Prostate-localized and Androgen-regulated Expression of the Membrane-bound Serine Protease TMPRSS2

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Abstract

Genes regulated by androgenic hormones are of critical importance for the normal physiological function of the human prostate gland, and they contribute to the development and progression of prostate carcinoma. We used cDNA microarrays containing 1500 cDNAs to profile transcripts regulated by androgens in prostate cancer cells and identified the serine protease TMPRSS2 as a gene exhibiting increased expression upon exposure to androgens. The TMPRSS2 gene is located on chromosome 21 and contains four distinct domains, including a transmembrane region, indicating that it is expressed on the cell surface. Northern analysis demonstrated that TMPRSS2 is highly expressed in prostate epithelium relative to other normal human tissues. In situ hybridization of normal and malignant prostate tissues localizes TMPRSS2 expression to prostate basal cells and to prostate carcinoma. These results suggest that TMPRSS2 may play a role in prostate carcinogenesis and should be investigated as a diagnostic or therapeutic target for the management of prostate cancers.

Introduction

The proteins encoded by the serine protease gene family are protein-cleaving enzymes that play important roles in normal and pathological physiological processes including digestion (e.g., trypsin and chymotrypsin), tissue remodeling (e.g., stratum corneum chymotryptic enzyme and urokinase), blood coagulation (e.g., plasminogen activator and thrombin), fertility (acrosin), inflammatory responses (elastase), tumor cell invasion (uPA), and programmed cell death (granzymes). Several members of the serine protease family are of relevance for the study of normal and neoplastic prostate development. Three of these, PSA, hK2, and prostase/PRSS18, exhibit an expression profile that is essentially restricted to the human prostate (1, 2). These proteases are hypothesized to participate in a proteolytic cascade that culminates in the cleavage of semenogelin and the liquefaction of semen. Interestingly, androgenic hormones regulate the expression of each of these three prostate-specific proteases (1, 2).

Exploiting the tissue compartmentalization of PSA has revolutionized the management of patients with prostate cancer by providing a tool for the early diagnosis and subsequent monitoring of patients with prostate cancer. In addition, studies designed to characterize the regulation of PSA expression, identify PSA activators and substrates, and identify the different molecular forms of PSA have provided new insights into the pathophysiology of the disease and identified new therapeutic approaches. Several novel treatment strategies aim to exploit the tissue-restricted expression profile of PSA for gene therapy and immunotherapies and to target specific cytotoxic compounds to prostate tumor cells (1).

Recently, serine proteases and, specifically, those serine proteases that are specifically expressed in prostate cells, have emerged as important molecules for understanding the pathophysiology and mechanisms of the prostate cancer metastatic process. The enzymatic activities of these proteases, when they are expressed in ectopic locations such as the bone, may alter the local environment to favor tumor cell invasion, tumor growth, and bone remodeling. PSA has been shown to directly degrade extracellular matrix glycoproteins and facilitate cell migration (3). PSA and hK2 are capable of interacting with a variety of growth-modulating factors, such as components of the insulin-like growth factor system, parathyroid hormone-related peptide, the bone morphogenetic proteins, and activators of the potent proteolytic enzyme plasmin (1). In addition, PSA has been an extremely useful molecule in studies involving the development of androgen-independent prostate cancer growth due to its properties of androgen-regulated expression.

Our objective in this study was to identify additional androgen-regulated genes in prostate cancer cells that could be of importance in normal and neoplastic prostate growth and that could potentially serve as markers for the diagnosis and treatment of prostate cancer. We used cDNA microarrays comprised of 1500 cDNAs derived from human prostate tissues to examine the transcript expression profiles of the androgen-responsive LNCaP prostate cancer cells under conditions of androgen deprivation or androgen supplementation. One of the cDNAs that was up-regulated by androgens, 10D11, is identical to the recently described serine protease TMPRSS2. TMPRSS2 is a serine protease originally cloned from chromosome 21 using exon-trapping strategies (4). Our data indicate that the expression of TMPRSS2 is regulated by androgen and is highly expressed in normal and neoplastic prostate epithelium, relative to other human tissues. We hypothesize that TMPRSS2 may play a role in prostate carcinogenesis by virtue of its serine protease activity and that TMPRSS2 may serve as a target for prostate cancer diagnosis and treatment due to its probable localization on the cell surface.

