Prostate Stem Cell Antigen Is Overexpressed in Human Transitional Cell Carcinoma

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Abstract

Prostate stem cell antigen (PSCA), a homologue of the Ly-6/Thy-1 family of cell surface antigens, is expressed by a majority of human prostate cancers and is a promising target for prostate cancer immunotherapy. In addition to its expression in normal and malignant prostate, we recently reported that PSCA is expressed at low levels in the transitional epithelium of normal bladder. In the present study, we compared the expression of PSCA in normal and malignant urothelial tissues to assess its potential as an immunotherapeutic target in transitional cell carcinoma (TCC). Immunohistochemical analysis of PSCA protein expression was performed on tissue sections from 32 normal bladder specimens, as well as 11 cases of low-grade transitional cell dysplasia, 21 cases of carcinoma in situ (CIS), 38 superficial transitional cell tumors (STCC), stages T1-T4, 65 muscle-invasive TCCs (ITCCs, stages T2-T4), and 7 bladder cancer metastases. The level of PSCA protein expression was scored semiquantitatively by assessing both the intensity and frequency (i.e., percentage of positive tumor cells) of staining. We also examined PSCA mRNA expression in a representative sample of normal and malignant human transitional cell tissues. In normal bladder, PSCA immunostaining was weak and confined almost exclusively to the superficial umbrella cell layer. Staining in CIS and STCC was more intense and uniform than that seen in normal bladder epithelium (P < 0.001), with staining detected in 21 (100%) of 21 cases of CIS and 37 (97%) of 38 superficial tumors. PSCA protein was also detected in 42 (65%) of 65 of muscle-invasive and 4 (57%) of 7 metastatic cancers, with the highest levels of PSCA expression (i.e., moderate-strong staining in >50% of tumor cells) seen in 32% of invasive and 43% of metastatic samples. Higher levels of PSCA expression correlated with increasing tumor grade for both STCCs and ITCCs (P < 0.001). Northern blot analysis confirmed the immunohistochemical data, showing a dramatic increase in PSCA mRNA expression in two of five muscle-invasive transitional cell tumors when compared with normal samples. Confocal microscopy demonstrated that PSCA expression in TCC is confined to the cell surface. These data demonstrate that PSCA is overexpressed in a majority of human TCCs, particularly CIS and superficial tumors, and may be a useful target for bladder cancer diagnosis and therapy.

Introduction

TCC of the bladder poses a significant worldwide clinical problem, with an estimated 54,200 new cases and 12,100 associated deaths reported in the United States in 1999 alone (1). The majority of patients present initially with superficial disease limited to the urothelium or lamina propria of the bladder wall. Such lesions are often amenable to transurethral resection. Intravesical immunotherapy with BCG may prevent recurrence or progression of high-risk tumors (e.g., high grade or T1) and CIS (2). However, despite these efforts, ~50% of superficial tumors will continue to recur and as many as 30% will progress to muscle-invasive disease (3). Although radical cystectomy can salvage many patients with muscle-invasive cancers, a significant number go on to die from metastatic disease, for which there is currently no effective treatment. These data underscore the urgent necessity for better diagnostic and treatment strategies for superficial and invasive bladder cancers.

Given the sensitivity of bladder cancer to BCG immunotherapy, there is a particular need to identify bladder cancer antigens for cellular and monoclonal antibody-based targeted immunotherapies. EGFR, for example, is overexpressed by a significant percentage of muscle-invasive bladder cancers (4). A recent study demonstrated that monoclonal antibody directed against EGFR slowed growth of a human transitional cell cancer in an orthotopic mouse model (5). Similarly, new bladder cancer markers have been identified that not only demonstrate high specificity for TCC but that also show early promise as a clinical tool. One such marker, uroplakin II, is an urothelium-specific differentiation antigen that is expressed by ~40% of TCCs (6). Detection of uroplakin-positive cells in human sera has been associated with metastatic spread of bladder cancer cells and may identify patients with micrometastatic spread prior to undergoing cystectomy (7).

