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REVIEW ARTICLE

Surface proteins and glycoproteins of human leucocytes

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Introduction

The essential condition for understanding the function of the immune system is to know as completely as possible its components, their properties, functions and mutual relations on a molecular level. That is, the first necessary step is to do a basic 'inventory' of all parts of the system. One of the most active areas in this respect is the investigation of surface macromolecules of leucocytes. Many leucocyte surface components have been identified, mostly with the aid of monoclonal antibodies, including such important molecules as various receptors and cell adhesion molecules. The final goal of these efforts is to identify and functionally define all surface components of all types of leucocytes. It is not clear how close to this ideal we are now, but it seems likely that many, perhaps most, of the leucocyte membrane proteins and glycoproteins are yet to be discovered.

In the present review we attempt to summarize the information available on the surface components of human leucocytes identified so far.

Because of space limitations and enormous extent of the field to be covered, we had to restrict the discussion only to the structurally and functionally best known and most interesting molecules. Also, we had to keep the number of citations to a minimum of those most recent and most relevant and wherever possible we cite detailed reviews on individual molecules. We apologize to the authors of all papers not cited for this reason. The Tables attached contain basic information on most human leucocyte surface antigens* for which at least a minimum of biochemical data (M_r) is available. For the sake of clarity, we grouped all these antigens in Tables according to their prevalent expression on different cell types [i.e. antigens of T lymphocytes, B lymphocytes, NK (natural killer) cells, myeloid cells (monocytes, macrophages and granulocytes) and finally antigens with broader expression]. We are aware that our classification is sometimes rather arbitrary, but, strictly speaking, there are very few molecules expressed absolutely specifically on a certain leucocyte subpopulation and most antigens should be in fact classified as 'lineage non-specific'. In this review we use as much as possible the 'CD nomenclature' of the International Workshops on Human Leucocyte Differentiation Antigens (Bernard *et al.*, 1984*a*; Reinherz *et al.*, 1986; McMichael *et al.*, 1987), which greatly clarifies certain confusion due to using different arbitrary names by different authors for identical molecules.

Thus, in the text we concentrate more on functional aspects, relations between various membrane molecules etc., while descriptive facts on M_r values, expression and nomenclature can be found mostly in the Tables.

Antigen-specific receptors and functionally related molecules

Recognition of substances foreign to an organism is the basis of immune response. The recognition is accomplished by soluble recognition molecules, i.e. immunoglobulins, and by membrane-bound antigen-specific receptors. There are basically two kinds of these receptors: membrane immunoglobulins of B lymphocytes and so called T cell antigen receptors of T lymphocytes. These are some similarities but also important differences between these two systems.

Membrane-bound immunoglobulins are structurally very similar to the secreted soluble immunoglobulins, except for a *C*-terminal hydrophobic stretch of amino acids in the heavy chain which serves to anchor the molecule in the lipid membrane of B lymphocytes (Rogers *et al.*, 1980). The membrane-bound immunoglobulins are mostly of IgM and IgD isotype; essentially nothing is known about possible functional differences between these isotypes but apparently both murine mIgM and mIgD (as well as mIgG) can act as signal transmission molecules (Mizuguchi *et al.*, 1986). Structure, mechanisms of generation of binding sites diversity and molecular genetics of immunoglobulins have been subjects of numerous reviews and therefore need not be discussed here. Each B lymphocyte clone carries mIgs of unique structure of combining site and thus exhibits unique antigen specificity. Recognition of the respective antigen by this surface receptor provides a signal necessary for activation of the B lymphocyte, its clonal expansion and terminal differentiation into either memory B cells or plasma cells, which secrete soluble immunoglobulin of structure and specificity identical with or very similar to that of the mIg on the originally stimulated B lymphocyte (somatic mutations during this proliferation/differentiation process can alter affinity and fine specificity of the resulting immunoglobulins). The biochemical basis of transmembrane signalling through mIg was thoroughly reviewed by Cambier *et al.* (1987*a*); it involves the second messenger system based on hydrolysis of phosphatidylinositol bisphosphate, rise of intracytoplasmic Ca^{2+} concentration and activation of protein kinase C. In most cases further 'helper' signals are necessary in addition to the primary signal provided by the antigen–mIg interaction to achieve proliferation and terminal differentiation of the B lymphocytes. These secondary signals are provided by lymphokines secreted mostly by helper T lymphocytes. Which of these second signals are necessary and sufficient under physiological conditions (and in which order) is not exactly known, but *in vitro* interleukins 1, 2, 4, 5 and 6, and IgE, C3d and probably also other factors, were shown to enhance B

Abbreviations used: BCGF, B cell growth factor; EGF, epidermal growth factor; GM-CSF, granulocyte-monocyte colony stimulating factor; mIg, membrane immunoglobulin; mAb, monoclonal antibody; MHC, major histocompatibility complex; NK, natural killer; T_c, cytotoxic T cell; T_h, helper T cell; T_s, suppressor T cell; Workshop, International Workshop on Human Leucocyte Differentiation Antigens.

* We will frequently use a convenient although imprecise term 'antigen', meaning here actually a 'protein or glycoprotein'. The use of this term is justified as practically all molecules described here have been identified by means of antibodies.

cell stimulation (for review see, e.g., Jelinek & Lipsky, 1987).

At least some of the complexes of mIg with the antigen recognized are internalized and the (protein) antigen is then cleaved into peptide fragments. Some of these peptides associate specifically with MHC class II glycoproteins (see below) and these complexes are then re-expressed at the cell surface where they can be recognized by specific helper T cell clones through their T cell receptors (Lanzavecchia, 1985). This interaction initiates activation and proliferation of these specific T_h cells which in turn produce the above mentioned helper factors to the B lymphocytes. Thus, mIg serves also to concentrate the antigen on specific B lymphocyte surfaces and transport it inside the cell where it is 'processed' to yield fragments capable of interaction with MHC glycoproteins and recognizable then by T_h. Although other cells, e.g. macrophages, are also efficient in processing antigens and presenting them to T_h in association with MHC glycoproteins, specific B cells are now thought to be the major antigen processing and presenting cells for soluble protein antigens occurring typically only in minute concentrations.

Major unresolved questions concerning mIg are as follows. (1) What are in exact molecular terms the mechanisms of signal transduction through this receptor? It is not exactly known what molecule(s) associated with mIg may be the first signal-transducing element triggering the phosphatidylinositol bisphosphate/Ca^{2+}/protein kinase C-mediated activation pathway. In this respect the 30 kDa molecule reported to be covalently linked to murine mIgM might be relevant (Haustein & van der Ahe, 1986). (2) What is the functional relevance of isotypic differences (IgM, IgD) of mIg expressed on different B cells? It is also unclear what is the role of unusual forms of mIg observed in mouse B cells: in addition to the usual L_2H_2 molecules, there are also LH 'half molecules', free heavy (H) chains and their dimers (Haustein & van der Ahe, 1986).

The antigen-specific surface receptors of T lymphocytes are structurally related to immunoglobulins. The structure, function and molecular genetics of these receptors have been recently reviewed several times (e.g. Collins & Owen, 1985; Kronenberg *et al.*, 1986; Marrack & Kappler, 1987). Briefly, these molecules are made up of two different chains of similar size (approx. 40–55 kDa) that structurally resemble the Ig light chains. Both these chains are anchored in the membrane through a hydrophobic stretch of amino acids in their *C*-terminal parts; the extracellular portions consist of a membrane-proximal constant domain and an *N*-terminal variable domain. The variable domains of both constituent chains form the antigen-binding site, as do the variable domains of the immunoglobulin heavy and light chains. The T cell receptor structure is therefore quite similar to an Fab fragment of immunoglobulins. The principles governing the clonotypic variability of T cell receptor chains are very similar to those operating in immunoglobulins, i.e. the germ line genes for T cell receptor chains are randomly rearranged during the T lymphocyte differentiation, so that individual T cells express receptors with clonally unique structures of antigen-binding sites. There is little or no somatic mutation of rearranged T cell receptor genes, which in immunoglobulins represents another additional source of diversity.

These are two basic types of human T cell receptor:

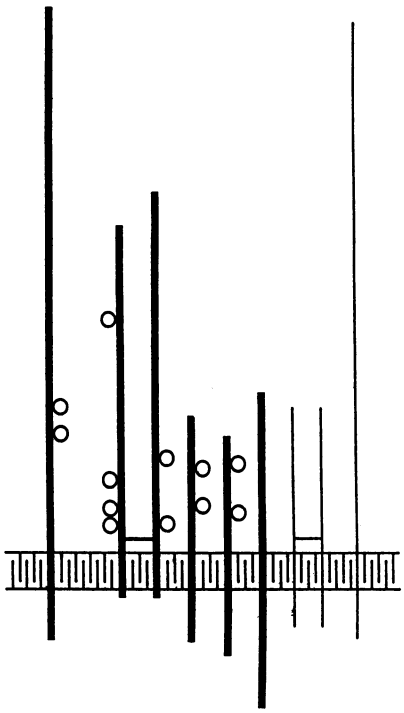

Fig. 1. Schematic representation of the $\alpha\beta$ T cell receptor and presumably associated proteins

The proteins for which complete amino acid sequence is known are drawn as thick vertical lines that represent the polypeptide backbones. The length of the lines corresponds approximately to the sizes of the polypeptides and the lengths of segments above and under the membrane are proportional to the true sizes of extracellular and intracellular domains, respectively. The horizontal bars connecting the chains represent cystine bridges. Small circles represent *N*-glycosidically linked carbohydrate chains. For proteins drawn in thin lines amino acid sequence is so far unknown and the sizes of their intracellular domains are drawn arbitrarily. As discussed in the text, the indications for association between the T cell receptor–CD3 complex with CD2 and with Tp45 (Carrel *et al.*, 1987) are so far rather indirect. True topological relations between different noncovalently associated components are unknown, except that the CD3-γ chain seems to be in contact with the T cell receptor β chain (Brenner *et al.*, 1985). CD8 instead of CD4 is probably associated with the T cell receptor complex in the $CD8^+CD4^-$ T cells. Abbreviation: TCR, T cell receptor.

the 'conventional' one (sometimes called Ti) consists of disulphide-linked chains called α and β and is expressed on most T lymphocytes. The other type is composed of chains called γ and δ and is expressed on embryonic thymocytes and on a small subpopulation of peripheral blood T lymphocytes which have a natural killer-like activity (Brenner *et al.*, 1986; Bank *et al.*, 1986). Actually, at least two kinds of the human T cell receptor γ chain exist (36–40 kDa and 55 kDa, respectively), differing in their constant domains and in glycosylation (Krangel *et al.*, 1987; Littman *et al.*, 1987), as well as in the mode of their association with the δ chain. The smaller form is disulphide-linked to the chain, while the larger form is associated noncovalently to it. A form of T cell receptor

consisting of two γ chains may also exist (Koning *et al.*, 1987). The structure of T cell receptor α, β and γ chains are all similar to each other; cDNA and the gene coding for the δ chain were cloned recently and the predicted corresponding protein also has a similar sequence (Hata *et al.*, 1987; Band *et al.*, 1987). Both the $\alpha\beta$ and $\gamma\delta$ T cell receptors are noncovalently associated with the so-called CD3 complex, consisting of CD3-γ, CD3-δ, CD3-ϵ and a covalent dimer of CD3-ζ chains (see Table 1 and Fig. 1). The association of the T cell receptor with CD3 is rather loose, but is preserved after solubilization in some detergents such as digitonin (Oettgen *et al.*, 1984). All CD3 chains are typical transmembrane proteins and have distant sequence similarities to the proteins of the immunoglobulin family (cf. Gold *et al.*, 1987) [For an excellent review on this family of proteins and on the criteria justifying classification of a protein as a member of that family see Williams (1987)]. The CD3 γ chain is in close contact with the T cell receptor β chain in the native complex (Brenner *et al.*, 1985).

