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PROSTATE-SPECIFIC GENES: PRESENT STATUS AND FUTURE DIRECTION

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1. ABSTRACT

Prostate cancer (prostatic adenocarcinoma) is the second highest cause of cancer mortality in men and the benign prostatic hyperplasia (BPH) affects 80% of men by age 80. The current diagnosis of prostate cancer relies on the serum levels of the well-known molecule designated as prostate-specific antigen (PSA). PSA, however, has limited sensitivity and specificity in appropriately detecting the earlier stages of abnormal prostate growth. Additional molecules need to be identified that are prostate-specific and have better sensitivity and specificity that can detect prostate cancer and BPH at an earlier stage for clinical management. Presently, several laboratories are actively engaged in searching for such molecules. The aim of this article is to review the current status of various prostate genes reported in the literature that have been claimed to be prostate-specific with a function in normal and abnormal prostate growth and development. The long-term objective is to define the lacunae that exist in the literature in our search for an ideal antigen.

2. INTRODUCTION

The prostate cancer is the most prevalent cancer in men including white, black, Asian/ Pacific islanders, American Indians/Alaska natives, and Hispanic men. As related to cancer mortality, it is second only to lung cancer. This is based upon the recent annual report published jointly by the American Cancer Society (ACS), the National Cancer Institute (NCI), the North American Association of Central Cancer Registries (NAACCR), and the Centers for Disease Control (CDC) (1). The present increase in the incidence of prostate cancer can be due to several factors including the explosion in the aging population. The availability of recent technologies (digital rectal exam and PSA test) has helped in the diagnosis of prostate cancer, which was difficult to diagnose previously (2-5). However, PSA has limited sensitivity and specificity in appropriately detecting the earlier stages of abnormal prostate growth. Additional molecules need to be identified that are prostate-specific and have better sensitivity and specificity. This will help to detect prostate cancer and

BPH at an earlier stage for clinical management. Presently, several laboratories are actively engaged in searching for such molecules. The various antigens/genes that have been isolated and characterized so far are described below. The molecular identities and functional parameters of the prostate-specific genes are found in Table 1 and their expression profiles are shown in Table 2.

3. DISCUSSION

3.1. Prostate-specific antigens identified by biochemical methods

3.1.1. Prostate-specific antigen (PSA)

Historically, Wang and associates have been credited for the name and purification of the prostate-specific antigen (PSA) from prostatic tissue (6, 7). PSA, a 34 kD protein, is produced exclusively by the columnar epithelium and periurethral glands. It is a member of the human kallikrein family, and thus has also been named hK3 (8). Kallikreins are proteases that cleave vasoactive kinin peptides from kininogen (9). PSA, however, functions as a chymotrypsin-like serine protease (10) cleaving substrates such as seminogelin I, seminogelin II, fibronectin, and insulin-like growth factor/binding protein in the seminal plasma which probably helps to maintain sperm motility (11-14).

PSA though specific to the prostate has limited sensitivity and specificity in appropriately detecting the earlier stages of abnormal prostate growth. A malignant prostatic cell produces less PSA than its normal or benign prostatic hyperplasia (BPH) counterparts (6, 15, 16). The elevated circulating PSA levels in urological patients can be due to PSA leakage into the bloodstream from abnormal prostate growth or inflammation such as prostatitis. PSA levels do not correlate to tumor size or density and it cross-reacts with other human glandular kallikreins. Thus, additional prostate-specific genes need to be identified.

3.2. Prostate-specific antigens identified by monoclonal antibodies

3.2.1. Prostate-specific membrane antigen (PSM/PMSℓ)

Prostate-specific membrane antigen (PSM) was recognized by using a monoclonal antibody (mAb), designated as 7E11-C5.3. This mAb, belonging to subclass IgG_1, was generated by immunizing mice with the membranes of the LNCaP cells (17). The full-length PSM cDNA was obtained by screening a LNCaP cDNA library with a PCR product coding for several of the PSM peptides. PSM is a 750 aa Type II integral membrane protein with a short intracellular amino terminal domain, and a large extracellular C-terminal domain. PSM has an apparent molecular weight of 100 kD after post-translational modification. PSM has poly-glutamate folate hydrolase activity thus functioning as a cell-surface peptidase in prostatic fluid (18).

