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Novel biomarkers and therapeutic targets for prostate cancer

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1. ABSTRACT

Prostate cancer is the most prevalent cancer in the Western male population and the second leading cause of cancer death in men, affecting over 10 million individuals. Present approaches to control the cancer mortality have focused on the detection of the cancer at early stages when it is still locally confined and may be curable. Identification of the prostate-specific antigen (PSA) has facilitated the early diagnosis of prostate cancer. However, PSA has limited specificity and sensitivity in appropriately detecting early stages of abnormal prostate growth. PSA levels fail to differentiate between indolent and aggressive cancers, do not correlate with tumor size, and cross-react with other serine proteases namely, glandular kallikreins 1 and 2. Besides cancer, its levels also increase in men with benign prostatic hyperplasia (BPH), prostatitis, and other non-malignancies. Additional prostate-specific genes and metabolites need to be identified to provide a better understanding of the molecular mechanisms of prostate physiology and pathophysiology. Novel markers for the diagnosis and development of new treatment modalities are urgently needed.

Table 1. Prostate specificity and prostate cancer expression of various genes/metabolites

Gene	Prostate-Specificity	Prostate Cancer Expression[1]
A. Transmembrane Proteins		
1. PSGR	Yes	↑
2. D-GPCR	Restricted	↑
3. STEAP	No	↑
4. hNPSA	Yes	↑
5. HPG-1	Yes	↑
6. NGEP-L	Yes	-
7. Trp-p8	No	↑
8. PMEPA1	No	-
B. Golgi membrane proteins		
9. Prostein	Yes	↑
10. STAMP1	Restricted	↑
11. GOLM1	No	↑
C. ER membrane proteins		
12. D-TMPP	Restricted	↓
D. Transcription factors		
13. PrLZ	Restricted	↑
14. AIbZIP	Restricted	↑
15. PCADM-1	Yes	↑
E. Carbohydrate binding proteins		
16. PCTA-1	No	↑
F. DNA repair enzymes		
17. PCA-1	No	↑
G. Growth factors		
18. PART-1	Restricted	Not known
H. Proteins of unknown function		
19. D-PCa-2	Restricted	-
20. KRIP1	Restricted	↓
21. NGEP-S	Yes	Not known
I. Metabolites		
22. Sarcosine	No	↑
23. Citrate	No	↓

[1]↑ indicates overexpression; - indicates no change; and ↓ indicates downregulation

2. INTRODUCTION

Among men, prostate cancer is the most frequently diagnosed malignancy and is responsible for the second most cancer-related deaths (1). While curable in containment, this disease is often fatal after metastisization or androgen independence, hence making early detection essential for patient survival. PSA is the standard biomarker for detection of prostate cancer. While it helps in diagnosis, it is not ideal. PSA has limited sensitivity and specificity and is not helpful in detecting the earlier stages of abnormal prostate growth. PSA serum levels are elevated in a non-tumor specific manner (2) and increase only after disruption of prostatic morphology; thus, it is not helpful in earlier detection. Once detected, the current treatment modalities include radical prostatectomy, radiotherapy, androgen ablation (3), and potential immunotherapy (4, 5).

Additional biomarkers (genes and metabolites) are needed that can be used for early diagnosis and therapeutic targets. An ideal biomarker should be expressed in a prostate-specific/restricted manner, detectable by noninvasive means, sensitive and specific to prostate cancer, and should provide an early detection sufficient enough to curtail the disease. An ideal therapeutic target should be prostate-specific, involved in the disease process, and preferably expressed on the surface for easy accessibility to drugs/antibodies. The main objective of this article is to review prostate-specific/restricted biomarkers (genes and metabolites) that have been identified over the last five years and have been proposed to have utility in the diagnosis and treatment of prostate cancer.