The antigen-recognition structures are the T cell receptor clonotypic dimers, while the CD3 complex transmits probably the signal inside the cell. Essentially nothing is known about the specific roles of individual CD3 chains in this respect.

Biochemical events following antigen recognition by the T cell receptor were extensively studied employing monoclonal antibodies (mAbs) against CD3 or receptor. Binding of such mAbs under appropriate conditions (usually the mAbs have to be immobilized on a solid surface) is thought to mimick the physiological interaction with the antigen. Similarly, the well-known mitogenic effects of some lectins on T cells are also probably due to their interaction with the carbohydrate moieties of the receptor–CD3 complex. The cascade process initiated by interaction of receptor–CD3 with an antigen, mAb or lectin involves rapid hydrolysis of phosphatidylinositol bisphosphate, rise of intracellular Ca^{2+} concentration and activation of protein kinase C (reviewed by Weiss *et al.*, 1986; Isakov *et al.*, 1987, Alcover *et al.*, 1987), i.e. a pathway similar to the signal transduction via mIg in B lymphocytes. The CD3 complex might be therefore linked to a G-protein, to a phosphodiesterase splitting the phosphatidylinositol bisphosphate and/or to a Ca^{2+} channel.

It is still possible that the T cell receptor–CD3 complex is an even more complicated structure and that additional components may be associated to it at least transiently. One of them may be the CD4 or CD8 molecule (see below), another perhaps CD2 (see the following section) and yet another a recently identified 45 kDa component (Carrel *et al.*, 1987*a*). Precise definition of complete structure and functions of all components of the T cell receptor supramolecular complex will be certainly of basic importance for understanding of signal transmission in T cells.

In spite of structural and molecular genetic similarities between mIg and T cell receptor, there is a major difference between these two receptors: while mIg can recognize the antigens as such, T cell receptors recognize it mostly in so called 'MHC-restricted' fashion, i.e. the antigen must be partially denatured and/or proteolytically cleaved (for review see Allen, 1987) and bound on cell surface to MHC glycoproteins. It is not entirely clear what is in fact recognized by the T cell receptor — whether only the processed antigen exposed on the MHC glycoprotein, or whether simultaneously there is a physical contact between receptor and the 'carrier' MHC molecule. According to the classical and so far very popular immunological hypothesis on MHC restriction the T cell receptor–MHC glycoprotein interaction is of essential importance, but recent data seem to indicate that all observed phenomena could be well explained without such a postulate.

A most exciting, so far unresolved question concerning the phenomenon of MHC-restricted recognition by T cell receptors is how only the cells carrying receptors with specificity for processed foreign antigens are selected during ontogeny (reviewed by Goverman *et al.*, 1986). There are several conceptually quite different hypotheses attempting to explain this, but probably the correct one is that the developing thymocytes encounter in thymus many different processed self-antigens associated with MHC glycoproteins and this recognition somehow leads to abortion of such T cell clones, e.g. by a mechanism similar to that suggested by Reinherz (1985). Only the T cell clones which have not met any complementary structure in thymus are then allowed to emigrate into the periphery and can recognize 'unfamiliar', i.e. mostly foreign, structures (Werdelin, 1987; Kourilsky *et al.*, 1987). This still does not explain why the antigen recognized must be associated with MHC glycoproteins. Perhaps this is because an effective recognition requires T cell receptor crosslinking by multiple interactions with the antigen displayed on a cell surface or because other additional interactions are needed to make the contact productive, or maybe because there is after all some indispensable interaction between the T cell receptor complex and the 'carrier' MHC molecule. It should be noted that at least some antigens can bind to the $\alpha\beta$-type T cell receptor without being complexed to MHC glycoproteins (Siliciano *et al.*, 1985), but it is not clear how general and physiologically relevant this phenomenon is. The T lymphocytes carrying the $\mu\delta$-type T cell receptor recognize their targets apparently without 'MHC restriction' (Brenner *et al.*, 1986; Bank *et al.*, 1986). It is not clear at present what are the structures recognized by this type of T cell receptor which should be much less clonotypically variable than the 'conventional' $\alpha\beta$-type (Quertermous *et al.*, 1986; Band *et al.*, 1987).

A puzzling phenomenon is that a large portion of T lymphocytes apparently recognize allogeneic forms of MHC molecules. This is usually interpreted as recognition of 'altered self' MHC molecules, which may appear to T cells like self MHC glycoprotein complexed with a foreign antigen. In our opinion, a more plausible (but so far unproven) explanation is that this 'alloreactivity' of T cells represents in fact recognition of various fragments of self antigens associated to the allogeneic MHC molecule — i.e. complexes never seen by the T cells during their development and therefore recognized as foreign (Werdelin, 1987).

The purpose of MHC restriction seems to be rather obvious. In this way cytotoxic T lymphocytes will concentrate on attacking, e.g., virally infected cells that express on their surface viral antigens and their fragments associated with MHC class I molecules and will not be distracted and in fact blocked by unproductive interactions with soluble viral antigens or single virus particles. Other T cells (T_h, T_s) can in this way specifically intimately interact with other cells of the immune system displaying processed antigens in association with MHC class II

Table 1. T-cell antigens

Asterisks denote the molecules for which cDNA was cloned and sequenced; the corresponding references with the sequence data are marked similarly. Abbreviations: TCR, T cell receptor; ALL, CLL, acute or chronic lymphoblastoid leukaemia; PHA, phytohaemagglutin; IL, interleukin.

Name (mAb)	Expression	Molecular mass (kDa)	Notes	References
TCR-α chain* (Ti-α)	T-cells, thymocytes	49	Associated with TCR-β and CD3 complex (see text)	See text
TCR-β chain* (Ti-β)	T-cells, thymocytes	43	Associated with TCR-α and CD3 complex (see text)	See text
TCR-γ chains*	Subpopulation of T-cells	40 or 55	Associated with TCR-γ and CD3 complex (see text)	See text
TCR-δ chain*	Subpopulation of T-cells	40–43	Associated with TCR-μ and CD3 complex (see text)	See text
CD1a* (T6, Leu-6)	Thymocytes, Langerhans cells	49	Associated with β_2-microglobulin on thymocytes covalently bound to CD8	Amiot *et al.* (1986*a*), van de Rijn *et al.* (1983), Knowles (1987), Snow *et al.* (1985*b*), Calabi & Milstein (1986)*
CD1b*	Thymocytes	45	Associated with β_2-microglobulin	Köller *et al.* (1987) (see also references for CD1a)
CD1c*	Thymocytes, some B-cells	43	Associated with β_2-microglobulin and with a 16 kDa subunit	Small *et al.* (1987) (see also references for CD1a)
CD2* (T11, Leu-5, E-receptor, LFA-2)	T-cells, thymocytes	50–55	Binds LFA-3; possibly associated with TCR (see text)	Plunkett & Springer (1986), Brown *et al.* (1987), Sewell *et al.* (1986)* (see also text)
CD3-γ chain* (T3-γ)	T-cells, thymocytes	27	See text	Gold *et al.* (1986)*, Kanellopoulos *et al.* (1983), Oettgen *et al.* (1984)
CD3-δ chain* (T3-δ)	T-cells, thymocytes	20	See text	van den Elsen *et al.* (1984)*, Kanellopoulos *et al.* (1983), Oettgen *et al.* (1984)
CD3-ϵ chain* (T3-ϵ)	T-cells, thymocytes	20	Not glycosylated; very hydrophobic	Krissansen *et al.* (1986)*, Kanellopoulos *et al.* (1983), Oettgen *et al.* (1984)
CD3-ζ chain	T-cells, thymocytes	$(16)_2$	Not glycosylated	Weissman *et al.* (1986)
CD4* (T4, Leu-3) (mouse homologue L3T4)	Subpopulation of T-cells, thymocytes, monocytes	55	HIV receptor; probably associated with TCR; probably receptor for MHC class II (see text)	Stewart *et al.* (1986), Maddon *et al.* (1985)* (see also text)
CD5* (T1, Leu-1) (mouse homologue Ly1)	T-cells, a small subpopulation of B-cells	67	Easily cleaved to a 56 kDa fragment; mAbs enhance T-cell stimulation	Jones *et al.* (1986*a*)*, Ceuppens & Baroja (1986), Thomas *et al.* (1984), Casali *et al.* (1987)
CD6 (T12)	T-cells, B-CLL	120	mAb blocks stimulation by anti-CD3	Haynes (1986), Yssel *et al.* (1987)
CD7* (3A1, Leu-9)	T-cells	35–40 and dimers; 29 kDa polypeptide core	*N*- and *O*-glycosylated; IgM receptor(?); sequence similarity to the Ig family	Carrel *et al.* (1984), Sutherland *et al.* (1984), Sandrin *et al.* (1987), Aruffo & Seed (1987)*
CD8* (T8, Leu-2) (mouse homologue Ly2)	Subpopulation of T-cells, thymocytes, some NK cells	32, 33	Possibly associated with TRC; probably receptor for MHC class I (see text)	Snow *et al.* (1985*a*), Littman *et al.* (1985)*, Sukhatme *et al.* (1985)* (see also text)
CD27(T14)	T-cells	$(55)_2$	mAb enhances stimulation by anti-CD3; after stimulation association with a 32 kDa subunit	Stockinger *et al.* (1986), van Lier *et al.* (1987)
CD28 (Tp44, antigen 9.3)	T-cells, plasma cells	44	Covalent dimers exist in equilibrium with the monomer; mAb mitogenic; expression strongly increases after T-cell activation	Gmünder & Lesslauer (1984), Lesslauer & Gmünder (1986), Lesslauer *et al.* (1986), Hara *et al.* (1985), Martin *et al.* (1986), Pantaleo *et al.* (1986)

Table 1. (*cont.*)

Name (mAb)	Expression	Molecular mass (kDa)	Notes	References
Human Thy-1 (mouse homologue Thy1)	Early thymocytes, some T-cell lines, neurons	26–29 and dimers	*N*- and *O*-glycosylated; homologue of mouse and rat Thy-1; member of Ig superfamily; anchored in membrane through a phospholipid moiety	Foon *et al.* (1984), Bonewald *et al.* (1984), Campbell *et al.* (1984), Campbell *et al.* (1981), Low & Kincade (1985)
Ta_1	Subpopulation of T-cells, strongly on activated T-cells	105	Marker of memory T-cells; possibly identical to Tp103	Fox *et al.* (1984), Hafler *et al.* (1986)
Tp103	Subpopulation of T-cells, activated T-cells	103	Involved in T-cell activation and T function; possibly identical to Ta_1	Fleischer *et al.* (1986*b*) Fleischer (1987)
TLiSA	Activated T-cells	70–95	mAb blocks stimulation of T-cells by interferon α or μ	Burns *et al.* (1985), Chen *et al.* (1986)
2H1	90% of resting T-cells, 10% thymocytes	138 (88 deglyco-sylated)	Increased expression after activation; mAb partially blocks E-rosette formation and enhances stimulation by PHA or anti-CD3	Morimoto *et al.* (1986*a*)
MW4	Thymocytes, lymphocytes	60	mAb inhibits antigen-induced proliferation	Pugliese *et al.* (1987)
Dipeptidylpeptidase IV	Broad	110	Marker of IL-2-producing CD4 T-cells	Mentlein *et al.* (1984)
D44	Immature leucocytes, T-cell subpopulation, NK cells	28, 30	Delineates a T_c subset of CD8 T-cells	Bernard *et al.* (1984*b*)
gp37	T-leukaemia, T-blasts (weak)	37	Does not modulate	Seon *et al.* (1986)
Vasoactive intestinal peptide receptor	T-lymphocytes, some ALL	47		Shannon *et al.* (1986)
TALLA	T-ALL	150	Does not modulate	Seon *et al.* (1983, 1986),
L35	Activated T-cells, granulocytes	97		Maino & Janszen (1986)
L36	Activated T-cells	90		Maino & Janszen (1986)
Tp90	Subpopulation of T-cells	90	mAb activates $Tp90^+$ T-cells	Carrel *et al.* (1987*b*)
(Unnamed)	PHA-activated or HIV-infected T-cells	18	Elicits autoantibody, possibly significant in AIDS pathogenesis	Stricker *et al.* (1987)
MLR3	Activated T-cells	28, 34	Possibly linked to IL-1 receptor	Cosulich *et al.* (1987)
H2	T-CLL	80		Janson *et al.* (1987)
IVF7	T-CLL, small subpopulation of T-lymphocytes	$(38)_2$	Idiotypic; possibly related to TCR?	Janson *et al.* (1987)
HML-1	Intestinal T-cells	(150, 105)	Marker of intestinal lymphocytes	Cerf-Benussan & Jarry (1987)
Tp45	subpopulation of T-cells (mostly CD8 cells)	45	mAb stimulates T-cells; probably associated with TCR	Carrel *et al.* (1987*a*)

glycoproteins (B lymphocytes, macrophages, activated T lymphocytes) and regulate their activities.

