Catalytic Cleavage of the Androgen-regulated TMPRSS2 Protease Results in Its Secretion by Prostate and Prostate Cancer Epithelia

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ABSTRACT

We identified TMPRSS2 as a gene that is down-regulated in androgen-independent prostate cancer xenograft tissue derived from a bone metastasis. Using specific monoclonal antibodies, we show that the TMPRSS2-encoded serine protease is expressed as a M, 70,000 full-length form and a cleaved M, 32,000 protease domain. Mutation of Ser-441 in the catalytic triad shows that the proteolytic cleavage is dependent on catalytic activity, suggesting that it occurs as a result of autoleavage. Mutational analysis reveals the cleavage site to be at Arg-255. A consequence of autocatalytic cleavage is the secretion of the protease domain into the media by TMPRSS2-expressing prostate cancer cells and into the sera of prostate tumor-bearing mice. Immunohistochemical analysis of clinical specimens demonstrates the highest expression of TMPRSS2 at the apical side of prostate and prostate cancer secretory epithelia and within the lumen of the glands. Similar luminal staining was detected in colon cancer samples. Expression was also seen in colon and pancreas, with little to no expression detected in seven additional normal tissues. These data demonstrate that TMPRSS2 is a secreted protease that is highly expressed in prostate and prostate cancer, making it a potential target for cancer therapy and diagnosis.

INTRODUCTION

Prostate cancer is a hormone-regulated disease that affects men in the later years of life. Untreated prostate cancer metastasizes to lymph nodes and bone in advanced cases. In such cases, the treatment consists of antagonizing the androgenic growth stimulus that feeds the tumor by chemical or surgical hormone ablation therapy (1). An unfortunate consequence of antiandrogen treatment is the development of androgen-independent cancer. Androgen-regulated genes, such as the gene encoding PSA,3 are turned off with hormone ablation therapy but reappear when the tumor becomes androgen independent (2). This suggests that alternative signaling pathways, such as activated tyrosine kinase receptors, can replace the androgen signal (3, 4).

To understand the molecular events surrounding the progression of prostate cancer to androgen independence, we used LAPC-9, a human prostate cancer xenograft derived from a bone metastasis, which can mimic the transition from androgen dependence to androgen independence (5). A subtractive hybridization method (6) was used to identify androgen-regulated genes by subtracting cDNAs from the AD xenograft. This strategy resulted in the identification of the TMPRSS2 gene, which encodes a putative transmembrane serine protease (7).

TMPRSS2 was predicted to be a type II transmembrane protein with an extracellular COOH terminus containing the protease domain and an intracellular NH2 terminus. TMPPRSS2 was recently shown to be regulated by androgens in the LNCaP prostate cancer cell model (8). To characterize the TMPRSS2 protein in prostate and prostate cancer, we generated Mabs toward the protease domain. Using these Mabs, we demonstrate that TMPRSS2 protein is highly expressed in prostate secretory epithelium and in prostate cancer and that the protein expression is also dependent on an androgen signal. The protease domain is released by an autocatalytic cleavage mechanism, resulting in its secretion into the extracellular space.

MATERIALS AND METHODS

Cell Lines and Human Tissues.
All human cancer cell lines used in this study were obtained from the American Type Culture Collection. All cell lines were maintained in DMEM with 10% FCS. Primary prostate epithelial cells (PrEC) were obtained from Clonetics and grown in prostate epithelial basal medium (PrEBM) media supplemented with growth factors (Clonetics). The AD LAPC-4 and LAPC-9 xenografts were routinely passaged as small tissue chunks in SCID male mice (5, 9). AI sublines of the xenografts were derived as described previously (5, 9) and passaged in castrated males or in female SCID mice.

Human tissues for RNA and protein analyses were obtained from the Human Tissue Resource Center at the University of California Los Angeles (Los Angeles, CA), from the National Disease Research Interchange (Philadelphia, PA), and from QualTek, Inc. (Santa Barbara, CA).