Several laboratories are actively involved in identifying prostate-specific /restricted genes and metabolites that can be used for earlier diagnosis and treatment of prostate cancer. An earlier review from our laboratory, published in 2001, described at least ten such genes (PSA, PSM, PTI-1, DD3, PCGEM1, PSCA, NKX3.1, PDEF, Prostase, and TMPRSS12) published in the literature (6). Since then, several additional genes/metabolites have been identified that may have a role in the diagnosis/treatment of prostate malignancy. The Pubmed database (www.pubmed.gov) was searched (2000-2009) using the keywords: "novel" AND "prostate-specific". It identified 786 articles describing several genes/metabolites. Further analysis of these articles identified at least 23 proteins/metabolites that were found to be novel and can provide potential biomarkers/therapeutic targets for abnormal prostate growth. These are reviewed in this article (Table 1).

3. DISCUSSION

3.1. Transmembrane proteins

3.1.1. Prostate-specific G-protein coupled receptor (PSGR)

PSGR is a transmembrane protein identified by using EST database. It is a 320 aa protein with a predicted molecular weight of 35.4 kDa and is localized on chromosome 11p15.4. PSGR has homology with other G-coupled protein coupled receptors (GPCRs) belonging to the odorant receptor (OR) gene family; it is an orphan OR with unknown function (7).

Its tissue-specific expression in prostate epithelial cells was confirmed by using Northern blot and RNA master blot analyses (7) and later by *in situ* hybridization procedure (8). The PSGR protein was detected in 76% of prostate cancer tissues at ~ 10-fold higher level than normal prostate. It is overexpressed in prostate intraepithelial neoplasia (PIN), a precursor of prostate cancer, and it is not expressed in benign prostate hyperplasia (BPH) (8). Due to its tissue-specificity, and malignant upregulation, PSGR may be a promising biomarker and a target for therapeutic application.

3.1.2. Dresden G-protein coupled receptor (D-GPCR)

D-GPCR was first discovered from EST database (9) and later identified as prostate-specific G-protein coupled receptor 2 (PSGR2) (10). It is a 317 aa protein with 57% identity and 73% similarity to PSGR and an apparent molecular mass of 28 kDa. The cDNA is 3077 bp long and is localized on chromosome 11p15.4, in opposing orientation, 30kb away from PSGR. D-GPCR is a seven-transmembrane protein localized on the plasma membrane and has high homology with GPCR OR family (9). Like PSGR, it is an orphan OR with unknown function.

D-GPCR has deemed prostate-specific expression as seen by Northern blot analysis (9, 10) and multiple tissue expression array (9). However, using quantitative RT-PCR procedure, low-level expression was also found in several other human tissues (9). A ~10-fold higher expression was found in prostate tumor samples compared to normal tissue (10). It also is expressed in androgen-dependent LNCaP cells, although at much lower levels than in tumor tissue, but not in androgen-independent prostate cancer cell lines (9). D-GPCR may have a role in early tumor progression and become quiescent during later stages. Its potential as a biomarker and therapeutic target needs further investigation.

3.1.3. Six transmembrane epithelial antigen of the prostate (STEAP)

STEAP is a type IIIa cell surface protein identified using suppressive subtractive hybridization. The protein is 339 aa long, and its gene is localized on chromosome 7p22.3 (11). It is expressed in other tissues besides prostate. Although upregulated during prostate carcinogenesis, it is also found in multiple non-prostatic tumor cell lines (11). Due to its lack of prostate-specificity, STEAP may not be an ideal prostate tumor marker or a target for cancer therapy.

3.1.4. Human novel prostate-specific antigen (hNPSA)

Identified by differential display PCR procedure, hNPSA is a 245 aa protein translated from a 1462 bp transcript (12). This 27.2 kDa protein is a type II membrane-anchored protein and has a 15 aa signal sequence. hNPSA has several potential phosphorylation and glucolysation sites (12).

