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Review

CD23 (the low-affinity IgE receptor) as a C-type lectin: a multidomain and multifunctional molecule

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Abstract. This review, regards the low-affinity receptor CD23 as a C-type lectin and compares it with other C-type lectins and C-type lectin-like receptors. C-type lectins such as the asialoglycoprotein receptor, as well as the dendritic cell immunoreceptor and the dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin on dendritic cell lectin, possess amino acid sequences which interact with Ca^{++} and sugar, and many of them possess an endocytosis signal sequence that includes tyrosine or serine in the cytoplasmic region. In contrast, natural killer receptors lack the Ca^{++} and sugar-binding amino acids but conserve homologous cysteines in the form of C-type lectin, and possess an immunoreceptor tyrosine-based inhibitory motif in the cytoplasmic region which inhibits killer activity when they recognize the self major histocompatibility (MHC) class I molecule. Since human CD23a form has a similar amino acid sequence, the possibility that this sequence is an endocytosis signal or an ITIM is discussed. The function of the reverse RGD and RGD-binding inhibitory peptide in human CD23 from the point of view of the relation between a C-type lectin and MHC class II molecules is also considered.

Key words. Low-affinity receptor for IgE; CD23; NK receptor; C-type lectin(-like) domain; inverse RGD sequence; RGD-binding inhibitory peptide; ITIM, endocytosis signal.

Introduction

During the 1970s and 1980s, three research groups independently discovered the low-affinity immunoglobulin (Ig)E receptor (FcεRII, CD23) either as an IgE receptor on human B lymphocytes [1], as a cell-surface marker specifically expressed on Epstein-Barr virus (EBV)-transformed B cells [2] or as a B-cell-activation antigen [3]. Its primary structure was found to have high similarity to C-type lectins such as the asialoglycoprotein receptor and the chicken hepatic lectin [4–6]. Subsequently, many C-type lectin(like) molecules have been cloned from immune cells and tissues. Several comprehensive [7–10] and focused [11–16] reviews have already been published. In this report, I compare six functional structures within human CD23, including the C-type lectin domain, with other molecules. New points reviewed here are comparison with natural killer (NK) receptors, which, it is becoming clear, constitute a large family of C-type lectin-like receptors; the reverse RGD sequence and RGD-binding inhibitory peptide at the root of the N-linked sugar chain; the four-amino-acid YSEI sequence in the cytoplasmic region of form a and the interaction of CD23 and tetraspanine. Human CD23 is certainly a mysterious but attractive multidomain and multifunctional molecule.

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Overview of the structure CD23

CD23 and the Fc receptor family

CD23 is the low-affinity receptor for IgE. Many Fc receptors on immunocytes bind the Fc portion of immunoglobulins [17], but of these only CD23 is a type II membrane protein (cytoplasmic N-terminus, extracellular C-terminus); all the others are type I (inverse orientation) [18, 19] (fig. 1). The IgE binding domain of CD23 has high similarity with C-type lectins such as the asialoglycoprotein receptor and chicken hepatic receptor, but all the other Fc receptors have two or three immunoglobulin-like domains through which they bind immunoglobulins (fig. 1). Another IgE receptor is the high-affinity receptor that consists of a type I IgE-binding α chain with immunoglobulin-like extracellular domains, which associates with a β and two γ chains whose cytoplasmic domains contain an immunoreceptor tyrosine-based activation motif (ITAM). Other Fc receptors make a complex with other chains containing ITAMs in their cytoplasmic domains, whereas FcγRIIb contains an immunoreceptor tyrosine-based inhibitory motif (ITIM) by itself [20] (fig. 1). Immunological reactions through immunocytes such as B, T and NK cells are controlled by the cell-surface receptors that have ITAM or ITIM motifs in their cytoplasmic domains. The tyrosine residues in both motifs are phosphorylated by protein tyrosine kinase, or dephosphorylated by SHP-1 phosphatase, which regulates the reaction for activation or inhibition of immune response [20, 21].

Thus, the low-affinity IgE receptor, CD23, is completely different in structure from all other Fc receptors. The affinity for IgE of the high-affinity receptor is 10^9 M^{-1} and that of the low-affinity receptor CD23 is 10^8 M^{-1} for IgE-antigen complexes, and $l0^7$ M^{-1} for IgE alone.

CD23 and the C-type lectin family

Many excellent reviews on lectins and animal lectins have been published [22–27]. Lectin, *legere* (select) in Latin, was named by Boyd and Shapleigh in 1954 as a protein in plant seeds which selects the blood types according to the different structure of carbohydrate. Plant lectin was originally discovered by Stillmark in 1860 [22]. Over a century later, hundreds of lectins are now well characterized and have been shown to be extremely useful reagents for detection and analysis of glycoproteins [28], and for the partial characterization of their carbohydrate moieties on the cell surface.

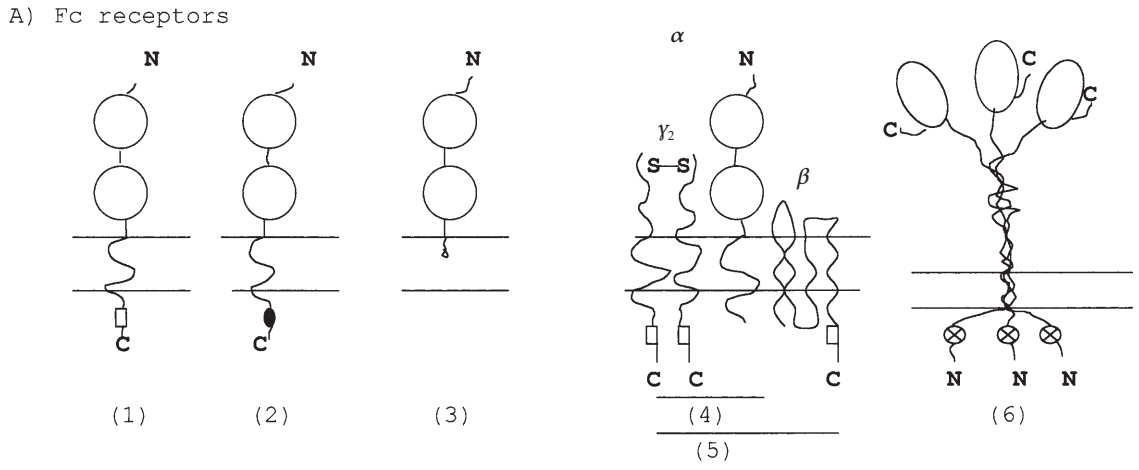
Animal lectins were discovered by Morell et al. and Ashwell [29], although recent evidence has dated the discovery back to 1860 and work done at that time on rattlesnakes [30]. By the 1970s, Morell et al. [31] had found that desialylated serum glycoproteins drastically reduce survival times in the circulation compared with native forms of the same proteins. They demonstrated a specific receptor on hepatocytes that mediates their clearance by recognition of terminal galactose residues exposed by the removal of sialic acid [29]. After that, many animal lectins were discovered and grouped [23, 24], and shown to act as mediators of cell recognition in a wide range of biological systems [24–27].

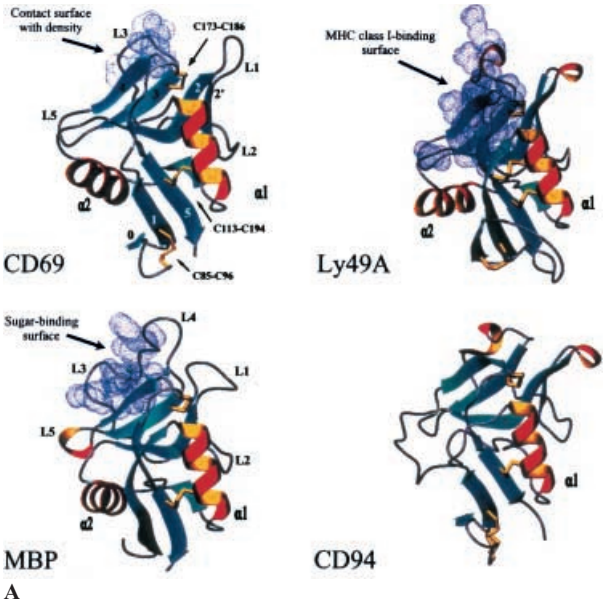
C-type lectins require Ca^{++} (thus, C-type) for binding to carbohydrate, for which their specificity is diverse. This group also contains some subgroups, described below. During the last 5 years, many NK receptors such as CD94, NKG, NKR and Ly49 were cloned, and it has become clear that they make a C-type lectin-like superfamily encoded by a conserved genomic region known as the NK gene cluster (NKC) [32]. Most of them have a C-type lectin-like domain that conserves typical cysteines but lacks sugar-binding properties, and shows a crystal structure similar to C-type lectin [33–36], while also mediating the innate immune response [32].