SSH. Tumor tissue and cell lines were homogenized in Trizol reagent (Life Technologies, Inc.) using 10 ml /g tissue or 10 ml /108 cells to isolate total RNA. Polyadenylated RNA was purified from total RNA using Qiagen’s Oligoex mini and Midi kits. SSH was performed using the PCR-Select cDNA Subtraction Kit (Clontech, Palo Alto, CA; Ref. 6). Tester cDNA was derived from the AD LAPC-9 xenograft, whereas driver cDNA was obtained from the AI subline of LAPC-9. SSH-derived gene fragments were processed and analyzed as described previously (10).

Expression Analysis. Northern blotting was performed on 10 µg of total RNA prepared from cell lines and LAPC xenografts using random hexamer-labeled (Boehringer Mannheim) TMPRSS2 cDNA. The human multitissue mRNA blots containing 2 µg of mRNA per lane were purchased from Clontech and probed with TMPRSS2 cDNA.

Constructs. TMPPRSS2 cDNA was isolated by screening a human prostate cDNA library (Life Technologies, Inc.) using clone 20P1F12, a TMPPRSS2 SSH-derived fragment, as a probe. For protein expression in 293T cells, TMPPRSS2 was cloned into pcDNA 3.1 Myc-His (Invitrogen, Carlsbad, CA) and retroviral vector PScrtnoe (11). Cells were transfected with either PScrtnoe expressing TMPPRSS2 or a COOH-terminal His-tagged TMPPRSS2.

Single point mutants of TMPPRSS2 were generated using a two-step PCR method. Arg-240, Arg-252, and Arg-245 were mutated to glutamines, and Ser-441 was mutated to alanine. Using a full-length cDNA clone as template, a 5′-TMPPRSS2 PCR fragment was generated using one mutagenic primer (5′-GGCCCTTCAGGCTACCC-3′ for S441A mutant, 5′-CGGAGGGTTACATGGTAAAGAAC-3′ for R240Q, 5′-CTGCTCTGGTTGCCTGAGTTC-3′ for R252Q, and 5′-CCCAATCTGTCCTGGCGG-3′ for R255Q) and one 5′-specific TMPPRSS2 primer containing the start codon, a kozak sequence, and an EcoRI site for cloning (5′-CGAATTCGACAGATG-TGCTTGA-3′). The 3′ fragment was generated by PCR using the reverse complement of the mutagenic primer (5′-GGCTTACGCGAGGCAGGGCC-3′ for S441A, 5′-GTTTCTTTTCAATGATAGCCTGG-3′ for R240Q, 5′-
RESULTS

Identification of TMPRSS2 as a Gene Down-Regulated in AI Prostate Cancer Xenografts. The prostate cancer bone metastasis-derived LAPC-9 xenograft (5) was used to identify genes that are differentially regulated during the transition from androgen dependence to androgen independence. A gene fragment corresponding to the 3' untranslated region of the TMPRSS2 gene was identified as down-regulated in LAPC-9 AI tissue. TMPRSS2 was originally discovered by exon trapping for chromosome 21 (7) and subsequently shown to be androgen regulated in the prostate cancer cell line LNCaP (8). We isolated a full-length cDNA for TMPRSS2 from a normal prostate library. Sequence analysis of the cDNA revealed an open reading frame of 492 amino acids, as reported previously (7). However, closer examination of the sequence showed eight differences in the nucleotide sequence that result in six amino acid differences at positions 160, 242, 329, 449, 489, and 491 compared with the previously published sequence (Fig. 1). All six differences were confirmed by sequencing additional TMPRSS2 cDNA clones and gene fragments derived from normal prostate and LAPC-4 and LAPC-9 xenograft cDNA libraries. All of these differences occur in the putative extracellular domain; two of them (amino acids 160 and 242) reside in the SRCR domain, whereas the others are all located within the protease domain.

**TMPRSS2 Is Expressed at High Levels in Prostate Cancer Tissues and Colon Cancer Cell Lines.** To analyze TMPRSS2 expression in cancer tissues and cell lines, Northern blotting was performed on RNA derived from the LAPC xenografts and a panel of prostate and non-prostate cancer cell lines. The results show high expression levels of a 3.8-kb TMPRSS2 transcript in all of the LAPC xenografts and in colon cancer cell lines (Fig. 2). Similar expression levels were detected in prostate, LAPC-4 AD, LAPC-4 AI, LAPC-9 AD, and LNCaP cell lines. Lower levels of TMPRSS2 were seen in LAPC-9 AI and PC-3 cells, with no expression seen in DU145. High levels of TMPRSS2 expression were also detected in three of four colon cancer cell lines, including LoVo, T84, and Colo-205 (Fig. 2). Analysis of other cancer cell lines, including breast, testicular, ovarian, pancreatic and cervical showed no detectable expression (data not shown).