PSA is a glycosylphosphatidylinositol (GPI)-anchored 123-amino-acid glycoprotein related to the Ly-6/Thy-1 family of cell surface antigens (8). PSA expression in normal tissues is largely prostate-specific, but we recently reported finding PSA transcripts and protein in transitional epithelium of the bladder and neuroendocrine cells of the stomach (9). In situ hybridization and IHC analyses demonstrated PSA expression in more than 80% of local and 100% of bone-metastatic prostate cancer specimens (9). Importantly, the intensity of PSA expression increased with tumor grade and stage, which suggests its potential as an immunotherapeutic target for high-risk and metastatic prostate cancer. Supporting this hypothesis, we recently demonstrated that monoclonal antibodies against PSA can inhibit tumor growth and metastasis formation and can prolong survival in mice bearing human prostate cancer xenografts (10). Also, Dannull et al. (11) recently reported that a PSA-derived peptide could elicit a PSA-specific T-cell response in a patient with metastatic prostate cancer.

Because PSA is present at low levels in normal bladder, we asked whether PSA is expressed in TCC. We also determined whether PSA is overexpressed in bladder cancer compared with normal bladder and whether the level of expression correlates with bladder cancer stage or grade. We demonstrate that PSA is expressed by a majority of both muscle-invasive and superficial tumors. Moreover,
PSCA is overexpressed in virtually all nonmuscle invasive bladder tumors and in >30% of invasive and metastatic cancers. As with prostate cancer, expression increases with increasing tumor grade. Interestingly, the overexpression of PSCA that we observed in TCC is quantitatively more than that seen in prostate cancer with respect to tumor stage. These results support PSCA as a potential diagnostic and/or therapeutic target in bladder cancer.

**Materials and Methods**

**Tissue Samples**

All of the tissue specimens were obtained with permission from the Human Tissue Resources Committee of the Department of Pathology at University of California-Los Angeles Medical Center. One hundred seventy-four formalin-fixed, paraffin-embedded human bladder tissues were obtained from 135 different patients. Blocks were then cut into 4-μm sections and mounted on charged slides in the usual fashion. H&E-stained sections of the neoplasms were graded by an experienced urological pathologist according to the criteria set forth in the International Histological Classification of Tumors. Staging was performed based on the 1997 Tumor-Node-Metastasis classification system. The tissue samples consisted of 32 normal bladder samples, 11 cases of low-grade transitional cell dysplasia, 21 cases of CIS, 38 cases of STCC and ITCC. In none of these patients was there evidence, either pre- or postoperatively, of CIS. Northern blot analysis was then performed as described previously (14). Briefly, 10 μm of DNA from each sample were loaded onto a 1% agarose gel. Equal loading and RNA integrity was confirmed by ethidium bromide staining. After electrophoresis, RNA samples were transferred onto a nitrocellulose membrane. Substantially all nonmuscle invasive bladder tumors and in >30% of invasive and metastatic cancers. As with prostate cancer, expression increases with increasing tumor grade.

**Immunohistochemistry**

**Methodology.** Specimens were stained using modifications of an immunoperoxidase technique previously described (12). Briefly, antigen retrieval was performed on paraffin sections using a commercial steamer and 0.01 M citrate buffer (pH 6.0). Slides were then washed in PBS and incubated with normal horse serum, diluted 1:20, for 10 min. PSCA monoclonal antibody 1G8 was generated in the CellPharm System 100 as described previously (9).

Monoclonal antibodies to PSCA were diluted 1:20 in PBS. After 50 min of incubation with the primary antibody, slides were treated sequentially with rabbit antimouse immunoglobulin, swine antirabbit immunoglobulin, and rabbit antiantiswine immunoglobulin (all biotin conjugated). Slides were then incubated with streptavidin-peroxidase, and antibody localization was performed using the diaminobenzidine reaction. Positive and negative controls were performed on tissues obtained from mouse xenograft tumors that were derived from the human prostate cancer cell lines LAPC-4 and PC3, respectively. Negative controls for each stained section consisted of substitution of the N-alkylated site of the primary antibody, as follows:

- 0 = no staining
- 1 = mild intensity
- 2 = moderate intensity
- 3 = severe intensity

