Overview of Prostate-Specific Membrane Antigen

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Efforts to evaluate and discover diagnostic and therapeutic markers for prostate cancer continue. One of these, prostate-specific membrane antigen (PSMA), a transmembrane protein expressed in all types of prostatic tissue, remains a useful diagnostic and possibly therapeutic target. The radioimmunoconjugate form of the anti-PSMA monoclonal antibody 7E11 is used in the commercially available and US Food and Drug Administration–approved diagnostic tool, the ProstaScint® (Cytogen Corporation, Princeton, NJ) scan. Recent studies have demonstrated other possible useful roles for PSMA as a target, not only in prostate cancer, but in other malignancies.
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Prostate-specific membrane antigen (PSMA) is a type II membrane protein originally characterized by the murine monoclonal antibody (mAb) 7E11-C5.3 and is expressed in all forms of prostate tissue, including carcinoma.[1-6] The PSMA protein has a unique 3-part structure: a 19-amino-acid internal portion, a 24-amino-acid transmembrane portion, and a 707-amino-acid external portion (Figure 1).[7,8] The PSMA gene is located on the short arm of chromosome 11 in a region that is not commonly deleted in prostate cancer.[9]

PSMA has known enzymatic activities and acts as a glutamate-preferring carboxypeptidase.[10-12] The impact of these enzymatic functions on human prostate tissue and perhaps elsewhere, however, remains unclear, as does the question regarding the existence of a natural ligand for PSMA. What has been demonstrated recently is that PSMA does have an internalization signal that allows internalization of the protein on the cell surface into an endosomal compartment.[13] This recently recognized characteristic might prove useful in future diagnostic and therapeutic maneuvers in which PSMA is used as an antigenic target.

Anti-PSMA Antibodies

Originally developed with a type of prostate cancer cell line known as LNCaP cells, the mAb 7E11 was the first anti-PSMA antibody. It recognizes and binds a PSMA intracellular or cytoplasmic epitope.[2,6,14] New mAbs, however, continue to be discovered and developed.[15-17] A key difference of these newer antibodies is where the binding interaction takes place, although this distinction may be less relevant for radionuclide-based imaging and therapeutic applications. The more recently developed anti-PSMA mAbs bind the extracellular portion of PSMA and, in fact, can be internalized by PSMA-expressing cells.[18] Recent anti-PSMA antibodies have identified dimer-specific epitopes on PSMA-expressive tumor cells.[19] In addition, several of these next-generation antibodies are now either fully human or humanized as opposed to murine antibodies, thus making them even more likely to be diagnostically and therapeutically effective without possible antimouse reactions, although the incidence of such antimouse reactions with ProstaScint (or capromab pendetide) have been extremely low.

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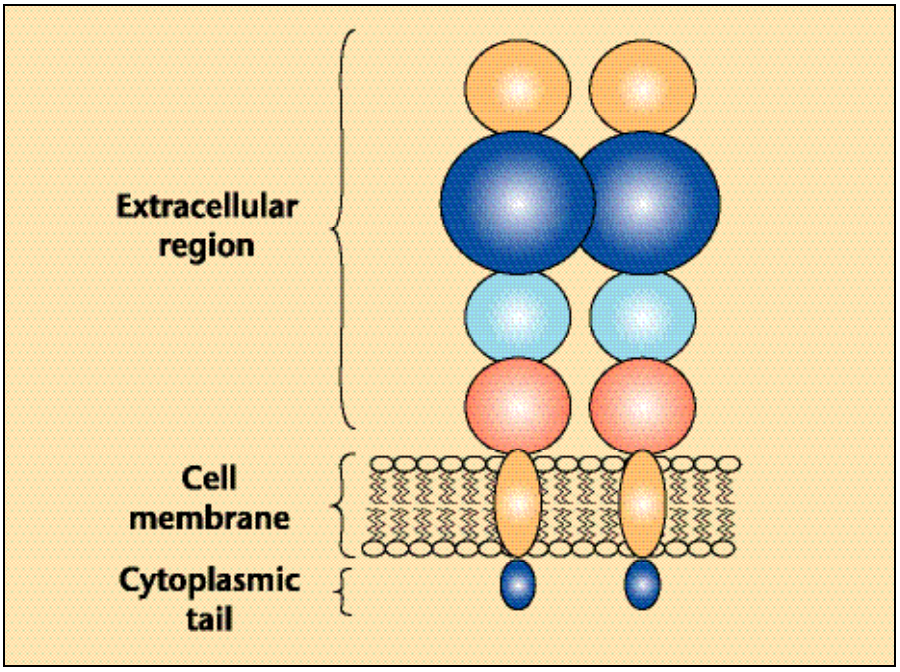