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![Fig. 1. Schematic representation of TMPRSS2. The TMPRSS2 cDNA was cloned from a normal prostate cDNA library. The sequence reveals eight differences in the nucleic acid sequence that result in six amino acid differences (shown with numbering) compared with the previously published sequence. The different domains are indicated with different shading and correspond to the following residues: 249–252 contains the protease; 149–242 contains the SRCR; 113–148 contains the LDLRA; and 84–106 contains the transmembrane (TM) region. The region in the protease domain contains the stop codon and an XbaI site for cloning (5'CGTCTA-GATTAGCCGTCTGGCCTTA-3'). For the second round of PCR, the 3' and 5' fragments were used as templates. The final PCR product was digested with EcoRI and XbaI and cloned into pSRαMSV-dNe. Protein expression was analyzed after transfection into 293T cells.](image1)

![Fig. 2. High expression levels of TMPRSS2 in prostate, prostate cancer, and colon cancer cells. Northern blots containing RNA derived from normal tissues, prostate cancer xenografts and cell lines, and colon cancer cell lines were probed using a TMPRSS2 cDNA fragment. Lane 1, prostate; Lane 2, LAPC-4 AD cells; Lane 3, LAPC-4 AI cells; Lane 4, LAPC-9 AD cells; Lane 5, LAPC-9 AI cells; Lane 6, LNCáP cells; Lane 7, PC-3 cells; Lane 8, DU145 cells; Lane 9, CaCo-2 cells; Lane 10, LoVo cells; Lane 11, T84 cells; Lane 12, Colo-205 cells. All RNA samples were normalized with a β-actin probe. Size standards (in kb) are indicated on the right.](image2)
TMPRSS2 showed the highest expression of the gene in small intestine (7), whereas a second report showed the highest expression of the gene in prostate tissue (8). Northern blotting of 16 normal tissues using TMPRSS2 cDNA as a probe showed the highest expression of a 3.8-kb transcript in normal prostate (Fig. 2), confirming the results obtained by Lin et al. (8). Lower expression levels were also detected in pancreas, kidney, and lung. No significant expression was detected in small intestine.

**TMPRSS2 Protein Is Proteolytically Cleaved in Tissues and Cell Lines.** In vitro-translated TMPRSS2 appears predominantly as the predicted Mr, 54,000 protein, with a minor breakdown product of Mr, 32,000 (Fig. 3A). Mouse Mabs were generated toward the protease domain of TMPRSS2 to study its expression pattern in cells and tissues. Western blotting of protein extracts from 293T cells using the 1F9 MAb showed equal expression of two protein species with apparent molecular weights of 70,000 and 32,000 only in TMPRSS2-transfected cells and not in control vector-transfected cells (Fig. 3). Similar results were obtained using other Mabs directed against TMPRSS2 (data not shown). The Mr, 70,000 cellular isoform of TMPRSS2 is larger than the predicted and in vitro-translated full-length protein, suggesting that it is modified, possibly by glycosylation. The TMPRSS2 protein sequence contains three possible N-linked glycosylation sites at residues 128, 213, and 249. Preliminary studies using N-glycosidase F-treated TMPRSS2 protein indicate that the protein is indeed glycosylated and that glycosylation accounts for some of the difference between the predicted and observed molecular weight of cellular TMPRSS2 (data not shown). The Mr, 32,000 form may be a proteolytically cleaved fragment containing the COOH-terminal epitopes recognized by the antibody.