Unique structural features of human CD23

Weis and Drickamer determined the three-dimensional structure of the mannose-binding protein (MBP) [37]. Conrad and his co-worker [38] presented experimental evidence for the formation of an oligomeric structure of CD23 showing 45- and 200-kDa molecules by cross-linking them with amino groups. Natarajan et al. [34] determined the crystal structure of human CD69, including their interaction sites with ligands (fig. 2A). Llera et al. [35] proposed similar results. Sutton and Gould [8] and Schult et al. [39] offered a three-dimensional model of CD23 (fig.2B) on the basis of these structures. Recently, Watson et al. [40] cloned complementary DNA (cDNA) that encoded equine and cattle CD23 and sequenced them; they listed the alignment of deduced amino acid sequences of horse, cow, human, mouse and rat CD23. Figure 3 shows a two-dimensional schematic model for human CD23 based on the amino acid sequence. This basic structure [16] was originally proposed by Sutton and Gould on the basis of the S–S bridges first proposed by Bettler [41].

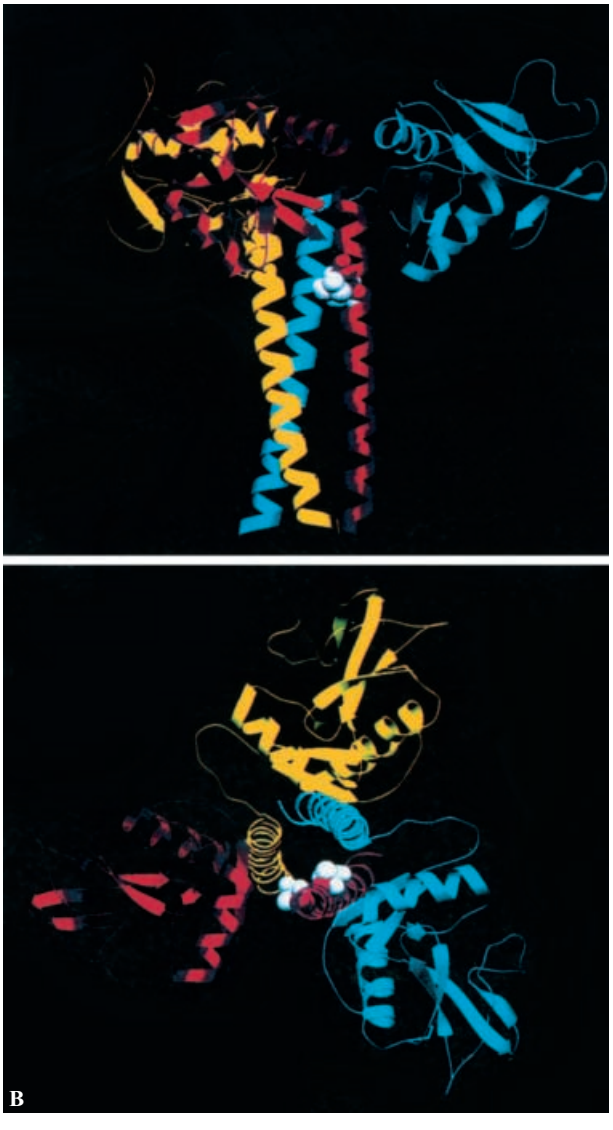
The six structural features to be discussed in this review are indicated (1)–(6) in figure 3, and are as follows: (1) the IgE-binding, C-type lectin domain; (2) the a and b forms of CD23 that differ in their cytoplasmic amino acid sequences, and the YSEI sequence; (3) the leucine-zipper structure; (4) the protease cleavage sites and soluble forms of CD23; (5) the reverse-RGD sequence near the C-terminus; (6) the 'RGD-binding inhibition peptide' at the root of the N-linked carbohydrate chain.


A) Fc receptors
N
C
(1)
(2)
(3)
α
γ2
S–S
β
(4)
(5)
(6)
B) C-type lectins
Collectin (MBP etc)
Type I membrane protein
2: CD62 (L)
6: CD62 (E)
9: CD62 (P)
macrophage receptor
x6
C) NKR
Ly49
CD94/NKG2
NKR-P1
CD69
Human KIR
S-S
SS
D) Others
GPIIb/IIIa
A
B



A

Figure 1. Structural models of Fc receptors and others. (*A*) Fc receptors. □, ITAM; ●, ITIM; C, C-terminus; N, N-terminus; **S–S**, cysteine-cysteine bridge. FcγRIIc, FcγRII$_b$ and FcγRIIIb belong to (1), (2) and (3), respectively. FcγRIa (possesses three Ig-like domains), FcαR and FcγRIIa (γ chain has ITAM) belong to (4), FcεRI (high-affinity IgE R) belongs to (5), whereas FcεRII (low-affinity IgE R, CD23) belongs to (6). (*B*) Example of C-type lectins. Example of collectin, MBP; this trimeric block forms a bouquet or cruciform shape. Example of type I membrane protein, CD62 and macrophage mannose receptor (human); ○ complement control domain, ⬭ EGF-like domain, ♡ C-type lectin domain, ▭ fibronectin type II domain. CD62 (L), CD62 (E) and CD62 (P) are L-, E- and P-selectin, and have two, six and nine complement-control (CC) domains, respectively. Macrophage receptor has eight C-type lectin domains. Example of type II membrane protein, CD23, described above. (*C*) NKR. Ly49, CD94/NKG2, NKR-P1 and CD69 have C-type lectin-like domains (or NK domain). Human KIRs are not members of the C-type lectin-like molecule but members of the Ig superfamily and contain either two or three Ig domains in the extracellular region. All members (except CD94 and CD69) contain ITIM (I/VxYxxL/V) sequences in the cytoplasmic domain. (*D*) Others. Platelet integrin GPIIb/IIIa. Ligands such as fibrinogen that contain RGD sequences interact with A (both chains). Peptide B inhibits this interaction.



B

Figure 2. Three dimensional structures of C-type lectins and CD23. (*A*) Ribbon diagrams of CD69, MBP-A, Ly49A and CD94. β Strands are blue, α-helices are red and yellow, and loop regions are shown as silver rope. The Ca^{2+} ions bound to MBP-A are drawn as blue spheres. The disulfide bonds are shown in yellow ball-and-stick representation. Secondary structure elements are labeled using the numbers for MBP-A. The surfaces shown in light blue illustrate the ligand-binding sites of MBP-A and Ly49A, and the surface within van der Waals contact distance of the uncharacterized electron density in the CD69 structure. (*B*) A model for the human CD23 trimer: the trace of the polypeptide chain is shown, and the arrows represent strands of β sheet. (***a***) shows the three lectin domains and the triple α-helical coiled-coil stalk and neck region. Residues Ser155 and Ser156 in the neck region, a site of proteolytic cleavage by *Der p* I, are shown in a space-filling representation for the magenta-colored subunit only. The modeled lectin domain (based upon Weis W. I. and Drickamer K. (1994) Structure **2:** 1227) terminates in β strand in the vicinity of the neck region adjacent to the serine residues. (***b***) The trimer model with Ser155 and Ser156 represented as in (***a***), viewed along the threefold axis of symmetry. [(*A*) [34] and (*B*) [39] are reproduced, respectively, with the permission of (*A*) Natarajan K., Sawicki M. W., Margulies D. H. and Mariuzza R. A. (2000) Crystal structure of human CD69: a C-type lectin-like activation marker of hematopoietic cells. Biochemistry **39**: 14779–14786. Copyright (2000) American Chemical Society, and (*B*) Schulz O., Sutton B. J., Beavil R. L., Shi J., Sewell H. F., Gould H. J. et al. (1997) Cleavage of the low-affinity receptor for human IgE (CD23) by a mite cysteine protease: nature of the cleaved fragment in relation to the structure and function of CD23. Eur. J. Immunol. **27:** 584–588. Copyright (1997) Wiley.]