**Scoring Methods.** Histopathological slides of the clinical specimens were read and scored by two pathologists (G.V.T. and J.S.) in a blinded fashion. There was a 90% inter- and intraobserver agreement. IHC intensity was graded on a scale of 0 to 3+: 0, no staining; 1+, mildly intense; 2+, moderately intense; 3+, severely intense. Staining density was quantified as the percentage of cells staining positive with the primary antibody, as follows:

- 0 = no staining
- 1 = superficial staining
- 2 = positive staining in <25% of the sample
- 3 = positive staining in 25–50% of the sample
- 4 = positive staining in >50% of the sample

Combining the intensity and density scores gives an overall score ranging from 0 to 15. The scores from normal tissues were 1.0, 1.0, and 1.1, respectively (Table 1). The mean intensity, density, and overall staining scores for normal tissues were 1.0, 1.0, and 1.1, respectively (Table 1). Expression of PSCA in normal bladders was significantly less than that found in CIS and both invasive and superficial tumors (P = 0.001; Table 3).

**Results**

**PSCA Protein Expression in Normal, Dysplastic, and Malignant Urothelium.** The expression pattern of PSCA in normal bladder tissues and TCCs of different stages and grades is summarized in Tables 1 and 2 and illustrated in Fig. 1, A–H. Thirty of 32 normal bladder specimens stained positively for PSCA. In these samples, PSCA expression was generally weak (i.e., 1+) and was localized almost exclusively to the superficial umbrella cell layer (i.e., density score of 1; Fig. 1A). The mean intensity, density, and overall staining scores from normal tissues were 1.0, 1.0, and 1.1, respectively (Table 1). Expression of PSCA in normal bladders was significantly less than that found in CIS and both invasive and superficial tumors (P = 0.001; Table 3).

PSCA expression was detected in all of the 11 low-grade dysplasia specimens surveyed (Table 1; IHC data not shown). The mean intensity, density, and overall score for these samples was 1.8, 2.0, and 3.6, respectively. Although PSCA staining intensity and density tended to be higher in dysplastic than in normal bladder, this was not statistically significant (P = 0.782; Table 3). In contrast, PSCA expression in CIS was intense and homogeneous in all but two specimens (19 of 21), with a mean intensity, density, and overall score of 2.7, 4.9, and 13.2, respectively (Table 1). Whereas PSCA staining in normal and dysplastic bladders was confined to the most superficial layers of urothelium, staining in CIS was detected in all of the neoplastic
urothelial cell layers (Fig. 1B). Overall, CIS expressed significantly higher levels of PSCA than any other specimen category in this study (P < 0.05, compared with normal bladder, dysplasia, STCC, ITCC, and metastases; Table 3). Nonmuscle invasive tumors (stages T a and T 1 ) also displayed an overall strong positivity for PSCA expression (Fig. 1C). Twenty-nine (76%) of 38 samples overexpressed PSCA, defined as an overall score of ≥8 (Table 1). The mean intensity, density, and overall scores for T a tumors were 2.0, 4.1, and 8.6, respectively, whereas T 1 lesions scored 2.2, 4.6, and 10.7, respectively. As a group, superficial tumors stained more strongly than normal, dysplastic, and invasive samples (P = 0.001; Table 3). PSCA expression increased significantly with worsening tumor grade in nonmuscle invasive tumors (Table 2). Grade 2 lesions had a mean overall staining score of 6.8 compared with a mean score of 11.2 for Grade 3 tumors (P < 0.001). We detected PSCA expression in 42 (65%) of 65 muscle-invasive tumors, of which 21 (32%) exhibited the highest levels of expression (i.e., overall score, ≥8). Locally advanced tumors tended to express higher levels of PSCA than organ-confined lesions, although this trend did not reach statistical significance. T 1 tumors had a mean overall score of 4.1, whereas T 2 and T 3 tumors had mean intensity versus density scores of 5.5 and 6.6, respectively (Table 1; Fig. 1D–F). As with superficial tumors, PSCA expression in muscle-invasive cancers increased significantly with tumor grade (Table 2). Eight (67%) of 12 grade 2 tumors displayed no detectable PSCA expression, whereas only 14 (27%) of 53 grade 3 lesions showed no expression. The mean overall score for grade 2 muscle-invasive tumors was 2.1, compared with a score of 5.9 for grade 3 tumors (P < 0.001). Several poorly differentiated muscle-invasive TCCs contained foci of squamous cell differentiation. PSCA expression in these cases was particularly prominent, as depicted in Fig. 1F. We also examined seven bladder cancer metastases. Four (57%) stained positive for PSCA (Fig. 1G), three of which were in the strongest immunoreactivity category (Table 1). The mean intensity, density, and overall scores for metastases were 1.4, 2.3, and 6.3, respectively. These results demonstrate that PSCA is expressed by a majority of TCCs. Expression is greatest in CIS and superficial tumors but is also extremely high in >30% of muscle-invasive and metastatic lesions. Importantly, within the subgroups STCC and ITCC, higher levels of PSCA expression correlate significantly with increasing tumor grade.

