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Editorial comment

CD antigens as promising tools for the functional analysis of solid tumours

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Homo- and heterotypic cell/cell interaction, cell/matrix adhesion, as well as signal reception and transduction via hormones and cytokines are mediated by cell surface molecules. For this reason, these structures are of paramount interest for all scientists working in the fields of cell and tumour biology. Monoclonal antibodies against these molecules are most suitable probes for their detection, isolation and functional analysis. However, both classical methods, the biochemical, by isolating a cell membrane component and subsequently raising an antibody against it or, alternatively, defining an antibody by the antigen it precipitates, have been fraught with a multitude of difficulties, and still are. Yet they remain the best approach to get hold of a molecular structure and to investigate its function. This kind of generating knowledge of one molecule might take years of life of an individual scientist or else requires open-hearted cooperation within the scientific community to speed up this process. Research in membrane antigens on epithelial and mesenchymal cells is – with few exceptions – still solipsistic and has led to a plethora of publications on antibodies and antigens. These are more or less ill-defined. However, the outstanding joint efforts made by the contributors and participants of the *International Workshops and Conferences on Leukocyte Differentiation Antigens* have provided us with up to date 78 different cell surface molecules (nearly all of them biochemically defined and a considerable number of them even cloned) together with a large number of well characterized hybridoma clones producing antibodies against them. These antibodies carry an official CD designation as do the antigens they define. The nomenclature states that the CD number identifies a clone officially assigned to it during one workshop (e.g., CD71 (BU54)) and the molecule (e.g., CD71 molecule) which may also carry other names (e.g., the CD71 antigen corresponds to the transferrin receptor). The term anti-CD (e.g., anti-CD71) should not be used to cite an antibody since in the strict sense, this designation implies anti-idiotypic reactivity. A 'w' before the number indicates a provisional clustering, an alphabetical index behind the number determines subtypes of very closely related molecules (e.g., isoforms) joined together in one cluster (Knapp et al. 1990).

As a consequence of their characterization as antibody-defined cell surface structures, CD molecules are very heterogenous. The CD list comprises membrane bound enzymes, members of a family of cystein rich molecules acting as cytokine receptors, phosphoinositol anchored molecules involved in signal transduction, activation antigens, members of the comprehensive immunoglobulin gene superfamily predominantly acting as adhesion molecules, and several members of the integrin family.

It has become increasingly clear that most of the CD molecules are not specific for a single haematopoietic lineage and a considerable number of them are not leukocyte restricted (Knapp et al. 1989). The so-called "non-lineage" and platelet-associated antigens, in particular, are very interesting molecules which are also expressed on various types of epithelial and mesenchymal cells. These are readily available for the functional characterization of solid tumours. What has been done so far in this respect will be outlined briefly.

CD10 antigen is identical with neutral endopeptidase, an enzyme cleaving peptide like angiotensin, bradykinin, encephalins, oxytocin, and substance P (for review: Le Bien and McCormack 1989). CD10 has been detected on renal tubular and glomerular cells (Metzgar et al. 1981) on the brush border of intestinal epithelium (Treijdosewicz et al. 1985), on myoepithelial cells (Gusterson et al. 1986), and in cultured human fibroblasts (Braun et al. 1983), in a germ cell tumour (Brox et al. 1986), on glioma cells (Monod et al. 1989), on melanoma cell lines (Carrel et al. 1983) and in various types of sarcomas (Mechtersheimer et al. 1989). *CD13* is identical with aminopeptidase N (Look et al. 1989a) an enzyme of the brushborder membranes of the small intestine and renal proximal tubules and was also found on synaptic membranes of the central nervous system. It is further ex-

pressed on fibroblasts, osteoclasts, and bile duct canaliculi (Hogg et al. 1984) and has been detected on several carcinoma cell lines (Look et al. 1989b; Finstad et al. 1985) and in various sarcomas (Mechtersheimer and Möller 1990a). Like CD10, CD13 is a member of the family of zinc-binding metalloproteases to which a role in cancer invasion and metastasis has been ascribed (reviewed by Murphy et al. 1989). The *CDw75* antigen, known as LN-1 antigen to many pathologists, was recently identified as an alpha 2,6 sialyltransferase. It is expressed on a large spectrum of nonlymphoid cells (Möller and Mielke 1989) and has been described in subsets of ductal and lobular epithelium of normal mammary gland and of mammary fibroadenomas (Mechtersheimer et al. 1990b).