It has prostate-specific expression as examined by Northern blot, and RT-PCR-Southern blot procedures using multiple human tissues. The hNPSA mRNA levels are ~ 3-fold higher in LNCaP cells as compared to normal prostate cells. Antisense oligonucleotides significantly inhibit growth of LNCaP cells *in vitro* indicating its role in carcinogenesis (12). Its applications as a biomarker in detection of prostate cancer and as a target for immunotherapy are currently being investigated.

3.1.5. Human prostate-specific gene-1 (*HPG-1*)

HPG-1 is a 1468 bp cDNA located on chromosome 3q26 which was identified by differential display PCR procedure. The ORF encodes a 127 aa protein of 14.8 kDa. It has two N-linked glycosylation sites, several O-linked glycosylation sites, and an N-myriostoylation site. Hydropathy plot analysis of HPG-1 indicates that it may be a plasma membrane-anchored protein, in addition to having a secreted form. Thus, it may have a function in signal transduction pathway (13).

Northern blot analysis using 16 human tissues and RT-PCR-Southern blot analysis using 10 human tissues showed that HPG-1 is expressed specifically in the prostate (13). It showed ~2-fold higher expression in LNCaP cells than the DU-145 line. It is also upregulated by androgens in LNCaP cells. Additionally, antisense HPG-1 oligonucleotides significantly decreased LNCaP cell proliferation by up to 86% *in vitro* (13). It is an exciting molecule and may provide a novel biomarker for early detection of prostate cancer and a target for immunotherapy.

3.1.6. New gene expressed in prostate-long (NGEP-L)

NGEP-L is a 934 aa seven-transmembrane protein located on the plasma membrane and has a predicted molecular mass of 95 kDa (14). It has a role in calcium-dependent intercellular adhesion (15). Multitissue dot-blot analysis showed NGEP-L to have specific expression in the prostate. Its expression was found only in the epithelium of normal and prostate cancer tissue samples and LNCaP cells, but not in the androgen-independent PC-3 or DU-145 cancer cell lines (14). Pilot studies indicate that it may have a useful role in prostate cancer immunotherapy (16).

3.1.7. Transient receptor potential (Trp)-p8

Originally identified by subtractive hybridization, trp-p8 is a 1104 aa protein transcribed from chromosome locus 2q37.1. The protein is predicted to have seven transmembrane domains, and has homology to *Drosophila* trp proteins that are involved in calcium channeling. It is expressed in various tissues, as well as several non-prostatic and prostatic cancer cell lines (18). It is upregulated in carcinogenesis. Its application as a biomarker and in therapy needs further investigation.

3.1.8. Prostate transmembrane protein, androgen-induced 1 (PMEPA1)

PMEPA1 is a novel 252 aa protein mapping onto chromosome locus 20q13. Identified by serial analysis of gene expression (SAGE)-tagging, it has a type Ib transmembrane domain. While being overexpressed in androgen-sensitive cell lines and xenografts, it is not prostate-specific, but has prostate–restricted expression. The transcript was found in several human tissues including heart and kidney. Additionally, it is not overexpressed in prostatic tumor tissue as compared to normal tissue (19). Therefore, PMEPA1 may not be an ideal candidate as either biomarker or for therapeutic endeavor.

3.2. Golgi membrane proteins

3.2.1. Prostein

Prostein is a 553 aa protein encoded by a 3410 bp segment located at chromosome 1q32.1. It was identified using cDNA subtractive library (20). It is a type IIIa membrane protein, having eleven possible transmembrane domains with a signal sequence and is localized in the Golgi (20). Prostein may be involved in signal transduction cascade and/or in peptide modification process.

Northern blot, microarray, and immunohistochemical analyses confirmed the prostate specificity of prostein (20). It is expressed in 94% of all prostate epithelial tissue (both normal and tumor) and 87% of tumor cells, with no correlation to tumor grade (21). Additionally, this protein is overexpressed in cancerous tissue compared to normal prostate tissue and is upregulated by androgens in LNCaP cells (20). It is thus possible that prostein has an important function in the

prostate and may provide a biomarker and target for therapeutic approaches.

