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SPECIAL ARTICLE

STRUCTURES ON THE CELL SURFACE

Update from the Fifth International Workshop on Human Leukocyte Differentiation Antigens

NORA G. SINGER, ROBERT F. TODD, and DAVID A. FOX

What is the value of the CD classification of leukocyte surface antigens?

Monoclonal antibody technology has led to the identification of a large number of leukocyte surface structures over the past 15 years. More importantly, the antibodies themselves have proven to be powerful tools for understanding the function and structure of these antigens. Many of these molecules now have defined roles in cell signaling, adhesion, and regulation of inflammatory processes. An in-depth understanding of the function of these molecules is essential to defining their importance in inflammatory and autoimmune diseases. Hopefully, many of these structures will ultimately be suitable targets for new pharmacologic and biologic therapeutic agents. A large number of the leukocyte surface markers have been classified in the CD nomenclature.

With the number of CD antigens now well in excess of 100, it becomes increasingly difficult to remember the identity of the specific structures in each CD cluster. In some ways, the assignment of more colorful or descriptive names to individual antigens is more compelling. Nevertheless, it is clear that the CD classification system is necessary to avert chaos in the rapidly expanding field of immunology. It has provided a mechanism for determining that investigators working with different antibodies in laboratories scattered around the world are, in fact, working with reagents to common surface antigens. In many instances this has allowed the assignment of as-yet-unclassified monoclonal antibodies to known CD clusters. More importantly, it has permitted the definition of new surface structures, for which information from any individual laboratory working with one reagent would not have been sufficient to properly characterize a new antigen. In some instances antibodies have been misclassified by submitting laboratories, and the workshop analyses provide a mechanism for correctly identifying the target antigen. This potentially averts many mistakes in research laboratories. It is also of value in clinical therapeutics, since misclassified antibodies have, on a rare occasion, already been in use in clinical protocols. Definition of the CD antigens provides a very helpful framework for further investigation. This is brought about by the direct exchange of information through The Human Leukocyte Differentiation Antigen Workshops.

At the First Workshop, completed in 1982, 137 antibodies were studied and 15 CD clusters designated. At the Fifth Workshop, with participation from more than 500 laboratories, culminating with a meeting in Boston in November 1993, 1,450 antibodies were studied and the list of classified CD antigens was extended to 130.

With the growth of the workshop effort, functional and biochemical studies have become an increasingly important part of the work undertaken, and often provide important clues to the physiologic role of the surface antigens. The use of transfectants and recombinant soluble forms of cell surface molecules has also accelerated the acquisition of new information regarding function and ligands of the various CD antigens. Thus, the Human Leukocyte Differentiation Antigen Workshops have become an important focus

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Nora G. Singer, MD: University of Michigan, Ann Arbor; Robert F. Todd, PhD, MD: University of Michigan; David A. Fox, MD: University of Michigan.

Address reprint requests to David A. Fox, MD, 200 Zina Pitcher Place, R4570 Kresge I, The University of Michigan, Ann Arbor, MI 48109-0531.

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Table 1. Examples of existing CDs with revisions/additions