Su and colleagues cloned and expressed an alternatively spliced variant of PSM, called PSM'. PSM' encodes for a 78 kD (266 aa) protein thought to be located in the cytoplasm since its cDNA lacked the transmembrane domain. PSM was found to be the predominate form in LNCaP cells and primary prostate cancer tissues, whereas PSM' predominates in the normal human prostate (19).

Subsequent studies have shown that PSM is not specific to the prostate. Both PSM and PSM' have been found to be expressed in the normal and coeliac disease duodenum. (20). PSM is also expressed in many other human tissues, thus PSM may not be appropriate marker for the specific diagnosis of prostate cancer (21).

3.3. Prostate-specific genes identified by a differential RNA display analysis

3.3.1. Prostatic carcinoma tumor-inducing gene-1 (PTI-1)

Fisher's group cloned and sequenced a gene designated as prostatic carcinoma tumor-inducing gene-1 (PTI-1). They hypothesized that specific prostatic carcinomas develop as a consequence of activation of cellular genes with transforming and tumorgenic potential so a gene that is overexpressed in the tumors will be prostate-specific (22). The experimental strategy involved extracting high molecular weight DNA from the LNCaP cells, and transferring the DNA with a neomycin-resistance selectable plasmid (pSV2-neo) into rat embryo fibroblast cells (CREF). They injected these cells into athymic nude mice to form tumors. Using the differential display technique using RNAs from these tumors, normal prostate, and BPH, a specific band corresponding to PTI-1 was identified that was expressed in tumor tissue (23).

The PTI-1 mRNA has a 630-bp 5′-untranlated region with 90% identity to Mycoplasma hyopneumoniae 23S ribosomal RNA, fused to base sequences which encode a truncated and mutated version of human translation elongation factor-1α (EF-1α). PTI-1 mRNA has been detected in carcinoma cell lines, 90% of prostate cancers, and is not expressed in normal prostate glands or in BPH. PTI-1 exhibits dominant transforming ability classifying it as an oncogene that is associated with prostate tumorgenesis. EF-1α is believed to ensure proper codon-anticodon binding interactions between mRNAs and transfer RNAs (tRNAs). Mutations in EF-1α could produce mutated proteins, disabling its proofreading task, a potentially dangerous event for prostate homeostasis (24). Fisher's group, furthermore, demonstrated that PTI-1 antisense RNA reverts the malignant phenotype in mice (22), thereby documenting PTI-1 as an oncogene which when directly blocked can nullify a cancer phenotype.

3.3.2. DD3

Isaacs' group identified DD3 by comparing mRNA expression patterns of normal, BPH, and tumor prostatic tissues. The full-length gene was obtained by screening a human prostate cancer cDNA library. The DD3 gene consists of four exons and spans a region of ~25 kb (25). The promoter of the DD3 gene has been isolated and characterized (26). There is no extensive open reading frame (ORF) which suggests that DD3 may function as a non-coding riboregulator. DD3 could not be detected in normal human tissue, tumor human tissue, and tumor human cell lines, indicating to be extremely restricted to the prostate. Bussemakers and associates found that DD3 is highly overexpressed in prostate cancer (25). Further studies are needed to examine its diagnostic potential in prostate carcinogenesis.

3.3.3. PCGEM-1

Similarly, Srikantan and associates used differential display analysis using normal and tumor prostate tissue RNAs to obtain a 530-bp partial cDNA fragment (27). This fragment was used to screen the normal prostate cDNA library and the resultant clone was designated as PCGEM-1. The 5′- and 3′- rapid amplification of cDNA ends (RACE) was preformed to obtain the full-length cDNA. It had no apparent ORF indicating that PCGEM-1 functions as a non-coding riboregulator. Analysis of normal human adult and fetal tissues, yeast RNA, and *E. coli* RNA revealed that PCGEM-1 is highly restricted to the prostate (27).

3.4. Prostate-specific genes identified by representational difference analysis

3.4.1. Prostate stem cell antigen (PSCA)

Prostate stem cell antigen (PSCA) was obtained by using representational difference analysis, a PCR-based subtractive hybridization strategy (28). PSCA encodes a 123 aa membrane-bound antigen related to stem cell antigen 2 (Sca-2), a member of the Thy-1/Ly-6 superfamily of glycosylphosphatidylinositol (GPI)-anchored cell surface antigens. The PSCA gene is overexpressed in 90% of high-grade intraepithelial neoplasia and hormone-resistant prostate cancers. PSCA is also expressed in a subset of basal epithelial cells in the normal prostate suggesting that prostate cancer may rise from the transformation of basal cells (28).

