 1 ml of a 1:1 mixture of gel and PBS; after rotary mixing for 2 hr at room temperature the gel was collected by centrifugation, washed once with PBS, and resuspended to the original volume). One hundred microliters of 1:1 antibody-coated gel suspension in PBS was added to each tube and rotated overnight. The beads were then centrifuged down and washed three times in 0.5 M NaCl/5 mM EDTA/1% NP-40/50 mM Tris/HCl (pH 8), three times in 0.5% deoxycholate/0.5% NP-40/0.05% $NaDodSO_4$/PBS, and twice in 5 mM $MgCl_2$/10 mM Tris/HCl (pH 8). The washed beads were boiled in Laemmli sample buffer (28) containing 2-mercaptoethanol, the beads were centrifuged down, and the supernatant was subjected to $NaDodSO_4$/10% PAGE. Dried gels were subjected to autoradiography using Amersham Hyper film and an intensifying screen.

RESULTS

Modulation of Surface CD23 Expression by IgE and BCGF. The kinetics of CD23 induction on high-density (resting, G_0) tonsillar B cells were followed by immunofluorescence using a mixture of biotinylated CD23 antibodies with specificities representative of the three epitope clusters previously mapped on the 45-kDa molecule. The improved sensitivity of this detection system over earlier methods (25) revealed that even deeply quiescent B lymphocytes of the highest buoyant densities displayed some CD23 at their cell surfaces. This low-level expression remained unchanged in simple culture, but in the presence of IgE at 100 μg/ml an approximate doubling of detectable CD23 antigenic sites was noted by 48 hr (Fig. 1*a*). At 68 hr of culture this profile remained essentially unchanged (data not shown).

High-density B cells that had been activated by phorbol 12-myristate 13-acetate (PMA) showed a level of CD23 expression at 48 hr appreciably higher than seen with control cultured cells (Fig. 1*b*). Again, the inclusion of IgE in these cultures resulted in an ≈2-fold augmentation of CD23 expression over that induced by PMA alone at day 2. By day 3 (68 hr) a further modest increase in CD23 induction had developed in the PMA cultures. Where IgE had been present, however, the increase was so great that the fluorescence intensity has been represented on a logarithmic scale to allow comparisons to be readily made (Fig. 1*c*). Also, by day 3, the result of having BCGF present in PMA-stimulated cultures was a level of CD23 expression only some 30% of that detected on cells cultured with PMA alone (Fig. 1*c*). These results show that the presence of IgE and BCGF during a

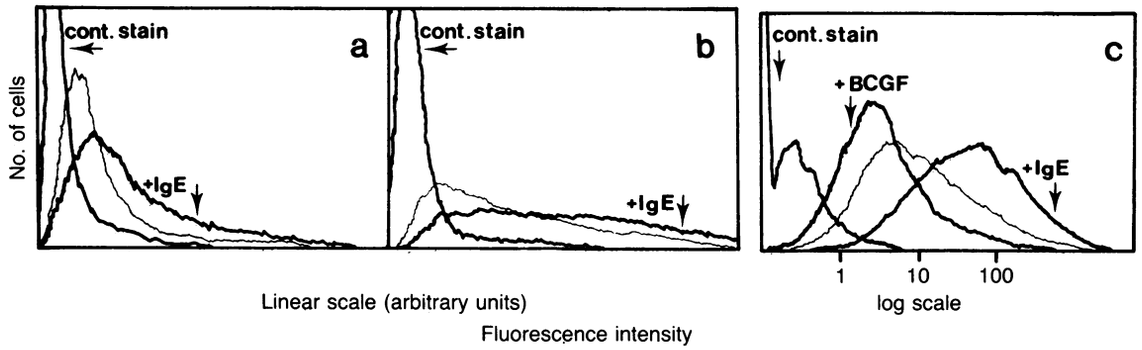

FIG. 1. Kinetics of CD23 expression. High-buoyant-density B cells were incubated at 5 × 10^5 per ml for 48 hr (*a* and *b*) or 68 hr (*c*) in the absence (*a*) or presence (*b* and *c*) of PMA (1 ng/ml), taken from culture, and washed, and the level of CD23 expression (faint line) was determined by staining with a mixture of biotinylated EBVCS antibodies followed by FITC-labeled avidin. The distribution of staining was determined by constructing histograms of the fluorescence profile collected from 50,000 cells in each test. Control staining (i.e., FITC-avidin only) is indicated by an arrow, as is the level of CD23 expression obtained when cells were cultured in the additional presence of either IgE (100 μg/ml) or BCGF (10%, vol/vol).

stimulation of resting B cells leads to opposing effects on subsequent CD23 expression.

