American Journal of Pathology, Vol. 160, No. 1, January 2002

Short Communication

Characterization of Prostate Cell Types by CD Cell Surface Molecules

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A set of monoclonal antibodies raised against lymphocyte cell surface molecules, the cluster designation (CD) antigens, was used to distinguish the constituent cell types of the prostate. The luminal secretory epithelial, basal epithelial, fibromuscular stromal, nerve sheath, and endothelial cells express distinctive complements of cell surface molecules that were identified by immunohistochemistry using 152 commercially available antibodies. Many of the CD antibodies stained lymphocyte populations in the prostate. These lymphocyte populations were grouped into abundance classes of rare, moderate, and high. Some of these molecules are expressed by multiple cell types, both parenchymal and lymphoid; others are expressed by only one cell type. Distinctive patterns of CD expression, which are most similar to the expression pattern of prostate luminal cells, also characterize a small series of Gleason score 6 prostate cancers. The cell-type specificity of CD molecules increases the prospect of isolating specific cell populations, using such techniques as laser capture microdissection and flow cytometry, for cell-specific molecular studies. *(Am J Pathol 2002, 160:37–43)*

Based on standard histology classification criteria there are more than 250 different cell types in the human body. The prostate gland has two generic cell types: epithelial and stromal. Epithelial cells form glands that are composed of the luminal secretory and basal cell types and rare neuroendocrine cells. The stroma surrounding the prostatic glands contains smooth muscle cells and fibroblasts.[1] Blood vessels, peripheral nerves and ganglia, and tissue infiltrating white blood cells are additional constituent cell elements of the normal adult human prostate. The fact that the prostate is a solid organ makes problematic the isolation of a specific cell type for study. This challenge forces us to rely on the use of cultured cell lines and animal models to investigate cell-specific changes in such prostatic diseases as cancer. Unfortunately, these *ex vivo* surrogates often do not faithfully represent the biology of cells *in vivo* in several ways, including cytogenetic changes and levels of gene expression. To identify and characterize prostate cancer cell-associated genes, for example, one would ideally compare the cohort of expressed genes, or the transcriptome, of a pure population of cancer cells with that of a pure population of non-neoplastic epithelial cells. However, the current practice is to characterize the transcriptome of fragments of cancer tissue rather than that of specific cell populations. Consequently, transcriptomes of tissue samples of carcinoma represent such non-carcinoma cells as stromal cells and lymphocytes in addition to carcinoma cells.

To characterize the transcriptome and biology of specific cell populations entails the identification and isolation of the respective specific cell populations from tissue using such techniques as flow cytometry or laser capture microscopy. Using these techniques a phenotypically homogeneous population of cells can be obtained. Monoclonal antibodies to cell surface antigens can be used as tools to isolate specific cell types. The cluster designation (CD) cell surface molecules are potentially specific targets.[2] Expression levels of CD antigens appear to both reflect the biology of prostate carcinoma and distinguish prostate cancer cells lines.[3,4] These molecules, of which there are >170, are defined by monoclonal antibodies that were originally raised against human leukemic cells (http://www.ncbi.nlm.nih.gov/prow/). Since many of these molecules are expressed in other cell types as well as lymphoid cells, we postulated that the parenchymal cells of the prostate would express unique patterns of CD. This study addresses our postulate.

Supported by the The Association for Cure of Cancer of the Prostate, Santa Monica, CA (CaP CURE Foundation).

Accepted for publication September 28, 2001.

