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Review

Surface molecules involved in B lymphocyte function*

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Introduction

For a long time, B lymphocytes were defined by their immunoglobulin expression. Surface-exposed immunoglobulin (sIg) serves as an antigen receptor and bears a considerable functional and structural resemblance to the T cell antigen receptor. Recent research has produced a huge amount of knowledge on other surface structures on B lymphocytes. Some of the B cell surface molecules are lineage restricted (e.g., CD19, CD20, CD22), but most of them are also expressed on other cells. Initially, these molecules and the corresponding antibodies were used for leucocyte typing, an approach that led to considerable progress in the diagnosis of leukaemia and lymphoma. Currently, there are two major routes of research, namely molecular cloning and protein sequencing of these molecules and their functional analysis. From molecular cloning it has become clear that evolutionary diversification of a limited number of molecules has led to the diversity in structure and function of surface molecules on mammalian cells; consequently, gene families are described to classify these molecules. Functional analysis has led to concepts of how surface molecules might be spatially adjusted in the membrane, which of them might act as receptor for soluble products or be involved in cell-matrix and/or cell-cell interaction, and whether there are functional or physical assemblies among these structures. Signalling through these molecules and second messenger properties linked to them currently constitute an exciting field of research.

The classification system of leucocyte surface molecules

By analogy with the workshops on HLA antigens, the Workshops and Conferences on Human Leucocyte Differentiation Antigens began by clustering monoclonal antibodies (mAb) statistically on the basis of their cellular reactivities. A cluster of differentiation (CD) was defined by a group of at least two mAb from different laboratories immunoprecipitating the same molecule or reacting with the respective transfectant/transformant. The CD nomenclature states that the CD number identifies a clone officially assigned to it during one workshop [e.g. CD74(BU45)] and the molecule (CD74) which may also carry other names (the CD74 molecule corresponds to the surface-expressed HLA-D-associated invariant chain). The term anti-CD (e.g. anti-CD74) should not be used to cite an antibody, as in the strict sense this designation implies anti-idiotypic reactivity. A 'w' before the number indicates a provisional clustering, an alphabetical index behind the number determines subtypes of very closely related molecules (e.g. isoforms) joined together in one cluster (Knapp et al. 1990). For historical and pragmatic reasons, HLA molecules, sIg and the T cell antigen receptor (TcR) are kept separately and mAb against these structures do not carry a CD designation. Initially it was thought best to group the molecules according to their main cellular reactivity (e.g., T cell, B cell, myelomonocytic, platelet antigens); during the IVth Workshop (Vienna, 1989), however, there were additional Workshop sessions dealing with 'activation' and 'non-lineage' antigens. Evidence is accumulating that cell line affiliation of surface molecules is (with very few exceptions) arbitrary and misleading and should be abandoned. Nevertheless, for the time being there are 21 CD molecules described as exclusively or predominantly expressed on B cells: CD10 (Paris, 1982), CD19, CD20, CD21, CD22, CD23, CD24 (Boston, 1984), CD37, CD38, CD39, CD40 (Oxford, 1986), CD45RA, CD45-like, CD48, CD72, CD73, CD74, CDw75, CD76, CD77, CDw78 (Vienna, 1989; Dörken et al., 1989a). Most of these molecules are only temporarily expressed during B cell ontogeny, thus determining different stages of B cell development by their presence or absence. Histologically, these stages of development are closely linked to microtopographically defined B cell compartments within the lymphoid tissues and, at the same time, cytologically discernible B cell types (Table 1).