PSCA Protein Is Expressed on the Cell Surface of Bladder Cancer Cells. To confirm that PSCA localizes to the cell surface of bladder cancer cells, we stained nonpermeabilized HT1376 bladder cancer cells and examined them by confocal microscopy. PSCA monoclonal antibody 1G8 detected PSCA expression in a subpopulation of these cells. As seen in Fig. 1H, PSCA protein expression is localized to the cell surface.

PSCA mRNA Expression in Normal and Malignant Urothelium. Northern blot analysis was performed on four normal and five invasive transitional cell cancer samples (Fig. 1J). As predicted, low levels of PSCA mRNA expression were detected in three of four normal bladder specimens. PSCA mRNA was also detected in three (60%) of five muscle-invasive tumors and an invasive transitional cell cancer cell line (HT1376). Consistent with the IHC findings, two of these invasive cancers (i.e., 40%) overexpressed PSCA when compared with normal bladder. The level of PSCA expression in these two cases was similar to that seen in LAPC 9, a prostate cancer xenograft. The corresponding IHC stain for a patient with a muscle-invasive transitional cell tumor of the renal pelvis is shown in Fig. 1E (lane with asterisk) and confirms the intense expression detected by Northern analysis. Of all of the tissues examined in this study, this was the only sample to be obtained from a site other than the bladder.

Discussion

PSCA is a cell surface antigen that has potential utility in the diagnosis and treatment of prostate cancer. In the present study, we demonstrate that PSCA is also expressed in normal bladder and in a large percentage of human TCCs. Interestingly, we found that expression in normal bladder is limited to the umbrella cell layer, a differentiated cell type believed to play a role in maintaining the integrity of the urothelium. Although the function of PSCA remains unknown, homologues of PSCA have been implicated in homotypic cell adhesion (15). Bahrenberg et al. (16) recently reported that PSCA expres-

### Table 1 Comparison of IHC staining intensity, density, and overall score by grade

<table>
<thead>
<tr>
<th>Intensity</th>
<th>Density</th>
<th>Overall Score</th>
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<tr>
<td>0–3</td>
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<td>8–15</td>
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<tr>
<td>Mean ± SD</td>
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### Table 2 Comparison of IHC staining intensity, density, and overall score by grade

<table>
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<th>Intensity</th>
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<th>Overall Score</th>
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<tr>
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<tr>
<td>Mean ± SD</td>
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*Two-way ANOVA using staining overall score as the dependent variable and grade and histopathologic subgroup (i.e., non-ITCC and ITCC) as factors was performed. Within each subgroup, higher grade correlated with higher overall score (P = 0.0002).
PSCA AND TCC