Relation of CD23 Expression to Cell Cycle Status. Experiments were performed to determine whether the above observations simply reflected the phase of the cell cycle to which B cells had been driven rather than any specific actions of IgE and BCGF on the CD23 molecule. Table 1 shows that by 64 hr, BCGF had driven a significant number of PMA-activated B cells into the S and G_2/M phases of the cell cycle. By contrast, the inclusion of IgE with PMA-activated cells, which resulted in a substantial increase in CD23 expression, yielded only a marginal increase in the number of cells found in S phase over cells cultured with PMA alone. Note that an equivalent amount of IgG influenced neither cell cycle status nor CD23 expression.

Where B cells had been coactivated with PMA and the calcium ionophore ionomycin, a large number of cells were, by 64 hr, cycling through the S and G_2/M phases. However, CD23 expression on these cells was increased relative to cells that had been cultured with PMA alone. Thus the apparent down-regulation of CD23 seen in the presence of BCGF was not a simple consequence of driving B cells through the cell cycle but, rather, reflected a more specific and direct effect of the BCGF on the CD23 molecule. This notion was strengthened by the observation that the addition of IL-2, which prompted a similar proportion of PMA-activated cells into S phase as did BCGF, nevertheless did not lead to a reduction in CD23 expression on these cells (Table 1). The presence of EBVCS4, an activating CD23 antibody, during PMA stimulation resulted in a reduced level of CD23 expression by 64 hr (Table 1) similar to that found when BCGF had been added. Where an antibody to a different epitope on CD23 had been included no such reduction was seen.

Regulation of CD23 Cleavage by IgE and BCGF. High-density tonsillar B cells cultured for 48 hr in the presence of PMA were surface-labeled with ^{125}I and then either lysed immediately or cultured for a further 4 hr to "chase" labeled material into the extracellular medium. PMA induced the appearance of a molecule on normal B-cell surfaces that, when precipitated with a CD23 antibody, had a mobility in $NaDodSO_4$/PAGE identical to that of the 45-kDa antigen expressed on transformed cell lines (Fig. 2). Consistent with the previously obtained immunofluorescence data, substantially more of this molecule could be precipitated from cells that had been cultured in the presence of IgE. As shown

Table 1. Relation of CD23 induction to cell cycle status

Addition to PMA culture*	CD23 expression†	% cells‡		
		G_0/G_1	S	G_2/M
None	56	95	5	<1
IgE	217	92	7	1
IgG	53	96	4	<1
BCGF	23	71	21	8
rIL-2	67	77	18	5
Ionomycin	89	59	25	16
EBVCS4	31	75	19	6
EBVCS5	75	93	6	<1

*Cells were cultured with PMA (1 ng/ml) as for Fig. 1, in the presence of IgE (100 μg/ml), IgG (100 μg/ml), BCGF (10%), recombinant IL-2 (rIL-2, 200 units/ml), ionomycin (1 μg/ml), EBVCS4 (10 μg/ml), or EBVCS5 (10 μg/ml).

†Cells were stained by indirect immunofluorescence using a mixture of EBVCS antibodies (nos. 1, 4, and 5) as first-stage reagent and developed with FITC-labeled sheep anti-mouse immunoglobulins in the second stage. The mean intensity of fluorescent staining (i.e., mean channel number) 64 hr after initiation of culture is given.

‡Cells stained with propidium iodide at 64 hr were assessed for their DNA content. The distribution of cells within the cell cycle is shown.