CD	Common name	Characteristics/function
CD2	T11	Expressed on T cells, thymocytes, and natural killer (NK) cells; ligands include CD58, CD59, and CD48
CD3	T3	Expressed on T cells and thymocytes; associated with the T cell antigen receptor; important in signal transduction
CD4	T4	Expressed on major subset of thymocytes and T cells; receptor for class II major histocompatibility complex (MHC) and human immunodeficiency virus
CD5	Tp67	Expressed on T cells and subset of B cells; reported to bind to CD72
CD6	T12	Distribution similar to CD5; both CD5 and CD6 may be involved in T cell activation
CD8	T8	Expressed on T cells and subset of NK cells; class I MHC receptor
CD11a	LFA-1α	Adhesion molecule expressed on leukocytes; receptor for CD50, CD54, CD102
CD11b	CR3, C3bi receptor, Mac-1, Mo-1	Receptor for C3bi and CD54
CD11c	gp150/95	Expressed on monocytes, granulocytes, NK cells
CD14	Mo-2	Expressed on monocytes and macrophages; receptor for endotoxin/endotoxin binding protein complex
CD15s	Sialyl Lewis^x	Neutrophil ligand for the selectin CD62E
CD16	FcRIIIA	Low-affinity receptor for IgG (FcγRIIIA, transmembrane form)
CD16b	FcRIIIB	Phosphatidylinositol-linked form of low-affinity Fc IgG receptor
CD18	LFA-1β	β subunit of leukocyte integrin family; noncovalently linked to CD11a, b, and c
CD20	Bp35, B1	Expressed on B cells; involved in B cell activation
CD21	C3d, receptor, EBV receptor	Receptor for C3d and Epstein-Barr virus; expressed on mature B cells
CD23	FcϵRII	Low-affinity Fc-IgE receptor; up-regulated by interleukin-4 (IL-4)
CD25	IL-2R, Tac antigen	Low-affinity subunit of IL-2 receptor
CD26	Ta-1	Dipeptidyl peptidase IV
CD28		Ligand on T cell for CD80; accessory pathway for T cell stimulation
CD29		Common integrin β1 subunit
CD32	FcγRII, p40	Low-affinity receptor for IgG
CD35	CR1, C3b receptor	Aids in binding and phagocytosis of C3b-coated particles
CD36	Platelet GPIV, GPIIIb	Endothelial cell receptor for *Plasmodium falciparum*–infected red blood cells; platelet and monocyte receptor for thrombospondin; member of the tetraspan family (includes CD9, CD37, CD53, CD63, and CD81)
CD40	gp50	Stimulation by monoclonal antibodies activates B cells; ligand expressed on T cells
CD41	GP IIb/IIIa	Mediates platelet aggregation; absent on platelets in Glanzmann's thrombasthenia
CD42a	GP IX	GP IX component of GP Ib/IX complex; von Willebrand factor–dependent adhesion receptor
CD42b	GP Ib,α	α is 135-kd chain
CD42c	GP Ib,β	β is 25-kd chain
CD42d	GP V	
CD44	Pgp-1	Homing receptor; role in T cell mitogenesis and cell adhesion; glycosaminoglycan receptor
CD44R		Restricted epitope of CD44; specific for exon V9
CD45		Important in cell signaling; is a tyrosine phosphatase; isoforms (CD45RA, CD45RO, CD45RB) identify functional lymphocyte subsets
CD46	MCP, gp45-70	Cofactor for the factor I–mediated cleavage of C3b, C4b
CD49a	VLA-1, α1 integrin chain	Receptor for collagen/laminin
CD49b	VLA-2, α2 integrin chain	Receptor for collagen/laminin
CD49c	VLA-3, α3 integrin chain	Receptor for epiligrin; weaker binding to collagen, laminin, fibronectin
CD49d	CDw49d, VLA-4, α4 integrin chain	$\alpha 4\beta 1$ is a ligand for vascular cell adhesion molecule 1 or CD106; $\alpha 4\beta 7$ is a ligand for the adhesion molecule termed MADCAM
CD49e	VLA-5, α5 integrin chain	Receptor for fibronectin
CD49f	CDw49f, VLA-6, α6 integrin chain	Receptor for laminin
CD50	CDw50, ICAM-3	Ligand for CD11a/CD18
CD51/CD61	GP IIbIIIa	Integrin expressed on platelets; involved in regulation of hemostasis
CD52	Campath-1	Antibodies have been used for prevention of graft-versus-host disease and treatment of autoimmune disease
CD54	ICAM-1	Intercellular adhesion molecule 1; ligand for lymphocyte function–associated antigen 1 (LFA-1) (CD11a/CD18) and Mac-1 (CD11b/CD18)
CD55	DAF	Decay-accelerating factor; limits complement activation
CD56	N-CAM, NKH-1	Useful for identification of NK cells
CD58	LFA-3	A ligand for CD2
CD59	MAC inhibitor	Inhibits the complement membrane attack complex
CD60	UM4D4	Carbohydrate epitope; expressed on a T cell subset that accumulates in autoimmune lesions
CD61	β3 integrin chain, GP IIIa, β chain of the vitronectin receptor	Can associate with CD51
CD62E	E-selectin, ELAM-1	Adhesion molecule expressed on activated endothelium
CD62L	L-selectin	Adhesion molecule widely expressed on leukocytes
CD62P	P-selectin, CD62, PADGEM, GMP-140	Adhesion molecule expressed on surface of activated platelets and endothelium
CD64	FcγRI	High-affinity Fc IgG receptor
CD70	CDw70, CD27 ligand	Homology to TNFα and the CD10 ligand; may be co-activating ligand for T cells
CD71	T9 antigen	Transferrin receptor
CD73	Ecto-5′-nucleotidase	Catalyzes dephosphorylation of purine/pyrimidine ribo/deoxyribo-nucleoside monophosphates
CD74	Invariant chain	Noncovalent association with class II MHC; role in intracellular MHC transport and antigen processing