The biological function of PSCA is not known. However, due to its homology with Thy-1/Ly-6 superfamily, it is hypothesized that PSCA may play a role in self-renewal (anti-apoptosis) and proliferation of basal epithelial cells. PSCA appears to be expressed in a prostate-cancer restricted manner that allows it to be a possible immunogen for anti-cancer vaccination therapy (28).

3.5. Prostate-specific genes identified by Expressed SequenceTag (EST) databases

3.5.1. *NKX3.1*

Bieberich and colleagues cloned *Nkx3.1*, a mouse homologue of the Drosophila NK-3 gene (29) The human homologue was identified using a large EST database of prostate-specific cDNA sequences and the full-length clone obtained by screening a normal prostate cDNA library. Northern blot analysis revealed that it is prostate-specific and is demonstrated to be androgen-dependent (30). *Nkx3.1* is the earliest known marker for prostatic epithelium, and its expression appears to demarcate areas where prostatic buds will arise from the urogenital sinus epithelium (UGS). During postnatal growth, it is a specific marker for ductal outgrowth and morphogenesis (31). The maintenance of *Nkx3.1* expression requires functional androgen receptors initially in the mesenchyme and subsequently in the epithelium. *Nkx3.1* mutant mice showed reduced or no production of prostatic secretory proteins (32).

Shen's group showed that *Nkx3.1* can be a candidate prostate tumor suppressor gene because mice expressing a mutant *Nkx3.1* gene display epithelial hyperplasia and dysplasia. In addition, overexpression of human or murine *NKX3.1* suppresses growth and tumorigenicity of prostate carcinoma cells in culture (32). Although human *NKX3.1* maps to 8p21, a region deleted in 80% of all prostate carcinomas (30), its role as a tumor-suppressor gene requires warning since prostate tumor samples fail to reveal any mutations in the coding region thus deviating from the classical attribute of a tumor suppressor (33).

3.5.2. PDEF

PDEF was identified in the Human Genome Sciences EST database as a human expressed sequence tag (EST) from a subtracted BPH cDNA library (34). Extensive sequence analysis of PDEF showed that it was a novel member of the Ets transcription factor/oncogene family. The full-length cDNA was obtained by the RACE method using human prostate. PDEF encodes a 335 aa protein with a molecular size of 37.5 kD. Its expression is restricted to the epithelial layers of the prostate and to other hormone-regulated tissues namely, ovary, mammary gland, and salivary gland. PDEF functions as a prostate epithelium-specific transcription factor enhancing PSA expression via co-activation of the androgen receptor and also by androgen-independent mechanisms (34).

3.6. Prostate-specific genes identified by subtractive libraries

3.6.1. Prostase

Hood's group identified an enzyme designated as prostase, an androgen-regulated serine protease with prostate-restrictive expression, by constructing an enriched prostate cDNA library subtracted with normal brain, liver, and placental cDNAs. The 128-bp prostase cDNA fragment was then used as a probe to screen the normal prostate library to obtain the full-length clone (35).

The prostase cDNA encodes a putative 254 aa polypeptide and exhibits features of a secreted protein. Prostase shares 78% sequence homology with enamel matrix serine proteinase 1 (EMSP1) and 35% sequence homology to PSA. EMSP1, a porcine protein, is thought to be involved in remodeling of the organic matrix in tooth development (36). Northern analysis showed that prostase mRNA is expressed in hormonally responsive normal and neoplastic prostate epithelial tissues but not in prostate stromal tissues. Although the exact role is not clear, prostase may have a role in the degradation of extracellular matrix and in the activation of PSA and other proteases (35).