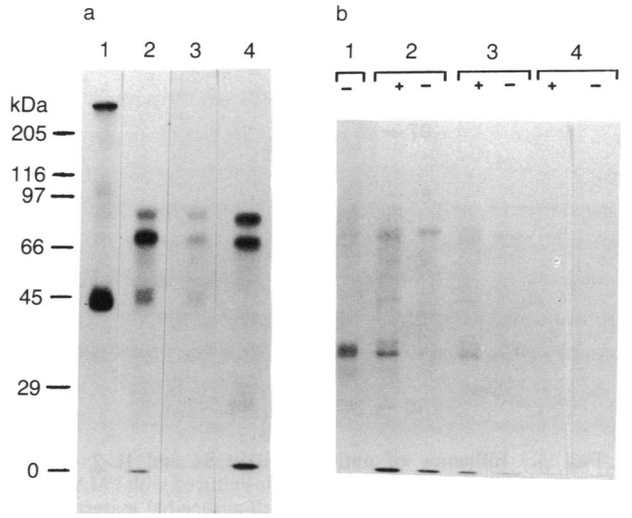

FIG. 2. Biochemical analysis of CD23 induction and cleavage. Cells were cultured as in Fig. 1 for 48 hr and then were surface-labeled with ^{125}I. (*a*) The material precipitated from cell lysates with antibody EBVCS5 was reduced and then analyzed by $NaDodSO_4$/PAGE followed by autoradiography. Lanes: 1, EBV-transformed lymphoblastoid cell line; 2, high-buoyant-density B cells cultured in the presence of PMA (1 ng/ml) and IgE (100 μg/ml); 3, B cells cultured with PMA only; 4, B cells cultured in the absence of any additions (i.e., control cultures). (*b*) Aliquots of the same cells labeled at 48 hr were cultured for a further 4 hr in the absence (−) or presence (+) of BCGF (10%) as indicated, and the medium collected was similarly analyzed, after immunoprecipitation, for released CD23 material. Positions of molecular size markers run in parallel are shown for *a*.

previously (29), material of 35 kDa could be precipitated from the medium of transformed cells that had been cultured for 4 hr after surface labeling. By contrast, no such molecule was precipitated from supernatants of activated normal cells, irrespective of whether IgE had been present during the stimulations or not (Fig. 2). However, if activated normal B cells were incubated in the presence of BCGF for 4 hr after surface labeling, material appeared in the culture medium that comigrated in $NaDodSO_4$/PAGE with the 35-kDa molecule released from the transformed cell line. Presumably reflecting the higher level of 45-kDa surface CD23, cells that had been originally cultured in the presence of IgE, labeled, and then cultured with BCGF released substantially more of the 35-kDa species than BCGF-pulsed cells that had previously been stimulated without IgE.

To explore the specificity of the BCGF-induced cleavage of CD23, labeled PMA-stimulated cells were cultured in the presence of recombinant IL-2. No detectable CD23 shedding was generated by the addition of IL-2 to labeled cells expressing the 45-kDa molecule (Fig. 3).

We also asked whether the stimulatory EBVCS4 anti-receptor antibody exerted any effect on receptor shedding. As before, the results with this antibody were indistinguishable from those observed with BCGF. That is, following PMA induction of 45-kDa CD23 on normal B-cell surfaces, the subsequent addition of a functional CD23 antibody resulted in the release of the 35-kDa form of the receptor into the medium (Fig. 3).

The appearance of labeled bands other than the 45-kDa material on the autoradiographs requires comment. Prominent specific bands at 70 and 85 kDa were regularly precipitated, particularly from labeled normal cells, with CD23 antibodies (Figs. 2 and 3). Other workers who have characterized the IgE receptor from B-lymphoblastoid cells described similar radioactively labeled proteins additional to the 45-kDa band (30, 31). Tryptic maps of the larger and

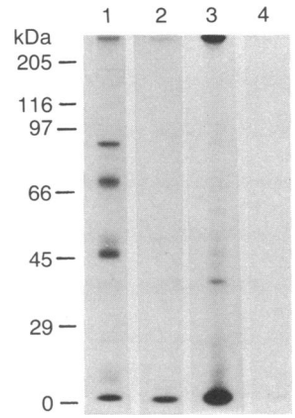

FIG. 3. Influence of antibody EBVCS4 and IL-2 on CD23 cleavage. High-buoyant-density B cells cultured with PMA for 48 hr were labeled with ^{125}I as in Fig. 2. Cell-associated material precipitated with antibody EBVCS5 and run reduced is shown in lane 1. Aliquots of the labeled cells were cultured for a further 4 hr either in medium alone (lane 2) or in the presence of EBVCS4 (10 μg/ml, lane 3) or recombinant IL-2 (100 units/ml, lane 4) and the labeled material in the culture supernatants was analyzed.

smaller peptides have been shown to be identical, indicating structural similarity between these components (31). It is possible that the larger form may represent an intracellular precursor of the 45-kDa external receptor that could be prone to labeling in cells rendered permeable by the iodination procedure.