Table 2. New CD antigens

CD	Common name	Characteristics/function
CD79a	mb-1, Ig-α	Signaling molecule associated with B cell surface immunoglobulin
CD79b	B-29, Ig-β	Signaling molecule associated with B cell surface immunoglobulin
CD80	B7/BB1	CD28 counterreceptor
CD81	Tapa-1	Member of the tetraspan family; antibody has antiproliferative effects on tumor cells in vitro
CD82	IA4, 4F9	Member of the tetraspan family (includes CD9, CD37, CD53, CD63, CD81)
CD83	HB15	Expressed on freshly isolated dendritic cells and on some activated peripheral blood cells
CDw84		Expressed on some resting and activated peripheral blood cells; function unknown
CD85	VMP-55, GH1/75	Expressed on plasma cells
CD86	Fun-1, BU63	Expressed on macrophages and activated and germinal center B cells
CD87	uPA-R	Receptor for urokinase plasminogen activator
CD88	C5aR	C5a receptor
CD89	FcαR	Fc IgA receptor
CDw90	Thy-1	Murine homolog expressed on T cells; human antigen present on hematopoietic precursors and some cell lines
CD91	α_2MR LDL-R–related protein	α subunit of α_2-macroglobulin receptor
CDw92	VIM 15	Expressed on granulocytes and monocytes; function unknown
CD93	VIM D2	Expressed on granulocytes and monocytes; function unknown
CD94		Expressed on granulocytes, monocytes, and natural killer (NK) cells
CD95	APO-1/FAS	Transmits signal for apoptosis
CD96	Tactile	Expressed primarily on T lymphocytes, late after activation
CD97		Expressed on myeloid cells and activated lymphocytes
CD98	4F2	Heterodimeric antigen expressed on most cells and cell lines; increased with activation; antibodies bind to the heavy chain
CD99	E2, MIC2	Pseudoautosomal, multiple epitopes on T lymphocytes; 2 epitopes involved in adhesion
CD100		Antibodies are co-mitogenic for T lymphocytes
CDw101		Expressed on myeloid cells; T cell subset
CD102	ICAM-2	One of several counterreceptors for LFA-1 (CD11a/CD18)
CD103	HML-1	Human mucosal lymphocyte antigen; αE subunit of $\alpha E\beta 7$
CD104	β4 integrin chain	Associates with CD49f
CD105	Endoglin	Transforming growth factor β1 and β3 receptor
CD106	VCAM-1	Counterreceptor for Very late activation antigen-4
CD107a	LAMP-1	Expressed on platelets and in lysosomes; up-regulated to cell surface on activated cells
CD107b	LAMP-2	Expressed on platelets and in lysosomes; up-regulated to cell surface on activated cells
CDw108		glycosylphosphatidyl inositol anchored; expressed on cultured NK cells and selected other cell types and lines
CDw109		Expressed on platelets, endothelial cells
CD115	CSF-1R	c-*fms* proto-oncogene product
CDw116	GM-CSFR	Colony-stimulating factor receptor
CD117	SCFR, c-*kit*	Stem cell factor receptor
CDw119	IFNγR	Interferon-γ receptor
CD120a	TNFR, 55 kd	Type 1 tumor necrosis factor receptor
CD120b	TNFR, 75 kd	Type 2 tumor necrosis factor receptor
CD121a	IL-1R, type 1	Interleukin-1 (IL-1) receptor, type 1
CD121b	IL-1R, type 2	IL-1 receptor, type 2
CDw122	IL-2R	IL-2 receptor
CDw124	IL-4R	IL-4 receptor
CD126	IL-6R	IL-6 receptor
CDw127	IL-7R	IL-7 receptor
CDw128	IL-8R	IL-8 receptor
CDw130	IL-6R, gp130SIG	Signaling molecule associated with IL-6 receptor and other receptors

for advancing understanding of the structure and function of the CD antigens, as well as classifying them.