Clearly, MHC glycoproteins are molecules functionally very relevant to the T cell receptor. They are the most thoroughly studied membrane glycoproteins; their structure, function and molecular genetics have been reviewed many times (e.g. Lew *et al.*, 1986; Harris & Gill, 1986; Korman *et al.*, 1985; Solheim *et al.*, 1986). Briefly, there are two structurally related types of human MHC glycoproteins: class I (HLA-A, -B and -C) and class II (DR, DQ and DP). MHC class I molecules are composed of a highly polymorphic heavy chain (approx. 45 kDa) which is a typical transmembrane glycoprotein noncovalently associated with β_2-microglobulin. MHC class II glycoproteins are noncovalent dimers of structurally similar chains α (approx. 34 kDa) and β (approx. 29 kDa) associated intracellularly but not at the cell surface with a third, so-called invariant, chain which occurs in several molecular forms (Quaranta *et al.*, 1984) and whose role is at present uncertain. Both α and β chains are transmembrane glycoproteins, and all chains except DRα are polymorphic. All constituent chains of MHC molecules bear sequence similarities to immunoglobulins. The three-dimensional structure of the HLA-A2 molecule

has been determined recently, providing for the first time detailed structural information on a human membrane-associated molecule (Bjorkman *et al.*, 1987*a*,*b*). It is almost certain now that the MHC molecules are generally 'receptors for processed antigens'. Although this has not been proven directly for MHC class I glycoproteins yet, a great deal of indirect evidence (e.g. Gotch *et al.*, 1987) as well as the three-dimensional structural data strongly suggest that these molecules do bind processed antigens. Direct binding experiments performed with mouse MHC class II glycoproteins repeatedly demonstrated that these molecules are capable of binding certain types of peptides, presumably those assuming a conformation of amphipathic α-helix (e.g. Buus *et al.*, 1987; Guillet *et al.*, 1987; Unanue & Allen, 1987; Margalit *et al.*, 1987). It seems quite likely that a peptide-binding site of similar character to that found in the three-dimensional structure of the HLA-A2 molecule also exists in the MHC class II molecules (Bjorkman *et al.*, 1987*b*). In spite of enormous progress in the understanding of structure and function of MHC glycoproteins and the T cell receptor, a number of important issues remain still unclear, and these are discussed below.

Why do some T cells (mainly T_c) recognize antigens mostly in association with MHC class I glycoproteins, while others (mostly T_h) in association with MHC class II molecules, although both these T cell subpopulations use the same kind of $\alpha\beta$ T cell receptor? A possible explanation of this puzzle is that 'accessory molecules', namely CD4 and CD8 (Table 1), mediate this MHC-type-specific interaction. There is a high correlation between CD4/CD8 expression and MHC class II/class I restricted T cell recognition (Swain, 1983). Moreover, anti-CD4 or anti-CD8 mAbs inhibit activation of the respective T cells induced by recognition of the antigen-presenting cell. CD4 may be physically associated with the T cell receptor complex (Saizawa *et al.*, 1987) and therefore it may really constitute a component of the supramolecular complex recognizing a conserved part of MHC class II molecules; CD8 may be similarly associated with the T cell receptor (Takada & Engleman, 1987) and specifically recognize the MHC class I molecules. Although direct measurements of the MHC glycoprotein–CD4/CD8 interactions have not been performed so far, several lines of evidence strongly suggest that such interactions do exist (Aparicio *et al.*, 1987; Doyle & Strominger, 1987). The direct binding experiments should become feasible after production of soluble recombinant forms of CD4, CD8 and MHC glycoproteins. In addition to the possible MHC class II receptor function, CD4 appears to be linked to an antigen-activated Ca^{2+} channel (Rosoff *et al.*, 1987) which may be another reason why some anti-CD4 mAbs block activation of T cells. Importantly, CD4 is also the receptor for human immunodeficiency virus (HIV) (Dalgleish *et al.*, 1984; McDougal *et al.*, 1986) and it may also be a receptor for peptide mediators of monocyte chemotaxis (Ruff *et al.*, 1987). Structure and function of CD4 and CD8 (both these molecules belonging to the Ig family) have been reviewed (Dalgleish, 1986; Parnes, 1986).

Another unresolved question concerning the MHC glycoprotein function is whether different MHC class II gene products (DR, DQ, DP) may have specific functions. There are reports that DR molecules present antigen fragments to T_h, and DQ to T_s (Hirayama *et al.*, 1987). Another so far poorly characterized type of human MHC class II molecules called DY (Wernet *et al.*, 1987) and possibly related to the molecule described by Carra & Accolla (1987) is presumably also involved in antigen presentation to T_s.

An important question is whether the peptide-binding ability is unique to MHC glycoproteins. A recent surprising finding indicates that a cell surface protein (72 and 74 kDa) exists that does bind peptides and presents them to T lymphocytes in an MHC-like manner (Lakey *et al.*, 1987).

Yet another incompletely resolved problem is what is the meaning of the extreme polymorphism of MHC glycoproteins, that led to the early identification of these molecules as the major transplantation antigens. It is usually assumed that the polymorphism is advantageous for the species, as it may ensure that at least some MHC allelic form will efficiently bind and present an antigen. However, it is difficult to explain how this polymorphism would be selected for, as in most cases there would be no apparent selective advantage for an individual carrying a new mutant form of the MHC molecule. An interesting alternative hypothesis was recently put forward, suggesting that the polymorphism might help to recognize quickly viruses coming from another individual of the species and carrying the MHC glycoproteins as captured components of the host cell membrane (Andersson *et al.*, 1987).

MHC glycoproteins may possibly have yet other functions in addition to serving as receptors (or rather carriers) for processed antigens: some anti-MHC class II mAbs can stimulate monocytes (Palacios, 1985) or B lymphocytes (Cambier *et al.*, 1987*b*) suggesting that interaction with a natural ligand (e.g. CD4?) may deliver a positive signal to the antigen-presenting cell; interestingly, one of the proteins apparently associated intracellularly with MHC class II glycoproteins in activated B cells is the regulatory subunit of cyclic AMP-dependent protein kinase (Newell *et al.*, 1986).

Some mAbs directed against MHC class I glycoprotein inhibit T and B lymphocyte functions (De Felice *et al.*, 1987; Taylor *et al.*, 1987), which may indicate an additional functional role for these molecules. Anti-MHC class I mAbs stimulate monocytes to production of a suppressive soluble factor (Dasgupta & Yunis, 1987). It can be speculated that these effects reflect functional association of MHC class I glycoproteins with some leucocyte surface receptors. It has been indeed shown that they are associated with receptors for insulin (Due *et al.*, 1986), epidermal growth factor (Schreiber *et al.*, 1984) and glucagon (Lafuse & Edidin, 1980). MHC class I glycoproteins may be involved in an as yet unclear carbohydrate-dependent way in the regulation of intercellular interactions (Lengerová *et al.*, 1977; Pimlott & Miller, 1986).

Finally, 'nonclassical' MHC class I molecules exist, the function of which is quite unknown (Paul *et al.*, 1987; Srivastava *et al.*, 1987). There are many genes in the major histocompatibility complex of man and mouse potentially coding for these molecules but so far little is known about their products (Lew *et al.*, 1986).

Structurally closely related to MHC class I glycoproteins are the CD1 molecules (van de Rijn *et al.*, 1983). They also consist of 43–48 kDa heavy chains non-covalently associated with β_2-microglobulin. At least three types (CD1a, b, c) are expressed on different cells (Table 1). CD1a on the surface of thymocytes is

covalently linked to CD8 (Snow *et al.*, 1985*a*,*b*). The CD1 gene complex is not linked to the MHC locus (Calabi & Milstein, 1986). The functions of CD1 are totally unknown.

It can be concluded that surprisingly much remains unknown about many aspects of the mechanisms used by lymphocytes for specific recognition of foreign antigens.

Adhesion molecules

Adhesion of various types of leucocytes to other cells is essential for many of their functions. Close cell–cell contact is, e.g., required during the attack of target cells by the T_c, during co-operation of T_h with antigen-presenting cells, during 'homing' of lymphocytes into lymph nodes and other organs, during phagocytosis, during differentiation of T cells in thymus etc. Some of the molecules mediating these intercellular interactions have now been identified and studied in detail. Actually, the T cell receptor complex, MHC glycoproteins, CD4 and CD8 discussed in the preceding paragraph also participate fundamentally in antigen-specific cell–cell contacts. Other, antigen-'non-specific' systems are discussed below.

(1) Fibronectin receptors and related molecules that mediate the interactions of leucocytes (but also of other types of cells) with extracellular matrix. These cell adhesion molecules of broad expression, called also 'integrins', have been recently reviewed (Hynes, 1987; Ruoslahti & Pierschbacher, 1987) and need not be discussed in detail here. It should be only noted that these receptors share sequential similarities and recognize the Arg-Gly-Asp sequence in fibronectin (Pytela *et al.*, 1986). Among this family of receptors expressed on leucocytes belong at least some of the VLA ('very late activation') antigens (Hemler *et al.*, 1987*a*; see Table 5) and the gpIIb/IIIa (CDw41) (Table 5). The VLA antigens (VLA-1 through VLA-5) share a common 135 kDa β-subunit noncovalently associated with different α-subunits (135–220 kDa) (Hemler *et al.*, 1987*a*). At least the VLA-3 and VLA-5 molecules are fibronectin receptors (Takada *et al.*, 1987).