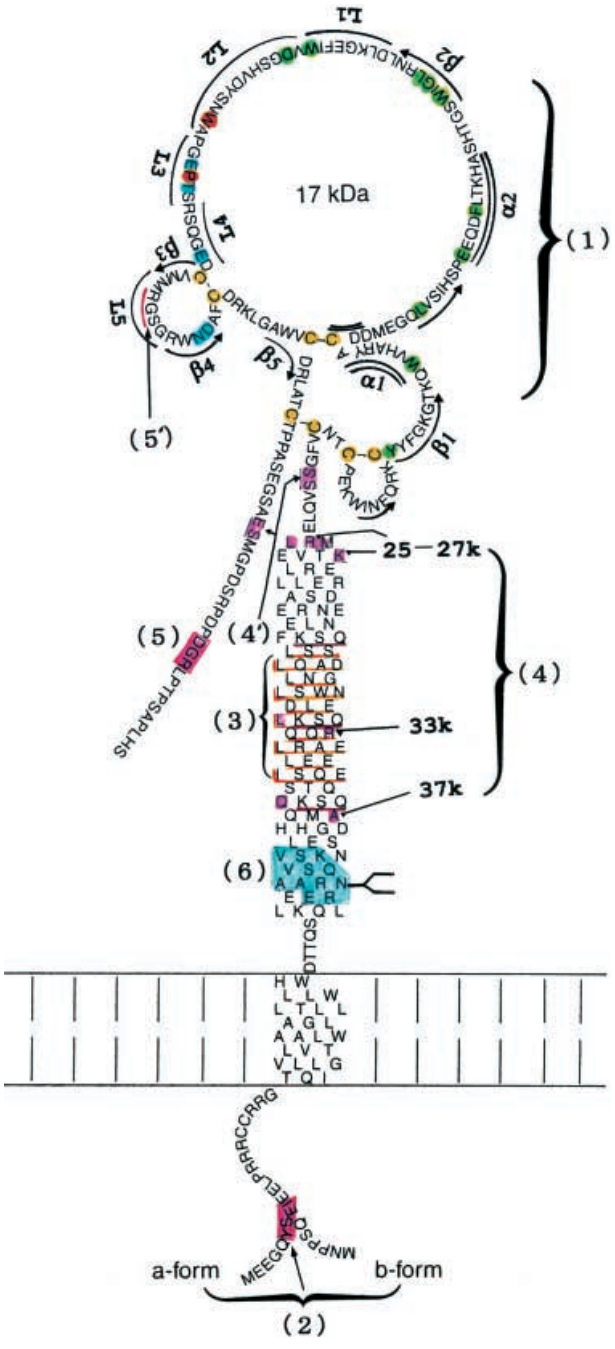


Figure 3. Two-dimensional schematic representation of human CD23. Double lines indicate α helix, arrows indicate β sheet and single lines indicate loops. These are numbered by analogy to the designation made for MBP [Weis W. I. et al. (1991) Science **254:** 1608–1615]. Numbers (1) to (6) refer to the discussion points in the text. The protease cleavage sites (4) are colored pink, and the sizes of the released soluble fractions are indicated. (The basic figure of the amino acid sequence was produced by Sutton and Gould, and is cited from *Immunology Today* [16] by the permission of Dr Sutton).

Characteristics of human CD23

IgE binding, C-type lectin domain – Relationship to NK cell receptors. Figure 4 shows the alignment of amino acid sequences of the C-type lectin domain and C-type lectin-like domain of NK cell receptors and other similar domains. Several features are indicated in this figure: amino acids in MBP bound two Ca^{++}; the carbohydrate binding site; the positions of highly conserved cysteine residues, summarized in table 1, which includes the chromosomal location of the gene, cytoplasmic sequence and others.

Figure 4 clearly shows that there are two structural groups. One group is of typical C-type lectins having Ca^{++} and sugar-binding amino acids. The members of this group are soluble collectins such as serum MBP and pulmonary surfactant proteins; type II transmembrane protein lectins, such as CD23, asialoglycoprotein receptor (ASGPR), chick hepatic lectin (CHL), macrophage C-type lectin, and dendritic cell-specific intercellular adhesion molecule (ICAM)-3-grabbing nonintegrin (DC-SIGN) and dendritic cell immunoreceptor (DCIR); type I transmembrane protein lectins, such as E-, L-, P-selectin (CD62) and human macrophage mannose lectin; macrophage-inducible C-type lectin (MINCLE) and DCIR, though these are encoded by the NK gene cluster, and two interesting lectins, lipopolysaccharide (LPS)-specific and inducible lectin from insect (ILM-2) and parasitic nematodes producing lectin (Tc) which has a domain charcteristic of host C-type lectin [52]. The other group is of C-type lectin-like molecules that lack Ca^{++} and sugar-binding amino acids but have conserved cysteines (thus, this domain regarded as an NK domain or a C-type lectin-like domain). The members are mainly NK receptors such as NKRP1, NKG2 family, CD94, murine Ly49 family, CD69 and human C-type lectin-like receptor (CLEC). The group also includes the low-density lipoprotein receptor [61].

MBP has a broad carbohydrate specificity that includes D-mannose, *N*-acetyl-D-glucosamine and L-fucose. The amino acid residues and the binding of sugars by Ca^{++} is well characterized by X-ray analysis of MBP [62]. Oxygen atoms from the side chains of E185, N187 (at the site B EPN), E193, N205 and D206 form one apex of the bipyramid coordination set of Ca^{++} 2; a carboxylate oxygen of D206 forms one apex of the bipyramid, and the 3- and 4-OH of mannose bisect the other apex. Site B in figure 4 has EPN or QPD sequences. EPN binds Man/GlcNAc and QPD binds Glc/Gal [25, 62]. ASGPR and macrophage C-type lectin have QPD, and others have EPN or modified EPN.

CD23 recognizes a motif in the Cε3 domain of IgE, and glycosylation of IgE is not required for binding [63]. But the IgE binding domain of CD23 has high sequence similarity with chicken ASGPR [4]. As figure 4 shows, CD23

Table 1. Data list of C-type lectin(-like) molecules.

Name	1 Ca^{++}	2 Sugar	3 S–S	4 Similarity	5 Gene	6 Cytoplasmic region	7 Expressed on	8 Ligand	9 Ref. & accession#
MBP-A rat	+	EPN	2	18.5					42, 62, 37
CD23	+	EPT	4	100	19p13	MEEGQ**Y**S**E**I	B, M	IgE, CR2, CR3, CR4	4–7, A10542, 65–68, 102, 106
human									
mouse	+	EPN	4			MEENE**Y**S**G**I			53
rat	+	EPN	4			MEENE**Y**S**G**Y			40
horse	+	EPN	4			MEEHA**Y**S**E**F			40
CHL chicken	+	EPN	3			MDEERL**S**DN	hepatocyte		43
DCIR human	+	EPS	3	27	12p13	MTSEIT**Y**AEV#	DC, B, M, G		44 CAA38997
DC-SIGN	+	EPN	4	34.6	19p13	**Y**KSL !	DC, End, Pl.,	ICAM-3,	45,46 AF209479
human								HIVgp120	55
L-SIGN human	+	EPN	4		19p13	HKSS	liver, LN		
MINCLE	+	EPN	3	34.6	#6 (12p13)		liver, LN		47
mouse									
ASGPR-1	+	QPD	3			MTKE**Y**QDLQ !	hepatic cells	ASGF	48
human									
ASGPR-2	+	QPD	3	36.2		MAKD**F**QDIQ !	hepatic cells	ASGF	49 CAA38997
human									
HML human	+	QPD	3	36.2		MTRT**Y**ENFQ !	macrophage	Tn (GalNAc-)	50 D50532
mMGL mouse	+	QPD	3			MI**Y**ENLQ !	macrophage		50
RML rat	+	QPD	3			MTMA**Y**ENFQ !	macrophage		50
IML-2 insect	+	EPN	3			M**Y**KSF- -**Y**FTS		LPS, mannan	51
Ly49 mouse	–	–	4	20	#6		NK	MHC class I	33, M352812, 72–74
human	–	–		13.8		VT**Y**SMV-IK**F**QDIQ#	NK	MHC class I	AAD44160
NKG2A mouse	–	–	4		NKC	VT**Y**AEL--I I**Y**SDF#	NK	MHC class I	56,57, AAD03419
human	–	–	4	25.4	12p13.1-3	VI**Y**SDL--IT**Y**AEL#	NK	MHC class I	33, 36, 70
CD94 human	–	–	3	21.5			NK	MHC class I	57, 70, 71
NKR-P1 human	(ref.72)				NKC	MDQQAI**Y**AEL#	NK	MHC class I	75, 32
CD69 human	–	–	3		NKC		hematopoietic cells		58, Z22576, 31,32
CLEC-1 human	–	–	3		NKC	MQAK**Y**SST	DC, Liver (intracell)		59, AF200949
CLEC-2 human	–	–	3	21.5	NKC	MQDEDG**Y**ITL	DC, Liver (cell surface)		59, AF124841