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Materials and Methods

All 152 monoclonal CD antibodies (mAbs) that were used in this study, [mouse IgG_1, IgG_{2a}, IgG_{2b}, IgG_3, IgM, and rat IgG_{2a} (CD49f, CD121a), IgG_{2b} (CD104, CD132)], were obtained from PharMingen (San Diego, CA) except for αCD49a, which was purchased from Endogen (Woburn, MA). Additional monoclonal antibodies to antigens that have not yet been assigned a CD number (cell membrane antigenic receptor TCR$\gamma\delta$, mannose receptor (R), NKB1, perforin, fusin (CXCR4), integrin β_7, interleukin (IL)-8RB, IL-10R, IL-12RB1, fMLPR, MDR1, epidermal growth factor receptor (EGFR), nerve growth factor receptor (NGFR), LAP, and LMP-1) were used. Isotype control was provided by monoclonal antibody clones MOPC21 (IgG_1) and G155–178 (IgG_{2a}). The cases that formed the basis of this study were 10 randomly selected radical prostatectomy specimens with prostate adenocarcinoma that had a Gleason score of 6 (3 + 3). Blocks of unfixed tissue containing both carcinoma and non-neoplastic prostate parenchyma had been frozen in OCT immediately after surgical resection and stored in a -80^{o} freezer. Immunohistochemistry was performed on serial 5 micron-thick, acetone-fixed, frozen sections. Sections from at least five specimens were stained with each primary antibody.

Immunolocalization of CD antigen was done using an indirect avidin-biotin-peroxidase method. Antibodies were used at a concentration of 8 ng/μl or less following a protocol described in a kit from Vector Labs (Burlingame, CA).[5] Secondary antibodies used for chromogen detection were either biotinylated anti-mouse IgG (BA-2000, Vector), which also reacts against rat IgG antibodies, or anti-mouse IgM (BA-2020). Reaction product was detected by incubating sections in a solution of avidin-biotin-peroxidase, followed by a solution of diaminobenzidine (Research Genetics, Huntsville, AL). The sections were lightly counterstained with hematoxylin.

Extent of immunoreactivity was determined by estimating the percentage of cells of a specific histological phenotype that expressed the antigen in five randomly selected fields at a final magnification of 40X (ocular 10X; objective 4X). The percentage of stained cells in a given section was averaged. The range in the percentage of stained cells in the different sections was tabulated and the standard deviation was calculated from these values (Table 2). A paired *t*-test compared extent of expression between benign epithelial cells and cancer cells for significance at the 95% level. Staining of individual cells was interpreted as intense immunoreactivity, faint immunoreactivity, or absent reactivity. The slides were reviewed simultaneously by both authors, who reached a consensus in evaluating each immunostain.

Results

The reactivity of 152 mAbs is summarized in Figure 1. Since the mAb to CD51/61 reacts with the complex and CD-specific mAbs to CD51 and CD61 were not used, results are listed under the single heading of CD51/61. Of these mAbs, 77 reacted with lymphocytes, 36 with epithelial cells (either luminal/secretory or basal), 22 with fibromuscular stromal cells, and 30 with specialized stromal cells (endothelial, nerve sheath, and/or perineural). Although neuroendocrine cells are presumably present, representing <5% of prostate acinar epithelial cells, no attempt was made to distinguish neuroendocrine cells from the luminal/secretory or basal cells. Parenchymal cells of different histological types expressed the same CD antigen, as is detailed in Figure 1. A small number of CD antigens were expressed by only one cell type (Table 1).

The extent and intensity of immunoreactivity for CD antigens varied (Figures 2 and 3; Table 2). Some antigens were expressed intensely by virtually all cells of a specific histological type, eg, CD107a by epithelial cells and CD49a by fibromuscular stromal cells. In contrast, the extent of immunoreactivity of other antigens in a specific cell type varied widely both within a given section and between sections. The pattern of expression by cells also varied. Most luminal cell antibodies stained both cytoplasm and cell membrane in a pan-membrane pattern. In contrast, CDw75 was expressed only in the apical membrane of luminal cells. No differences in expression of CDs by parenchymal cell were seen by zone, by proliferative state of glandular epithelium (proliferative *vs*. atrophic), or by the nodularity of the parenchyma of the transition zone (nodular *vs*. non-nodular).

In general, the majority of carcinoma cells also expressed CD antigens expressed by luminal cells. However, CD13 and CD10 were exceptions; although expressed intensely by the secretory cells, none of the carcinomas studied expressed these antigens. None of the antigens expressed by basal cells and not by secretory cells were expressed at a convincing intensity of immunoreactivity by the carcinomas. No CDs expressed only by non-epithelial cells were expressed by carcinomas.