Analysis of human tissue and cell lines, which vary expressing levels of TMPRSS2 by Northern blotting, showed the same pattern of protein expression as seen in TMPRSS2-transfected 293T cells. TMPRSS2 expression was detected in protein lysates from LAPC-4 AD, LAPC-9 AD, and LNCaP cells, but not in the LAPC-9 AI, AI PC-3, and DU145 AI cells (Fig. 3, B and C). Analysis of three prostate cancer specimens and the matched adjacent tissue with apparently normal morphology showed significant expression of TMPRSS2 protein in all samples (Fig. 3D). High expression was also detected in the colon cancer cell line Colo-205 (Fig. 3B).

**TMPRSS2 Protein Expression Is Dependent on the AR Signal.** Our analysis above shows that expression of TMPRSS2 protein is undetectable in the AI LAPC-9, PC-3, and DU145 cell lines. To extend these findings, as well as the observation by Lin et al. (8) that TMPRSS2 message is androgen regulated in LNCaP cells, we androgen-deprived LNCaP cells and an LAPC-9 AD cell line derived from the LAPC-9 AD xenograft, which expresses the wild-type AR and PSA (data not shown). TMPRSS2 protein expression in the androgen-deprived cells was compared with expression in LNCaP cells (Fig. 4A) and LAPC-9 AD cells (Fig. 4B) after treatment with mibolerone, a synthetic androgen. The results show that TMPRSS2 expression was significantly reduced during androgen deprivation in both cell lines and reappeared during mibolerone treatment. PSA protein levels were measured in parallel, showing a similar regulation (data not shown).

PC-3 cells, which do not express the AR and grow in an AI manner, express only low levels of TMPRSS2 (Fig. 4C). However, PC-3 cells that have been engineered to express the wild-type AR (PC-3 AR) express significant levels of TMPRSS2 when treated with mibolerone (Fig. 4C). Interestingly, only the full-length TMPRSS2 protein is detected in untreated PC-3 AR cells and control PC-3 neo cells. Treatment with mibolerone not only increases total TMPRSS2 expression but also induces expression of the Mr, 32,000 cleavage product. This indicates that TMPRSS2 expression in prostate cancer cells is dependent on an androgen signal and that cleavage may be a function of expression level.

**TMPRSS2 Protease Is Released into Cell Culture Medium and Mouse Serum by Prostate Cancer Cells.** Structural predictions for TMPRSS2 suggest that it is a type II transmembrane protein with an extracellular protease domain (Fig. 1). The size of the cleaved Mr, 32,000 TMPRSS2 fragment suggests that it contains the entire protease region. Cleavage of this domain is thus predicted to result in the release of the protease into the extracellular space. To test this hypothesis, media were collected from androgen-starved and androgen-stimulated LNCaP cells. The media were then analyzed for the presence of TMPRSS2 protein by Western blotting using anti-TMPRSS2 Mab. The results show a clear detection of cleaved TMPRSS2 protein in the media of androgen-stimulated cells, but not in androgen-deprived cells (Fig. 4D). The amount of protease present in the media is directly correlated to the amount of TMPRSS2 protein present in the cell extracts, which increases with an increased dose of mibolerone (Fig. 4D). Similar release of protease into cell media was also observed for PC-3 AR cells that were treated with mibolerone (Fig. 4D). Secreted TMPRSS2 protease is also detected in the sera of male mice that harbor LNCaP tumors, but not in sera derived from naive males (Fig. 4D). The Mr, 70,000 form of TMPRSS2 is not detected in the cell media of TMPRSS2-expressing cells or in the sera of LNCaP tumor-bearing mice.

**TMPRSS2 Cleavage Is a Consequence of Autocatalytic Activity.** To determine whether the cleavage of TMPRSS2 is dependent on its own catalytic activity, Ser-441 of the catalytic triad in the protease domain was mutated to alanine (S441A). Mutant TMPRSS2 cDNA was cloned into a retroviral vector for expression in 293T cells. Western blot analysis of cell extracts of 293T cells transfected with either wild-type or S441A mutant TMPRSS2 showed that in contrast...
to wild-type protein, TMPRSS2 S441A appeared as a single protein species with an apparent molecular weight of 70,000 (Fig. 5). Cell media analysis shows the presence of the cleaved M₄ 32,000 protease domain only in media collected from cells transfected with wild-type TMPRSS2 and not in media from S441A-transfected cells (data not shown). TMPRSS2 with a COOH-terminal myc-His tag also showed predominant expression of the full-length tagged protein, although some cleavage product is detected (Fig. 5). The myc-His tag at the COOH terminus of the protease domain may exert some inhibitory activity on the proteolytic cleavage. These results suggest that the proteolytic cleavage of TMPRSS2 in cells and tissues is a consequence of autocatalytic activity.