Materials and Methods

Cell Culture and General Methods. DNA manipulations, including transformation, plasmid preparation, gel electrophoresis, and probe labeling, were performed according to standard procedures (5). The prostate carcinoma cell lines LNCaP, DU145, and PC3 were cultured in RPMI 1640 supplemented with 10% FCS (Life Technologies, Inc., Rockville, MD). LNCaP cells were transfected into RPMI 1640 with 10% CS-FCS (Life Technologies, Inc.) 24 h before androgen regulation experiments. This medium was replaced with fresh CS-FCS medium or CS-FCS supplemented with 1 nM R1881, a synthetic androgen (NEN Life Science Products, Inc., Rockville, MD). Cells were harvested for RNA isolation at 0, 1, 2, 4, 8, 24, 48, and 72 h.

Microarray Construction. A nonredundant set of 1500 prostate-derived cDNA clones was identified from the Prostate Expression Database, a public sequence repository of expressed sequence tag data derived from human...
prostate cDNA libraries (6). Individual clone inserts were amplified by PCR using primers corresponding to priming sites flanking the insert cloning site of the pSPORT1 plasmid (Life Technologies, Inc.) as described previously (7). PCR products were purified through Sephacryl S500 (Amersham Pharmacia Biotech, Inc., Piscataway, NJ), mixed 1:1 with denaturing Reagent D (Amersham Pharmacia Biotech, Inc.), and spotted in duplicate onto coated Type IV glass microscope slides (Amersham Pharmacia Biotech, Inc.) using a Molecular Dynamics GenII robotic spotting tool.

**Probe Construction, Microarray Hybridization, and Analysis.** Total RNA was isolated from LNCaP cells after 72 h of androgen depletion or supplementation using TRIZol (Life Technologies, Inc.) according to the manufacturer’s directions. Poly(A)+ RNA was purified using oligo(dT) magnetic beads (Dynal, Lake Success, NY). Fluorescence-labeled probes were made from 1 µg of poly(A)+ RNA or 30 µg of total RNA in a reaction volume of 20 µl containing 1 µl of anchored oligo(dT) primer (Amersham Pharmacia Biotech, Inc.); 0.05 mM Cy3-dCTP (Amersham Pharmacia Biotech, Inc.); 0.05 mM dCTP, 0.1 mM each dGTP, dATP, and dTTP; and 200 units of Superscript II reverse transcriptase (Life Technologies, Inc.). Reactants were incubated at 42°C for 90 min, followed by heating to 94°C for 3 min. Unlabeled RNA was hydrolyzed by the addition of 1 µl of 5 M NaOH and heating to 37°C for 10 min. One µl of 5 M HCl and 5 µl of 1 M Tris-HCl (pH 7.5) were added to neutralize the base. Unincorporated nucleotides and salts were removed by chromatography (Qiagen, Valencia, CA), and the cDNA was eluted in 30 µl of distilled H₂O. One µg of dA/dT 12–18 (Amersham Pharmacia Biotech, Inc.) and 1 µg of Cot1 DNA (Life Technologies, Inc.) were added to the probe, heat-denatured at 94°C for 5 min, combined with an equal volume of 2× microarray hybridization solution (Amersham Pharmacia Biotech, Inc.), and placed onto the microarray slide with a coverslip. Hybridization was carried out in a humid chamber at 52°C for 16 h. The slides were washed once with 1× SSC-0.2% SDS at room temperature for 5 min and then twice with 0.1× SSC-0.2% SDS at room temperature for 10 min. After washing, the slide was rinsed in distilled H₂O to remove trace salts and dried. Fluorescence intensities of the immobilized targets were measured using a laser confocal microscope (Molecular Dynamics, Sunnyvale, CA). Intensity data were integrated at a pixel resolution of 10 µm using ~20 pixels per spot and recorded at 16 bits. Local background hybridization signals were subtracted prior to comparing spot intensities and determining expression ratios. For each experiment, each cDNA was represented twice on each slide, and the experiments were performed in duplicate producing four data points per cDNA clone per hybridization probe. Intensity ratios for each cDNA clone hybridized with probes derived from androgen-stimulated LNCaP and androgen-starved LNCaP were calculated (stabilized intensity/starved intensity). A gene expression level change was treated as significantly different between the two conditions if all four replicate spots for a given cDNA demonstrated a ratio of 2 or <0.5 and the signal intensity was >2 SDs above the image background. We previously determined that expression ratios of <2-fold were not reproducible in our system (data not shown).