Regarding lymphocytes, CD45 identified virtually all these cells; other antibodies reacted with subpopulations of lymphocytes that were either rare or moderate in abundance. Most lymphocytes were localized to the stroma. In exception, the majority of $CD8^+$ cells appeared to infiltrate the glandular epithelium.

Discussion

We have identified a subset of greater than 150 commercially available mAbs against cell surface CD molecules that can be used to identify the different prostate cell types, both parenchymal and lymphoid. Our findings agree, for the most part, with previous studies of CD expression in the prostate, ie, CD10,[6] CD13,[7,8] CD26,[7,9] CD38,[10] CD82,[11] CD104 and other integrins,[12] and CD107a/b.[13] Some of our findings contrast with prior reports. Although a prior publication reported lack of expression, we identified basal cell expression of CD55.[14]

A problematic aspect of trying to isolate genes and gene products from human cancer tissue is that obtaining a pure population of cancer cells using microdissec-

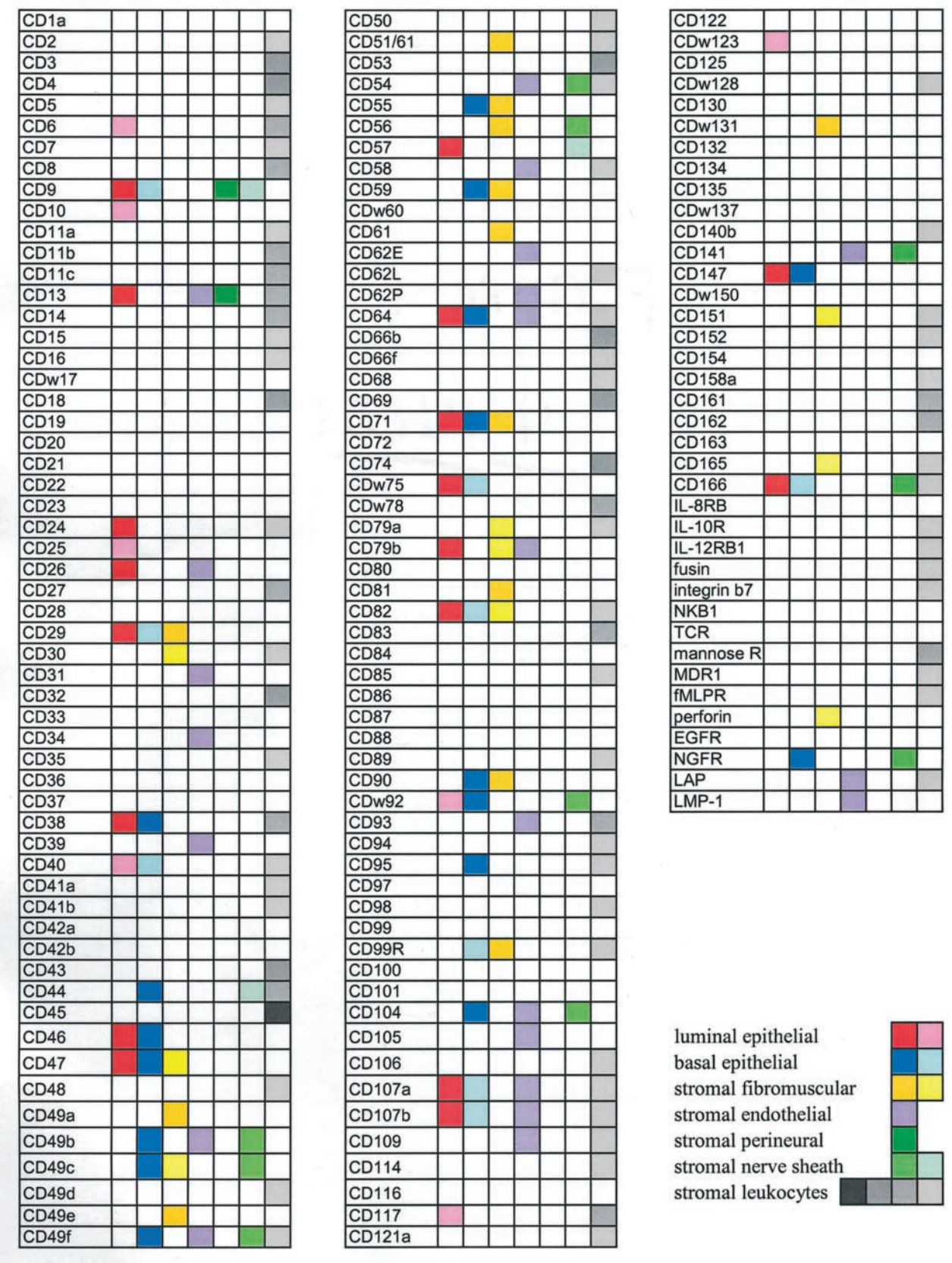

Figure 1. Prostate cell-type specificity of CD molecules. Reactivity is indicated by colored boxes. Lighter hues of the parenchymal cell markers indicate faint or equivocal staining. The color code for respective cell types (intense *vs.* faint) is: red/rose for luminal epithelial cells, blue/turquoise for basal epithelial cells, gold/yellow for fibromuscular stromal cells, lavender for endothelial cells, and lime/light green for nerve sheath cells. Perineural cells only stained intensely when stained (bright green). The lymphocyte gray scale indicates lymphocyte abundance; the darkest shade designates the most abundant CD types. Low abundance (the two lightest shades of gray) is defined as <10 lymphocytes, moderate abundance as 10 to 100 lymphocytes, and high abundance as >100 lymphocytes per 40X field of magnification, respectively.