(2) The CD2–LFA-3 system is used during interactions of T cells with their targets (Dustin *et al.*, 1987; Takai *et al.*, 1987). CD2 is expressed on all T cells, while its partner, LFA-3, is broadly expressed on various cell types. Both CD2 (Table 1) and LFA-3 (Table 5) are strongly glycosylated, and, interestingly, have significant sequence similarities to each other (Seed, 1987) indicating common evolutionary origin; both these molecules have certain sequence similarities to the immunoglobulin family. CD2 has an unusually large intracytoplasmic *C*-terminal domain suggesting a potential for interactions with cytoskeleton or other intracellular components (Sewell *et al.*, 1987). Two alternative forms of LFA-3 exist, one of them being a typical membrane-spanning protein, while the other is anchored in the membrane via a covalently linked phosphatidylinositol moiety (Seed, 1987; Wallner *et al.*, 1987). So far nothing is known about functional differences between these two forms of LFA-3. There are reports on carbohydrate-binding activity of CD2 (Semenyuk & Brain, 1985) but it is not clear whether CD2 recognizes a carbohydrate structure in LFA-3. It is possible that CD2 can bind yet another so far unknown ligand in addition to LFA-3; this is indirectly suggested by the fact that after T cell activation, a novel epitope appears on CD2 (called $T11_3$), arising probably by a poorly understood conformational change (Meuer *et al.*, 1984; Peterson & Seed, 1987). mAbs against this epitope stimulate T cells *in vitro*, when simultaneously LFA-3 or mAbs against other CD2 epitopes are present (Hünig *et al.*, 1987; Olive *et al.*, 1986). Thus, it can be speculated that *in vivo* an unidentified lymphokine or some cell-bound ligand can bind to CD2 after it has bound LFA-3 on the target cell. The ability of some anti-CD2 mAb pairs and of LFA-3 plus anti-CD2 mAb to stimulate T cells, as well as the structure of the CD2 molecule, suggest that it is not only a 'passive' adhesion molecule, but that activation signals can be delivered through it. Activation through CD2 is functionally linked to the T cell receptor-mediated activation (reviewed by Alcover *et al.*, 1987) and in fact CD2 might be a transiently associated component of the T cell receptor supramolecular complex (Breitmeyer

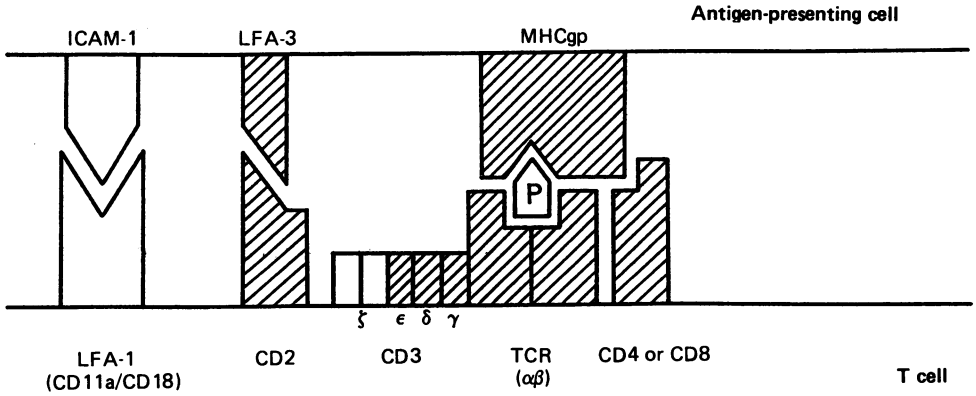

Fig. 2. Schematic representation of adhesion systems used during functional contact of T cells and antigen-presenting (target) cells

The components known to be structurally related to the Ig family are hatched. The small entity denoted P is the processed antigen (mostly a peptide fragment) associated with the MHC glycoprotein. Little or nothing is known about the nature of interactions between CD2 and the T cell receptor–CD3 complex, T cell receptor and MHC glycoprotein, and CD4 (or CD8) with T cell receptor and MHC glycoprotein. Receptors for fibronectin and homing receptors are not shown in this Figure. Abbreviation: TCR, T cell receptor.

Table 2. B-cell antigens

Surface antigens of human B lymphocytes were recently reviewed by Zola (1987). Abbreviations: EBV, Epstein–Barr virus; IL, interleukin; BCGF, B-cell growth factor; CLL, chronic lymphoblastoid leukaemia.

Name (mAb)	Expression	Molecular mass (kDa)	Notes	References
Membrane IgM*	B-cells	$(75+25)_2$	Receptor of B-cells for antigen (see text)	See text
Membrane IgD*	B-cells	$(60+25)_2$	Receptor of B-cells for antigen (see text)	See text
CD19 (B4, Leu-12)	B-cells	87–95	mAbs block B-cell stimulation	Nadler *et al.* (1983), Horibe & Knowles (1986), LeBien *et al.* (1986), Pezzutto *et al.* (1987*a*)
CD20 (B1, Leu-16)	B cells	35, 37 (dimer?)	mAbs stimulatory to B-cells; mAbs inhibit proliferation induced by EBV or anti-μ	Horibe & Knowles (1986), LeBien *et al.* (1986), Clark & Ledbetter (1986), Tedder *et al.* (1985)
CD21* (B2, CR2, EBV receptor)	B cells	140	Receptor for C3d and C3g; receptor for EBV (see text)	Weis & Fearon (1985), Siaw *et al.* (1986), Weis *et al.*, (1986)*, Frade *et al.* (1985), Fingeroth *et al.* (1984), Frade (1986) (review)
CD22 (Leu-14)	Most B-cells	130, 140 (complex?) 85, 100 polypeptide cores	mAbs enhance stimulatory effects of anti-μ, anti-CDw40 and of IL-4	Dörken *et al.* (1986), Clark & Einfeld (1986), Pezzutto *et al.* (1987*b*)
CD23* (Blast-2)	Lymphocytes; strongly on activated B-cells	45	Expression induced by IL-4; a 33 kDa soluble fragment is shed; low affinity IgE receptor; (see also text)	Defrance *et al.* (1987), Thorley-Lawson *et al.* (1986), Kikutani *et al.* (1986)*, Ikuta *et al.* (1987), Swendeman & Thorley-Lawson (1987)
CD24 (BA-1, OKB-2)	B-cells, granulocytes, some non-haematopoietic cells	45	Glycoprotein	Pirrucello & LeBien (1986)
CD37	B-cells; weakly on other leucocytes	40–45	Heavily glycosylated (25 kDa polypeptide core)	Poncelet *et al.* (1987), Schwartz *et al.* (1987)
CD39	Stimulated B-cells, plasma cells, macrophages, epithelia	80–85	Possibly involved in regulation of intracellular Ca^{2+} level	Ledbetter *et al.* (1987)
CDw40 (Bp50)	B-cells, bladder carcinoma	50	Anti-CDw40 antibodies augment stimulation of B-cells	Clark & Ledbetter (1986), Gordon *et al.* (1987)
Blast-1	Activated B-cells	45	Probably associated with a 55 kDa chain	Thorley-Lawson *et al.* (1982, 1986)
PC-1	Plasma cells	28		Anderson *et al.* (1984)
PCA-1	Plasma cells	24		Anderson *et al.* (1983)
AB-1	Activated B-cells	55	mAb blocks BCGF-dependent proliferation	Jung & Fu (1984)
BB1	B-blasts	37	Appears 4–7 days after stimulation	Yokochi *et al.* (1982)
BB2	B-blasts	76	CD39?	Clark & Yokochi (1984)
B5	Activated B-cells	75	CD39?	Freedman *et al.* (1985)
BL2	B-cells	68	Sometimes coprecipitates with DR	Wang *et al.* (1984)
BL3	B-cells	105		Wang *et al.* (1984)
BLCA	B-cells, carcinomas	55	'B-lymphocyte–carcinoma cross-reacting antigen'	Yip *et al.* (1987)
MN-1	B-cells	42		Link *et al.* (1986)
KB61	B-cells, tissue macrophages	40		Pulford *et al.* (1986)
Bac-1	Activated B-cells	59		Suzuki *et al.* (1985)
B7.2	Activated B-cells	45–50	Glycosylated	Southern *et al.* (1987)
HC2	Activated B-cells	52–63		Posnett *et al.* (1984)

Table 2. (*cont.*)

Name (mAb)	Expression	Molecular mass (kDa)	Notes	References
gp54	Tonsillar B-cells	54		Wang *et al.* (1979)
gp70	Burkitt lymphoma	70	Soluble form in sera of patients	Gazitt *et al.* (1986)
p80 (LB-1)	Lymphoblastoid cells	80	CD39?	Clark & Yokochi (1984)
7F7	B-cells, some neutrophils	85 (precursor 65)	Different from CD39, may be associated with a complement receptor	Schulz *et al.* (1987)
41.H16	B-cells, CLL	39	CD37?	Zipf *et al.* (1983)
BCGF receptor	B-cells	(90, 48)	Receptor of high-M_r BCGF	Ambrus *et al.* (1986)
IgM-binding protein	Activated B-cells, CLL	60		Sanders *et al.* (1987)
cCLLA	CLL	69		Faguet & Agee (1987), Agee *et al.* (1986)

et al., 1987). Similarly, LFA-3 may not be only a passive adhesion molecule, since its cross-linking on the surface of antigen-presenting cells stimulates them to interleukin-1 production (Le *et al.*, 1987).

(3) The LFA-1-based adhesion system (reviewed by Martz, 1987) appears to be critically important for adhesion of T_c to their targets (Krensky *et al.*, 1983; Shaw *et al.*, 1986*a*) and probably also in other leucocyte interactions. The LFA-1 molecule (Table 5) is broadly expressed on leucocytes; it consists of two glycoprotein transmembrane subunits: α (CD11a) and β (CD18) (170 kDa and 95 kDa, respectively). The β subunit is sequentially similar to fibronectin receptors (Kishimoto *et al.*, 1987; Law *et al.*, 1987) and can be associated with two other α subunits called now CD11b and CD11c (Krensky *et al.*, 1983; see Table 4). During the cell–cell contact LFA-1 probably binds to a so far poorly characterized molecule called ICAM-1 (Dustin *et al.*, 1986). Defective expression of CD18 (the β subunit) in some individuals causes severe dysfunctions of their immune system, obviously due to impaired leucocyte adhesivity (Springer *et al.*, 1984).

(4) 'Homing' systems are used to target leucocytes to specific organs and tissues. The murine receptor responsible for homing of lymphocytes to lymph nodes is a 95 kDa glycoprotein with unusual branched structure due to covalent attachment of several ubiquitin chains (for review see Gallatin *et al.*, 1986) and recognizes complex carbohydrates containing 6-phosphomannosyl residues (Yednock *et al.*, 1987). A very similar molecule seems to be involved also in homing of human lymphocytes to lymphoid organs (Jalkanen *et al.*, 1986, 1987).

In conclusion, multiple systems of intercellular adhesion are used by leucocytes (Fig. 2); the relative importance of individual systems in different situations remains to be established.

Receptors for lymphokines, growth and differentiation factors etc.

Multiple soluble mediators of polypeptide or glycoprotein nature are essential in regulation of leucocyte growth differentiation and proliferation. All these soluble factors act through specific receptors expressed on the surface of target cells. In many cases these receptors are present only in very small amounts, which has so far prevented their isolation and thorough biochemical characterization. Here we will only briefly mention several well characterized receptors of this kind. Several others, for which less information is available, can be found in Tables 2, 4 and 5.

The receptor for interleukin-2 is by far the most thoroughly studied lymphokine receptor. The high-affinity receptor consists of noncovalently associated subunits α (55 kDa, called also Tac or CD25) and β (75 kDa), both of which have a medium affinity for interleukin-2 themselves (Sharon *et al.*, 1986; Smith, 1987). Both subunits can exist independently on the cell surface. The free β subunit is present on the surface of, e.g., resting T cells or NK cells (Bich-Thuy *et al.*, 1987; Siegel *et al.*, 1987) and serves as the functional IL-2 receptor. After T cell activation, the α chain (CD25) is rapidly expressed and after its association with the β chain an apparently more efficient receptor is formed (Wang & Smith, 1987).

Interaction of interleukin-2 with isolated α chain seems to deliver a negative signal to the cell (Kumar *et al.*, 1987). Crosslinking experiments revealed recently the presence of a third, 95–100 kDa, subunit associated with the interleukin-2 receptor (Szöllösi *et al.*, 1987; Saragovi & Malek, 1987). The structure of the α subunit is known in great detail (reviewed by Waldmann, 1986, and Greene & Leonard, 1986), while little is known about the β subunit (Robb *et al.*, 1987) and the 95–100 kDa 'γ' subunit. The mechanism of signal transduction through the interleukin-2 receptor is unclear; apparently the β subunit (75 kDa) is phosphorylated by a receptor-associated protein kinase after interleukin-2 binding (Benedict *et al.*, 1987); it is possible that the subunit itself is the protein kinase. Internalization of interleukin-2 is mediated by the β subunit but not the α subunit (Robb & Greene, 1987) but it is not clear whether the internalization has any functional importance. A soluble form of the α chain (CD25), produced probably by proteolytic cleavage of the membrane-bound molecule, occurs in serum and may have an immunoregulatory role (Rubin *et al.*, 1986);

high concentrations were observed in the sera of patients with leukaemia (Semenzato *et al.*, 1987).