1, Presence of Ca^{++}-binding amino acids; 2, amino acid sequence of $Ca^{++}$and sugar binding; EPN binds Man/GlcNAc, and QPD binds Glc/Gal; 3, number of S–S bridges; 4, similarity in lectin domain (%); 5, location of gene; 6, cytoplasmic sequence – !, reported as internalization signal; #, reported as ITIM in each reference. Human and mouse CD72 (Lyb-2) also contain ITIM , IT**Y**ADL sequence; 7, expressed cells and tissues: M, macrophages; G, granulocytes; B, B lymphocytes; DC, dendritic cells; End, endometrium; Pl, placenta; LN, lymph node. Insect, *Drosophila*, has a group of C-type lectin families related to development and immune reactions [60]. Human langerin [54] also has C-type lectin having EPN.

belongs to the C-type lectin group, though the sequence of site B is not EPN but EPT. When EPN is substituted for EPD, MBP loses its mannose- but not its Ca^{2+}-binding activity [62]. We therefore ask whether CD23 that contains EPT rather than EPN is able to bind sugar and act as a lectin. Since EBV-transformed B cells express a high level of CD23, and cells grow in single and aggregated form [64], we used the EBV-transformed human B cell line, L-KT9, to test the sugar-binding activity of CD23 [65]. The crude membrane fraction from L-KT9 cells was solubilized and incubated with asialofetuin-coupled Sepharose in the presence of Ca^{2+}. CD23 was detected in the eluate of 0.3 M lactose (fig. 5A) [65]. We found that CD23 bound rather to the carbohydrate chain having Gal-GalNAc- or GalNAc-stucture (O-linked sugar chain) than to the Gal-GlcNAc-structure (N-linked sugar chain) (fig. 5B). We also found, by glycosidase treatment, that the aggregation of LKT9 cells occurred mainly through the interaction of CD23 as a lectin with galactose residues as its ligand [66] (fig. 6).

Another experiment that supports the interaction of CD23 with sugar chains has been reported by Bonnefoy's group working with the CD21/CD23-liposome system [67]. Human CD21 is one of the ligands of CD23 [68]. By mutating the asparagines on CD21, they [67] have clearly shown that N-linked sugar chains on CD21 are involved critically in the binding of CD23.

The next point to consider is the number of S–S bridges. As figure 2 indicates, MBP has two, CD69 and CD94 have three S–S bridges, and CD23 has one more bridge between cysteines pair number 4 (fig. 4), as in the case of Ly49A (fig. 2), although the position of the S–S bridge

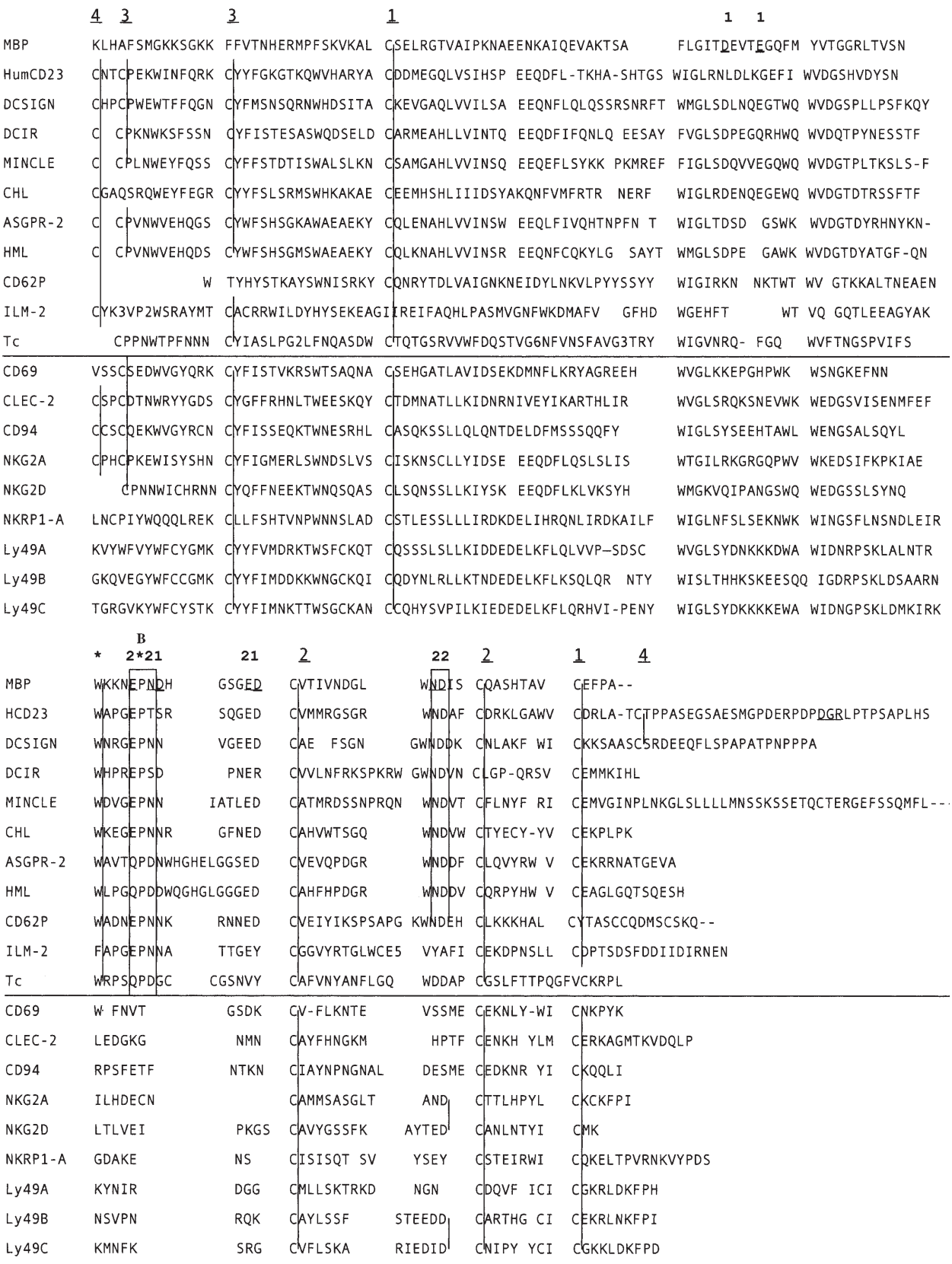


Figure 4. Alignment of C-type lectin(-like) molecules. The residues of MBP-A that bind the two Ca^{++} ions are indicated by numerals **1** and **2**; asterisks (W and P) indicate hydrophobic residues involved in the Ca^{++} binding site [59]; the asterisked W of MBP in the lower panel is 181th from N-terminal. *B* The carbohydrate binding specificity; the paired numbers indicated by underlined 1–4 correspond to the bonded cysteines in CD23. In order to put the cysteine or other amino acids on the same position, space was inserted. - - - in the C terminal means the amino acid sequence continues. Similar figures are shown in [33–36], [45] and [59].