What revisions were made to previously established CD clusters?

Table 1 indicates revisions to previously established CD clusters (CD1–CD78) made at the Fifth Workshop, and contains information about the function of some of these antigens. When possible, the terminology used has been selected to fit well with other names for known antigens. For example, the selectins have all been clustered within the CD62 grouping as CD62E, L, and P, respectively, designating E-selectin, L-selectin, and P-selectin. Similarly, the expanded CD49 grouping sequentially follows the previously defined VLA and α integrin chain designations. One CD antigen, CD67 (not shown in Table 1), has been left as a vacant cluster, since its structure has been found to be most properly grouped in the CD66

cluster. Additional information about these antigens (1) and their cluster revisions (2) has been published.

What new CD clusters were established?

Table 2 lists the new CD antigens clustered at the Fifth Workshop. Many of these are molecules of known functional importance, and many will be of interest to investigators in the rheumatic diseases. When possible, workshop committees attempted to make CD designations easy to remember. For example, ICAM-2 is CD102. Even more helpful, a variety of cytokine receptors for interleukins 1–8 are designated CDw121–CDw128. Known receptors for which antibodies were not available at this workshop, such as the interleukin-3 receptor, earned vacant CD slots for future assignment. Although specific cell lineage panels for many of the new CD antigens are indicated in Table 2, it is increasingly clear that very few antigens are strictly lineage restricted. A more complete description of the distribution of these various structures is contained in the complete description of the Fifth Workshop proceedings (3). Molecular weights of these structures have been summarized elsewhere (2).

What is the future role of the Human Leukocyte Differentiation Antigen Workshops?

The results achieved at the Fifth Workshop and at all previous workshops provide strong momentum for continuation of the workshop effort. The magnitude of the collaborative efforts involved in these workshops provides a model for international scientific cooperation. However, the workshops will have an important role only as long as there are new antigens to be identified, and new structural and functional information to be learned about the CD antigens. That this is the case seems to be beyond question. Even at the Fifth Workshop, several very interesting surface structures were discussed that have been identified so recently that antibodies were not available for exchange at the time of organization of the workshop. Examples of such structures on T lymphocytes include the CD40 ligand and the CTLA4 antigen. New approaches used during the Fifth Workshop are beginning to extend the scope of CD antigens to submembrane and cytoplasmic locations. Endothelial cell and platelet antigens as well as other adhesion ligands are now included within the scope of the workshops, representing an expansion beyond the surface of leukocytes. It seems likely that other nonleukocyte cell types could be added to later workshops.

It can also be expected that information established through workshop framework will be increasingly useful in clinical medicine, both for defining cell markers useful in monitoring diagnoses or stages of disease, and for defining reactivity of antibodies that may be used in clinical therapeutics. It will become increasingly important to develop new models and approaches for understanding the interactions of multiple surface receptors in regulating cell functions in a coordinated manner. The complexity involved is further accentuated by the growing realization that most of the defined surface receptors have multiple ligands, both physiologic and microbial. The tasks for future workshops, therefore, are more complex and difficult than those accomplished to date. Planning for the Sixth Workshop is already well under way, with the workshop conference scheduled for 1996 in Osaka, Japan.

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REFERENCES

1. Knapp W, Dörken B, Gilks WR, Rieber EP, Schmidt RE, Stein H, von dem Borne AEGKR (editors): Leukocyte Typing IV. Oxford: Oxford University Press, 1989
2. Schlossman SF, Boumsell L, Gilks W, Harlan JM, Kishimoto T, Morimoto C, Ritz J, Shaw S, Silverstein RL, Springer TA, Tedder TF, Todd RF: CD antigens 1993. J Immunol 152:1–2, 1994
3. Schlossman S, Boumsell L, Gillis W, Harlan J, Kishimoto T, Morimoto C, Ritz J, Shaw S, Silverstein R, Springer T, Tedder T, Todd R (editors): Leukocyte Typing V. Oxford: Oxford University Press, 1994