The protease domain of TMPRSS2 belongs to the S1 family of serine proteases with cleavage activity after Arg or Lys residues. Examination of the protein sequence reveals the presence of three Arg residues (amino acids 240, 252, and 255) near the NH₂-terminal region of the TMPRSS2 protease domain. To identify the actual cleavage site of the protease domain, the three Arg residues were mutated to Gln residues. The mutants were expressed in 293T cells by transient transfection and analyzed by Western blotting. Only the R255Q mutation resulted in a loss of cleavage, identifying the Arg-255-Ile-256 bond as the proteolytic cleavage site. 293T cells were transfected with the different mutants that are underlined in bold. The actual cleavage site at Arg-255 is indicated by an arrowhead. Western blots of 293T cell lysates (20 μg of protein) were probed with 1F9 MAb. TMPRSS2 staining of androgen-deprived LNCaP showed very little staining of the cells. In contrast, the majority of androgen-stimulated LNCaP cells growing in regular media exhibited staining similar to that seen in androgen-stimulated cells (data not shown). The majority of staining appeared to be localized to granular structures within the cell.

Analysis of 20 prostate clinical specimens showed moderate to strong staining in the glandular epithelia of all normal prostate, prostatic intraepithelial neoplasia (PIN), and prostate cancer samples tested (Fig. 6, c and d; Table 1). The signal appeared to be strongest at the apical side of the secretory cells, and in most cases granular staining was seen, as observed in LNCaP. The prostate tissue staining was specific because GST-TMPRSS2 immunogen could competitively inhibit staining of prostate cancer tissue, whereas GST alone could not (Fig. 6, e and f). Similar to PSA, TMPRSS2 protein was found to accumulate within the lumen of the epithelial glands (Fig. 6,
and h), indicating that TMPRSS2 protein is secreted by the secretory epithelia. This staining pattern is in contrast to the RNA in situ hybridization analysis, which showed expression of TMPRSS2 RNA primarily in the basal cell layer of normal prostate glands and not in the secretory epithelium (8). It is possible that TMPRSS2 RNA is present in both compartments, but that basal cell RNA is more stable.

Analysis of 10 non-prostate tissues showed no staining in most tissues (Table 1), including kidney and lung, which express some TMPRSS2 message. Protein expression was detected in normal pancreas samples and normal colon and colon cancer tissues (Table 1). The pancreatic staining was restricted to the pyramidal exocrine acinar cells, with no staining detected in the islets of Langerhans (data not shown). The staining in normal colon appeared primarily within crypts of the mucosal lining but was significantly less intense than normal prostate staining (data not shown). The staining in colon cancer seemed to concentrate in luminal areas, indicating possible secretion of the antigen by colon cancer cells.

### DISCUSSION

TMPRSS2 was identified during an effort to discover genes that are differentially expressed between hormone-dependent and hormone-independent prostate cancer tissue. We found TMPRSS2 to be down-regulated in LAPC-9 AI, a prostate cancer xenograft originally derived from a bone metastasis. Our sequence, which was derived from a normal prostate library, contains several differences compared with the previously published sequence, which was cloned from a heart library (7). These differences occur primarily in the protease domain and could have functional implications for protease activity or substrate specificity of the TMPRSS2 protein. Extensive expression profiling by us and others (8) has determined that TMPRSS2 is most highly expressed in prostate and prostate cancer cell lines and tissues. However, our studies show that TMPRSS2 protein is also expressed in pancreatic, colon, and colon cancer tissue. High expression levels were...
detected particularly in colon cancer cell lines, indicating a possible up-regulation of TMPRSS2.