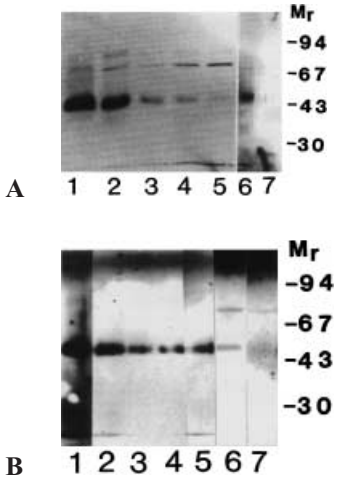


Figure 5. (*A*) Effect of various carbohydrates on the elution of bound CD23 from ASF-Sepharose. L-KT9 cell lysate was incubated at 4 °C for 2 h with ASF-Sepharose gel (lanes 1–6) (~2 mg of cell lysate per 0.2 ml of packed volume of Sepharose). The gel was eluted with 0.3 M carbohydrate or 10 mM EDTA. The eluates were immunopurified by anti-CD23-coupled beads, subjected to SDS-polyacrylamide gel electrophoreses (PAGE) and detected by the immunoblot method. Carbohydrates used for elution were lactose (lane 1), galactose (lane 2), N-acetylglucosamine (lane 3), mannose (lane 4) or glucose (lane 5). ASF-Sepharose gel was also eluted with 10 mM EDTA alone (lane 6), then the gel was further eluted with 0.3 M lactose (lane 7). (*B*) CD23 mainly interacts with O-linked sugar chains. L-KT9 cell lysate was incubated at 4 °C for 2 h with glycoprotein-coupled Sepharose (~1 mg protein of the cell lysate per 0.1 ml of packed volume of Sepharose) and analyzed as in (*A*). Lane 1: the cell lysate was directly immunopurified without incubation with Sepharose gel; lanes 2–5, Sepharose gel coupled with asialocasein (lane 2); asialofetuin (lane 3), asialofetuin-β-eliminated (lane 4); asialobovine submaxillary mucin (lane 5). Lane 6, Sepharose; lane 7, acetylated Sepharose. [Kijimoto-Ochiai S. et al. (1994) Immunol. Lett. **40:** 49–53 [65]. Copyright (1994) Elsevier Science.]

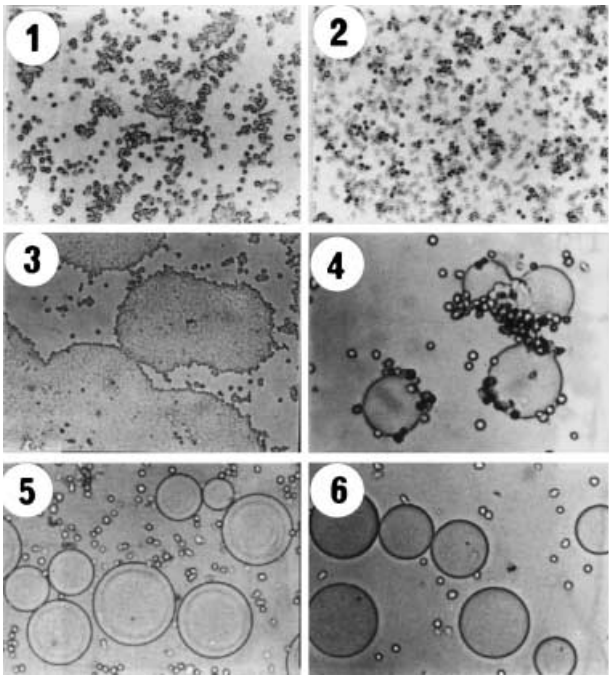


Figure 6. Effects of glycosidases on L-KT9 cells and association with ASF-Sepharose. The aggregated-cell-rich fraction of L-KT9 cells was incubated for 30 min in a CO_2 chamber without (1) or with (2) β-galactosidase from *Escherichia coli* (1.5 U). (3) The single cell-rich fraction was incubated with sialidase from *Arthrobacter ureafaciens* of 2 mU. Cells were incubated with asialofetuin-Sepharose (4) or asialoagalactofetuin-Sepharose (5) or in the presence of anti-CD23 (BG-6 at 7.5 µg/ml) with ASF-Sepharose (6). [These photos are rearranged and combined from figures 1, 2 and 3 in Kijimoto-Ochiai S. and Uede T. (1995) Glycobiology **5:** 443–448 [66]. Copyright (1995) Oxford University Press.]

differs between Ly49A and CD23. Bettler et al. [69] emphasized the importance of these critically placed cysteines in CD23 on finding that the deletion of cysteines has a deleterious effect on IgE binding. Furthermore, despite differences in the number of S–S bridges, these C-type lectin domains all have very similar three-dimensional structures, with exposed ligand binding sites formed by residues within loops L3 or L4 (fig. 2), except for CD94, which does not have the α2 helix. Although the position and structure of two of the S–S bridges in MBP are highly conserved in other C-type lectins, the amino acids between the bridges display much less similarity. CD23 shows higher similarity with ASGPR, DC-SIGN, MINCLE and HML but less similarity with MBP (table 1).

The next question concerns the location of the CD23 gene. Soilleux et al. [45] have found that the human CD23 gene is mapped on chromosome 19p13, near the DC-SIGN and DC-SIGNR (DC-SIGN related, 73% identical to DC-SIGN at the nucleic acid level) genes. DC-SIGN was reported in 1992 as a C-type lectin that is able to bind to the human immunodeficiency virus (HIV) surface protein gp120 [46]. DC-SIGN binds the highly glycosylated molecule ICAM-3, as its name indicates (see abbreviation). Bashirova et al. [55] very recently suggested L-SIGN as a more appropriate name for DC-SIGNR because it became clear that it expresses on liver sinusoidal cells and lymph node but not on DCs. These two genes and CD23 are all encoded within a 105-kb region of 19p13 [45], and all three have four S–S bridges, which suggests that they seem to have a very close relationship. On the other hand, the genes in table 1 are located on human chromosome 12, mouse chromosome 6 and rat 4 in the NK gene complex or cluster (NKC), comprising a C-type lectin-like superfamily of receptors [32]. In humans, the encoded proteins are NKR-P1, CD94, NKG2, and the Ly49 family is added to mouse. CD94/NKG2 forms disulfide-linked heterodimers on human NK cells and is defined as an inhibitory NK cell receptor involved in MHC class I recognition [70, 71]. Ly49 makes homodimer and recognizes polymorphic H-2 class I molecules on potential target cells. These are expressed on NK cells.

CD69 antigen shares functional features with these NK-specific receptors, but CD69 is expressed on a wide variety of hematopoietic cells. Human C-type lectin-like receptors CLEC-1 and -2 [59] on dendritic cells are identified as homologous to the NK cell receptors in linkage with NKC. Recently, Matsumoto et al. [72] revealed the binding site between the MHC class I/β2-microglobulin complex and Ly49. The carbohydrate chain on MHC class I is not involved in binding to Ly49 [73, 74]. Among the NK gene group, DCIR is unique. Bates et al. have pointed out [44]: 'Unlike members of the NK gene complex, DCIR displays a typical lectin domain rather than an NK cell type domain, and was expressed on dendritic cells, monocytes, macrophages and so on. DCIR is differentially expressed on dendritic cells depending on their origin and stage of maturation/activation. DCIR represents a novel surface molecule expressed by Ag presenting cells, and of potential importance in regulation of dendritic cell function.' Akira and his co-worker [47] have found a novel LPS-inducible C-type lectin, MINCLE (the murine homologue of human DCIR), and its gene has been located on mouse chromosome 6 (0.6c Molgans) proximal to CD4 and corresponding to 12p12 in the human chromosome.

In humans, the killer cell-inhibitory cell receptor (KIR) genes, located on chromosome 19q13.4, encode glycoproteins of the Ig superfamily (fig. 1) that bind human leukocyte antigen (HLA) class I ligand and inhibit NK cell-mediated cytotoxicity [32].

The above description allows us to group C-type lectin (like) molecules as follows:

1) ASGPR (HHL), CHL and macrophage lectins recognize sugars and endocytose glycproteins and so on.
2) CD94/NKG2, Ly49 encoded in NKC and expressed NK cells do not bind sugars, but recognize MHC class I.
3) CLEC-1 and -2 are homologous to 2) in dendritic and hepatic cells, whereas CD69 is expressed on a wide variety of hematopoietic cells.
4) NKR-P1 (homolog of LOX-1) is encoded in NKC but is not an essential member for MHC class I recognition [32]. Though it is reported to bind Ca^{++} and sugar [75], no amino acid binds them in MBP as shown in figure 4, except for one Glu (E) that corresponded to 165 and 185 (for #1 and #2 Ca^{++}, respectively) in MBP.
5) DCIR and MINCLE are members of NKC, but have a typical lectin domain.
6) DC-SIGN and L-SIGN are typical C-type lectins and have ligands of highly glycosylated proteins such as HIVgp120 and ICAM-3. DC-SIGN is highly expressed on term placenta and may be related to vertical transmission of HIV [45]. The genes of these lectins are located on 19p13 very close to CD23.
7) Human CD23, one of whose ligands is CD21 – the receptor for EBV – is able to bind not only the IgE-protein portion but also the other glycoprotein with carbohydrate chains containing a terminal galactose. Thus, CD23 functions as a lectin.