* Dedicated to Prof. Dr. Dres. h.c. W. Doerr at the occasion of his 77th birthday

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Table 1. Antigen expression in microtopographically and cytomorphologically defined peripheral B cell subsets as determined by immunohistochemistry

CD/antigen	Molecular weight (kDa)	Clone	MZ	FC	EF[a]	PCC
CD10	100–95	J5	−	(+)	−	−
CD19	90	HD37	+	+	+	−
CD20	37/35	B1	+	+	+	−
CD21	140	B2	−/+	−	−	−
CD22	135	HD39	+	(+)	+	−
CD23	50–45	HD50	+	−	−	−
CD24	41/38	SN-3	+	−	−	−
CD30	105	Ber-H2	−	−	−	−>+
CDw32	48–43/39	41H16	(+)	−	−	−
CD37	52–40	HD28	+	+	+	−
CD38	45	OKT10	−	(+)	−	+
CD39	100–70	AC2	(+)	−	+	−/+
CD40	48/44	G28-5	+	+	+	−
CD45RA	220	F8-11-13	+	+	+	+
CD45-like	220	KiB3	+	−	−/+	−
CD69	34/28	TP1/55-3	+	−>+	+	+
CD72	43/39	J3-109	+	−/+	+/(+)	−
CD73	69	AD2	−	+	−	−
CD74	(41)/35/33	BU-45	+	+	+	−
CDw75	?	LN1	−/(+)	+	−/+	−
CD76	85/67	HD66	+	−	−/+	−
CD77	Galα-1–4 Galβ1–4 Glc1–1 ceramide	424/4A11	−	+	−	−
CDw78	?	Leu-21	+	−	−	−
B-ly7/HML-1	175, 143, 112/122, 100	B-ly7	−	−	−>>+	−
B7/BB-1	44/54	BB-1	−>+	−	−>+	−

MZ, mantle zone; FC, follicular centre; EF, extrafollicular B cell compartment; PCC, plasma cell compartment; +, strong positivity; (+), weak positivity; −, no reactivity; x/y, composite pattern of reactivity; −>+, more negative than positive cells

[a] The extrafollicular (EF) compartment is the peri(/supra-)follicular area, which has different names in different lymphoid tissues. It corresponds to the marginal zone of the spleen, to the peri- and intrasinusoidal region of the lymph node, to the so-called dome area of the gut-associated lymphoid tissue, to the intraepithelial compartment in the tonsil, and, probably, to the medullary B cell compartment of the thymus (reviewed by Möller and Mielke 1989)

B cell antigens comprise different types of molecules

CD19, CD22, CD48, and the (still unclustered) B7/BB-1 antigen are members of the very complex immunoglobulin superfamily (Stamenkovic and Seed 1988a; Williams and Barclay 1988; Tedder and Isaacs 1989; Freeman et al. 1989) acting predominantly as adhesion molecules; all members of this family are integral transmembrane structures and so-called type I molecules; that is to say the C-terminus of the protein is located inside and the N-terminus outside the cell. CD22 has considerable molecular homology to the adhesion structures neural cell adhesion molecule N-CAM and myelin-associated glycoprotein (MAG) and is a mediator of B-B cell homotypic adhesion (Wilson et al. 1991). CD48 is a glycosylphosphatidylinositol-anchored early-activation-associated glycoprotein (formerly known as BLAST-1 antigen) which mediates adhesion (Fisher and Thorley-Lawson 1991). The B7/BB-1 molecule is the natural ligand of the T cell antigen CD28 contributing to T-B cell adherence and signalling (Linsley et al. 1990). Transmembrane molecules with an intracytoplasmic N-terminus and an extracytoplasmic C-terminus are called type II integral membrane proteins. CD23, CD38 (Jackson and Bell 1990), CD72, and CD74 belong to this group. CD20 and CD37 are proteins with multiple transmembrane domains; both ends of the CD20 molecule are directed towards the cytosol and therefore it is classified as a type III molecule (Tedder et al. 1988; Stamenkovic and Seed 1988b; Einfeld et al. 1988); CD37 has an intracytoplasmic N-terminus, two membrane-spanning regions and an extracellular C-terminus. Together with CD5, the nerve cell growth factor (NGF) receptor and the low and high-molecular-weight tumour necrosis factor (TNF) receptor, CD40 belongs to the group of cysteine-rich cytokine receptor-like structures (Clark 1990). CD10, CD45, CD73, and CDw75 are cell-surface-associated enzymes: CD10 is identical with neutral endopeptidase, an enzyme hydrolysing peptides such as angiotensin, bradykinin, encephalins, oxytocin, and substance P (LeBien and McCormack 1989). CD45 comprises a family of surface molecules the cytoplasmic portion of which has protein tyrosine phosphatase activity (Charbonneau et al. 1988); CD45 molecules interact with other surface (glyco-)proteins and dephosphorylate their tyrosyl residues (see below). CD73 is identical with ecto-5′nucleotidase, a glycosyl phosphoinositol-anchored molecule serving as purine salvage enzyme (Thompson et al. 1990). Molecular cloning of CDw75 revealed that this molecule is a surface-expressed α2,6-sialyl-transferase (Stamenkovic et al. 1990).