3.7. Prostate-specific genes identified by exon trapping

3.7.1. *TMPRSS2*

The serine protease, *TMPRSS2*, was first cloned from chromosome 21 using exon-trapping methods. A 216-bp PCR product derived from a trapped exon was used as a probe to screen a human heart cDNA library to obtain a longer 2.4- kb cDNA fragment. To generate the full-length cDNA, 5′- and 3′- RACE was preformed. Paoloni-Giacobino and associates demonstrated that the *TMPRSS2* 3.8-kb mRNA was strongly expressed in the small intestine (37). By utilizing cDNA microarray technology, it was shown that serine protease *TMPRSS2* exhibited increased expression in the presence of androgens and is overexpressed in prostate epithelium relative to other normal human tissues. The expression of *TMPRSS2* was localized to the prostate basal cells and to prostate carcinoma (38).

Table 1. Molecular identities and functional parameters of prostate-specific genes

		TISSUE SPECIFICITY[b]			
Gene	**Molecular Identity[a]**	**Immuno-histo-Chemistry**	**Northern Blot Analysis**	**RT-PCR Analysis**	**Function**
A. Identified by biochemical methods					
1. PSA	34 kD 240 aa	X	X	X	serine protease
B. Identified by monoclonal antibodies					
2. PSM	2.65 kb 100 kD 2653 nt	X	X	X	folate hydrolase
3. PSM′	2.08 kb 78 kD 2387 nt			X	folate hydrolase
C. Identified by differential RNA display					
4. PTI-1	2.0 kb 46 kD		X	X	oncogene
5. DD3	25.0 kb		X	X	non-coding riboregulator
6. PCGEM1	1.643 kb		X	X	non-coding riboregulator
D. Identified by representational difference analysis					
7. PSCA	1.0 kb 24 kD 123 aa		X	X	antiapoptosis/proliferation of basal epithelial cells
E. Identified by expressed sequence tag databases					
8. NKX3.1	3.5 kb 234 aa		X		homeobox gene/ tumor suppressor
9. PDEF	1.477 kb 37.5 kD 335 aa		X	X	co-regulator of androgen receptor
F. Identified by using a subtractive library					
10. Prostase	1.347 kb 254 aa		X		serine protease
G. Identified by exon trapping					
11. TMPRSS12	3.8 kb 492 aa		X		serine protease

[a]amino acids (aa), kilobase (kb), kilodalton (kD), nucleotides (nt), [b]method used for examining tissue specificity (X)

Table 2. Expression profile of prostate-specific genes

		EXPRESSION PROFILE[a]							
Gene	**Human Prostate tissue**			**Human tissue/cell line**		**Prostate cell line**		**Prostate xenographs**	
	N[1]	PC[2]	BPH[3]	Normal	Tumor	LNCaP	ANR[4]	AD[5]	AI[6]
1. PSA	+	++	++/±	-	-	+	-	NK	NK
2. PSM	+	++	+	+	NK	+	-	NK	NK
3. PSM′	+	-	+	NK	NK	+	NK	NK	NK
4. PTI-1	-	++	-	NK	+	+	+	NK	NK
5. DD3	+	++	-	-	-	+	-	NK	NK
6. PCGEM-1	+	++	NK	-	NK	+	-	NK	NK
7. PSCA	+	++	NK	+	NK	NK	NK	++	++
8. NKX3.1	+	±	±	+	-	+	-	NK	NK
9. PDEF	+	NK	NK	+	-	+	NK	NK	NK
10. Prostase	+	NK	NK	NK	NK	+	-	+	
11.TMPRSS12	+	+	NK	+	NK	+	-	+	+

[a]expression (+), overexpression (++), down-regulated expression (±), not known (NK), [1]normal (N), [2]prostate cancer (PC), [3]benign prostatic hyperplasia (BPH), [4]androgen non-responsive (ANR), [5]androgen-dependent (AD),[6]androgen-independent (AI)

4. CONCLUSIONS

Besides PSA, there are at least nine other proteins/genes that have been reported to have prostate-restrictive expression (Table 1). Five proteins namely, PSM, PTI-1, PSCA, prostase, *TMPRSS12* are found to be secreted in the bloodstream, and the first three are up-regulated during carcinogenesis (Table 2). However, their application in specific diagnosis and in immunotherapy of prostate cancer and BPH has not been extensively investigated. Additional prostate-specific genes need to be identified to provide a better understanding of the molecular mechanisms

of prostate physiology and pathophysiology. Novel markers for the diagnosis and treatment of benign prostate disease and cancer are urgently needed.

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