Table 1. Number of CDs Expressed by Each Cell Type

Cell type	Number of CDs expressed	Number of CDs expressed only by specified cell type	Cell type-specific CD antigens
Luminal/secretory	25	2	10, w123
Basal	26	0	
Fibromuscular stromal	22	5	49a, 49e, 61, 81, w131
Endothelial	22	7	31, 34, 39, 62E, 62P, 105, LMP-1
Perineural	2	0	
Nerve sheath	13	0	
Lymphocyte	77	52	43, 45, etc. (see Figure 1)

"Expressed" cites the number of CD antigens expressed by the specified cell type; "Expressed only by specified cell type" cites the number of CD antigens that are expressed only by the listed cell type. The specific CD antigens that are expressed only by one cell type are listed in the final column.

tion is impossible; stromal cells are invariably included in extracts of tissue. In characterizing the sets of CD antigens that are expressed by the prostate cell types, we have found tools that might be used to isolate single types of cells. Labeled mAbs to cell surface molecules can be used in either a flow cytometric sorting method or by laser capture microdissection[15] to identify and isolate cells of a single phenotype. We have previously demonstrated the value of using flow sorting to separate a specific CD-expressing cell population from which a cDNA library was made (http://pedb.org). Laser capture microscopy can be made more specific by using antibodies that are labeled with a precipitating substrate that can be visualized at the light microscopic level. The laser beam can be directed to capture only those cells that are immunostained.

There are potential problems with this approach. Any technique that isolates epithelial cells from the stroma may introduce artifacts in the gene expression profile. As previously reported, separation of normal prostate luminal cells from the prostate stroma is followed by markedly decreased expression of prostate specific antigen within

