

An update on human CD23 (FcεRII). FcεRII and IgE-BFs (soluble CD23) play an essential role in the regulation of human IgE synthesis

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Four families of IgE-binding molecules have now been characterized at the molecular level (Table 1). In spite of a common functional property these molecules are unrelated and have no sequence homology. The aim of this work is to briefly summarize recent acquisitions regarding the low affinity receptor for IgE (FcεRII, CD23 antigen) and its soluble fragments (sCD23 or IgE-binding factors).

1. CD23 STRUCTURE

- 1.1 The cDNA coding for mouse CD23 has been cloned and functionally expressed (4). It has no homology with that of rodents IgE-BFs described by Ishizaka (5) whereas it displays a significant homology with human CD23. A comparison of mouse and human CD23 is shown in Table 2.
- 1.2 CD23 exists in 2 isoforms (named A and B) differing only by a few amino acids in the intracytoplasmic tail of the molecule (6). Freshly isolated normal B cells express type A only; upon IL4-stimulation they coexpress types A and B. Normal monocytes do not express type A, even after IL4 stimulation. Cell lines of the T cell, monocyte or eosinophil lineage express only type B CD23. According to preliminary results, type B (but not type A) is capable of internalization after binding to IgE.
- 1.3 Surface CD23 is cleaved into soluble fragments by an autoproteolytic mechanism (7). The cleavage is inhibited by IgE and it is increased by agents preventing the N-linked glycosylation of the molecule. Soluble CD23 is first released as unstable 37-33 kDa molecules which are subsequently transformed into stable 25 kDa fragments (8).

2. CELLULAR EXPRESSION OF CD23

CD23 is mainly expressed on sIgM/sIgD bearing B cells before isotype-switching. It may also be found on monocytes/macrophages, platelets, follicular dendritic cells and on Langerhans cells (9). The expression of CD23 on T cells and eosinophils is still questioned. CD23 was recently found within Read-Sternberg cells (10) and on carcinoma cells from the nasopharynx

TABLE 1IgE-BINDING MOLECULES

-	MAC 2 (1) (rIgEBP, GBP 35)	GALACTOSE-SPECIFIC LECTIN
-	α CHAIN Fc ϵ RI (2)	HIGH AFFINITY IgE RECEPTOR
-	Fc ϵ RII (CD23)	LOW AFFINITY IgE RECEPTOR
-	IgE-BINDING FACTOR (3)	RODENTS - HOMOLOGY TO RETROVIRAL POLYMERASES

TABLE 2COMPARISON OF MOUSE AND HUMAN Fc ϵ RII

	<u>HUMAN</u>	<u>MOUSE</u>
- DGR-SEQUENCE	YES (aa309-311)	NO
- NO. OF AMPLIFIED EXONS	3	4
- NO. OF N-GLYCOSYLATION SITES	1	2
- SOLUBLE FcεRII FRAGMENTS	BIND TO IgE	NO BINDING TO IgE
- FUNCTION OF sFcεRII FRAGMENTS	MULTIPLE	NOT KNOWN

harboring the EBV genome (11).

3. REGULATION OF CD23 EXPRESSION

On B cells, CD23 may be upregulated not only by IL4 but also by IL2, LTB4 and PAF (12-14). Moreover, cognate interactions with T cells also increase CD23 expression in the absence of apparent interleukin secretion (15). IL5 by itself has no effect whereas it increases the induction of CD23 by suboptimal concentrations of IL4 (16). The expression of CD23 on B cells stimulated with a saturating dose of IL4 may be further increased (superinduction) either upon stimulation of the B cells (with anti-IgM or SAC) or upon incubation with T cells or their culture supernatant (17, 18). The LMW-BCGF was recently shown to transiently inhibit type A and to induce type B CD23 on an EBV-transformed and BCGF-dependent cell line (R. Sharma, personal observation). It is not known whether this growth factor exerts the same effect on normal B cells. The expression of CD23 on normal B lymphocytes is inhibited by IFN- γ , IFN- α and PGE 2 as well as by glucocorticoids and TGF- β (11, 19). CD23 is not constitutively expressed on resting monocytes, it is induced by IL4, LTB4, PAF and IFN- γ (9, 13, 20). The latter triggers the release of sCD23 by monocytes but not the expression of surface CD23, suggesting that IFN- γ increases the cleavage of the membrane CD23 (21). The expression of CD23 on monocytes is inhibited by IFN- α , glucocorticoids, 1-25 OH vitamin D3 and TGF- β (20, 22).

4. FUNCTION OF CD23

A unique feature of CD23 is that its membrane-form (the IgE receptor) and its soluble fragments are endowed with distinct and sometimes antagonistic functions.

4.1 Fc ϵ RII

Although CD23 Ag has a striking homology with type C lectins, including some adhesion molecules, the known functions of this molecule are IgE-dependent, i.e., it works as a low affinity receptor for IgE. Its function depends upon the cell type on which it is expressed. On monocytes/macrophages, CD23 was shown to mediate the following IgE-dependent activities; (1) cytotoxicity against some parasites (23); (2) release of inflammatory mediators (24) and (3) internalization of IgE-immune complexes (25). The triggering of a cytotoxic reaction requires a functional interaction of CD23 with CD11b, a member of the LFA1 family, also known as the receptor for iCD3b (26). CD23 was also reported to mediate IgE-dependent cytotoxicity by platelets (27) and eosinophils (28).