Table 3 One-way ANOVA** mean overall score versus histopathology

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
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<th>Low-grade dysplasia</th>
<th>CIS</th>
<th>STCC</th>
<th>ITCC</th>
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<tbody>
<tr>
<td>Abs difference</td>
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<td>Normal</td>
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<td>Low-grade dysplasia</td>
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<tr>
<td>CIS</td>
<td>12.1 ± 0.782</td>
<td>9.6</td>
<td>0.761**</td>
<td>3.5</td>
<td>3.5</td>
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<tr>
<td>STCC</td>
<td>8.6 ± 0.001b</td>
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<td>0.046b</td>
<td>3.4</td>
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<tr>
<td>ITCC</td>
<td>4.0 ± 0.001b</td>
<td>1.5</td>
<td>8.0</td>
<td>4.5</td>
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<tr>
<td>Metastases</td>
<td>5.2 ± 0.006</td>
<td>2.0</td>
<td>0.012</td>
<td>1.1</td>
<td>1.1</td>
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** One-way ANOVA-Sidak multiple comparison procedure using mean immunostaining overall score as the dependent variable and grade and histopathological subgroup as factors.

*Statistically significant.

Fig. 1. IHC staining and Northern analysis of PSCA in benign and malignant urothelial tissue. All of the sections were stained with PSCA monoclonal antibody 1G8. Brown color, positive stain. A, normal bladder tissue displayed weak, superficial staining. B, intense, homogeneous staining was seen in CIS specimens. Positive staining can be seen in all layers of neoplastic urothelium. C, nonmuscle invasive superficial TCCs showed prominent PSCA expression. D and E, high-grade muscle-invasive transitional cell tumors displayed moderate-to-strong PSCA immunoreactivity. PSCA mRNA analysis from the tumor in E may be seen in I, Lane with asterisk. F, high-grade muscle-invasive tumors occasionally contained areas of squamous cell differentiation that were hot spots of PSCA expression (arrow). G, several metastatic tumors, as seen in this example from a metastatic lesion to the lung, displayed significant PSCA expression. Note the intensely positive island of metastatic transitional cells (arrowhead) surrounded by normal lung parenchyma. H, immunofluorescent staining of the cell line HT1376 shows PSCA expression (green, fluorescein) exclusively at the cell surface. Positive staining was seen in only a subpopulation of cells. The nuclei are counterstained with propidium iodide (red). I, Northern blot analysis of PSCA expression in normal and malignant urothelium. Three of four normal bladder specimens showed weak PSCA mRNA expression. The human bladder cancer line HT1376 displayed weak PSCA expression. Two of five muscle-invasive TCCs expressed high levels of PSCA mRNA when compared with normal bladder. Weak expression of PSCA was seen in an additional bladder tumor. All of the transitional cell tumors were muscle invasive. The human prostate cancer cell lines LNCaP and LAPC 9 were used as negative and positive controls, respectively. See “Results” for discussion of sample that was labeled with asterisk.

As noted above, increasing levels of PSCA expression correlated with increasing tumor grade in both superficial and muscle-invasive tumors. One possible mechanism for PSCA overexpression is that it may result from PSCA gene amplification. PSCA maps distal to the MYC oncogene on chromosome 8q24.2 (8). In prostate cancer, PSCA overexpression is associated with PSCA and MYC coamplification (17). Christoph et al. (18) and Sauter et al. (19) have shown that low-level MYC amplification is a common feature of both nonmuscle-invasive and invasive bladder cancers and correlates with worsening tumor grade. Fluorescent in situ studies of bladder cancers should clarify whether PSCA overexpression is caused by gene amplification. Also, it will be interesting to determine whether PSCA overexpression correlates with MYC amplification.

We observed intense PSCA staining in poorly differentiated tran-
tional cell tumors with squamous features, which suggests that PSCA expression may be associated with squamous differentiation. We recently created a transgenic mouse model using the PSCA promoter to drive green fluorescent protein (GFP) expression.\(^5\) In this model, we noted GFP expression in keratinized skin as well as in the adult urothelium of a single founder line. Likewise, Bahrenberg et al. (16) recently reported that PSCA is expressed by keratinocytes in tissue culture, although we have not seen PSCA expression in adult skin. These observations suggest that PSCA may be a marker of both transitional and squamous differentiation patterns in the bladder and may provide another possible mechanism whereby PSCA expression levels may increase in poorly differentiated bladder tumors.