The interleukin-2 receptor appears to be an interesting multicomponent complex, the elucidation of whose functions will become possible only after thorough structural description of its components.

Another well characterized receptor is that for a haemopoietic growth factor called CSF-1 (colony stimulating factor 1, also called M-CSF), expressed mainly on human macrophages (Table 4). This typical integral membrane glycoprotein of 165 kDa has a large cytoplasmic domain with ligand-dependent tyrosine-kinase activity (Coussens *et al.*, 1986). A form of the feline receptor modified in the *C*-terminal domain was shown to be identical to the product of the v-*fms* oncogene. This truncated receptor phosphorylates itself constitutively, which results in deregulated cell proliferation (Sherr *et al.*, 1985; Wheeler *et al.*, 1986).

Basic biochemical properties of human receptors for interleukin-6 (Coulie *et al.*, 1987, see Table 2) and for so-called GM-CSF (Park *et al.*, 1986; see Table 4) have been determined, while only murine receptors for interleukin-3 and GM-CSF have been studied so far (for review of the CSF receptors see Nicola, 1987). Some basic information is also available on the nature of the murine receptor for interleukin-4 (Park *et al.*, 1987), which may be associated with the LFA-1 molecule (Mishra *et al.*, 1986).

Recent data on interferon γ receptor have been reviewed (Rubinstein *et al.*, 1987); little is known about the biochemical character of this important receptor except that molecules of 90 kDa and 50 kDa have the receptor activity (Auget & Merlin, 1987).

Little is also known about the receptor for an important multifunctional cytokine, interleukin-1. The cell-surface receptor is a 60 kDa molecule as determined by affinity-crosslinking experiments (Matsushima *et al.*, 1986; see also review by Dower & Urdal, 1987). An immunosuppressive urinary glycoprotein called uromodulin appeared to be a soluble form of an interleukin-1 receptor (Muchmore & Decker, 1986); apparently, interleukin-1 binds in a lectin-like fashion to the carbohydrate moiety of this glycoprotein. Recently uromodulin was identified as the major urinary Tamm–Horsfall glycoprotein (Hession *et al.*, 1987). Interleukin-1 seems to have two separate binding sites through which it interacts with this soluble glycoprotein and with the cellular receptor, respectively (Hession *et al.*, 1987). The physiological meaning of the interaction with the urinary glycoprotein is unknown.

The antigen CD23 (discussed in more detail in the following paragraph on Fc receptors) was reported to be the receptor for so-called 'low-molecular-weight B cell growth factor' (Guy & Gordon, 1987).

Identification and thorough elucidation of structure and function of cytokine receptors on leucocytes will certainly become one of the central topics of leucocyte membranology, as it should bring an understanding of the principles governing the regulation of leucocyte growth and differentiation and of their defects in malignant transformation, with potentially important practical medical implications.

Transferrin and insulin can be considered as growth factors of proliferating leucocytes (and of other cells as well). Transferrin receptor is a typical 'activation antigen' expressed on a variety of dividing cells including activated lymphocytes and early thymocytes. Its structure and function have been reviewed in detail (Testa, 1985; Huebers & Finch, 1987). This covalent homodimer of a 90 kDa subunit is unusual in that the polypeptide is oriented with *N*-terminus intracellularly (Schneider *et al.*, 1984; McClelland *et al.*, 1984). An open question is whether transferrin receptor on tumour cells serves as the target molecule recognized by NK cells (Vodinelich *et al.*, 1983; Dokhélar *et al.*, 1984). Also, it is not quite clear whether the interaction of transferrin with the receptor does provide a growth-stimulatory signal independent of the iron-delivery function (Manger *et al.*, 1986).

Structure and function of the insulin receptor (Table 5) have been recently thoroughly reviewed elsewhere (Van Obberghen & Gammeltoft, 1986).

Receptors for immunoglobulins

Several types of receptors for the Fc portion of immunoglobulin molecules exist on different subpopulations of human leucocytes. Recently great progress is being made toward detailed molecular characterization of these receptors. Among the relatively well characterized human leucocyte Fc receptors are CD16, CDw32 and the monocyte high-affinity Fc receptor (all receptors

Table 3. NK-cell associated antigens

Name (mAb)	Expression	Molecular mass (kDa)	Notes	References
HNK-1 (Leu7)	NK cells	110	Cross-reactive carbohydrate epitopes occur also on some neuronal surface molecules	Abo & Balch (1981), Schröder *et al.* (1983)
NKH-1 (Leu19)	NK cells and MHC-unrestricted T-cells	220	Probably a member of the 'T200' (CD45) family	Lanier *et al.* (1986)
NK-9	NK cells	220, 200, 190	Closely related to or identical NKH-1; *O*-glycosylated	Nieminen & Saksela (1986)
KC-1	NK cells, granulocytes, monocytes, weakly lymphocytes	145	Antibody blocks NK cytotoxity	Clayberger *et al.* (1986)
NKH-2	Subpopulation of NK cells	60		Hercend *et al.* (1985)

for IgG; see Table 4), CD7 (probably the receptor of T cells for IgM; see Table 1), CD23 (lymphocyte low affinity receptor for IgE; Table 2), and the mastocyte/basophil high affinity receptor for IgE (Table 4). Structural relationship between various human Fc receptors should be clarified after cloning and sequencing of corresponding cDNAs (so far these data are available only for CD23 and CD7). Murine cDNA coding for the Fc receptor called Ly17 was recently cloned and sequenced (Lewis *et al.*, 1986; Ravetch *et al.*, 1986); the sequence had significant similarities to the proteins of the immunoglobulin family. Also, the existence of at least three closely related forms of murine Fc receptors was demonstrated (Ravetch *et al.*, 1986), expressed in different leucocyte subsets. It would be interesting to know which are the corresponding human equivalents – presumable candidates are CD16, CDw32 and the monocyte 72 kDa Fc receptor. Although physiological functions of Fc receptors (especially those for IgG and IgM) are largely yet to be defined, at least some of their functions appear to be clear. First, Fc receptor-mediated attachment of IgG molecules to the monocyte and NK surface may endow these cells with certain antigen-specific recognition potential. Such 'armed' cells may then more effectively recognize and attack microbial pathogens, infected or possibly tumour cells and destroy them by this 'antibody-dependent cellular cytotoxicity' mechanism. Second, pathogens coated by specific immunoglobulins (opsonized) can be recognized by the Fc receptor-bearing cells and destroyed by phagocytosis. Third, soluble immune complexes (complexes of antigen with specific immunoglobulins) can be recognized and endocytosed after recognition through Fc receptors. In addition to these effector functions mediated by Fc receptors, these molecules clearly play regulatory roles. Binding of immunoglobulins or immune complexes to the B lymphocyte Fc receptors down-regulates immunoglobulin production, which seems to be a simple negative feedback regulatory mechanism (for review see Sinclair & Panoskaltsis, 1987). B lymphocyte Fc receptor was reported to have a phospholipase A_2 activity (Suzuki *et al.*, 1981), which is a key enzyme in the prostaglandin synthesis. The regulatory effects of this Fc receptor on immunoglobulin production could then be due to affecting the synthesis of prostaglandins, substances with strong immunomodulatory effects. Most is known about the mechanism of action of the basophil/mastocyte high affinity receptor for IgE which mediates the familar allergic reactions. Its structure and function have been reviewed extensively recently (Metzger *et al.*, 1986). The α subunit of this multichain complex (Table 4) binds the Fc part of monomeric IgE and after interaction with the corresponding antigen the resulting crosslinking of receptors leads to rapid 'degranulation' of the mastocytes or basophils, which causes a strong local tissue reaction. The amino acid sequence of the α subunit of the rat receptor predicted from the structure of cDNA has significant similarities to murine Fc receptor Ly17 (Kinet *et al.*, 1987).

Another IgE receptor is the CD23 antigen which is weakly expressed on resting lymphocytes and strongly on activated B cells (Table 2). In addition to a relatively low-affinity binding of IgE it was reported to be also the receptor for 'low-molecular-weight B cell growth factor' (Guy & Gordon, 1987), a so far rather poorly defined lymphokine. The CD23 molecule has several other interesting features: it has a significant sequential similarity to the hepatic receptors for asialoglycoproteins, which might indicate that CD23 also is a lectin (Kikutani *et al.*, 1986; Ikuta *et al.*, 1987). Further, it is unusually oriented in the membrane, with the *C*-terminus being extracellular, similar to, e.g., the transferrin receptor. Most interestingly, a soluble fragment of the CD23 molecule produced probably by proteolytic cleavage appears to be an autocrine growth factor for B cells (Swendeman & Thorley-Lawson, 1987); it is not known what is the mechanism underlying this phenomenon, e.g. what is the receptor for this fragment. Thus, CD23 seems to be an extremely interesting receptor with perhaps too many functions identified; it may be a molecule of key importance for B cell growth regulation (Guy & Gorden, 1987) and IgE may well prove to be an important B cell cycle regulatory molecule in addition to its known effector functions.

Existence of soluble forms of Fc receptors may be a more general phenomenon of uncertain physiological importance; in addition to soluble CD23 also CDw32 is easily shed as a soluble fragment (Looney *et al.*, 1986). It is not quite clear what is the structural relationship of so called 'immunoglobulin binding factors' present in serum to the known Fc receptors (see e.g. MacLean *et al.*, 1986).

Complement receptors and related molecules

This is a group of often structurally related membrane receptors capable of recognizing different complement components and their fragments. As these receptors were reviewed elsewhere (Fearon, 1984; Gresham & Volanakis, 1986) we will only very briefly point out some interesting or most recently described features. Basic data on these molecules can be found in Table 2 [complement receptor type 2 (CD21)], Table 4 [complement receptor type 3 (CD11b/CD18), CD11c/CD18 and C5a receptor] and Table 5 [complement receptor type 1 (CD35), decay accelerating factor, C1q receptor, GP45-70 (MCP) and HRF]. These receptors serve apparently several different functions: first, they help to recognize by phagocytic cells the pathogens 'opsonized' with complement fragments (complement receptor type 3); interaction of the C3d fragment with CD21 (complement receptor type 2) seems to be an important signal regulating the lymphocyte cell cycle (Melchers *et al.*, 1985) and moreover, CD21 is the receptor for Epstein–Barr virus (Fingeroth *et al.*, 1984). The C5a receptor is important for chemotaxis of monocytes and granulocytes toward the inflammation sites.

A group of these receptors have regulatory functions (decay accelerating factor, MCP and HRF) as they prevent spontaneous deposition of activated complement fragments on the self-cells (Atkinson & Farries, 1987). The complement receptors CD35, CD21 and decay accelerating factor display significant sequence similarities and the genes for these homologous proteins form a cluster on human chromosome 1 (Weis *et al.*, 1987).

CD11b/CD18 (complement receptor type 3) is structurally similar to the LFA-1 adhesion molecule [the β chain (CD18) is common for these two molecules] and appears to be multifunctional: first of all it binds to iC3b fragment [the sequence recognized in this complement fragment involves the Arg-Gly-Asp sequence similar to that recognized by fibronectin receptors in fibronectin

Table 4. Myeloid cell antigens

A number of other myeloid cell surface antigens were tentatively identified by unique mAbs, during the 3rd Leucocyte Workshop (Hogg & Horto, 1987). Abbreviations: AML, acute myeloblastoid leukaemia; ADCC, antibody-dependent cell cytotoxicity; MIF, migration inhibition factor.