On B cells, the function of CD23 is twofold: (1) IgE-dependent presentation of Ag to T cells and (2) regulation of B cell activation/differentiation. Clearly CD23 is not the receptor for the LMW-BCGF (29).

Antigen-bound to IgE antibodies may be processed by CD23 bearing B cells and presented to Ag-specific T cells (30). Hence, CD23 and IgE may amplify the T cell response to that antigen by expanding the pool of Ag-specific T cell clones. Our recent results (31) further indicate that the binding of IgE-immune complexes to CD23 prevents B cell activation, proliferation and differentiation into Ig secreting cells. Hence, CD23 bearing B cells presenting Ag to T cells via CD23 are paralyzed and play the role of APC. These two observations have several implications regarding the isotype-regulation of the immune response. First, the paralysis of CD23, sIgM and sIgD triple bearing B cells (playing the role of non Ag-specific APC) prevents their differentiation into plasma cells producing antibodies of irrelevant specificities. Second, the turnoff signal mediated by CD23-IgE-IC interaction is observed only when the density of CD23 is sufficient, i.e., after the B cells have been exposed to IL4. Since the sIgM/sIgD CD23 triple bearing lymphocytes are the precursors of IgE producing cells, their inactivation prevents the recruitment of new IgE B cells. Hence, CD23 is mediating the IgE induced negative feedback regulation of IgE synthesis; this prediction has been recently verified in our laboratory. This also explains why in hay fever patients most of the serum IgE protein is made of pollen-specific IgE antibodies (32). Third, the amplified pool of Ag-specific T cells may induce activation and proliferation of Ag-specific B cells expressing no or little CD23. i.e., of switched B cells or of B cells which have not been in contact with IL4. In each case the result is in favor of the production of isotypes other than IgE.

4.2 SOLUBLE CD23 OR IgE-BINDING FACTORS (IgE-BFs)

Unstable 37-33 kDa IgE-BFs have a potent effect on the synthesis of IgE by activated IgE B cells. They act at a stage of B cell differentiation and activation which is IL4-independent. For example, they may increase the spontaneous synthesis of IgE by in vivo activated B cells isolated from the blood of atopic donors (33, 34). Moreover, some anti-CD23 mAbs completely inhibit this ongoing IgE synthesis (35). Since these antibodies cannot interact with IgE secreting cells (because CD23 is lost after switching) it is most likely that the IgE inhibition is due to the neutralization of IgE-BFs. Finally, and most importantly we have recently developed a novel model of human IgE synthesis where IgE-BFs clearly appear to have a permissive effect.

Hence, FcεRII may inhibit IgE synthesis (feedback down regulation) whereas IgE-BFs have the opposite effect. Moreover, IgE inhibits the cleavage of FcεRII into IgE-BFs (potentiating IgE synthesis) providing a second negative feedback signal.

The stable 25 kDa IgE-BFs have no IgE regulatory effect whereas they exert an important role in the differentiation of T cells and of myeloid precursor cells. Indeed, it was recently observed that 25 kDa IgE-BFs in synergy with IL1 is capable of inducing the differentiation of early thymocyte precursors (CD4⁺, CD2⁻, CD3⁻, CD4⁻/CD8⁻, CD25⁻, TCR⁻, CD5⁻) into more mature T cells (CD2⁺, CD3⁺, CD4⁺/CD8⁺, TCR⁺ and CD25⁺) capable of proliferating upon stimulation with anti-CD2 and IL2 (36). The differentiation does not require cellular proliferation and it is observed within 48 h of incubation. Sequential addition of IgE-BFs and IL1 indicates that IL1 may be added first and washed out prior to the addition of IgE-BFs, whereas the reverse is not true. The *in vivo* significance of these observations stems from the recent finding that CD23 is expressed on some thymic cells. Another striking finding is that 25 kDa IgE-BFs, in synergy with IL1, induces the proliferation of early bone marrow myeloid precursor cells (CD34⁺). The response is IL3-independent, it is accompanied by colony formation and 30-40% of the colonies contain basophils (37). Finally, a recent study suggested that IgE-BFs may also affect the migration and the differentiation of monocytes (38).

CONCLUSIONS

Like most lymphokines, CD23 appears to exert multiple effects on a large variety of cells. The unique feature of this molecule is that its membrane form (FcεRII) undergoes an autocatalytic proteolysis leading to soluble fragments (IgE-BFs) displaying distinct and multiple biological activities, depending upon their size. Whereas, as of to date, all the functions ascribed to FcεRII are IgE-dependent, at least some of the activities of the IgE-BFs do not involve their interaction with IgE (e.g., differentiation of thymocytes, myeloid precursors and monocytes). It is now becoming increasingly clear that both FcεRII and IgE-BFs play a pivotal role in IgE specific isotype regulation as well as in IgE-mediated inflammatory reactions.

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