Signal transduction via sIg requires additional molecules

Triggering a B cell via sIg leads – analogously to triggering a T cell via its TcR – to a rapid appearance of tyrosine phosphorylated proteins. This effect is associated with inositol phospholipid turnover and a transmembrane $[Ca^{2+}]_i$ flux (Lane et al. 1991). The intracytoplasmic portion of sIg consists of only three amino acids. Therefore, it has been assumed that membrane IgM and IgD transduce signals via closely associated proteins (analogous to the TcR/CD3 complex). Recently, further constituents of the B cell antigen receptor complex have been identified in the mouse (reviewed by Reth et al. 1991): Two genes, *mb-1* and *B29*, have been identified that encode type I integral membrane proteins probably assembling to a $\alpha\beta$-heterodimer non-covalently associated with sIgM and sIgD (Wienends et al. 1990; Campbell and Cambier 1990). These proteins have been reported to bear sequence homologies with the proteins of the CD3 complex (Hombach et al. 1990). Their human equivalents have not yet been identified.

Surface molecules functionally linked to sIg

There are CD molecules known to be functionally linked to sIg, namely CD19, CD21, CD22, and CD40. CD21 is the human complement receptor type 2. Anti-Ig crosslinking leads to phosphorylation of CD21; sIg co-cap with ligand-loaded CR2; CD21 crosslinking contributes a co-stimulating signal to anti-μ stimulation (Dörken et al. 1989b). CD22 might also be functionally linked with sIg since CD22 mAb have been shown to augment $[Ca^{2+}]_i$ fluxes induced by anti-Ig when cross-linked (Pezzutto et al. 1988). During the developmental stage this antigen is expressed on the cell surface. The activation antigen CD40 (Clark and Ledbetter 1986; Gordon et al. 1988) is a phosphoprotein involved in growth signal transduction (Paulie et al. 1989; Braesch-Andersen et al. 1989). Its cell surface density can be enhanced by phorbol esters (Law et al. 1990) and interleukin-4 (Vallé et al. 1989). Meanwhile, it has come to seem very likely that CD40 serves as a cytokine receptor (Clark 1990), and it might indeed be the receptor for interleukin-6 or a spatially closely associated structure as it has been shown that interleukin-6 induces increased phosphorylation of CD40 molecules (Clark and Shu 1990). CD40 mAb together with anti-Ig was shown to prevent centrocytes from cell death by apoptosis (Liu et al. 1989). Crosslinking of CD40 molecules on normal, non-transformed B cells through immobilized CD40 mAb together with interleukin-4 was shown to deliver a prolonged clonal expansion signal to these cells, which otherwise survive only for a short time in culture. This effect was most pronounced when CD40 mAb were exposed Fc-bound via CDw32 molecules expressed by a CDw32 transfectant mouse fibroblast monolayer (Banchereau et al. 1991; Rousset et al. 1991). CD40 mAb together with interleukin-4 induce IgE production in tonsillar B cells in an isotype-specific manner (Zhang et al. 1991). Furthermore, by delivering a signal via the CD40 molecule, CD40 mAb induce homotypic adhesion in freshly isolated B cells. This adhesion was at least partly due to up-regulation of surface expression of intercellular adhesion molecule-1 (CD54), a ligand for LFA-1 (CD11a/CD18) (Barrett et al. 1991). Taken together, these data show that CD40 signalling modifies the B cell in very different ways depending on the nature of co-signals.