Cytoplasmic amino acid sequence – Is the YSEI amino acid sequence an endocytosis signal sequence or ITIM? In human CD23, the two subtypes FcεRIIa and FcεRIIb (CD23a, CD23b) differ only in their N-terminal cytoplasmic sequence, as shown in figure 3. CD23a has a tyrosine in the cytoplasmic sequence, whereas CD23b does not. These species appear to be generated by utilization of different transcriptional initiation sites and alternative RNA splicing [76]. CD23a is constitutively expressed only in normal B cell and EBV-transformed B cell lines, whereas CD23b is expressed on interleukin (IL)-4-activated B cells, macrophage, eosinophils and so on. In the mouse, only one FcεRIIa-like receptor has been reported, although a new cDNA subtype for murine CD23 homologous to the human subtype b has been cloned by polymerase chain reaction (PCR) [77].

Tyrosine exists as a member of the YSEI sequence in human CD23a (YSGT in mouse). In 1994, Gordon [12] pointed out that 'Kolb and colleagues noted that Tyr6 and Ser7 of CD23 are predicted sites for sulphation and casein kinase II phosphorylation, respectively'. He also suggested that Tyr7 of CD72 should be highlighted; now, Tyr7 of CD72 is known as ITIM, a member of the IT**Y**ATL sequence, although Tyr6 and Ser7 of CD23 have not yet been shown to act as signals.

The YXXL-like motifs in the cytoplasmic region of C-type lectin(-like) molecules are listed in table 1. Typical endocytosis signals [78–81] are those of ASGPR-1 and -2 [48, 49]. Macrophage lectins also follow these sequences [50]. At endocytosis, these sequences (YQDL, FQDL, YRIC(I), YXRF) are recognized by the adaptins of cargo receptors [81]. A characteristic stretch of four amino acid residues, which are thought to form a sharp turn in the polypeptide chain (YXRF), form an essential part of the endocytosis signal shared by those cell-surface receptors that function in receptor-mediated endocytosis from the plasma membrane. The amino acids at the RF position in YXRF have large side chains. From this point of view, YSEI in human CD23a fits into this category, i.e. as an endocytosis signal. CHL has no tyrosine, but it is known that the Ser7 is known to be phosphorylated, and its residue is implicated in endocytosis [80]. If we look at the serine adjoined to tyrosine that exists in all other CD23s, we find that this serine corresponds precisely to that of CHL. Thus, the serine residues in CD23 may act in the same way as CHL.

Another group showed ITYADL and I/VXYXXL/V sequences that are known to be typical ITIMs [20]. DCIR, Ly49, NKG2-A and the B-cell-differentiation antigen CD72 have this sequence (table 1). It is of interest that

Ly49 has one more signal sequence, which is the same as ASGPR-2, described above.

The YXXL sequence is also known as an ITIM motif, and if Leu can substitute for Ile, YXXI might be a kind of ITIM motif; in that case, then the YSEI in human CD23 is a variant of the YXXL, ITIM motif. In CD23-knockout mice, antigen-specific IgE-mediated enhancement of antibody responses was severely impaired [82]. If we consider that the suppression of IgE production was released in CD23-knockout mice, it is reasonable to suppose that CD23 contains an inhibitory signal within the molecule, or is coupled with another molecule having an ITIM motif.

In conclusion, the meaning of this sequence remains unclear, and further study will be required to find an answer.

Leucine zipper structure

Human CD23 has a leucine-zipper sequence near the transmembrane domain of its extracellular region and makes an α-helical coiled-coil stalk, which mediates the formation of trimers. This leucine-zipper structure has a seven-amino-acid motif beginning with Leu or Ile that is repeated five times in the case of human CD23 (fig. 3). DC-SIGN has a long sequence of two complete and one irregular, longer leucine-zipper sequences, and this long sequence is repeated eight times [45]. These long stalks do not have the collagen type I sequence of GXY triplet repeats that is in the MBP structures [25]. CD69 does not possess this stalk region [58], and makes a dimer with the S–S bridge near the cell surface (fig. 1). An α-helical coiled-coil stalk will be a more convenient means of making polymer than an S–S bridge. In the case of the binding of carbohydrate and lectin, clustered carbohydrate shows very high affinity [83]. Similarly, the clustered receptor will show high affinity to the carbohydrate chain, and the clustered form will be more convenient for cell-cell interaction.

Klein et al. [84] have reported that vimentin shows significant homology with CD23, as well as having a leucine-zipper-like motif (fig. 7). Vimentin is the most widely distributed of the cytoplasmic intermediate filament proteins [85]. The many types of intermediate filament protein monomers have an amino-terminal head, a carboxyl-terminal tail, and a central rod domain that consists of an extended α-helical region containing a heptad repeat. The variable regions of the different intermediate filament proteins, the head and tail domains, serve a function similar to those of the accessory proteins of actin filaments and microtubules, but the variable regions are an integral part of the intermediate filament subunit, rather than being a separate protein [85]. Thus, intermediate filament-protein, vimentin, itself has a multidomain character like CD23.

Soluble CD23 formation by proteolytic cleavage

Human CD23 is cleaved at four points, releasing soluble forms of CD23 with sizes 25, 27–29, 33 and 37 kDa, as indicated in figure 3 [86]. The release of 33-kDa–soluble CD23 from cell membranes is mediated by a membrane-bound metalloprotease [87]. From the primary structure of CD23, the cleavage site that releases 33-kDa sCD23 is expected to be the carboxyl side of Arg, and thus it is expected to be a trypsin-like protease whose substrate specificity is the carboxyl side of Arg or Lys. Soluble CD23 of 25–27 kDa is also cleaved by the same or a similar protease, as judged by sequence specificity: Lys 147 and Arg 149 are reported to be the cleavage sites for this fragment [86].

Gu et al. [88] reported that ATP induces the shedding of CD23 and L-selectin (CD62) from lymphocytes. The release of L-selectin is the result of a cleavage at the Lys-Ser (KS) peptide bond. A different protease has been suggested to cleave CD23 [88], despite the presence of three KSQ sequences (fig. 3, underlined in red) in CD23. Thus, there is no evidence for the cleavage of the KSQ sequence in CD23. It is likely that many different proteases are involved in the cleavage of L-selectin from leukocytes, and perhaps also for CD23.