Figure 1. *Schematic of prostate-specific membrane antigen.*

Clinical Evaluation of PSMA

Tissue Expression

Studies have consistently demonstrated PSMA expression in all types of prostate tissue and increased PSMA expression in cancer tissue.[2,3,5,6,20,21] The binding occurs in the epithelial cells of the prostate but not in the basal or stromal cells. Bostwick and colleagues[22] described PSMA immunohistochemical expression in 184 prostate specimens examined, all of which had PSMA expression and demonstrated a correlation between this expression and severity of cancer. There was an increase in the percentage of PSMA staining from benign epithelial tissue (69.5% of cells positive) to high-grade prostatic intraepithelial neoplasia (77.9% of cells positive) to malignant cells (80.2% of cells positive).[22]

Prostate-specific antigen (PSA) and PSMA are different in several ways (Figure 2). Importantly, PSMA expression seems to be inversely related to androgen levels.[23] Denmeade and colleagues[24] recently examined cell lines in different states of androgen deprivation and discovered that PSMA activity in prostate cancer cell lines increased as cells became more androgen independent. Such manipulation could improve the efficacy of any antibody-directed, diagnostic/therapeutic targeting. Short-term (3-month) neoadjuvant deprivation therapy in clinically localized prostate cancer patients, however, did not increase immunohistochemical PSMA expression within prostate tissue.[25]

Antibody binding to PSMA does

not seem to be restricted absolutely to prostate tissue. Anti-PSMA mAbs consistently bind duodenal epithelial (brush border) cells and proximal tubule cells in the kidney.[15,17] More excitingly, PSMA seems to be expressed in other cancers, more specifically in the neovasculature associated with these cancers.[5,15] We have examined a wide range of carcinomas, including conventional (clear cell) renal cell, transitional cell of the bladder, testicular–embryonal, neuroendocrine, colon, and breast, and the different types of malignancies consistently and strongly expressed PSMA in their neovasculature.[17] Interestingly, this binding of the neovasculature does not seem to occur in prostate cancer.[5,17,22]

Diagnostic Applications

Researchers have attempted to use PSMA as a serum-based marker, but results have been variable at best.[2,26-28] Murphy and colleagues[29] examined the results of a number of reverse transcriptase polymerase chain reaction (RT-PCR) studies and found that RT-PCR of serum PSMA was not accurate enough to be the basis of a decision to treat and did not independently contribute more than the currently established prognostic indicators of Gleason sum, serum PSA, or clinical stage. Current RT-PCR strategies have much to overcome, especially in the reproducibility of these techniques. Better differentiating primers need to be identified as well. As a result, PSMA is not used as a serum-based diagnostic or screening marker.

What has been clinically useful and safe is the ProstaScint® scan (Cytogen Corporation, Princeton, NJ), the US Food and Drug Administration–approved radiographic test that uses the mAb 7E11 by linking it to ^{111}indium to produce a radiodiagnostic marker, ^{111}indium-capromab pendetide.[26,30,31] The majority of studies in high-risk metastatic prostate cancer and recurrent prostate cancer have demonstrated a sensitivity rate of 60% to 80% and a specificity rate of 70% to 90%, which are better than the accuracy of current CT scans or MRIs.[31,32] A combination of algorithms, nomograms, and the ProstaScint scan was analyzed, and the combination of algorithms and ProstaScint scan provided an improved 72% positive predictive value for metastatic disease.[33] A recent study also found that no minimum serum PSA value was needed to detect radiographic disease after surgery.[34] Importantly, however, a recent study by Thomas and colleagues[35] revealed that the ProstaScint scan did not predict biochemical control after radiation therapy.