The *CD40* molecule, a B lymphocyte-associated antigen, is now assigned to the family of cystein rich molecules involved in signal transduction (Paulie et al. 1989) comprising the receptors for tumour necrosis factor and nerve growth factor. Although the ligand of CD40 is still unknown, it is very likely to be a cytokine (Clark 1990). CD40 antigen has been found expressed on several types of epithelial cells (Möller and Mielke 1989) as well as on colon carcinomas and melanomas (Ledbetter et al. 1987). *CD30*, better known as the Ki-1 antigen, has become an important lymphocyte activation antigen defining Hodgkin cells (Stein et al. 1982) and the so-called Ki-1 lymphomas (Stein et al. 1985; O'Connor et al. 1987). It has been suggested that CD30 might also be a cytokine receptor. Outside the lymphatic system, CD30 has been observed in embryonal carcinomas (Pallesen and Hamilton-Dutoit 1988), in some other types of carcinoma and even in melanomas (Schwarting et al. 1989). Moreover, Ki-1 reactivity has been detected in a subset of sarcomas of different histogenesis (Mechterheimer and Möller 1990c). Although no longer lineage restricted, the CD30 antigen might nevertheless become helpful in defining special variants or subtypes within otherwise defined tumour entities.

The linkeage of cell surface molecules via glycosyl phosphatidylinositol is a characteristic of another group of molecules involved in signal transduction (for review: Low 1989). *CD24* belongs to this category (Fischer et al. 1990); it is a single chain sialoglcycoprotein expressed on endothelial and some neural and chromaffin cells as well as on neuroblastoma cell lines (Sugimoto et al. 1984; Ebener et al. 1990). In addition, the CD24 molecule has been found in primitive subcortical nephrons of fetal and in distal nephrons of adult kidneys (Platt et al. 1983). *CD73* is identical to ecto-5'nucleotidase, another glycosyl phosphoinositol-anchored molecule serving as purine salvage enzyme. The CD73 molecule is expressed on a comprehensive panel of non-haematopoietic cell types (Thompson et al. 1990). In addition, it has been observed on a subset of fibrocytes/fibroblasts and, recently, a positive correlation between the expression of estrogen receptor of neoplastic cells and CD73 expression of stromal fibroblasts of breast carcinoma has been found (Krüger et al. 1991). Another molecule differentially expressed on fibrocytes/fibroblasts and also detectable on endothelial cells is the haematopoietic progenitor antigen *CD34*, the structure and exact function of which are still unknown (Sutherland et al. 1988; Fina et al. 1990; Schlingemann et al. 1990).

The steadily growing immunoglobulin gene superfamily comprises several well-known surface molecules, for example, carcinoembryonic antigen (CEA), the secretory component of IgA, HLA-molecules, and the CD "classics" and T cell antigens CD1, CD2, CD3, CD4, and CD8 (for review: Williams and Barclay 1988). Recently, CD31, CD54, CD56, CD57, and CD58 have been included in this family. These molecules are all mainly involved in intercellular adhesion phenomena. CD31 has recently be found to show a strong sequence homology with CEA (Simmons et al. 1990). Like CD34 and *CD36* molecules it is detectable on vascular endothelial cells and, in addition, in lymphatic endothelium (Parravicini et al. 1989). *CD54*, which corresponds to the intercellular adhesion molecule 1 (ICAM-1) is a broadly distributed structure also expressed on endothelial cells, fibroblasts and several epithelial cell types (Dustin et al. 1986). It has been shown to be the natural ligand for the lymphocyte function molecule 1 (LFA-1) which, in turn, is identical with the CD11a/CD18 heterodimer (Makgoba et al. 1989). CD54 is exploited as receptor by rhinovirus (Staunton et al. 1988); a potential role of CD54 in metastasis formation of malignant melanoma has recently been suggested (Stade et al. 1989). *CD56* is identical to the neural cell adhesion molecule (NCAM) known to be involved in embryonic development and cell migration (Lanier et al. 1989); it is transiently expressed in embryonic smooth (Akeson et al. 1988) and diseased adult skeletal muscle cells (Walsh and Moore 1985). As Roth et al. (1988) pointed out, variations in length of polysialic acid chains on this molecule accounts for the differences in its adhesive potential observed during embryogenesis. CD56 is expressed in nephroblastoma (Roth et al. 1988) and turned out to be the antigen bound by many antibodies co-recognizing small-cell lung carcinoma and neuroblastoma (Patel et al. 1989). Antibodies of the *CD57* cluster detect a sulphated carbohydrate epitope on NCAM (Kruse et al. 1984) and also recognize the myelin associated glycoprotein (MAG; McGarry et al. 1983). This situation explains the complex binding spectrum of CD57 antibodies, the prototype clone of which (NKH-1) was initially published as a marker for natural killer cells. The list of solid tumours expressing CD57 comprise small-cell lung carcinoma (Bunn et al. 1985), neurogenic tumours (Smolle et al. 1985), prostatic adenocarcinomas (Rusthoven et al. 1985), spindle cell sarcomas (Swanson et al. 1987), and Ewing's sarcoma of bone (Pinto et al. 1989). *CD58* corresponds to the lymphocyte function antigen 3 (LFA-3), existing in a transmembrane and a phosphatidylinositol anchored form. It is broadly distributed among non-haematopoietic cell types and is the natural ligand of the T lymphocyte specific CD2 molecule. The physical interaction of CD58 and CD2 induces antigen-independent aggregate formation and T cell activation (Makgoba et al. 1989). The observation of sporadic loss of CD58 in colon carcinoma (Smith et al. 1989) and transitional cell carcinoma (Nouri et al. 1990) has led to the concept