CD19 and CDw32 as signal-transducing molecules antagonizing sIg-induced activation

CD19 mAb have been shown to inhibit B cell activation and proliferation and, at the same time, induce a strong $[Ca^{2+}]_i$ flux in resting B cells (Pezzutto et al. 1987). Pretreatment with CD19 mAb can completely block anti-Ig induction of a calcium signal (Pezzutto et al. 1987). However, it has been shown that anti-IgM mAb co-modulate CD19, in that the antibody-mediated internalization of sIg also leads to a depletion of surface CD19 (Pesando et al. 1989). Indirect evidence suggests that this signal pathway is distinct from others (Barrett et al. 1990), and it has been suggested that it might interfere directly with the membrane Ig-associated, inducibly tyrosine-phosphorylated protein complex described in mouse (see above) (Rijkers et al. 1990). Recently, three additional transmembrane chains associated with CD19 have been described (p50, p20, p14), which form a CD19 complex that itself may physically associate with the complement receptor type 2 (CD21) (Matsumoto et al. 1991). This multimolecular p50, p20, p14/CD19/CD21 complex might be the structure by which complement modulates B cell function. Fc receptors for IgG (FcRII; CDw32) are expressed on resting B cells (roughly corresponding to B cells of the mantle zone; cf. Table 1). In contrast to the situation found in macrophages, CDw32 is less involved in antibody-mediated endocytosis than in modulating B cell activation; these different modes of function might be due to the fact that there are different isoforms of this structure (Stuart et al. 1989; Hunziker et al. 1990). Although crosslinking of sIg can result in B-cell activation and differentiation (see above), crosslinking CDw32 with sIg via specific antigen bound to soluble IgG delivers a dominant inhibitory signal that prevents or aborts activation (Köhler et al. 1977). This form of regulation was proposed to induce tolerance by IgG and to control the B cell repertoire by anti-idiotypes (Sinclair and Panoskaltsis 1987). Hence, antigen bound to soluble IgG and complexing with sIg might either turn the antigen-specific B cell *off* (via CDw32) or *on* (via complement-loaded CD21; see above).

sIg-independent B cell activation

CD20 has been known for several years to be functionally linked with B cell activation, as some (but not all) CD20 mAb induce a transition from G_0 to G_1 in normal resting B cells (Tedder et al. 1985; Clark and Shu 1987).

CD20 was proposed to be a B-lymphocyte-specific Ca^{2+} channel (Bubien et al. 1989) independent of sIgM. CD20 signalling might possibly involve the protein kinase C pathway, presumably in an inositol triphosphate-independent mechanism (White et al. 1989). CD20 function may be regulated by modulation of CD20 protein phosphorylation (Tedder and Schlossman 1988), which can be induced by CD40 mAb and anti-μ (Genot et al. 1991). Another surface glycoprotein inducing Ca^{2+} mobilization and B cell activation is CD39 (Valentine et al. 1988). According to Kansas et al. (1991), CD39 mAb directed against certain epitopes induce rapid aggregation of B cells. Thus, it was suggested that CD39 is involved in the activation-associated homotypic adhesion. Activation/adhesion is also mediated by CD48. Although CD48 is already expressed at moderate levels on resting B cells the molecule might be complexed at this stage, resulting in masking of the epitope critical for function; activation probably causes dissociation of the complex revealing the functionally active domain (Yokoyama et al. 1991).