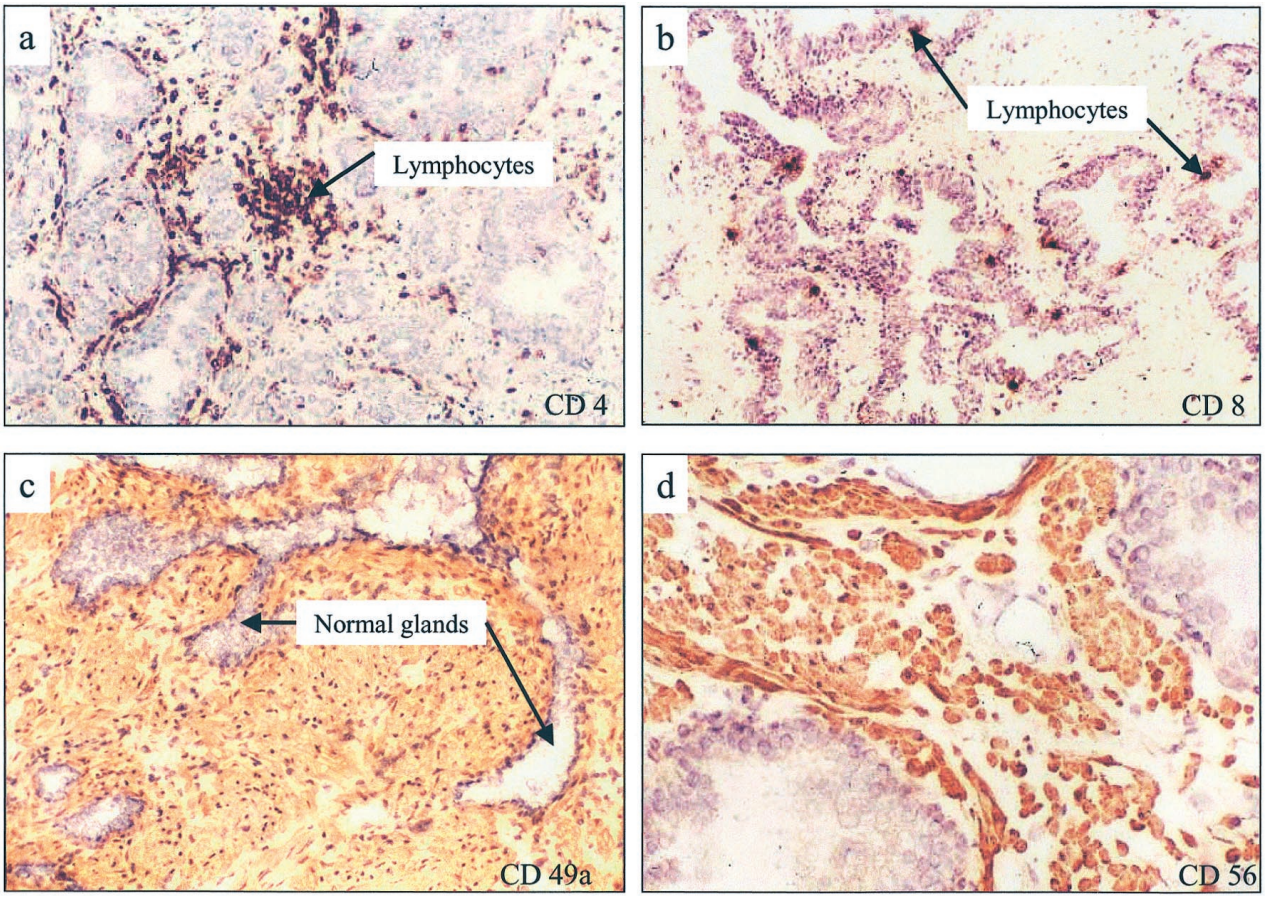

Figure 2. CD immunoreactivity of prostate cells (immunoreaction product red-brown; pale blue hematoxylin nuclear counterstain) in benign prostate (**a–d**). **a:** CD4 (T helper/inducer cells); focus of abundant $CD4^+$ lymphocytes between benign glands. **b:** CD8 (T cytotoxic/suppressor cells). Low abundance $CD8^+$ lymphocytes within the glandular epithelium. **c, d:** Fibromuscular stromal cells uniformly express CD49a (**c**) and CD56 (**d**). Glandular epithelial cells lack CD49a and CD56 immunoreactivity. Edematous stroma separates $CD56^+$ fibromuscular stromal cells in **d**.