In prostate cancer cells and tissues, TMPRSS2 is regulated by an androgen signal. Androgen deprivation and stimulation experiments in LAPC-9 xenograft and LAPC-9 cell line, which express the wild-type AR (5), and in LNCaP cells show that TMPRSS2 protein expression is increased with androgen stimulation. PC-3 cells, which do not normally express the AR (12) and grow in an AI manner, express little TMPRSS2. However, constitutive expression of the wild-type AR in PC-3 cells and simultaneous stimulation with androgen induce the expression of TMPRSS2 protein. PSA expression in PC-3 cells can also be induced by heterologous expression of the AR and concomitant androgen stimulation (13). These studies demonstrate that, similar to PSA, TMPRSS2 protein expression is critically dependent on the AR pathway.

Prostate tissue expresses a number of androgen-regulated proteases, including PSA, human glandular kallikrein and prostate/KLK-L1 (14–16). TMPRSS2 is unique among these proteases due to its structural features. It is a putative type II transmembrane protease with a SRCR and a LDLRA domain (7). The protease domain is located at the COOH terminus, which is postulated to be extracellular. These features suggested that TMPRSS2 protein is expressed at the cell membrane and could function as a receptor for other proteins or small molecules. The TMPRSS2 protease domain is most homologous to hepsin (also a type II transmembrane protease), which lacks the SRCR and LDLRA domains (17) and is up-regulated in ovarian cancer (18). Subcellular fractionation studies localized hepsin to the membraneous fraction of cultured HepG2 cells (19). Our studies show that a significant fraction of TMPRSS2 protein is proteolytically cleaved and secreted. The remaining regions, including the LDLRA and the SRCR domains, are possibly still membrane associated and could function as receptors independent of the protease domain.

Mutational inactivation of the TMPRSS2 protease shows that the cleavage of the protease is a consequence of its own catalytic activity, suggesting that TMPRSS2 may be its own substrate. Alternatively, TMPRSS2 activates a secondary protease that then cleaves the TMPRSS2 protease. Both interpretations require an active TMPRSS2 protease. Similar autocatalytic cleavage has also been observed for hepsin (20). Site-directed mutagenesis shows that the cleavage of TMPRSS2 occurs at Arg-255 and results in the release of the protease domain. Western blot analysis using anti-TMPRSS2 MAb, directed to the protease domain, demonstrated that only the Mr 32,000 protease fragment is secreted by prostate cancer cells and xenografts into the media or sera, respectively (Fig. 4D). These findings suggest that the protein accumulated in the glandular lumen of normal and cancerous prostate tissues is the cleaved protease fragment. Proliferation and metastasis of cancer cells, associated with destruction of the normal tissue architecture, may cause a rise in serum TMPRSS2 levels that would signify the presence of cancer cells. These data suggest that released TMPRSS2 protease may be useful as a potential serum diagnostic or prognostic marker for prostate and possibly colon cancer.

Secreton TMPRSS2 protease may be involved in processing and activating growth factors present in the extracellular space. Recent work with PSA and human glandular kallikrein have shown that they may play a role in activating growth factors important in the osteoblastic response of bone-metastasized prostate cancer (21). One of these factors, parathyroid hormone-related protein, has been shown to increase the rate of prostate tumor growth in vivo and protect LNCaP cells from apoptosis (22). IGFBP-3, an inhibitor of insulin-like growth factor I, has also recently been shown to be a substrate for PSA (23,24). Cleavage of IGFBP-3 results in an increase in active insulin-like growth factor I, a growth factor implicated in prostate cancer cell growth (23,25). It remains to be seen whether TMPRSS2 is capable of acting on parathyroid hormone-related protein, IGFBP-3, and/or other factors that could influence prostate cancer growth. The expression pattern and localization of TMPRSS2 make it a potential target for therapy in cancers of the prostate.

ACKNOWLEDGMENTS

We thank Drs. Robert Eisenman, Owen Witte, and William Isaacs for helpful suggestions and critical reading of the manuscript; Frank Lynch and Page Erickson at QualTek Molecular Laboratories for their expertise in immunohistochemistry; and Celeste Jones for help in preparation of the manuscript.

REFERENCES


Table 1 Immunohistochemical staining of human tissues with anti-TMPRSS2 MAb

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* PIN, prostatic intraepithelial neoplasia.
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