**Northern Analysis.** Total RNA was isolated from cell lines, normal prostate tissue, and prostate cancer xenografts using TRIZol according to the manufacturer’s directions. Ten µg of total RNA were fractionated on 1.2% agarose denaturing gels and transferred to nylon membranes by capillary denaturation. Blots were hybridized with DNA probes labeled with [α-32P]dCTP by random priming using the Random Primers DNA labeling kit (Life Technologies, Inc.), according to the manufacturer’s protocol. Filters were imaged and quantitated by using a phosphor-capture screen and ImageQuant software (Molecular Dynamics).

**In Situ Hybridization.** For mRNA in situ hybridization, recombinant plasmid pCRII-TOPO (Invitrogen, Carlsbad, CA), containing a 489-bp TMPRSS2 fragment (nucleotides 513–1002 of the published TMPRSS2 sequence; Ref. 4), was linearized to generate sense and antisense digoxigenin-labeled RNA probes. In situ hybridization was performed according to the manufacturer’s protocol on the Ventana GenII automated instrument (Ventana Medical Systems, Tucson, AZ). Programmed recipe files consisting of buffer rinses, probe digestion, hybridization, detection, and counterstains were optimized for the use of poly(A)+ RNA or 30 µg of total RNA in a reaction volume of 20 µl containing 1 µl of anchored oligo(dT) primer (Amersham Pharmacia Biotech, Inc.); 0.05 mM Cy3-dCTP (Amersham Pharmacia Biotech, Inc.); 0.05 mM dCTP, 0.1 mM each dGTP, dATP, and dTTP; and 200 units of Superscript II reverse transcriptase (Life Technologies, Inc.). Reactants were incubated at 42°C for 90 min, followed by heating to 94°C for 3 min. Unlabeled RNA was hydrolyzed by the addition of 1 µl of 5 M NaOH and heating to 37°C for 10 min. One µl of 5 M HCl and 5 µl of 1 M Tris-HCl (pH 7.5) were added to neutralize the base. Unincorporated nucleotides and salts were removed by chromatography (Qiagen, Valencia, CA), and the cDNA was eluted in 30 µl of distilled H₂O. One µg of dA/dT 12–18 (Amersham Pharmacia Biotech, Inc.) and 1 µg of Cot1 DNA (Life Technologies, Inc.) were added to the probe, heat-denatured at 94°C for 5 min, combined with an equal volume of 2× microarray hybridization solution (Amersham Pharmacia Biotech, Inc.), and placed onto the microarray slide with a coverslip. Hybridization was carried out in a humid chamber at 52°C for 16 h. The slides were washed once with 1× SSC-0.2% SDS at room temperature for 5 min and then twice with 0.1× SSC-0.2% SDS at room temperature for 10 min. After washing, the slide was rinsed in distilled H₂O to remove trace salts and dried. Fluorescence intensities of the immobilized targets were measured using a laser confocal microscope (Molecular Dynamics, Sunnyvale, CA). Intensity data were integrated at a pixel resolution of 10 µm using ~20 pixels per spot and recorded at 16 bits. Local background hybridization signals were subtracted prior to comparing spot intensities and determining expression ratios. For each experiment, each cDNA was represented twice on each slide, and the experiments were performed in duplicate producing four data points per cDNA clone per hybridization probe. Intensity ratios for each cDNA clone hybridized with probes derived from androgen-stimulated LNCaP and androgen-starved LNCaP were calculated (stabilized intensity/starved intensity). A gene expression level change was treated as significantly different between the two conditions if all four replicate spots for a given cDNA demonstrated a ratio of 2 or <0.5 and the signal intensity was >2 SDs above the image background. We previously determined that expression ratios of <2-fold were not reproducible in our system (data not shown).