3.2.2. Six transmembrane protein of prostate 1 (STAMP1)

STAMP1 (22) is also known as six transmembrane epithelial antigen of the prostate 2 (STEAP2) (23). It is a 26 kb transcript translating to a 490 aa polypeptide. Identified by differential expression technique (22) and subtraction/cDNA array hybridization procedure (23), this gene maps to chromosome locus 7q21.13. STAMP1 is localized to the TGN of the Golgi complex (22) as well as the plasma membrane (23). Indeed, it was found to shuttle between the Golgi and plasma membrane, as well as to endosomes (22). Functionally, it is a ferrireductase as well a cupric reductase, and stimulates uptake of iron and copper into the cell (24).

Northern blot (22) and real-time quantitative RT-PCR procedure (23) revealed that it is not strictly prostate specific, but has a 10-20 fold higher expression in prostate than other tissues. Also, its expression is 2.5-fold higher in malignant prostate epithelium than in normal tissue. It is not expressed in the DU-145 or PC-3 cells. Although overexpressed in LNCaP cells, it is not regulated by androgens (22). Its role as a biomarker and in therapy needs to be investigated.

3.2.3. Golgi membrane protein 1 (GOLM1)

A type II *cis*-Golgi membrane protein, GOLM1 has been described as a urine biomarker for prostate cancer. It has a significant, almost 3-fold upregulation, in urine of prostate cancer patients (25). However, it is dysregulated not only in prostate cancer but also in other cancers (26). Indeed, under the name Golgi phosphoprotein 2 (GOLPH2), this protein has also been investigated as a serum marker for hepatocellular carcinoma (27). Despite its lack of prostate cancer specificity, it may provide a useful noninvasive prostate tumor biomarker. Although its levels rise in blood in several cancerous conditions, the upregulation and detection in urine has only been reported in prostate cancer.

3.3. Endoplasmic reticulum membrane proteins

3.3.1 Dresden transmembrane protein of the prostate (D-TMPP)

D-TMPP is an 883 aa polypeptide with a molecular mass of 99.8 kDa. It is localized in the endoplasmic reticulum and is predicted to have seven transmembrane domains of unknown function. It is expressed in several tissues, albeit at much lower levels than in the prostate. Its expression has not been correlated with tumor grade. Its expression is regulated by androgens (27). Its application as a biomarker and as a target for therapy needs to be investigated.

3.4. Transcription factors

3.4.1. Prostate leucine zipper (PrLZ)

PrLZ is a 224 aa cytoplasmic transcription factor with a coiled leucine zipper flanked by multiple enzymatic substrates. It was identified by microarray expression analysis of LNCaP and C4-2 cell lines. It is a 2573 bp cDNA located on chromosome locus 8q21.1 (28). Besides the prostate, it is also expressed in other secretory tissues at low levels.

Although the exact role of PrLZ in prostate cancer is unknown, it has been shown that its expression decreases in normal prostatic tissue with age, it is upregulated in prostate cancer, and modulated by androgens (28, 29). Thus, PrLZ may be an androgen-regulated transcription factor involved in prostate carcinogenesis. Its application as a biomarker and as a target for therapy needs further investigation.

3.4.2. Androgen induced bZIP (AIbZIP)

AIbZIP was identified using PCR-select cDNA subtraction procedure (30). It is an androgen-induced protein that is a member of the bZIP superfamily which has a basic region adjacent to a leucine zipper (30). The 395 aa protein is encoded by a 1564 bp cDNA localized on chromosome 1q21.3.

Northern blot analysis detected AIbZIP only in the prostate; however RNase protection assay indicated its expression also in human breast cancer cell lines (30). Its levels are higher in prostate cancer compared to normal tissue. It shows a late-response expression pattern when LNCaP cells are treated with androgens (30). AIbZIP seems to be a gene expressed in an androgen-dependent manner in secretory cells and could provide an interesting target for therapy of androgen-responsive tumors.