Name (mAb)	Expression	Molecular mass (kDa)	Notes	References
CD11b/CD18* (Mo1, Mac1, CR3) (mouse homologue Mac1)	Myeloid cells, NK cells	(170, 95)	Receptor for iC3b (see text)	Krensky *et al.* (1983), Le Bien *et al.* (1983), Miller *et al.* (1987), Cosgrove *et al.* (1986), Miller & Springer (1987), Kishimoto *et al.* (1987), Law *et al.* (1987)
CD11c/CD18 (p150/95, Leu-M5)	Myeloid cells, NK cells, some B-cell lines and cloned T_c; strongly on tissue macrophages	(150, 95)	Complement receptor type 3; adhesion molecule	Hogg *et al.* (1986), Micklem & Sim (1985), Keizer *et al.* (1987*a*,*b*)
CD13 (MY7)	Myeloid cells	150	cDNA cloned	Look *et al.* (1987)
CD14* (MH4, Leu-M3)	Monocytes	53–55	Soluble form occurs in serum	Maliszewski *et al.* (1985), Bažil *et al.* (1986) S. A. Goyert, unpublished work*
CD15	Granulocytes, embryonic cells	50–180	A group of proteins carrying 'hapten X' (2′-fucosyl-*N*-acetyl-lactosamine), also occurs on glycolipids	Knowles *et al.* (1982), Gooi *et al.* (1983), Skubitz & August (1985), Paietta *et al.* (1986)
CD16 (low affinity Fc receptor for IgG)	Granulocytes, NK cells	50–70	(See also text)	Bernstein & Self (1986), Tetteroo *et al.* (1987)
CD31	Monocytes, granulocytes, 130–140 platelets, some T-cells	130–140	Possibly identical with the TM2, TM3 antigens	Hogg & Horton (1987)
CDw32 (FcRII)	Myeloid cells, platelets, B-cells	40	Receptor for IgG; easily cleaved to a 33 kDa soluble fragment (see text)	Looney *et al.* (1986), Tetteroo *et al.* (1987), Vaughn *et al.* (1985)
CD33 (MY9)	Myeloid progenitors	67		Hogg & Horton (1987)
CD34 (MY10)	Myeloid progenitors	115		Look *et al.* (1987)
CD36	Monocytes, platelets	85		Hogg & Horton (1987)
OKM5	Monocytes (70%)	88	Thrombospondin receptor	Asch *et al.* (1987)
OKM6	Subpopulation of monocytes, platelets	130		Talle *et al.* (1983)
IgE receptor*	Mast cells, basophils	45 (α) 33 (β) $(9)_2$ (γ)	High-affinity IgE receptor rat subunit binds IgE; rat subunit cDNA cloned	Metzger *et al.* (1986) (review), Perez-Montfort & Metzger (1982), Kinet *et al.* (1987)*
Monocyte high-affinity Fc receptor (FcRI)	Monocytes, macrophages	68–72	Heavily glycosylated; binds human IgG1 and murine IgG2a and IgG3	Lubeck *et al.* (1985), Anderson *et al.* (1985), Tetteroo *et al.* (1987), Frey & Engelhardt (1987), Dougherty *et al.* (1987)
GM-CSF receptor	Myeloid cells, myeloid progenitors	130	Easily cleaved to a 70 kDa fragment	Park *et al.* (1986)
CSF-1 receptor	Monocytes, macrophages	165	Identical with the product of c-*fms* proto-oncogene; protein kinase activity	Coussens *et al.* (1986)*
Mo3e	Stimulated monocytes	80+50	Related to MIF receptor?	Liu & Todd (1986)
Mo4	Monocytes, platelets	100		Todd *et al.* (1984)
Mo5	Myeloid precursors, monocytes, neutrophils	94		Todd *et al.* (1984)
Mo6	Myeloid cells	80	Lost from cultured monocytes	Todd *et al.* (1984)
MoU26	Monocytes, platelets	130–140		Goyert *et al.* (1986)
MY26	Granulocytes	18–20		Warren & Civin (1985)
MY901	AML, NK cells	65		Griffin & Schlossman (1984)
MY906	AML	72		Griffin & Schlossman (1984)
M206	Monocytes, weakly granulocytes	180		Maruyana *et al.* (1983)

Table 4. (*cont.*)

Name (mAb)	Expression	Molecular mass (kDa)	Notes	References
Mac120 (Leu-M2)	Macrophages	120		Raff *et al.* (1980), Hausman *et al.* (1980)
MAC387	Myeloid cells	72, 56	In granulocytes 13, 14 kDa	Jones *et al.* (1987)
SG 133	Immature myeloid cells	26–28		Goyert *et al.* (1986)
SG 185	Granulocytes	185		Goyert *et al.* (1986)
MAX1	Macrophages	64		Emmrich & Andreesen (1985)
MAX3	Macrophages	68		Emmrich & Andreesen (1985)
A1-3	Activated monocytes	52	mAb inhibits monocyte procoagulant activity	Ewan *et al.* (1986)
LP3, LP5, LP7	Monocytes, macrophages, other tissues	$(100)_2$	M_r similar to growth hormone receptor	Partridge *et al.* (1987)
UC45	Spreading monocytes, neurons	45		Hogg *et al.* (1981)
YB5.B8	AML, tissue mast cells	150		Ashman *et al.* (1987)
GFA-2	Granulocytes	95	mAb stimulates ADCC; possibly related to CD18	López *et al.* (1985)
Bsp-1	Basophils	45		Bodger *et al.* (1987)
AML antigen NHL-30.5	AML	180		Askew *et al.* (1986)
1–15	Neutrophils	180	Membrane protease	King *et al.* (1987)
Membrane proteinase	Neutrophils	300	After stimulation released into medium	Pontranoli *et al.* (1986)
12B1	Cultured monocytes, dendritic reticular cells	86–93 (40+44 after deglycosylation)	Possibly related to 25F9 (Zwadlo *et al.*, 1985)	Farace *et al.* (1986)
'24 antigen'	Monocytes, macrophages	174		Dougherty *et al.* (1986)
25F9	Macrophages	86		Zwadlo *et al.* (1985)
27E10	Subpopulations of myeloid cells	17	Strongly expressed on Sezary cells	Zwadlo *et al.* (1986)
61D3	Monocytes	65	Lost after culture	Nunez *et al.* (1982)
LDL receptor	Macrophages	130		Soutar & Knight (1986)
CEA-crossreactive antigen	Granulocytes	90, 160		Audette *et al.* (1987)

(Wright *et al.*, 1987)]. Further, this receptor has a lectin-like carbohydrate-binding activity which may be important for recognition of some microbial cell wall carbohydrates (Ross *et al.*, 1985). Complement receptor type 3 also appears to be a cell adhesion molecule (Dana *et al.*, 1986), as does the other member of the CD11 family with complement receptor activity, p150,95 (CD11c/CD18) (Keizer *et al.*, 1987*a*). CD35 (complement receptor type 1) is predicted to be an unusual rod-like molecule consisting of 30 short consensus repeats of 60 amino acid residues (Klickstein *et al.*, 1987). Interestingly, allelic forms exist which considerably differ in the number of these basic structural units but still normally bind C3b and C4b (Dykman *et al.*, 1985).

Decay accelerating factor belongs to the receptors anchored in membrane by the phosphatidylinositol moiety (Davitz *et al.*, 1987). Multiple forms of decay accelerating factor exist (Seya *et al.*, 1987), including a soluble one produced by unusual mRNA splicing involving a frame-shift in the *C*-terminal region (Caras *et al.*, 1987), but nothing is known about the roles of these alternative forms.

Activation antigens

Activation of leucocytes by various stimuli normally leads to expression of new surface components or greatly increased expression of molecules already present on the resting cells. Many of these molecules have been already discussed in previous paragraphs. The kinetics of expression is very different for different antigens (hours for early activation antigens, days or even weeks for late or very late activation antigens).

Among the activation antigens belong typically CD25 (low-affinity interleukin-2 receptor), transferrin receptor, CD23 and the Blast-1 antigen (Table 2). Another characteristic activation antigen of many cell types is the 4F2 molecule (Haynes *et al.*, 1981), which appears to be a Na^+/Ca^{2+} exchanger (Bron *et al.*, 1986) of interesting two-chain structure (Table 5). Some of these molecules, such as transferrin receptor or 4F2, may be recognized by NK cells as markers of rapidly growing tumour cells (Vodinelich *et al.*, 1983; Moingeon *et al.*, 1985).

Other activation antigens of so far unknown function are, e.g., CD30 (Table 5) or the 18 kDa antigen of

Table 5. Molecules with 'broad expression'

A number of other leucocyte surface molecules were tentatively identified by means of unique mAbs during the International Workshops on Human Leucocyte Differentiation Antigens; not all of them are included here. Several possibly new antigens were described also in a paper by Pesando *et al.* (1986*c*). Abbreviations: ALL, acute lymphoblastoid leukaemia: IL, interleukin; PHA, phytohaemagglutinin; AML, acute myeloblastoid leukaemia.

Name (mAb)	Expression	Molecular mass (kDa)	Notes	References
HLA-A*, -B*, -C* (mouse homologues H-2K, -D)	Broad	45	Associated with β_2-microglobulin; see text for functions	See text
HLA-DR*, -DQ*, -DP* (mouse homologues I-E, -A)	B-cells, monocytes,	(34, 29)	See text	See text
CD9 (p24)	Pre-B-cells, ALL, platelets, monocytes, activated T-cells, carcinomas	24, 26	Molecular species differing in glycosylation but possibly also in polypeptide backbone exist; membrane anchored via a lipid; related to PDGF and *sis*-oncogen product; growth-promoting activity	Hercend *et al.* (1981), Shaw *et al.* (1986*b*), Le Bien *et al.* (1986*a*), Wood *et al.* (1986), Zipf *et al.* (1986), Zeleznik *et al.* (1987)
CD10 (CALLA)	Pre-B-cells, ALL, granulocytes, kidney parenchyma	95–110	M_r different in different cell types (common 78 kDa polypeptide core); probably anchored via a lipid moiety	Newman *et al.* (1981), Metzgar *et al.* (1981), Addis & Letarte (1986), Pesando *et al.* (1986*b*)
CD11a/CD18* (LFA-1)	Leucocytes	(180, 95)	Cell-adhesion molecule (see text)	Martz (1987) (review), Springer *et al.* (1985), see also text and references for CD11b (Table 4)
ICAM-1	Broad	90	Interacts with LFA-1	Dustin *et al.* (1986)
LFA-3*	Broad	40–70	Cell-adhesion molecules, (interacts with CD2); heavily glycosylated; (see also text)	Dustin *et al.* (1987), Wallner *et al.* (1987)*, Seed (1987)*
CD25* (Tac)	Activated lymphocytes and monocytes	55	Low-affinity IL-2 receptor, heavily glycosylated (see text)	Waldman (1986) (review), Greene & Leonard (1986) (review), Leonard *et al.* (1985*a*,*b*)* (see also text)
p75	Lymphocytes	70–75	Low-affinity IL-2 receptor; in association with CD25 forms a high-affinity receptor (see text)	Sharon *et al.* (1986), Smith (1987), Robb *et al.* (1987), Robb & Greene (1987) (see also text)
CDw29 (4B4)	Myeloid cells, thymocytes, subpopulation of T-cells	135	CDw29$^+$, CD45R$^-$ T cells are true helpers of B cells	Morimoto *et al.* (1985), Amiot *et al.* (1986*b*)
CD30	Hodgkin's disease cells, activated lymphocytes	120, 105	90 kDa precursor	Stein *et al.* (1987), Froese *et al.* (1987)
CD35* (CR1)	Broad	160–250 (allotypic variation)	Receptor for C3b and C4b; sequence similarity to other complement receptors (see text)	Sim (1985), Klickstein *et al.* (1987)*, Weis *et al.* (1987)
CD38 (T10)	Thymocytes, monocytes, some cell lines, plasma cells	45	Associated with β_2-microglobulin or another 12 kDa protein	Terhorst *et al.* (1981), Cotner *et al.* (1981), Ling *et al.* (1987)
CD43 (gp115, leukosialin, sialophorin) (mouse homologue Ly-9)	Leucoytes, neurons	95–115 (lymphocytes) 135 (neutrophils, platelets)	Major sialoglycoprotein; migration on SDS/PAGE strongly decreased after desialylation; heavily *O*-glycosylated; expression defective in Wiskott-Aldrich syndrome	Remold-O'Donnell *et al.*, (1984, 1987), Carlsson & Fukuda (1986), Axelson *et al.* (1985), Mentzer *et al.* (1987), Carlsson *et al.* (1986), Reisinger & Parkman (1987), Borche *et al.* (1987)
T305	Activated T cells	140–160	Probably a form of CD43	Sportsman *et al.* (1985), Carlsson & Fukuda (1986)