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**Results**

**Microarray Hybridization.** We performed transcript profiling with microarrays of prostate-derived cDNAs to identify genes that are transcriptionally regulated by androgens in human prostate cancer cells. Of a total of 1500 distinct cDNAs represented on the microarray, we identified 9 with a >2-fold expression level increase in LNCaP cells after stimulation with androgens. These included PSA and hK2, two genes containing androgen response elements located in the 5'-flanking regions that have been shown to confer androgen responsiveness by functional studies (8, 9).

One androgen-regulated cDNA, 10D11, was homologous to the recently described serine protease TMPRSS2. Full-length sequencing of the microarray cDNA confirmed the identity of 10D11 as TMPRSS2 and provided additional 3' sequence information to the mRNA sequence available in the public databases. The expression level of TMPRSS2 increased 6-fold in androgen stimulated LNCaP cells, relative to androgen-deprived cells as assayed by microarray hybridization (Fig. 1A). Androgen-regulated expression of TMPRSS2 was confirmed by Northern analysis using the same LNCaP RNA that was used to construct the probes for microarray hybridization. Phosphorimaging quantitation of the Northern demonstrated a 9-fold induction of TMPRSS2 expression after 72 h of androgen exposure (Fig. 1B).

**Androgen-regulated and Prostate-localized Expression of TMPRSS2.** LNCaP cells were used to determine the time-course of androgen-induced TMPRSS2 expression. After steroid depletion, the cells were supplemented with 1 nm synthetic androgen R1881. TMPRSS2 expression could be detected in the normal prostate tissue and the steady-state LNCaP cells grown in FCS, but it was not detectable after 24 h of androgen depletion (Fig. 2A). TMPRSS2 expression could be detected after 2 h of androgen supplementation and increased steadily through the 48-h time point. We did not detect TMPRSS2 expression in the androgen-unresponsive PC-3 and DU-145 cell lines or in a short-term culture of prostate stroma consisting of fibroblasts and smooth muscle cells (Fig. 2A).

Normal secretory prostate epithelial cells and early-stage prostate carcinomas depend on androgens for growth. The emergence of an androgen-independent AI phenotype is a hallmark of advanced prostate cancer. In addition to androgen-independent proliferation, these neoplastic cells are also capable of androgen-independent PSA expression.

Expression of the Serine Protease TMPRSS2

We examined the expression of TMPRSS2 in human prostate cancers propagated in a xenograft system that recapitulates the androgen-dependent and -independent characteristics of human prostate cancer growth (10). TMPRSS2 was expressed in both the androgen-dependent and -independent tumors (Fig. 2A, PXe-AD and PXe-AI, respectively), a finding that parallels PSA expression in this system, indicating a possible dysregulation of TMPRSS2 control.

The distribution of TMPRSS2 transcripts in normal human tissues was determined by Northern analysis. Of 16 adult tissues examined, TMPRSS2 message was predominantly expressed in prostate, with very low expression levels in colon, lung, liver, kidney, and pancreas, and no detectable expression in spleen, thymus, testes, ovary, peripheral leukocytes, heart, brain, placenta, or skeletal muscle (Fig. 2B).

**TMPRSS2 Expression in Prostate Basal Cells and Prostate Carcinoma.** Normal prostate contains two major epithelial cell populations, the luminal secretory cells and the basal cells. *In situ* hybridizations were performed on sections of normal prostate by using an antisense RNA probe specific for TMPRSS2 to localize its expression. TMPRSS2 was expressed exclusively in the normal basal cell population (Fig. 3A and B). Little to no staining was seen in stroma, secretory cells, or infiltrating lymphocytes. Hybridization with sense TMPRSS2 RNA probes showed no background staining (Fig. 3C). *In situ* hybridizations with TMPRSS2 antisense and sense probes were also performed on sections of primary prostate adenocarcinoma obtained from radical prostatectomy specimens. Adenocarcinoma cells were uniformly positive for TMPRSS2 expression (Fig. 3D and E). Hybridization with sense TMPRSS2 RNA probes showed no background staining (Fig. 3F).