Our results differ somewhat from those reported recently by Bahrenberg et al. (16). Similar to Bahrenberg, we saw dramatically increased levels of PSCA expression in superficial tumors. Likewise, we saw lesser overall expression of PSCA in muscle-invasive tumors. However, unlike Bahrenberg, we found that a majority of invasive and metastatic tumors expressed PSCA and >30% overexpressed it. In addition, although Bahrenberg et al. concluded that PSCA expression was a marker of differentiated bladder tumors, we found that PSCA expression was highest in poorly differentiated invasive and superficial tumors. One possible reason for these differences is that the study of Bahrenberg et al. did not include cases of CIS or high-grade superficial cancer. Also, their study was small and included only two well-differentiated (presumably superficial) and eight poorly differentiated (presumably invasive) cancers.

Another difference between this study and that of Bahrenberg is that we primarily evaluated PSCA protein expression, whereas the latter looked at mRNA levels exclusively. Importantly, Bahrenberg et al. reported finding several PSCA splice variants. One of these, denoted Δ(1–17), results in the substitution of the 17-amino-acid signal sequence of exon 1 with a new 31-amino-acid sequence. This splice variant is transcribed and would be predicted to contain the epitope in exon 2 that is recognized by PSCA monoclonal antibody 1G8. It is possible, therefore, that, in at least some instances, our immunostaining would have detected a PSCA splice variant. That said, we did not detect any aberrant messages by Northern analysis, and we were clearly able to correlate PSCA mRNA and protein expression in a patient with muscle-invasive TCC. Also, our Northern analysis was consistent with the IHC data, showing expression in 60% of cases and overexpression in 40%.

Confocal microscopy studies demonstrated cell surface expression of PSCA in a subset of cells from the bladder cancer cell line HT1376. IHC analysis of PSCA shows cell surface as well as apparent cytoplasmic staining of PSCA in benign and malignant transitional epithelia (Fig. 1, A–G). One possible explanation for this is that anti-PSCA antibody can recognize PSCA peptide precursors that reside in the cytoplasm. In addition, it is possible that the positive staining that appears in the cytoplasm is actually from the overlying cell membrane. We have observed similar results with prostate cancer vis-a-vis confocal/immunofluorescent and IHC data (9). These data seem to indicate that PSCA is a novel cell surface marker for TCC.

Our results suggest that PSCA may have a number of potential uses in the diagnosis and treatment of human TCC. Because neoplastic transitional cells are naturally sloughed from the bladder, differential expression of PSCA in voided samples might form the basis for a diagnostic test. Detection of PSCA on the surface of circulating cells in blood and bone marrow might be useful in identifying some patients with bladder cancer micrometastases, particularly those whose primary tumors express PSCA. We have recently shown that immunomagnetic beads conjugated with PSCA monoclonal antibodies can detect as few as 1 in 107 PSCA-positive cells in bone marrow.\(^6\) Similar approaches have been tested using urolphin II as a marker of metastatic transitional cells (7).

PSCA might also be a valuable target for bladder cancer immunotherapy. One potential approach is to use monoclonal antibodies intravascularly to treat localized disease (particularly CIS) or systemically to treat advanced disease. We have recently shown that naked PSCA antibodies inhibit prostate cancer tumorigenesis and metastasis, which suggests that they may have utility in TCC as well (10). Similar approaches have been reported in bladder cancer using antibodies against EGFR systemically and against the MUC 1 mucin antigen intravascularly (5, 20). PSCA might also be useful for local or systemic vaccine approaches. Dannull et al. (11) recently demonstrated that amino acids 14–22 of PSCA can elicit a PSCA-specific T-cell response in a patient with prostate cancer. Given the profound immunosensitivity of bladder cancer to nonspecific agents such as BCG, this is a particularly promising approach, especially in the local setting.

In summary, we have shown in this study that PSCA is expressed by a majority of superficial and muscle-invasive transitional cell tumors. Furthermore, PSCA is overexpressed in a majority of superficial tumors and a significant percentage of invasive and metastatic transitional cell cancers. These results suggest that PSCA may be a valuable target for bladder cancer diagnosis and therapy.

References


\(^6\) Z. Gu and R. E. Reiter, unpublished data.


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