Table 5. (*cont.*)

Name (mAb)	Expression	Molecular mass (kDa)	Notes	References
CDw44	Leucocytes, erythrocytes (weak), neurons	65–85	Heavily glycosylated	Haynes *et al.* (1983), Dalchau *et al.* (1980), Letarte (1986)
CD45* (T200, L-CA) (mouse homologue Ly-5)	Leucocytes	220, 205, 190, 180	The different M_r forms are products of alternatively spliced mRNA and differ at *N*-terminus; heavily *N*- and *O*-glycosylated; (see also text)	Judd *et al.* (1980), Morishima *et al.* (1982), Ralph *et al.* (1987)*, (see also text)
CD45R* (B220, 2H4)	Monocytes, B-lymphocytes, subpopulation of T-lymphocytes	220, 205	The large forms of CD45; expression defines functional T-cell subpopulations (see text)	Ralph *et al.* (1987)*, Morimoto *et al.* (1986*a*,*b*), Beverley (1987)
UCHL-1*	Myeloid cells, subpopulations of T-cells	180	The smallest form of CD45	Smith *et al.* (1986), Beverley (1987), Ralph *et al.* (1987)*
Leu8	Broad	80	Defines functional subpopulation of T-cells. Probably identical to TQ1 antigen	Kansas & Engelman (1987)
Human MRC OX-2	Leucocytes, neurons, trophoblast	65, 55	Homologue of rat antigen MRC OX-2 (an Ig-family member) (Clark *et al.*, 1985)	Stern *et al.* (1986)
HuLym3	Most lymphocytes	47		Vaughan *et al.* (1983)
CIPanHu	Broad	16		de Kretser *et al.* (1986)
Act-1	Activated lymphocytes	63	Appears 1–2 days after DNA synthesis maximum	Lazarovits *et al.* (1984)
EA-1	Thymocytes, activated lymphocytes, some non-lymphoid cell lines	(28, 32)	Both chains are phosphorylated	Hara *et al.* (1986)
Ea1	(Activated) lymphocytes, other cells	78	Early activation antigen	Newman *et al.* (1986)
Ea2	Activated lymphocytes, other cells	(86, 73)	Association with a 23 kDa component	Newman *et al.* (1986)
Ea3	PHA-activated lymphocytes	31	mAb blocks PHA-induced activation	Newman *et al.* (1986)
MD	B cells, subpopulation of T-cells, NK cells	220–240, (non-red), 70–80 (red.)	Possibly related to the homing receptor	Koning *et al.* (1986)
SN6	Bone marrow, various leukaemic cell lines	$(80)_2$		Haruta & Seon (1986)
P-glycoprotein*	Broad, e.g. leukaemic cells	170	Causes multiple drug resistance	Ueda *et al.* (1987)*
A-3A4	Broad (cell lines)	45		Peters *et al.* (1984)
L24	Lymphocytes	$(140)_2$	mAb blocks T_c	Clayberger *et al.* (1987)
L25	Lymphocytes	150, 85, 75	mAb blocks T_c	Clayberger *et al.* (1987)
B.3.C.5	Multipotential progenitors	110–120		Katz *et al.* (1986)
44E3	Broad	94		Quackenbush & Letarte (1985)
44H6	Lymphoid precursors, ALL, AML, macrophages	(125, 87)		Quackenbush & Letarte (1985)
44H7	Broad	57, 47, 41		Quackenbush & Letarte (1985)
44G4	ALL, endothelia	$(95)_2$	Heavily sialylated glycoprotein	Quackenbush & Letarte (1985), Gougos & Letarte (1986)
44H9	ALL, AML, bone marrow, thymocytes	51		Quackenbush & Letarte (1985)

Table 5. (*cont.*)

Name (mAb)	Expression	Molecular mass (kDa)	Notes	References
53.6	Some leucocytes, many cell lines	34	Non-glycosylated	Yagi *et al.* (1987)
BRIC 110	Broad	70 (and dimer)	Heavily sialylated, carries some erythrocyte blood group antigens	Spring *et al.* (1987)
Lymphocyte homing receptor	B-cells, subpopulation of T-cells	90	Mediates attachment to endothelia in lymph nodes	Jalkanen *et al.* (1986)
IL-1 receptor	Broad (?)	60		Dower & Urdal (1987), Matsushima *et al.* (1986)
Interferon γ-receptor	(isolated from a B-cell line)	90, 50		Auget & Merlin (1987)
Transferrin receptor* (T9)	Activated cells, tumour cells	$(90)_2$	Probably a target for some NK cells; *C*-terminal domain extracellular; (see also text)	Testa (1985) (review), Huebers & Finch (1987) (review), Schneider *et al.* (1982, 1984)* McClelland *et al.* (1984)*
Insulin receptor*	Broad	$(130+90)_2$	Insulin-activated protein kinase; associated with MHC class I; sequence similarity to EGF receptor and to *src* product	Van Obberghen & Gameltoft (1986) (review), Fujita-Yamaguchi *et al.* (1983), Van Obberghen *et al.* (1983), Fehlmann *et al.* (1985), Ullrich *et al.* (1985)*
Growth hormone receptor	Broad	$(120)_2$	Sialylated, 20% *N*-linked carbohydrates	Asakawa *et al.* (1986)
4F2*	Broad; strongly on activated cells	(90+41)	Probably Na^+/Ca^{2+} exchanger	Haynes *et al.* (1981), Hemler & Strominger (1982), Bron *et al.* (1986), Teixeira *et al.* (1987)*, Quackenbush *et al.* (1987)*
VLA 1	Activated T cell clones, fibroblast lines	(210, 130)	β subunit (130 kDa; can be expressed independently) is common for all VLA and probably identical to the fibroblast fibronectin receptor	Hemler *et al.* (1984, 1987*a*)
VLA 2	Long term T cell lines, platelets, fibroblast lines	(165, 130)		Hemler *et al.* (1983, 1987*a*)
VLA 3	Fibroblast and carcinoma lines, some T-lines	(135, 130)	α-subunit possibly disulphide-linked to a 20 kDa subunit; fibronectin receptor	Takada *et al.* (1987) Hemler *et al.* (1987*a*)
VLA 4	T cell line	(150, 130)		Hemler *et al.* (1987*a*,*b*)
VLA 5	Cell lines K562, U932	(135, 130)	α subunit possibly disulphide-linked to a 20 kDa subunit; fibronectin receptor	Takada *et al.* (1987) Hemler *et al.* (1987*a*)
gp IIb (a subunit of CDw41)	Platelets, monocytes, NK cells	(114+22)	Subunits are disulphide-linked; associated non-covalently (Ca^{2+}-dependent) with gp IIIa to form a fibronectin and fibrinogen receptor	Calvette & Gonzáles-Rodriguez (1986), Eirín *et al.* (1986), Burns *et al.* (1986), Pytela *et al.* (1986), Poncz *et al.* (1987)
gp IIIa (a subunit of CDw41)	As gpIIb	92	Associated with gp IIb (see above); sequence very similar to vitronectin receptor	Ginsberg *et al.* (1987), Fitzgerald *et al.* (1987) (see also references for gp IIb)
C1q receptor	Leucocytes, other cells	85	Associated with a proteoglycan	Ghebrehiwet (1986)
DAF* (decay accelerating factor)	Broad (most strongly on myeloid cells)	75	Heavily glycosylated; binds activated C3b and C4b (see text); anchored through phosphatidylinositol; sequence similar to other complement receptors	Lublin *et al.* (1986), Davitz *et al.* (1986), Medof *et al.* (1987)*, Caras *et al.* (1987)*, Seya *et al.* (1987)

Table 5. (*cont.*)

Name (mAb)	Expression	Molecular mass (kDa)	Notes	References
HRF (homologous restriction factor)	Broad	65	Prevents the C8, C9 complex formation on autologous cells	Zalman *et al.* (1987)
MCP (membrane cofactor protein; gp 45–70)	Broad	45–70	Receptor for C3b, C4b; together with DAF prevents activation of deposited complement on autologous cells	Seya *et al.* (1986), Atkinson & Farries (1987)
(Unnamed)	LAK cells and their precursors, some T cell lines, myeloid cells	120	mAb blocks LAK cell function	Zocchi *et al.* (1987)
(Unnamed)	Lymphocytes	150, 50	Easily shed to medium	Sundqvist & Otteskog (1987)

stimulated or HIV-infected T cells (Stricker *et al.*, 1987). As already mentioned, a new, 'activation' epitope of CD2 called $T11_3$ appears on activated T cells. MHC class II glycoproteins can also be considered activation antigens, as their expression on activated B-lymphocytes and monocytes is strongly increased and they are even expressed on activated T lymphocytes (Zier *et al.*, 1986) which do not express them at all in the resting state; the role of these MHC class II molecules on activated T cells is a potentially important and so far rather neglected question.

Also the 'very late activation antigens' (VLA) which appear after 2–3 weeks of culture on activated T cells (Hemler *et al.*, 1984) and are apparently related to the fibronectin receptors (Takada *et al.*, 1987), have been shortly discussed in the paragraph on adhesion molecules. Their molecular mass, subunit composition and expression suggest that the molecules called CDw26 (Haynes, 1986) and LDA_1 (Suciu-Foca *et al.* 1985) may be related to the VLA family.

Some other 'interesting' molecules

Function of some leucocyte suface molecules can be inferred from the effects of mAbs recognizing these molecules. Thus, when a mAb has a cell-stimulatory effect, it may be because the mAb mimicks the effects of a so far unknown physiological ligand, such as a lymphokine. If on the other hand a mAb blocks some of the leucocyte functions, this may be interpreted as interference by the mAb with the respective function, such as intercellular contact, or 'nonproductive' blocking of some receptor presenting the physiological ligand to activate the cell. Thus, under appropriate conditions, mAbs against T cell receptor complex or membrane Ig may stimulate the cells (mimicking of the antigen action), and mAbs against MHC class II glycoproteins, CD4, CD8 or against various adhesion molecules do block a number of leucocyte functions. Many other examples of this kind can be found in Tables 1–5.

However, it is quite possible that some of these effects may be artifacts and that perhaps modulation of a surface molecule under non-physiological conditions by mAbs can cause such effects. Nevertheless, even with this possibility in mind, functional effects of mAbs can be considered as first clues to possible receptor or other functions of the target antigens. Among well-known examples of such leucocyte surface molecules without a clearly defined function (but where some of the corresponding mAbs exert observable effects *in vitro*) are, e.g.: CD5, CD6, CD27, CD28, Tp103, TLiSA, MW4, Tp90 (Table 1); CD19, CD20, CD22, CDw40, AB-1 (Table 2); Ea3, L24, L25 (Table 5). Obviously, finding physiological ligands for these molecules would be of major importance.

Among other functionally important molecules are, e.g., CD43 and CD45 (Table 5). CD43 is the major leucocyte sialoglycoprotein described also under the names leukosialin or sialophorin (Carlsson & Fukuda, 1986; Mentzer *et al.*, 1987; Borche *et al.*, 1987). There is one report on mitogenic activity of a mAb against this antigen (Mentzer *et al.*, 1987); moreover, the expression of this sialoglycoprotein is defective in patients affected by Wiskott–Aldrich syndrome (Remold-O'Donnell *et al.*, 1984). It is possible that sialic acid residues carried by this antigen protect the cells from premature removal from circulation through the asialoglycoprotein receptors in liver (Reisinger & Parkman, 1987). Moreover, similarity in molecular size might indicate a relation of CD43 (or of a similar sialoglycoprotein CDw44) to the homing receptor (Jalkanen *et al.*, 1986).