3.4.3. Prostate cancer-associated diagnostic marker-1 (PCADM-1)

PCADM-1 protein has a 99% homology with human ribosomal protein S2 (RPS2), differing only by five amino acids at the NH_2-terminus (31). RPS2 has DNA-binding and leucine zipper-like regions, while PCADM-1 has four mutations at those locations which may enhance the DNA binding function (31).

PCADM-1 protein is specifically expressed in epithelial cells of cancerous prostatic tissue and it is not expressed in other tissues (normal or malignant), normal prostate, and BPH. Furthermore, the mutated protein is expressed at low levels in high grade PIN and increases with prostate tumor grade (31). Due to its high specificity and exciting expression pattern, PCADM-1 is currently being investigated as a tumor-specific biomarker.

3.5. Carbohydrate binding proteins

3.5.1. Prostate carcinoma tumor antigen (PCTA-1)

PCTA-1 is a 317 aa protein identified by monoclonal antibodies. It is part of the carbohydrate-binding human galectin family and is secreted by prostate cancer cells (32). PCTA-1 is localized in the cytoplasm before secretion (33). Despite being overexpressed in prostate cancer, it is also ubiquitously expressed at high levels in all human tissues studied (33). Hence, PCTA-1 may not be an ideal target as a biomarker or therapeutic interventions.

3.6. DNA repair enzymes

3.6.1. Prostate cancer antigen-1 (PCA-1)

PCA-1 is a 286 aa protein, identified by the fluorescent differential display method. It is localized on chromosome 11p11.12. It seems to be an alkylated DNA-repair protein. PCA-1 is overexpressed in prostate tumors; however it is also expressed ubiquitously in all human tissues tested, with highest levels in pancreas and testis (34).

3.7. Growth factors

3.7.1. Prostate androgen-regulated transcript 1 (PART-1)

PART-1 was identified using a prostate microarray (35). It is a 60 aa protein that is transcribed from a 2109 bp transcript mapped onto chromosome 5q12.1. Northern blot and RNA Master dot blot analyses showed prostate-restricted expression of PART-1 (with low-level expression in salivary gland) (35), RT-PCR showed some expression in several tissues (36). Its expression is upregulated by androgens in LNCaP cells up to 3.5-fold (35) and in malignant prostate tissue (36). Even though the function of PART-1 is unknown, it putatively contains two protein kinase C phosphorylation sites and one tyrosine kinase site (35), thus it may play a role in signal transduction pathway (36). Its role in carcinogenesis needs to be investigated.

3.8. Proteins of unknown function

3.8.1. Dresden prostate cancer 2 (D-PCa-2)

D-PCa-2 was identified using an EST database (37). It is localized on chromosome 15q15.1 and translates to a 150 aa sequence. It does not have homology with any known protein. It has two monopartite nuclear localization signal (NLS) regions (37).

A multiple tissue expression array of 57 adult tissues showed prostate-specific expression of D-PCa-2. However, real-time PCR showed low-level expression in human heart, liver, and leukocytes: albeit 2000-fold lower than in prostate. Its expression does not increase in prostate cancer.

3.8.2. Kallikrein-related in prostate 1 (KRIP1)

Kallikrein-related in prostate (KRIP1) is a unique transcript encoding a 134 aa protein from the *KLKP1* gene localized on chromosome 19q13.4 (38). It is the only member of the Kallikrein family that is not a serine protease. It has binding domains essential for signal transduction and is located in both the nucleus and cytoplasm. Northern blot analysis showed KRIP1 to be prostate-restricted, but not specific. Its expression is regulated by androgens and downregulated during prostate carcinogenesis (38). This is very similar to PSA, which is a member of the same family. It has not been examined whether KRIP1 is secreted or not.