Table 2. CD Expression by Prostate Parenchymal Cells (Excluding Lymphocytes) and by Prostate Cancers

CD	Normal epithelial	FM stromal	Spec. stromal	Cancer
CD6	85 ± 9			0
CD9	90 ± 10		67 ± 21	73 ± 10
CD10	80 ± 13			25 ± 5
CD13	93 ± 5		75 ± 13	5 ± 5*
CD24	71 ± 8			80 ± 7
CD25	47 ± 13			
CD26	97 ± 5		98 ± 3	90 ± 10
CD29	97 ± 3	100		95 ± 5
CD31			95 ± 7	0
CD34			95 ± 2	0
CD38	97 ± 5			100
CD39			65–80	
CD40	77 ± 13			ND
CD44	73 ± 13			0
CD46	90 ± 5			87 ± 8
CD47	90 ± 5	72 ± 8		ND
CD49a		100		100
CD49b	95 ± 2		95 ± 2	3 ± 2*
CD49c	90 ± 5	68 ± 8		ND
CD49e		97 ± 5		ND
CD49f	90 ± 5		87 ± 12	95 ± 5
CD51/61		80 ± 15		0
CD54			85 ± 8	0
CD55	80 ± 5	70–95		0
CD56		97 ± 5		0
CD57	75 ± 8			85 ± 5
CD58			90 ± 5	0
CD59	72 ± 8	92 ± 3		0
CD61		90 ± 5		0
CD62E			90 ± 5	0
CD62P			95 ± 5	0
CD64	90 ± 5		85 ± 9	95 ± 5
CD71	100	100	92 ± 5	100
CDw75	95 ± 5			ND
CD79a		58 ± 11		0
CD79b	85 ± 5	65 ± 5	92 ± 5	90 ± 5
CD81		85 ± 5		0
CD82	92 ± 5	75 ± 5		65 ± 15*
CD90	92 ± 5	75 ± 8		0
CDw92	90 ± 5		85 ± 5	ND
CD93			90 ± 5	0
CD95	92 ± 8			0
CD99R	53 ± 10	50 ± 8		0
CD104	92 ± 3		87 ± 5	0
CD105				0
CD107a	100			100
CD107b	100			100
CD109			90 ± 5	0
CD117	80 ± 5			ND
CDw123	80 ± 5			ND
CDw131		90 ± 3		0
CD141			87 ± 5	0
CD147	100			100
CD151		65 ± 18		0
CD165		63 ± 19		0
CD166	90 ± 5		90 ± 5	ND

*$p < 0.05$ (cancer *vs.* normal epithelial cells).

The percentage of cells of each category and of the 10 prostate adenocarcinomas that were studied are reported as ranges that were immunostained, with standard deviations. "Epithelial" includes luminal and/or basal cells; "FM stromal" cells are the fibromuscular stromal cells; "Spec. stromal" includes endothelial, perineural, and/or nerve sheath cells; ND, not done.

hours.[2] The solution to this potential problem is more rapid specimen processing. Furthermore, since many of the CD mAbs that react with non-lymphoid prostate cells immunoreact with other cell types, both parenchymal and lymphoid, care must be taken to ensure that only a single type of cell is being studied and characterized. A limitation to our study is that we cannot be sure that all isoforms of a given gene are immunostained. For instance, splice variants of CD44 have different patterns of expression in the prostate.[16] We do not know if our monoclonal anti-CD44 detects all splice variants of CD44.

There are additional benefits of developing a CD catalogue of the prostate. First, a set of markers is made available to use clinically in both diagnosing cancer and in potentially providing prognostic information. Second, knowing the pattern of CD expression may provide clues to the function(s) of the specific cell types and to understanding phenotypic differences between cell lines and intact tissue. And, third, questions of histogenesis can be addressed with more certainty.

There is precedence in the leukemia literature regarding the use of CD antigens to diagnose prostate cancer. Antigens not co-expressed in non-neoplastic hematopoietic cells may be co-expressed in leukemia.[17] Identification of such anomalously co-expressed antigens provides a tool for diagnosing leukemia. These observations raise the prospect of diagnosing prostate cancer based on co-expression of CD antigens that are not normally co-expressed, eg, basal cell antigen CD49b and luminal cell antigen CD57. We are investigating whether this phenomenon occurs in prostate carcinoma.