Interestingly, Hewitt et al. [89] have reported that the cysteine protease from the house dust mite cleaves CD23. The major house dust mite allergen, *Der p* I, has a high similarity with animal and plant cysteine proteases [90]. On the other hand, the human respiratory tract contains

```
                    *       *       *       *       *
CD23  87 QISQE-LEELRAEQQRLKSQDLELSWNLNGLQADLSSFKS  QELNERNE  133

Vim. 149 LYEEEMRELRRQVDQLTNDKARVEVERDNLAEDIMRLREKLQEEMLQREE 198


CD23 279 AWVCDRLA   TCTPPASEGSAESMGPDSR              PDPDGRL 312

Vim. 313 STEYRRQVQSLTCEVDALKGTNESLERQMREMEENFAVEEAANYQDTIGRL 365
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Figure 7. Comparison of CD23 and vimentin amino acid sequences. This is a part of the figure originally made by Klein N. J., Rigley K. P. and Callard R. E. (1993) IL-4 regulates the morphology, cytoskeleton, and proliferation of human umbilical vein endothelial cells: relationship between vimentin and CD23. Int. Immunol. **5:** 293–301 [84], and cited with the permission of the authors and the Oxford University Press. The leucine-zipper-like motif is indicated with asterisks, and the area of the inverse RGD sequence is underlined.

α1-antiprotease, and it has been found to inhibit *Der p* I protease [89, 91]. But once *Der p* I crosses the tract, it disrupts the IgE network by selectively cleaving CD23 and CD25 (α subunit of the IL-2 receptor) [89, 16]. The cleavage site of CD23 Ser-Ser and Glu-Ser is indicated in figure 3 by an arrow (4′), and a 17-kDa lectin domain fragment is released [16]. No other CD23 or DCIR contains these cleavage sites, but vimentin and the high-affinity IgE receptor do have them, though there is no evidence that *Der p* I is able to cleave these sites.

On the other hand, anti-CD20 (CD20 regulates B cell activation and so on) or anti-CD40 (CD40 on B cell interacts with the CD40-ligand on T cells) cause an increase in sCD23 cleavage [92]. This illustrates that T-B cell cooperation plays a role in sCD23 release.

Moreover, the binding of anti-CD23 monoclonal antibody to the leucine-zipper motif of CD23 on the B cell membrane promotes its proteolytic cleavage, whereas IgE inhibits this cleavage [93]. In contrast, the antibody that recognizes the lectin domain, as well as IgE, protects CD23 from proteolytic cleavage and stimulates its endocytosis [93].

Released soluble CD23 activates monocytes to produce proinflammatory mediators such as IL-1b, IL-6 and tumor necrosis factor α (TNF-α) [93]. Soluble CD23 is reported to function like a cytokine [10, 11]. Thus, this leucine-zipper structure is not simply a stalk supporting a lectin domain.

Reverse RGD sequence

Human CD23 has a reverse RGD (read from the C-terminus, thus inverse) sequence near the C-terminus, as shown in figure 3. The RGD sequence is well known as a cell-adhesion sequence in integrin ligands such as fiblonectin, vitronectin and so on. Integrins are a family of cell-surface heterodimeric glycoprotein receptors that mediate cell-cell and cell-matrix interactions through integrin ligands. Another RGD-containing family is that of the cellular disintegrins, defined by their sequence similarity to snake venom integrin ligands and metalloproteases [94]. Kratzshmar et al. [95] have reported that the role of the RGD sequence in disintegrin works in the same way as integrin ligand, cell adhesion and information signaling. On the other hand, the presence of distinct sites of RGD ligand recognition on the integrin gpIIb/IIIa was reported, using two distinct venom-derived RGD proteins together with a negative allosteric relationship between these RGD recognition sites [96]. This might be the result of the reflection of integrin and disintegrin RGD sites.

Two different functions for the RGD motif, distinct from cell adhesion, have been proposed; one by Buckley et al. [97] is that RGD peptides induce apoptosis by direct caspase-3 activation, whereas the other deals with the cellular trafficking of proprotein convertase 1: the RGD motif is critical for its cellular trafficking but not for its intracellular binding to integrin $\alpha5\beta1$ [98, 99].

In human CD23, but not in other species of CD23 nor in other C-type lectins, an inverse RGD sequence is present near the C-terminus (fig. 3(5), fig. 4). Macrophage C-type lectin also possesses a reverse RDG sequence in the C257–C273 loop (fig. 3(5′), fig. 4), though it is unclear whether this RGD sequence has any function. The human CD23 gene may possibly have acquired this reverse RGD sequence from some other molecule – perhaps from vimentin. Vimentin, as shown in figure 7, has particularly high similarity with CD23 around the RGD sequence of CD23 (residues 307–312), although the sequence of vimentin is RGI (fig. 7). A monoclonal antibody against CD23 (BU-38) has been reported to cross-react with vimentin around RGD as an epitope [84].

In the following section, I will consider the interaction of this reverse RGD motif with the sequence at the root of the N-linked sugar chain.

RGD-binding inhibitory peptide at the root of the N-glycosidic sugar chain

The presence of an ‘RGD-binding inhibitory peptide’ [fig. 3(6)] was first pointed out by Moulder in relation to the RGD sequence [100]. This peptide is in the gpIIIa chain of platelet-integrin gpIIb/IIIa (though Moulder described it as an ‘RGD-binding site’). This peptide (amino acids 211–222 of gpIIIa, fig. 1 D, site B) blocks the binding of platelet-integrin and fibrinogen that has an RGD sequence [101]. Human CD23 has an inverse sequence with homology to this RGD-binding inhibitory peptide (8 residues identical out of 12 amino acids), located at the root of the N-glycosidic chain [100]. The two peptides are as follows: GpIIIa (COOH) EPADRNRS-VSQK (peptide 2 in [102]); CD23 (NH2) ERAARNVSQVS-K (peptide 3 in [102]). The human CD23 molecule, therefore, has interesting peptides in one molecule, i.e. a reversed RGD sequence near the C-terminus, and a reversed RGD-binding inhibitory peptide around the N-sugar chain. Yet why should the CD23 molecule contain these two opposing peptides when their function seems to be contradictory?

We synthesized three peptides to clarify their functions [102]: peptide 1 included an inverse RGD sequence near the C-terminus ((GCY)DPDGRLPTPSAPLHS-COOH); peptides 2 and 3 were as mentioned above. Of the three peptides, only peptide 3 inhibited aggregation of L-KT9 cells (fig. 8). In order to identify the molecule that binds to these peptides, a tyrosine was introduced into peptides 1 and 3(CY)ERAA-- near to the terminus, and the tyrosine-OH was labeled with ^{125}I to avoid modification of the $-NH_3$ or $-COO^-$ groups of the side chains of other amino acids. The labeled peptides 1 and 3 bound to the EBV-transformed B cells (L-KT9) and also to the Western blot

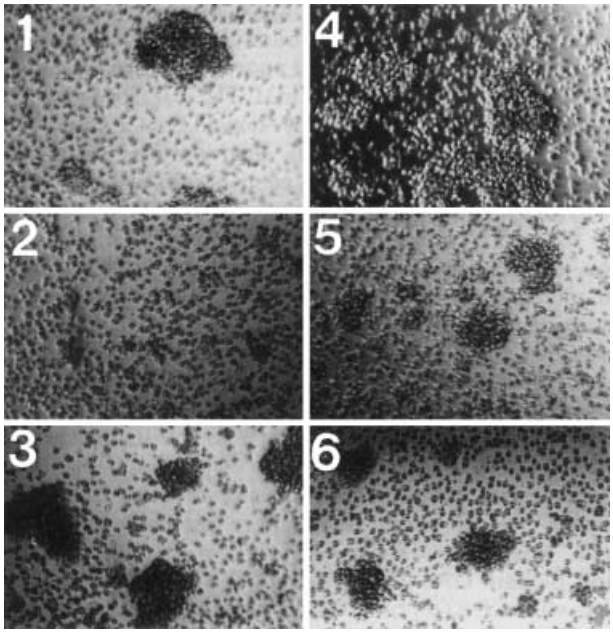

Figure 8. Inhibition of homotypic cell aggregation by peptide 3. L-KT9 cells were harvested, and aggregated cells were pipetted. Single-cell suspension, thus obtained, was incubated ($2.5–3.8 \times 10^5$ cells/30 µl/well of 96-well plate) in the presence of the medium alone (1); peptide 3 (2); peptide 2 (3); peptide 1 (4); GRGDSP (5); and GRGESP (6) at 3 mM of each peptide. [Kijimoto-Ochiai S. and Noguchi A. (2000) Biochem. Biophys. Res. Comm. **267:** 686–691 [102]. Copyright 2000 by Academic Press.]

of solubilized membrane proteins from these cells [102]. The labeled band indicated almost the same molecular size as MHC class II. MHC class II was therefore immunoprecipitated, subjected to two-dimensional electrophoresis [103], and the blotted nitrocellulose (NC) sheets were incubated with the labeled peptides 1 or 3 (fig. 9). Both peptides bound to MHC class II molecules, but peptide 1 (the RGD-containing peptide) did not bind to CD23. Peptide 3 showed a higher affinity for MHC class II than peptide 1 [102].

On the basis of the result that peptide 1 bound to MHC class II but did not bind to the CD23-enriched band, whereas peptide 3 did, we assumed [102] that the physiological function of peptides 1 and 3 was as follows. Peptide 1 probably interacts with the sequence around the sugar chain of MHC class II (or other glycoproteins). CD23, however, has a peptide 3 at the position, signifying that it is an RGD-binding inhibitory peptide, and indeed, no interaction of peptides 1 and 3 was observed by Bio-Gel P4 column chromatography. This means that no homotypic interaction of CD23 molecules through the lectin domain and sugar chain occurs (though CD23 showed low affinity for N-glycoside chain). Peptide 3 may thus be present in CD23 in order to avoid the homotypic interaction of CD23 molecules. Thus, the amino acid sequence around the sugar chain is important for the (positive or negative) interaction of CD23 and glycoproteins, i.e. it may be one of the factors which determines the specificity of the glycoproteins that are ligands for CD23 as a lectin.