HLA molecules as signal transducing structures

Mature resting B cell constitutively express HLA-A,B,C/β_2m and HLA-DR, HLA-DP, and HLA-DQ molecules (Guy and van Heyningen 1983); it could be further shown that B cells also express the HLA-D-associated invariant chain (CD74) on the cell surface (Wraight et al. 1990). HLA antibody effects suggest that HLA molecules might confer signals to the B cell. Anti-HLA-A,B,C antibodies inhibit the T-cell-independent proliferation of B cells (Taylor et al. 1987). Crosslinking of HLA-D molecules on resting B cells can initiate phosphatidyl inositol turnover and increases the intracellular calcium to levels comparable to those seen after anti-μ stimulation (Lane et al. 1990). This activation might involve a protein kinase C pathway (Mooney et al. 1990). Triggering B cells via HLA-D enhances B7/BB-1 expression (Koulova et al. 1991); B7/BB-1-CD28 interaction was shown to co-stimulate proliferation and to increase interleukin-2 transcripts in T cells (Linsley et al. 1991) and might, therefore, be a second signal for primary alloactivation of $CD4^+$ T cells by B blasts. A signal from a $CD4^+$ T cell might also be delivered through CD72, which was recently identified as the human homologue of mouse *Lyb-2*, known to be the natural ligand for *Ly1*, the human homologue, in turn, is CD5 (Van de Velde et al. 1991; DeFranco 1991). In this respect it is noteworthy that there is a spatial association of HLA-DR and CD23 on B lymphocytes (Bonnefoy et al. 1988). Apart from other functions ascribed to the CD23 molecule (see below), it was suggested that CD23 could serve as a co-stimulatory adhesion molecule in antigen presentation (Flores-Romo et al. 1990).

CD23, a multifunctional molecule

The CD23 antigen is a B cell structure identified as the low-affinity IgE receptor (Yukawa et al. 1987; Bonnefoy et al. 1987) expressed on sIgM/sIgD double-positive B cells. CD23 expression can be induced by Epstein-Barr virus nuclear antigen 2 (Wang et al. 1987), interleukin-4 (Defrance et al. 1987), can be enhanced by IgE (Guy and Gordon 1987), and is down-regulated by interferon-γ. CD23 acts as an early activation antigen synthesized and expressed prior to the entrance in the cell cycle (Thorley-Lawson and Mann 1985) and triggers the cell cycle progression of activated B cells (Gordon et al. 1986). CD19 mAb, which inhibit B cell proliferation in response to interleukin-4 in conjunction with anti-Ig, was found to inhibit interleukin-4 induced CD23 but not sIgM expression, suggesting that CD23 and sIgM are regulated independently (Rigley et al. 1991). CD23 mAb were found to trigger polyphosphoinositide hydrolysis in B blasts co-stimulated by *Staphylococcus aureus* Cowan I (SAC) and interleukin-4 and induce a rise in $[Ca^{2+}]_i$ flux which could be attributed to mobilization from intracellular pools; a specific phosphoinositidase C was found to be involved in this process (Kolb et al. 1990). First reports on shed CD23 and the effects of soluble fragments date back to 1987 (Swendeman and Thorley-Lawson 1987). Meanwhile, the CD23 molecule has been sequenced (Letellier et al. 1989) and is described as a type II transmembrane molecule with an IgE-binding domain, followed by a lectin homology region and an inverted RGD region close to the C-terminus. Cleavage products, most probably resulting from autoproteolytic activity (Letellier et al. 1990), have different molecular weights, M_r 33/37 kDa and M_r 25/27 kDa. Soluble CD23 (sCD23), which can be detected at low levels in normal serum (Lowe et al. 1989), is released by B cells upon interleukin-4 stimulation (Pfeil et al. 1989; Delespesse et al. 1989) and this particular interleukin-4 effect can be enhanced by CD40 mAb (Cairns et al. 1988); sCD23 production by B cells was shown to be suppressible by interferon-γ and interferon-α (Delespesse et al. 1989). sCD23 has cytokine function and acts as autocrine growth factor (BCGF) (Swendeman and Thorley-Lawson 1987) and differentiation factor for B cells (BCDF). The more stable 25/27 kDa fragment, which retains the IgE-binding capacity, promotes in synergy with interleukin-1α survival of otherwise short-lived germinal centre B cells and drives them towards a plasmocytoid stage of differentiation (Liu et al. 1991). Effects of sCD23 are not B cell restricted; in synergy with interleukin-1 sCD23 also induces early thymocyte maturation (Mossalayi et al. 1990a) and proliferation of early myeloid progenitor cells (Mossalayi et al. 1990b).