**Sequence Analysis of the Putative TMPRSS2 Promoter.** We used a genome-walking strategy to clone DNA sequence 5’-upstream of the TMPRSS2 coding region to identify potential androgen-regulatory sites. An 1100-bp DNA fragment overlapping the TMPRSS2 cDNA by 100 nucleotides was obtained. It contained 870 bp of sequence 5’ to the putative transcriptional start site. Analysis of this upstream sequence with a neural network promoter prediction algorithm5 recognized a 51-bp sequence beginning 250 nucleotides 5’ of the putative translational start site that correlates highly (score of 0.97, indicating a 0.1% false-positive prediction rate) with consensus promoter elements. Numerous putative transcription-factor binding sites were identified using SIGSCAN,6 including consensus sites for SP1, Z-box, AP1, and AP2 regulation. A 15-bp sequence with significant homology to the consensus androgen response element is located at position −148, relative to the putative transcriptional start site (Fig. 4).

**Discussion**

Transcript profiling by hybridization to microarrays of cDNAs allows for the simultaneous analysis of the expression levels of thousands of genes (11). The technique is ideally suited to determine individual and global gene expression level changes that occur in a well-controlled biological system (12). We used the cDNA microarray method to identify genes that are transcriptionally regulated by androgens in the androgen-responsive prostate cancer cell line LNCaP. This study determined the androgen-regulated expression of the serine protease TMPRSS2, a gene that we have subsequently shown to be localized in expression to normal and neoplastic prostate epithelium.

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**Fig. 1.** Androgen induction of TMPRSS2 expression in LNCaP cells. A, representative duplicate cDNA microarray hybridizations of TMPRSS2 with (+A) or without (−A) exposure to androgen. Arrow, TMPRSS2 cDNA clone. B, Northern analysis with a TMPRSS2 probe hybridized to the same LNCaP RNA used for the microarray hybridization (+A) or (−A) androgen treatment.

**Fig. 2.** Androgen-regulated and prostate-localized TMPRSS2 expression. A, Northern analysis using a TMPRSS2 probe with RNA extracted from normal prostate (Lane NP), LNCaP at steady state (Lane SS), LNCaP after 24 hr of androgen deprivation (Lane 0), LNCaP at specified times (in h) after androgen exposure (Lanes 1, 2, 4, 8, 24, and 48), the PC3 (Lane PC3) and DU145 (Lane DU145) prostate cancer cell lines, the androgen-dependent (Lane PXe-AD) and androgen-independent (Lane PXe-AI) prostate cancer xenografts, and prostate stroma (Lane PS). A probe for β-actin was used to estimate RNA loading (bottom). B, Northern blot analysis of TMPRSS2 expression in 16 human tissues. The filter was obtained from Clontech and contained 2 μg of poly(A)+ RNA in each lane. A β-actin control probe (bottom) was used to verify equivalent loading of RNA.

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The *TMPRSS2* gene encodes a predicted protein of 492 amino acids, with five distinct domains (4). On the basis of homology to other proteins, these regions comprise a serine protease domain of the S1 family; a scavenger receptor cysteine-rich domain, possibly involved in binding to cell surface molecules; a class A low-density lipoprotein domain; a transmembrane domain; and a cytoplasmic domain (4). The published study describing *TMPRSS2* reported high *TMPRSS2* expression in small intestine and weak expression in several other tissues (4). In contrast, our data indicate that *TMPRSS2* is highly expressed in normal human prostate tissue relative to other human tissues and that *TMPRSS2* is androgen-regulated in prostate cancer cells. A low level of *TMPRSS2* expression is present in colon, lung, kidney, and pancreas. We believe that the original description of high *TMPRSS2* expression in small intestine resulted from an error in the Northern analysis due to a transposition of the commercially prepared Northern blot, such that the lane containing prostate mRNA was interpreted as containing small intestine mRNA.

Analysis of the predicted *TMPRSS2* protein indicates that *TMPRSS2* is a type II integral membrane protein that is most similar to the mammalian hepsins, a class of proteins that are important for cell growth and maintenance of normal cell morphology (13). Hepsin has been shown to be overexpressed in ovarian carcinomas and is suggested to be a candidate mediator of the invasive process and growth capacity of ovarian tumor cells (14).