As a result of limitations inherent to SPECT imaging, ProstaScint imaging techniques continue to evolve in an attempt to improve accuracy and clinical utility and are discussed elsewhere in this supplement. In addition, PSMA is being used as a radiographic imaging target by newer, second-generation antibodies that bind the external portion of PSMA. Early promising results from phase I trials have demonstrated 90% correlation with conventional scans, but pathological confirmation studies are needed.[36]

PSMA expression might also be a predictor of disease recurrence in prostate cancer patients. In a recent

Table 1
Prostate-Specific Membrane Antigen Expression Status in Prostate Cancer Treated by Radical Prostatectomy

	Non-overexpressing (n = 71)	Overexpressing (n = 65)	*P*
Incidence of recurrent disease	20/71 (28%)	37/65 (57%)	.001
Mean time to recurrence (months)	43.75	34.78	.001

Prostate-specific membrane antigen overexpression independently predicts disease recurrence. Data from Ross JS et al.[1]

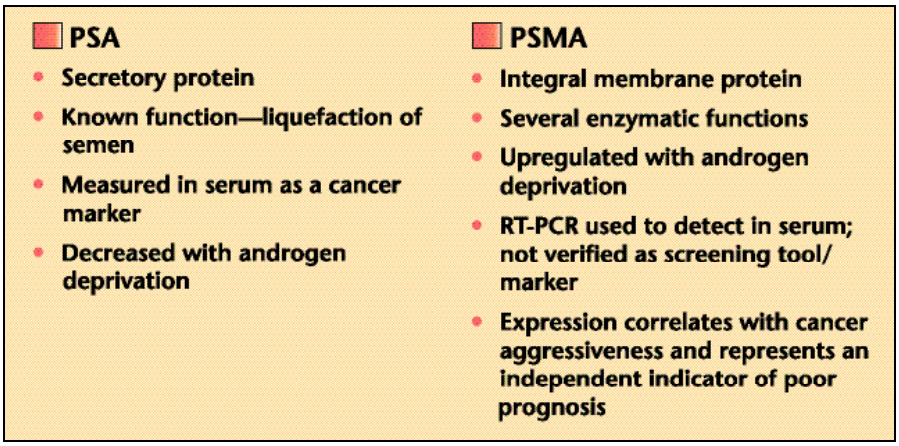

Figure 2. *Comparison of prostate-specific antigen (PSA) and prostate-specific membrane antigen (PSMA). RT-PCR, reverse transcriptase polymerase chain reaction.*

series by Ross and colleagues,[1] examination of postprostatectomy specimens revealed PSMA expression determined through immuno staining with the mAb 7E11 that correlated with tumor grade, pathologic stage, PSA, and aneuploidy. Importantly, in a multivariate analysis, PSMA expression independently predicted the likelihood of biochemical recurrence (Table 1).[1]

Expanding the possible role of PSMA as a radiographic marker was an incidental renal cell carcinoma discovered by ^{111}indium-capromab pendetide scan. The scan revealed suspicious uptake in a kidney, which subsequent conventional imaging revealed to be a solid renal mass with necrosis.[37] In an in vivo setting, this example might have demonstrated the recognition by the anti-PSMA mAb 7E11 of tumor-associated neovasculature. Other malignancies such as non-Hodgkin's lymphoma, neurofibromatosis, and meningioma have been detected as well.[38-40] More research is necessary to determine the in vivo activity of anti-PSMA monoclonal antibodies with regard to nonprostatic primary and metastatic malignancies.

Therapeutic Interventions

The use of PSMA as a therapeutic antigenic target for antibodies has recently become more than a hypothetical proposal. Recent studies with an anti-PSMA mAb have used linkages to radionuclides to treat metastatic prostate cancer. In an early trial, no toxicity has been noted, and as important, the antibody-radionuclide compound localized to tumor in vivo, even to bony sites of metastatic disease.[36,41] This technique of combining an antibody with some type of therapeutic intervention has also been used in nonprostate cancer lesions, including renal cell cancer, in which phase II trials have combined anti-PSMA mAb with interleukin-2.[42]