CD45, a family of membrane-associated tyrosine phosphatases modulating receptor function

CD45 mAb recognize an epitope common to all isoforms of CD45 leucocyte common antigen, whereas other mAb bind only one of the known isoforms presently designated CD45RA, CD45RB, and CD45RO (Pulido and Sanchez-Madrid 1989). Leucocytes differ in CD45 isoform patterns they express; furthermore, the actual combination/concentration of CD45 isoforms on a cell

is modulated by events of maturation and activation (Akbar et al. 1988; Clark and Ledbetter 1989; Zola et al. 1990; Deane et al. 1991). The isoform predominantly expressed on B cells appears to be CD45RA (Dörken et al. 1989c; Schwinzer 1989). During the *IVth Workshop and Conference on Human Leucocyte Differentiation Antigens*, a small group of antibodies was found to recognize a B-cell-restricted molecule of a molecular range identical with CD45 but differing in its expressional pattern from CD45RA (Table 1); since it is not clear at the moment which isoform of CD45R is recognized by antibodies like Ki-B3, a preliminary group, "CD45-like", was temporarily defined (Dörken et al. 1989c). The natural ligand(s?) for CD45 molecules have not yet been found. Functional studies revealed that CD45 regulates signal transduction in lymphocytes. On resting B cells crosslinking CD45 with either sIg or CD19 negatively affects the calcium signal transduced by these molecules (Mittler et al. 1987; Clark and Ledbetter 1989). CD45 can also inhibit signalling when crosslinked with CD40 (Gruber et al. 1989); this interaction does not lead to alteration in Ca^{2+} but might inhibit the alleged cytokine-binding capacity of the CD40 molecule (see above). Thus, CD45 can participate in *on* and *off* signalling of B cells depending on the receptor with which it interacts. These data, however, will have to be re-evaluated against the background of our knowledge on functional differences among CD45 isoforms which have been worked out in the T cell system (Akbar et al. 1988; Birkeland et al. 1989; Yamada et al. 1990; Miyawaki et al. 1990).

Outlook

Data on the molecular structure and/or function of the recently defined B-cell-associated antigens CD73 (Thompson et al. 1990), CDw75, CD76, CD77, and CDw78 are still too sparse, preliminary and/or conflicting to be reported here. Matters are likewise not settled enough to include CD1c, CD5, CD27 and the (still unclustered) B-ly7/HML-1 antigen in the complex picture of B cell physiology. These antigens are known as T cell antigens but are also expressed in *subsets* of B cells (Smith et al. 1988; Raveche 1990; Maurer et al. 1990; Moldenhauer et al. 1990; Möller et al. 1990), probably defining functional subpopulations. Furthermore, the *activation antigens* CD25 (interleukin-2 receptor), CD30 (reviewed by Schwarting and Stein 1989a), CD69 (AIM; Sanchez-Mateos et al. 1989; Gerosa et al. 1991), and CD71 (transferrin receptor; reviewed by Schwarting and Stein 1989b) are deliberately neglected in this presentation, although it is evident from the data currently available that these molecules are most likely to become important Knots in the functional network governing the B lymphocyte. This is especially true for the large number of *adhesion molecules* that control lymphocyte migration, homing and intercellular adhesion (reviewed by Stoolman 1989; Patarroyo and Makgoba 1989; Hemler 1990); a considerable number of them is differentially expressed during B cell ontogeny (Möller et al. 1991). Since in the life of a B lymphocyte adhesion and activation seem to be two sides of the same coin (Clark and Lane 1991), close functional relationships between activation and adhesion molecules will surely emerge in the near future.

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