that an abrogation of CD58/LFA-3 might contribute to the putative escape of tumours from cytotoxic T cell attack (Smith et al. 1989).

Clustered adhesion molecules outside the immunoglobulin gene superfamily are CD36, CD44, and members of the integrin family. *CD44* is mainly involved in cell adhesion and T cell activation. It has been independently described under different names including "phagocytic glycoprotein (Pgp-1)", "extracellular matrix receptor III (ECM-III)", "B cell p80 antigen", and "Hermes class of lymphocyte homing receptor" (Haynes et al. 1989). It has a cartilage proteoglycan homology domain, may be involved in CD2/CD53 interaction, is broadly distributed on non-haematopoietic cells, and may promiscuously bind to multiple molecules. Recent experimental data suggests a major role of CD44 in metastatic tumour growth (Walter et al. submitted). *CD36*, identical with glycoprotein IV, which is a collagen receptor on platelets (Tandon et al. 1989), was also found on epidermal cells of the stratum granulosum in normal and diseased skin (Parravicini et al. 1989; Lisby et al. 1990), on endothelial cells and adipocytes (von dem Borne et al. 1989). A subgroup of integrins is traditionally called "very late antigens" (VLA), since it is expressed on T cells during the "very late" phase of activation. These non-lineage antigens are expressed on a large number of cell types and are crucially involved in cell/matrix interaction (for review: Hemler 1990). Three members of this complex family of heterodimeric molecules carry cluster designations: VLA-2 (CD29/CD49b), VLA-4 (CD29/CD49d), and VLA-6 (CD29/CD49f), the common β chain of which is *CD29* and the different α chains are joined in the *CD49* cluster. A downregulation/loss of these molecules in tumour cells might cause a disturbed cell/matrix interaction that might augment their invasive porperties. It could recently be shown that CD29/CDw49b molecules tend to be lost in colorectal carcinomas and that a reduced CDw49b expression statistically correlates with Dukes' stage C/D (Koretz et al. 1991).

The comprehensive study by *G. Mechterheimer* in this issue of *Virchows Archiv A* is a very promising approach to characterize normal mesenchymal cells and soft tissue tumours by CD molecules. As she points out, each morphologically defined type of normal adult mesenchymal cell can also be defined by the complex profile of CD molecules expressed. Disappointingly but not unexpectedly, immunophenotypic patterns emerging in neoplasia are far less distinct and discriminative. This is in accordance with results of comparable studies in other tumour entities (for example malignant lymphomas, cf. Mielke and Möller 1991). Nevertheless, several antigenic constellations that emerged from her study will surely gain practical application since they seem to be of help in solving a number of differential diagnostic problems in soft tissue tumour typing. Apart from this pragmatic point of view, abnormalities in antigen expression may turn out to be important clues for a better understanding of the biology of soft tissue tumours and, hence, ultimately, of the individual tumour. Against the background of obvious or alleged histogenetic relationships of soft tissue tumours to normal cellular counterparts, deviant antigen expression on tumour cells might be due to i) down- or upregulatory events (e.g., induced by local or systemic cytokine effects), ii) regulatory regression towards earlier developmental stages or, iii) irreversible (regulatory, chromosomal) defects. For the functional understanding of soft tissue tumours – hopefully justifying new routes for therapeutic intervention! – much remains to be done: the results of *G. Mechtersheimer* will have to be confirmed by studying even larger series of soft tissue tumours. Moreover, sarcoma cell lines will have to be investigated for their immunoprofile and its dynamics, and, last but not least, fetal development will once again have to be studied with respect to CD antigen expression during histo- and organogenesis.

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