The normal function of *TMPRSS2* is not known. Activators and substrates of this protease have yet to be determined. The features of the protease domain of *TMPRSS2* are compatible with the S1 family of serine proteases with chymotrypsin as the prototype member (15). The Asp435 residue in the substrate-binding site indicates that *TMPRSS2* will have trypsin-like proteolytic activity, with cleavage after Lys or Arg residues. Thus, *TMPRSS2* could be a natural activator of the precursor forms of PSA and hK2. The zymogen form of *TMPRSS2* is also predicted to be proteolyzed by trypsin-like enzymes that cleave the Arg-Ile bond of the NH₂ terminus of the protease domain. Thus, *TMPRSS2* could be autocatalytic or could be activated by other trypsin-like proteases in the prostate, such as hK2 or prostase/PRSS17. The characterization of *TMPRSS2* as a serine protease expressed in prostate epithelium adds another member to a group of proteases that may participate in a cascade mechanism of enzymatic activity.

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**Fig. 3.** In situ hybridization with antisense RNA probe for *TMPRSS2* expression in normal and malignant prostate tissue. Low-power (A) and high-power (B) magnification showing *TMPRSS2* expression in basal cells of normal prostate tissue (closed arrowheads) but not in secretory luminal epithelium (open arrowheads). C, sense control *TMPRSS2* probe showing no background staining in normal prostate tissue. Low-power (D) and high-power (E) magnification showing *TMPRSS2* expression in primary prostate carcinoma cells. F, Sense control of *TMPRSS2* probe showing no background staining in cancerous prostate tissue. The in situ images were digitally acquired, and the staining intensity was enhanced to show contrast in A and B.

**Fig. 4.** Putative androgen response element in the *TMPRSS2* gene. An analysis for putative promoter and regulatory elements was performed with the SIGSCAN program. A sequence with high homology to consensus androgen response element (ARE) sequence is shown boxed in a position relative to the putative transcriptional start site. Consensus androgen response elements and specific functionally tested androgen response element sequences are aligned below the putative *TMPRSS2* androgen response element. Sequence codes: F, C or T; W, A or T. *GPX5*, an androgen-regulated epididymis-specific gene (25). Superscript 26, 8, and 25 are reference numbers.
reactions in seminal fluid that is analogous to the fibrinolytic and blood coagulation system (16, 17).

As has been suggested for other prostate serine proteases, the enzymatic activities of TMPRSS2 may also play a direct role in the process of prostate carcinogenesis. PSA has been shown to degrade components of the extracellular matrix (3), an essential step in the process of tumor cell invasion and metastasis. HK2 is able to activate the proteolytic enzyme uPA, a protease that has been associated with prostate cancer invasion and metastasis (17, 18). The activation of pro-uPA occurs by cleavage of the Lys^{158}-Ile^{159} bond, a site that should also be susceptible to proteolysis by TMPRSS2. The activity of TMPRSS2 on these and other substrates remains to be determined in the laboratory.

The localization of TMPRSS2 expression to neoplastic prostate cells and to the basal cell compartment of normal prostate tissue is intriguing, in that other prostate serine proteases are predominantly expressed in the secretory luminal cells. The phenotypic similarities between normal luminal cells and prostate cancer cells, including common cytokeratin profiles and the expression of PSA and hK2, suggest a secretory luminal cell origin of prostate adenocarcinomas (19). However, a number of recent studies propose that at least some prostate cancers may arise from the transformation of basal cells (20, 21). Prostate stem cell antigen, a recently describedgene with expression localized to a subset of basal cells in normal prostate tissues is overexpressed in the majority of prostate carcinomas (21). The expression of other basal cell genes, such as c-met, Bcl-2, and high molecular weight cytokeratins have also been identified in populations of prostate carcinoma cells (22, 23). The expression profile of TMPRSS2 provides further support that some prostate cancers may arise from the transformation of basal cells. An alternative explanation is that malignant transformation of the luminal cells results in the re-expression of previously silenced basal cell genes. However, it will be important to determine the expression of TMPRSS2 protein because it is possible that, although TMPRSS2 message was not detected in luminal cells, TMPRSS2 protein may be present.

The predicted cell surface expression of TMPRSS2 suggests that it may be exploited as a diagnostic or therapeutic target for treating prostate cancers. It is also possible that membrane-bound TMPRSS2 could be cleaved to generate a circulating form as has been suggested for the hepsin protease (24). In view of the significant biological and clinical attributes of prostate serine proteases such as PSA, further studies are indicated with the TMPRSS2 protein.

References

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