3.8.3. New gene expressed in prostate-short (NGEP-S)

NGEP-S is 179 aa protein with a molecular mass of 19.6 kDa. It is localized in the nucleus and cytoplasm. It may undergo some form of post-translational modification. It has prostate-specific expression, with expression in both normal and cancerous prostate tissue (14). Currently, its function is unknown.

3.9. Metabolites

3.9.1. Sarcosine

Sarcosine is the N-methyl derivative of glycine. It is metabolized to glycine by the enzyme sarcosine dehydrogenase, while glycine-N-methyl transferase generates sarcosine from glycine. Sarcosine is a natural amino acid. Using differential metabolomic profiling of normal and cancer tissue it was found that sarcosine increases significantly in prostate tumors (39).. Using liquid and gas chromatography coupled with mass spectrometry found that this amino acid is secreted in higher amounts in urine of prostate cancer patients. An area under the curve (AUC) analysis found its predictive ability is better than standard PSA tests. Furthermore, analysis of multiple prostate cancer cell lines showed that sarcosine is higher in metastatic disease than organ-confined, and that it may play a role in disease progression (39). It seems that sarcosine detection may provide a useful biomarker in determining disease presence and progression.

3.9.2. Citrate

Nuclear Magnetic Resonance Spectroscopy (NMR) indicated that citrate may be an interesting diagnostic marker for prostate cancer. This metabolite is produced and stored at high levels in the prostate, and is a normal constituent of semen. A recent study found that there is a 2.8 fold increase in citrate levels in semen of prostate cancer patients compared to those with a normal gland (40). When examined in expressed prostatic secretions (EPS), there was a 2.7 fold decrease in citrate levels in cancer patients. Interestingly, citrate levels in BPH patients were not different from normal men. An AUC analysis of its predictive ability showed that it is a better indicator of cancer than PSA, with levels in semen being a slightly better predictor than levels in EPS (40). Hence, citrate levels may provide a diagnostic tool for the prostate cancer.

4. CONCLUSIONS

During the last five years, at least 21 genes/proteins and 2 metabolites have been identified that show prostate-specific/restricted expression patterns and may have application in diagnosis and treatment of prostate cancer.

Of the 12 cell surface transmembrane proteins, all except PMEPA1 are upregulated during prostate carcinogenesis, indicating that these transmembrane proteins have an important role in tumorogenesis. Three Golgi transmembrane proteins may be involved in modifications of several proteins implicated in prostate cancer. Indeed, a connection between Golgi membrane proteins and prostate cancer has been reported (27). The transcription factors described here seem to be specific to the prostate and three have been shown to be overexpressed in prostate cancer. Other genes may have several other functions unknown at this time.

Interestingly, a single locus contains three of these genes, namely NGEP-L and –S and D-TMPP, which are splice variants found within the anoctamin 7 (ANO7) gene on chromosome 2q37.3. ANO7 spans 36.6 kb and has 24 exons. While the two NGEP proteins and D-TMPP were discovered independently using EST databases, the NCBI Entrez Gene server attributes them to the same locus (http://www.ncbi.nlm.nih.gov/sites/entrez?db=gene). ANO7 gene/locus may have special significance in prostate carcinogenesis.

Recent research in prostate metabolomics has revealed an exciting potential area for future diagnostic measurements. While invasive, magnetic resonance spectroscopy and imaging (MRS/MRI) have advanced knowledge in this field, however *ex vivo* NMR techniques are at the forefront of current cancer detection research. Further work on other metabolites is being done and continues to carve the direction for the future (41).

It seems that multiple tumor markers used together provide a better diagnostic tool to diagnose carcinogenesis (42). Additionally, individual tumors express different markers and targeting several markers provides better treatment modalities (43). Whether used individually or in combination, biomarkers for the early detection and therapeutic targets against prostate cancer are urgently needed.

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