Regarding cell function, since expression of CD molecules is linked to the physiological state of cells,[18] these molecules may be used to study cell function and cellular differentiation. At least some of the functions of the CD molecules have been determined. For instance, the integrin complexes and their ligands are well characterized.[19] CD49a/CD29 ($\alpha_1\beta_1$), whose ligand is laminin, is present only on stromal cells. CD49b/CD29 ($\alpha_2\beta_1$), whose ligand is collagen, is present only on basal cells. This complex has been shown to promote adhesion of prostatic cancer cells to bone cell matrix.[20] The prostate cancer cell lines LNCaP, PC3, and DU145 all express this integrin complex.[4] CD47 may promote tumor cell chemotaxis;[21] all three prostate cancer cell lines tested are positive for this molecule. CD46, CD55, and CD59 appear on epithelial cells; all three molecules can be detected in proliferating cells.[4,22] CD71, CD81, CD95, CD147, and CD98 appear to play a role in cell proliferation. These molecules are found in cultured epithelial and stromal cells.[23,24]

Regarding the influence of the *ex vivo* state on gene expression, we have reported that cultured stromal fibromuscular cells or cultured epithelial cells express a set of the CD molecules that is different from the CD pattern of these respective cell types in tissue. For instance, CD44, CD13, and other "non-stromal" markers are found in cultured stromal cells.[24] A marker that is not found by immunohistochemistry in the prostate, CD98, is expressed by cultured epithelial cells and by cancer cell lines (unpublished data). Since expression of CD98 and of some other CDs is common to non-confluent cultured cells of all types, their expression is likely to be associated with cell proliferation.