Combined Actions of IgE, BCGF, and Anti-Receptor Antibody on B-Lymphocyte Stimulation. Given the coordinated actions observed for IgE, BCGF, and EBVCS4 on CD23 expression, we next explored the influence of combinations of these ligands on B-cell stimulation. Addition of IgE during PMA-driven activation could, of itself, provide some contribution to the DNA synthesis occurring in these cultures (Fig. 4). EBVCS4 antibody augmented stimulation to a far greater extent but, more importantly, the influence of the CD23 antibody was over and above that observed with IgE even where both agonists were present at concentrations sufficient for their maximal individual activities. With such combinations, the resultant increase in DNA synthesis was more than

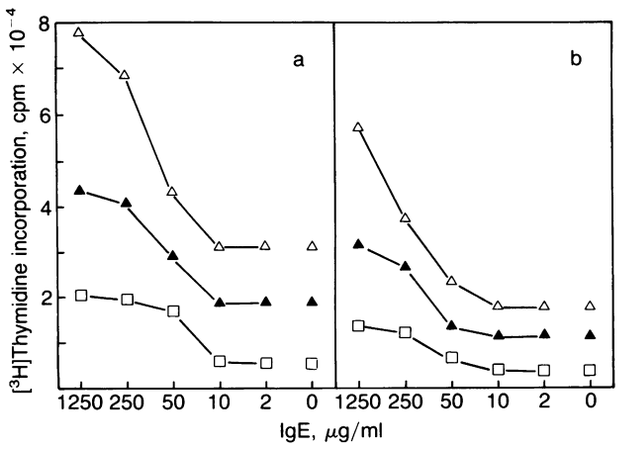

FIG. 4. Influence of IgE and EBVCS4 on B-cell stimulation, as assessed by incorporation of [^{3}H]thymidine. High-buoyant-density B cells were cultured with PMA (1 ng/ml) as in Fig. 1 in the presence of IgE at concentrations indicated (□). Antibody EBVCS4 was also included in some culture wells at either 10 μg/ml (△) or 1 μg/ml (▲), representing optimal and suboptimal concentrations, respectively, of stimulating antibody. Results from two individual tonsil preparations (*a* and *b*) are shown.

Table 2. Interaction of IgE and BCGF in B-cell stimulation

% BCGF added	[^{3}H]Thymidine incorporation			
	No Ig	IgE (50 μg/ml)	IgE (250 μg/ml)	IgG (250 μg/ml)
0	4,360	6,025	11,571	5,740
1	10,356	14,892	27,983	12,821
5	21,295	23,426	48,797	21,086
10	23,674	24,393	60,488	24,460
20	20,892	22,255	57,036	22,505

Cells were cultured as for Fig. 1 but were incubated with [^{3}H]thymidine at 52 hr for a further 16 hr. Results are given as means of triplicate determinations.

additive (Fig. 4). Similar supraadditive stimulations were observed when IgE, but not IgG, was combined with BCGF during PMA activation of high-density B cells (Table 2). We have previously shown that no additional effects are generated when a functional CD23 antibody is used in combination with BCGF (10), a finding confirmed in this study for EBVCS4 (results not detailed). These findings indicate further that IgE and BCGF are exerting individual influences on B-cell stimulation and that the actions of the latter, but not the former ligand, are mimicked by an appropriate CD23 antibody.