Yet we must ask three questions as to why the CD23 molecule repulsed the reverse RGD peptide (1), whereas the MHC class II molecule accepted it. Was this result really caused by the presence or absence of the reverse RGD-binding inhibitory peptide (3) in both molecules at the root of the N-linked carbohydrate chain? Is the functional site of reverse RGD peptide (1) really the DGR motif? Does reverse RGD, i.e. DGR, react in the same way as the RGD?

To answer the first and second questions, we shall need first to carry out an experiment of substitution or deletion of the amino acids in both peptides (1 and 3). As to the third question, sequences RGD and DGR are fundamentally different because of the chiral nature of proteins. Yamada and Kennedy [104], however, have reported that the

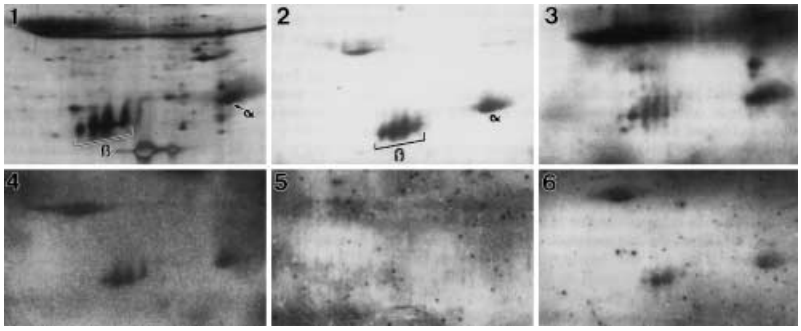

Figure 9. Interaction of ^{125}I-peptide with MHC class II and CD23 molecules. Two-dimensional electrophoresis was performed on immunopurified MHC class II molecules. The proteins on the gel were transferred to an NC membrane. (1) Silver-stained gel. (2) An NC bot was stained with biotinyl RCA lectin and peroxidase reagents. (3) An NC bot was incubated with ^{125}I peptide 1 (5×10^7 cpm/ml for 1 h), washed with TTS, dried and detected by a BAS-1000 image analyzer. (4) ^{125}I peptide 3 was used instead of 1 in 3. (5) Nonlabeled peptide 3 was incubated, washed, and then ^{125}I-peptide 1 was incubated. (6) Nonlabeled peptide 1 and than ^{125}I-peptide 1 were incubated as in 5. [Kijimoto-Ochiai S. and Noguchi A. (2000) Biochem. Biophys. Res. Comm. **267:** 686–691 [102]. Copyright 2000 by Academic Press.]

reverse RGD sequence (SDGR) inhibited cell adhesion and cell spreading in the same manner as RGDS, whereas Dufour et al. [105] have reported almost negative results with regard to the SDGR effect. In the reverse RGD peptide of CD23, DGR lies between proline (-PDGRLP-). This part, therefore, does not make an α helix. Our the results show that both reversed peptides (1 and 3) functioned reasonably. Was this result arrived at incidentally or was it inevitable? We can speculate variously to explain these situations. Before we can decide the answer to this question, however, we shall need more studies, including ones to determine the precise mechanism by which RGD interacts with integrin molecules.

Ligands and function

Ligands for CD23 have been reported, such as IgE, EBV receptor CD21 (CR2) [68], complement receptor and adhesion molecules CR3 (Mac-1, CD11b/CD18) and CR4 (CD11c/CD18, gp150/95)[106]. (For detailed reviews see [9]). On L-KT9, an EBV-transformed B cell line, such ligands are expressed to an almost negligible extent, with the exception of a low level of CD21 [66, unpublished data], but the L-KT9 cells form large aggregates in a growing culture medium. What is the ligand and receptor for this aggregation? Although CD23 is not wholly responsible for the aggregation (more than 50% of the aggregation was inhibited by anti-CD23 or soluble CD23 [66]), it is likely that there is (or are) ligand(s) for CD23 other than those described above. In the physiological state, CD23 is induced by IL-4 during the maturation of B cells at the μ+δ+ stage [107]. If the B cells at this stage aggregate with each other or with T cells through CD23, what is the ligand? It seems to be of interest and important to make clear the natural ligand (including MHC class II) of this μ+δ+ stage.

The function of CD23 has been reviewed by others [9, 10, 14, 82]. CD23 is suggested to act as a negative regulatory feedback signal for IgE level, which in the knockout mice is removed, analyzed in vivo with CD23-knockout mice [82]. The same phenomenon was observed in FcγRII knockout mice [108]. Only FcγRIIb has an ITIM in the cytoplasmic domain; all other Fc receptors have either ITAM (or are coupled with other polypeptides containing ITAM), or no signal motif at all (fig. 1 A).

The B cell in the CD23 knockout mice was reported to maturate normally [109–111], but its capability to protect against infection was not tested. There is a possibility that an infected microorganism is covered with serum glycoproteins and, when recognized, phagocytosed by macrophage lectin or CD23 on macrophage as a lectin. If such a infection-protection mechanism does work in vivo, CD23 knockout mice will provide some information about the function of CD23 as a lectin, though it might be difficult to get clear results because of the presence of many alternative pathways.

Mossalayi [10] and Hebet [27] have reviewed CD23 signal transduction. Several reports have been published: that cyclic-AMP generation was increased in human B lymphocytes following ligation of CD23, by Kolb et al. [112]; that the cross-linking of surface Ig and CD23 on B cells induced apoptosis [113]; that the cytoplasmic domains of CD23 and CD69 are important for Ca^{2+}-mediated signaling [114]; that CD23 couples with I-κ-B kinase [115]; and that soluble CD23 acts as a cytokine, and the cytokine domain differs from IgE binding domain [10]. Membrane-bound CD23, thus, probably acts as a signal-transducing molecule, in association with other B-cell-surface molecules such as MHC class II [116, 117], or tetraspanines such as CD9, CD81 and CD82 [118, 119]. Indeed, we have evidence for the association of CD23 and CD81 [unpublished].

The mysterious and attractive molecule: CD23

Human CD23, as mentioned above, is able mainly to bind the O-glycoside chain (this means that it is possible to bind asialoganglioside series), and act as a C-type lectin, while having high homology with such ASGPR as take glycoproteins into cells by endocytosis. On the other hand, CD23 binds IgE with a protein portion but not with carbohydrates of IgE, and the structure of CD23 differs completely from other Fc receptors. In evolutionary terms, IgE is the latest in the immunoglobulin family to appear. But because CD23 has multifunctional, multistructural characteristics, it is difficult to put it in a typical one-only category. There are many fragmental facts that seem to be related with this CD23 as a lectin, and as a Fcε receptor: eggs are also likeky to have animal lectin, as many seeds have plant lectins; sialic acid-binding lectin from bullfrog (*Rana catesbeiane*) eggs has ribonuclease activity and has been named 'leczyme' by Nitta et al. [120]. Other lectins are related with such enzyme activities as protease or lysophospholipase [24]; MBP recognizes abundant mannose on yeast cell surfaces, whereas some lectins recognize abundant LPS on bacterial surfaces or are induced by it [51], and an insect lectin was induced by injury [121]; Kawasaki et al. found that MBP activates the complement system [122], whereas it kills cancer cells by an unknown complement-independent manner [123]; recognition of non-self by macrophage, and the recognized molecules transported into cells by endocytosis through macrophage lectins or CD23; recognition of non-self by NK cells with NK receptors through MHC class I molecules and inhibition of killer activity by NKRs; the appearance of immunoglobulins that recognize non-self with high specificity, and some of the lectins were probably used as Fc

receptors, as discussed in the review 'Were lectins primitive Fc receptors?' by Hajela [124]; the appearance of complement system is coupled with an immunoglobulin system. EBV's ligand is C3bi, which is one of the members of complement system; the EBV receptor CD21 is a receptor for complement CR2; CD21, one of the receptors of CD23, and CD23 also use CR3 (CD11b/CD18, Mac-1) and CR4 (CD11c/CD18) as ligands, whereas CR3 and CR4 are members of the β2-integrin adhesion molecule family; moreover, CD23 is a low-affinity receptor for IgE, which appears last in the list of immunoglobulins.

How can we arrange these fragmental factors, including the cellular expression of C-type lectins, of NK cell receptors, and of CD23, on the reasonable path of evolution? Where should the human CD23 molecule of today be positioned? One trial was proposed on the basis of gene arrangement by Santis et al. [125]. For me, human CD23 is still a mysterious and attractive molecule.

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