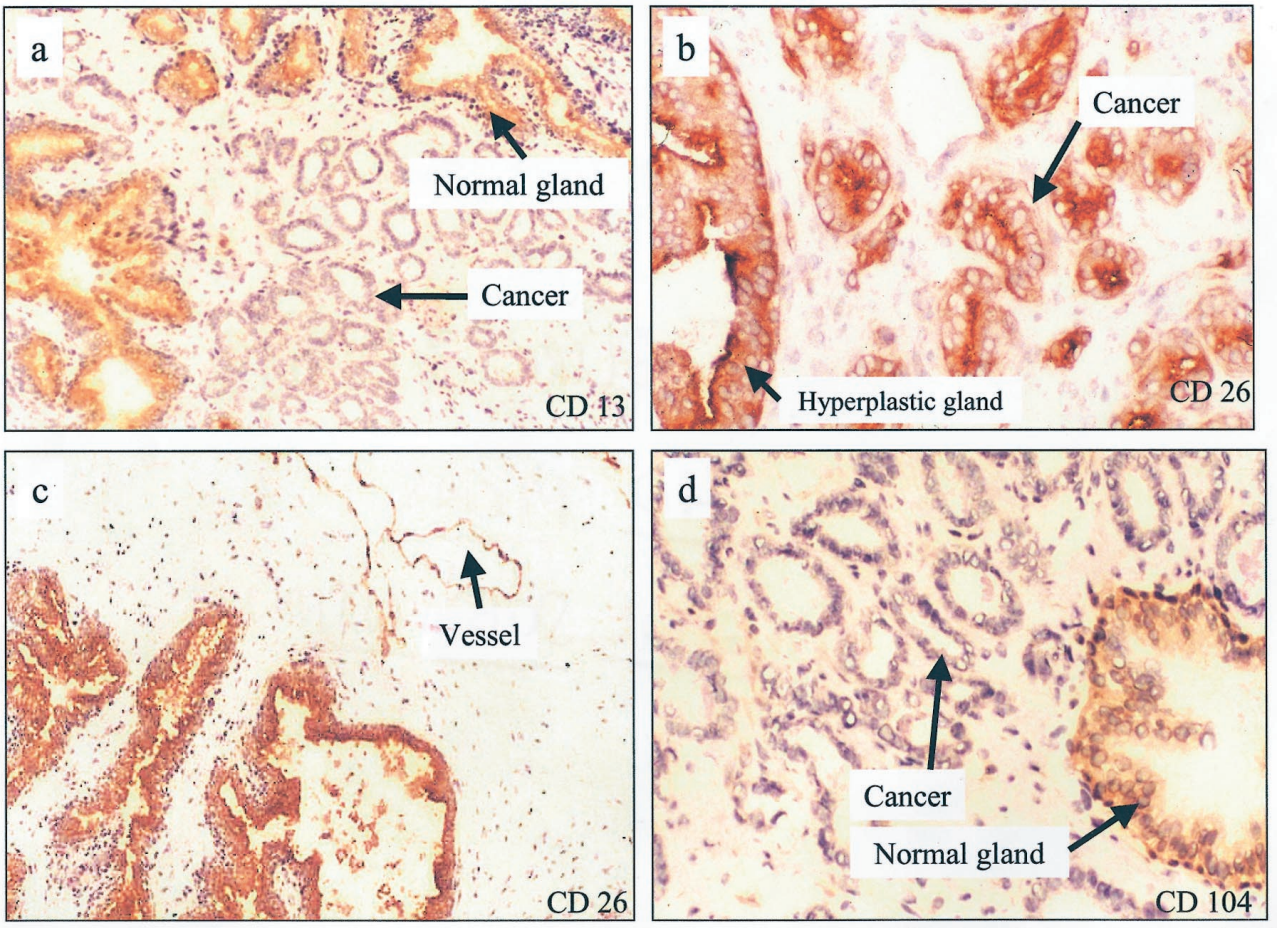

Figure 3. CD immunoreactivity of cells (immunoreaction product red-brown; pale blue hematoxylin nuclear counterstain) in prostate cancer (**a–d**). **a:** Luminal epithelial cells express CD13 and prostate carcinoma cells between benign glands lack immunoreactive CD13. **b:** Both prostate cancer cells and luminal cells of a benign gland that exhibits epithelial hyperplasia express CD26. **c:** The luminal secretory cells and endothelial cells express CD26. **d:** Cancer cells fail to express CD104, which is a basal cell marker.

A comparison of the CD profiles of non-neoplastic cells with profiles of cancer cells gives support to the hypothesis that prostate carcinoma cells arise from luminal rather than basal cells. Most primary tumors contain $CD57^+$ cancer cells; these cells are not stained by the basal cell markers CD44, CD104, or CD99R. One marked difference between $CD57^+$ cancer cells and $CD57^+$ luminal cells is the absence of CD13 expression in the former.

There are not many reports on the types of lymphocytes that populate the prostate,[25,26] even though inflammatory diseases of the prostate are a cause of morbidity. We have observed a great diversity of white blood cell populations as shown by the different CD antibodies. It would be interesting to compare the lymphocyte types and their abundance in normal prostate tissue with diseased prostate.[27,28] The presence of T-cell markers such as CD6 in epithelial cells is not unexpected since T-cell receptor transcripts have been found in prostatic epithelial cells.[29]

In summary, we have demonstrated the utility of CD molecules in the phenotyping of prostate cell populations. Specific cell populations can be readily identified and, potentially, isolated from tissue by flow cytometry or laser capture microdissection. Although we have studied a small series of prostates for tumor cell reactivity, a systematic study of a large number of cases is required to characterize the reactivity of the differentially expressed CD molecules in prostate carcinomas of different grades, volumes, and stages. This task can be productively carried out with the use of tissue microarrays.[30] In ongoing investigations we have shown that within a populations of cells of a single histological type are cells that have different CD profiles. These molecules, augmented by newly discovered cell surface molecules such as PSCA[31] or STEAP[32] and other previously characterized antigens,[33] provide a set of potentially useful markers for prostate cell isolation and characterization, and for disease diagnosis.

Acknowledgments

We are greatly indebted to Susan Saiget of PharMingen and our undergraduate students Michael Feddersen and Laurie Nakashima for their contributions. We thank Agnes Gawne and Dr. Martine Roudier for help with computer graphics.

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