Another type of therapy is immunotherapy, which avoids foreign DNA and uses a patient's own cells to provide the mechanism for treatment. Currently, several novel treatment options use PSMA in this manner. Gong and colleagues[43] have developed a unique approach involving creation of an artificial T cell receptor to target cells expressing PSMA. This artificial T-cell receptor incorporates a PSMA-specific single-chain antibody fused to a zeta chain signal transduction domain. Promising in vitro results demonstrate successful lysis of PSMA-positive prostate cancer cells with no effect on PSMA-negative cells. This model can successfully produce large amounts of interleukin-2. In addition, the amplified cell populations retain their antigen-specificity.[44]

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PSMA peptides have been used to generate an immune response by infusing dendritic cells pulsed by these PSMA peptides. In a recent trial, a small number of patients with advanced or metastatic disease had a partial clinical response, defined as greater than 50% reduction in serum PSA.[45]

Gardner and colleagues[46] recently presented findings of early studies of a newly developed vaccine based on a novel recombinant soluble PSMA protein representing the extracellular domain of PSMA.[19] This vaccine was administered to patients with progressive disease following local therapy, and was well tolerated in this patient population. Results showed that the vaccination elicited antibodies that reacted strongly with prostate cancer cells, and that antibody levels increased with repeated dosing.

Based on the evaluation of fully human mAbs against PSMA in a preclinical setting, Ma and colleagues[47] recently selected a lead fully human antibody for testing in naked, radiolabeled and toxin-conjugated forms. Focusing on novel recombinant forms of PSMA and XenoMouse™ technology (Abgenix, Fremont, CA), they evaluated these mAbs' cytotoxic effects and their ability to deliver cytotoxic agents to PSMA-expressing tumor cells. Results showed naked mAbs induced antibody-dependent cell-mediated cytotoxicity of human prostate cells; the mAb labeled with isotope ^{177}Lu was well tolerated and was effective in targeting PSMA and increasing survival in animals by more than 3-fold. In addition, toxin-conjugated mAbs quickly internalized and killed PSMA-expressing cells and eradicated prostate tumors in mice without toxicity.

By using different combinations of anti-PSMA antibodies or antibodies to other previously described targets such as GM2, KSA, Thomsen-Friedenreich antigen, or others yet to be identified, one could perhaps develop a more powerful and/or more precisely targeted treatment strategy for prostate cancer.[48] This approach would attempt to decrease any nonspecific binding that can occur. Current antibodies used to target PSMA are not absolutely prostate-specific,[27] but this has been true with current therapeutic antibodies available for cancer therapy.[49,50]

Finally, what we know now about PSMA is that its promotor and gene, or surrounding gene sequence, must contain transcriptional enhancer regions that selectively activate PSMA transcription. This activation seems to occur in tumor-associated

neovasculature but not in benign vessels. By manipulating these sequences or better understanding the impact of certain sequences, one could develop an antiangiogenic gene therapy construct. Studies have demonstrated the effect of modulating the promotor region on PSMA expression,[51] but actually utilizing this in vivo is currently hypothetical.

Conclusions

The possible diagnostic and therapeutic role of PSMA continues to evolve. In prostate cancer, PSMA continues to be a useful antigenic target that will continue to be of diagnostic and therapeutic value as newer targeting agents are developed and imaging systems and techniques continue to improve. In addition, beyond prostate cancer, PSMA might represent a unique angiogenic target for a variety of neoplasms. ■

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Main Points

- Studies have consistently demonstrated prostate-specific membrane antigen (PSMA) expression in all types of prostate tissue and increased PSMA expression in cancer tissue.
- PSMA seems to be expressed in other cancers (conventional renal cell, transitional cell of the bladder, testicular–embryonal, neuroendocrine, colon, and breast), specifically in the neovasculature associated with these cancers.
- Reverse transcriptase polymerase chain reaction of serum PSMA is not accurate enough to be the basis of clinical therapy and does not independently contribute more than the currently established prognostic indicators of Gleason sum, serum prostate-specific antigen, or clinical stage.
- What has been clinically useful and safe is the ProstaScint® scan (Cytogen Corporation, Princeton, NJ), the US Food and Drug Administration–approved radiographic test that uses the monoclonal antibody 7E11 by linking it to an ^{111}indium to produce a radiodiagnostic marker, ^{111}indium-capromab pendetide.

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