Numerous mAbs against the 'leucocyte common antigen' CD45 (Table 5) enhance stimulation of T cells (Martorell *et al.*, 1987), inhibit activation of B cells (Mittler *et al.*, 1987) and block cytotoxic activity of NK cells (Sparrow & McKenzie, 1983). In addition, expression of alternative forms of CD45 correlates with functions of T lymphocyte subsets (see the following paragraph). The CD45 molecules have a large intracellular domain (Ralph *et al.*, 1987) interacting specifically with cytoskeleton (Bourguignon *et al.*, 1985). All these observations strongly suggest a functional importance of these molecules, but the natural ligand is still to be found.

Yet another functionally important but so far incompletely understood molecule is CD9 (Table 5). This antigen, attached to the cell membrane via a lipid anchor (LeBien *et al.*, 1985), is structurally closely related to the platelet derived growth factor (PDGF) and to the product of *sis* oncogen (Wood *et al.*, 1986), it has a protein kinase activity (Zipf *et al.*, 1986) and the isolated antigen has a

growth-promoting activity (Zeleznik *et al.*, 1987). It may be speculated that CD9 could be a membrane-bound PDGF just as both soluble and membrane-bound interleukin-1 exist (Weaver & Unanue, 1986).

Molecules whose expression defines functional leucocyte subpopulations

As discussed to some extent in the previous paragraphs, the expression of some surface antigens is more or less restricted to certain leucocyte types and subpopulations. Detection of such molecules with restricted expression is invaluable for identification of the respective cell subsets. Thus, mIg and T cell receptor complex are characteristic markers (and most important functional molecules) of B and T lymphocytes, respectively. In addition there are a few other absolutely T cell-specific (CD7, CD27) or B cell-specific (e.g. CD19, CD20) antigens and CD14 and CD15 are reliable markers of monocytes and granulocytes, respectively. In most cases, the expression of other leucocyte surface antigens is not absolutely cell-type specific, but there are, e.g., molecules expressed on T cells and plasma cells (CD28), on T cells and a subpopulation of B cells (CD5), T cells and monocytes (CD4), etc. (see Tables 1–5). However, there are a few molecules that define, mostly in combination with other markers, a smaller functional subset of lymphocytes. Thus, T cell receptor the $\gamma\delta$ type is expressed on a subpopulation of T lymphocytes with 'NK-like' activity (Brenner *et al.*, 1987) which seems to be a lineage of T cells completely different from the major subpopulation carrying the $\alpha\beta$-type T cell receptor (Allison & Lanier, 1987). The nearly mutually exclusive expression of CD4 and CD8 molecules on T lymphocytes defines two subsets: the CD4 pool consists mostly of (1) T_h secreting lymphokines enhancing differentiation and proliferation of B lymphocytes and (2) so-called inducers of suppressor cells (i.e. cells helping in development of T_s); the $CD8^+$ subpopulation of T cells is responsible for most of the MHC-restricted cell-mediated cytotoxicity (T_c) and for suppressive activity (T_s).

The two subsets of $CD4^+$ T cells can be phenotypically distinguished by expression of molecules called CDw29 (Table 1) and UCHL-1 (a 160 kDa form of the CD45 antigen) on the 'true' T_h, and CD45R (205 kDa and 220 kDa forms of the CD45 antigen) on the suppressor-inducer subset (Morimoto *et al.*, 1986*a*; Beverley, 1987)

It is not quite clear what are the surface molecules reliably distinguishing T_c from T_s; it was reported that the cells expressing both CD8 and CD28 are T_c while the cells expressing CD8 and CD11/CD18 (previously called Mo1), but not CD28 are T_s (Yamada *et al.*, 1985). Also, the expression of a so far poorly biochemically characterized antigen Leu8 (Table 1) may differentiate between T_c and T_s and even between different subsets of T_s (Kansas & Engelman, 1987). It should be noted that the nature and perhaps even the very existence of T_s as a separate subpopulation remains controversial. A critical review on T lymphocyte subpopulations and their surface markers was recently published by Beverley (1987).

There are several antigens more or less specifically expressed on NK cells (Table 3). Interestingly, there are apparently NK-specific forms of CD45 (NKH-1, NK-9) which again stresses the functional importance of this family of molecules. It should be noted that there is some confusion concerning the definition of 'true' NK cells, which should be the non-T, non-B cells expressing the markers given in Table 3 and also the CD11a/CD18 and CD16 molecules (Lanier & Phillips, 1986).

Another useful marker is the CD5 antigen (Table 1) which is expressed on all T lymphocytes but also on a minor functionally important subpopulation of B lymphocytes which produce IgM autoantibodies against immunoglobulin and other self-antigens (Casali *et al.*, 1987).

The Ta_1 antigen (Table 1) appears to be a marker of memory T cells, i.e. the T cells that had been previously activated by specific antigen (Hafler *et al.*, 1986). Unfortunately, so far no surface molecule specific for memory B cells has been found; discovery of such a marker would be of major importance for better understanding of the nature of this very important but so far rather elusive subset.

Plasma cells, i.e. the terminal differentiation stage of B lymphocytes, are characterized by their expression of PC-1 and PCA-1 molecules (Table 2); in addition these cells express also the T cell molecules CD28 (Kozbor *et al.*, 1987) and CD38 (Ling *et al.*, 1987).

The recently described antigen HML-1 (Table 5) identifies an interesting subset of intestinal lymphocytes (Cerf-Benussan *et al.*, 1987).

From a practical point of view, it would be extremely useful to have markers specific for various malignant leucocytes. Such markers do exist, e.g. the expression of CD9 and CD10 is of diagnostic value for identification of acute lymphoblastoid leukaemia, the TALLA and cCLLa molecules (Tables 1 and 2, resp.) appear to be markers of T-cell acute lymphoblastoid leukaemia and chronic lymphoblastoid leukaemia, respectively, CD14, CD33 and CD34 are useful markers of myeloid leukemias (Foon & Todd, 1986). However, all these molecules are also present on some normal leucocytes, e.g. some bone marrow cells; CD10 is strongly expressed on kidney parenchymal cells and normal granulocytes (Metzgar *et al.*, 1981). Expression of these leukaemia-associated antigens on normal cells prevents, to large extent, e.g. the use of specific mAbs for therapeutic purposes.

Types of association with membrane and soluble forms of leucocyte surface antigens

The great majority of leucocyte surface glycoproteins are integral membrane proteins associated with the lipid membrane via a hydrophobic stretch of amino acid residues located usually in the *C*-terminal part of the polypeptide; in most cases the *C*-terminal domain is intracellular, but the orientation of several leucocyte antigens is reversed, with *C*-terminal part being extracellular. Among these 'upside-down' antigens (sometimes called 'type II membrane proteins') are transferrin receptor, CD23 and heavy chain of the 4F2 activation antigen.

The second type of association with membrane is via a phospholipid (phosphatidylinositol) moiety covalently bound usually to a hydrophobic region in the *C*-terminal part of the polypeptide chain (see the review by Low, 1987). It is not exactly known what are the basic functional differences between this latter type of membrane proteins and the more common previous type, but it is conceivable that both types may greatly differ in their lateral mobility in the membrane plane, in their potential to be modulated and to associate with intracellular components. Examples of these phos-

pholipid-anchored leucocyte molecules are Thy-1, CD9, probably CD10, decay accelerating factor and one form of LFA-3.

In many cases soluble forms of otherwise membrane-associated leucocyte molecules occur. Sometimes, these are translation products of alternatively spliced mRNA from which the membrane-spanning segment is absent. The best known example is immunoglobulins, and a similar situation was described for decay accelerating factor (Caras *et al.*, 1987). It seems likely that soluble Fc receptors ('immunoglobulin binding factors') are similarly related to the membrane-bound Fc receptors (MacLean *et al.*, 1984).

In other cases the soluble forms arise by proteolytic cleavage of the originally membrane-bound molecule which is in agreement with the usually observed smaller size of the soluble forms. This is probably the case for CD25 (Rubin *et al.*, 1986), CD8 (Fujimoto *et al.*, 1984), CD28 (Gmünder & Lesslauer, 1984), CD23 (Thorley-Lawson *et al.*, 1986), CD21 (Myones & Ross, 1987), CDw32 (Looney *et al.*, 1986; Vaughn *et al.*, 1985) and CD35 (Yoon & Fearon, 1985). It is not clear what is the relation between the soluble and membrane-bound forms of CD14, as both appear to be of identical size (Bažil *et al.*, 1986).

Conceivably, soluble forms of phosphatidylinositol-anchored molecules can be produced by enzymic cleavage of the lipid moiety; soluble CD10 might be perhaps produced in this way (Komada *et al.*, 1986).

It is not clear what are the physiological roles of the soluble forms. Soluble forms of CD9 (Zeleznik *et al.*, 1987) and CD23 (Swedeman & Thorley-Lawson, 1987) were reported to have growth-factor activities, and soluble CD25 may regulate the level of interleukin-2 (Rubin *et al.*, 1986). The serum level of soluble CD14 is higher in some patients, especially those with some autoimmune diseases (Bažil *et al.*, 1986), but the relevance of this finding is so far unclear. Soluble forms of Fc receptors immunoglobulin binding factors have possibly immunoregulatory functions (MacLean *et al.*, 1984) and soluble forms of T cell receptors may function as antigen-specific suppressor factors (De Santis *et al.*, 1987).

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Note added in proof

A number of relevant papers have been published since submitting the manuscript. Among them are, e.g., those describing diversity of TCR γ/δ [Konig *et al.* (1988) J. Exp. Med. **167**, 676–681; Elliot *et al.* (1988) Nature (London) **331**, 627–630]; cloning and sequencing of cDNA coding for CD20 [Einfeld *et al.* (1988) EMBO J. **7**, 711–718; Tedder *et al.* (1988) Proc. Natl. Acad. Sci. U.S.A. **85**, 208–212], CD28 [Aruffo & Seed (1987) Proc. Natl. Acad. Sci. U.S.A. **84**, 8573–8577], α-subunit of human high-affinity IgE receptor [Shimizu *et al.* (1988) Proc. Natl. Acad. Sci. U.S.A. **85**, 1907–1911], CD14 [Goyert *et al.* (1988) Science **239**, 497–499], ICAM-1 [Simmons *et al.* (1988) Nature (London) **331**, 624–627], Fc receptor CDw32 [Stuart *et al.* (1987) J. Exp. Med. **166**, 1668–1684], CD11c [Corbi *et al.* (1987) EMBO J. **6**, 4023–4028], ζ chain of CD3 [Weissman *et al.* (1988) Science **239**, 1018–1021] and rat leukosialin/CD43 [Killeen *et al.* (1987) EMBO J. **6**, 4029–4034]. Five different groups obtained recombinant soluble CD4 [reviewed by Weiss (1988) Nature (London) **331**, 15]. Structure of CD37 antigen was described in more detail [Schwartz-Albiez *et al.* (1988) J. Immunol. **140**, 905–914], association of CD5 and CD21 molecules in leukaemic cells was reported [Bergui *et al.* (1988) Eur. J. Immunol. **18**, 89–96], as well as apparent association of a small fraction of CD4 molecules with TCD–CD3 complex [Anderson *et al.* (1988) J. Immunol. **140**, 1732–1777]. Several new molecules apparently involved in T lymphocyte stimulation were identified, such as antigen 5/9 [Risso *et al.* (1987) Cell. Immunol. **110**, 413–424], TH5.2 [Thieme *et al.* (1987) Cell. Immunol. **108**, 28–41] and TM1 [Hara *et al.* (1988) J. Immunol. **140**, 1028–1033]. Finally, an antigen called E2 participating probably in T cell adhesion [Bernard *et al.* (1988) J. Immunol. **140**, 1802–1807] and possibly another CD4-binding receptor [Beretta *et al.* (1987) Eur. J. Immunol. **17**, 1793–1798] have been described recently.