DISCUSSION

The findings of this study demonstrate an interplay between IgE and a T-cell-derived BCGF in regulating a B-cell response, with both activities being focused on a single receptor molecule, CD23. It has yet to be determined whether the low-affinity IgE receptor (i.e., CD23) actually binds the BCGF or, instead, is functionally and, possibly, physically linked to a distinct BCGF receptor. Affinity crosslinking would help to resolve this question, but such studies must await the arrival of a more highly purified or a cloned form of the BCGF. However, the observation that particular CD23 antibodies mimic the actions of the BCGF but contrast with those of IgE does suggest that the one receptor contains the potential for more than one ligand—whether it be BCGF itself, a closely associated surface effector protein, or a distinct factor elicited following BCGF binding. One precedent for such pleiotropy in a receptor is provided by the binding of thymopoietin to the acetylcholine receptor (32). The remarkable sequence homology between CD23, asialoglycoprotein receptors, and chicken hepatic lectin has suggested that the binding of IgE to its receptor on B cells may be mediated through carbohydrate residues (15). It is possible, therefore, that homologous sugar moieties on the BCGF allows it to interact with the same binding domains on CD23 as IgE but with different effects. Another possibility is that CD23 comprises one component of a BCGF-receptor complex, in a manner analogous to that recently demonstrated for Tac antigen in the two-chain IL-2 receptor (33). Whatever the precise relationship between CD23 and BCGF, it is clear that the actions of the T-cell-derived factor and the expression of the IgE receptor are tightly linked.

Whereas IgE up-regulated its receptor, the presence of BCGF resulted in reduced CD23 expression. This reflected the ability of BCGF to stimulate receptor release from activated cells. The demonstration that anti-receptor antibody could also induce receptor release, coupled with our previous observation that the growth-promoting effects of CD23 antibodies are both epitope-restricted and independent of receptor crosslinking (13), indicates that an allosteric mechanism may be responsible for the shedding of CD23. From the amino acid sequence deduced from the cDNA clone, it has been proposed that the B-cell IgE receptor

contains a potential arginine cleavage site (14, 15), and it may be here that the actions of the BCGF and the functional antibodies are being focused. One possible mechanism for the two agonists is that their binding generates an autoproteolytic activity in the receptor molecule, as was recently described for the estradiol receptor following binding to its ligand (34). While we have no information on the fragment of CD23 that presumably remains bound to the cell after cleavage, the released extracellular fragment has been associated with a number of biological activities. Particularly intriguing is the observation that affinity-purified preparations of shed CD23 from EBV-transformed B cells possess autostimulatory activity (21). Thus the cleaved receptor may be related to the 25- to 30-kDa autocrine factor originally described by J.G. and coworkers as being an essential component for growth of transformed B cells (22) and more recently implicated in normal B-cell responses (23, 24).

The process by which IgE up-regulates CD23 remains unclear, although it may stabilize the receptor by binding at or near the cleavage site and preventing degradation. The outcome of IgE being present during a B-cell stimulation is the availability of more CD23 on which the BCGF can act to generate more autocrine growth activity and thus provide a stronger growth stimulus. Thus, as long as the B- and T-cell arms were being triggered by free immunogen, the consequence of generating an IgE response would be to establish a positive feedback amplification loop centered on CD23. Given the relatively high concentrations of monomeric IgE required to observe such a circuit *in vitro*, it is likely that the appropriate conditions would be met *in vivo* only when IgE was bound to antigen. In this regard it is worthy to note that dimers and trimers of IgE are orders of magnitude more efficient than monomeric IgE in up-regulating IgE receptors on a mouse B-cell hybridoma line (35).

In conclusion, we believe that this report firmly establishes CD23 as a molecule pivotal to the control of B-lymphocyte function. This one receptor has been shown to be regulated at B-lymphocyte surfaces by the coordinated actions of two ligands, one of which can be replaced by an anti-receptor antibody. Their influence results in a controlled release of the receptor, which itself is endowed with autocrine growth-promoting activity and is probably responsible for many of the properties ascribed to the so-called IgE-regulants (20). If we accept that it has a key position in B-lymphocyte control, CD23 becomes a prime candidate for deregulation in oncogenic transformation. The high constitutive levels of CD23 on B cells that have been infected with EBV and its prerequisite expression for EBV transformation lend support to this notion (36). Thus, for both normal and deregulated B-lymphocyte processes, CD23 appears to assume a role somewhat equivalent to that of the IL-2 receptor on T lymphocytes. Perhaps the "unique" features associated with CD23 will provide a model for other receptors, some of which are known similarly to be released as cleavage products (37, 38).

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