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***TMPRSS2-ERG* Gene Fusion in Small Cell Carcinoma of the Prostate**

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Abstract

Recent studies have shown that most prostate cancers carry the *TMPRSS2-ERG* gene fusion. Here we evaluated the *TMPRSS2-ERG* gene fusion in small cell carcinoma (SCC) of the prostate (n=12) in comparison with SCC of the urinary bladder (n=12) and lung (n=11). Fluorescence *in situ* hybridization demonstrated rearrangement of the *ERG* gene in 8 cases of prostatic SCC (67%), and the rearrangement was associated with deletion of the 5' *ERG* gene in 7 cases. But rearrangement of the *ERG* gene was not present in any SCC of the urinary bladder or lung. Next we evaluated the *TMPRSS2-ERG* gene fusion in nude mouse xenografts that were derived from two prostatic SCCs carrying the *TMPRSS2-ERG* gene fusion. Two transcripts encoded by the *TMPRSS2-ERG* gene fusion were detected by RT-PCR, and DNA sequencing demonstrated that the two transcripts were composed of fusions of exon 1 of the *TMPRSS2* gene to exon 4 or 5 of the *ERG* gene. Our study demonstrates the specific presence of *TMPRSS2-ERG* gene fusion in prostatic SCC, which may be helpful in distinguishing SCC of prostatic origin from non-prostatic origins. The high prevalence of the *TMPRSS2-ERG* gene fusion in prostatic SCC as well as adenocarcinoma implies that SCC may share a common pathogenic pathway with adenocarcinoma in the prostate.

Keywords

TMPRSS2-ERG gene fusion; prostate cancer; small cell carcinoma; mouse xenograft

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Conflict of interest

We have no conflict of interests to declare.

Introduction

Primary small cell carcinoma (SCC) of the prostate is a rare variant of prostate cancer, accounting for less than 2.0% of *de novo* prostate cancers.¹ Prostatic SCC exhibits clinicopathologic features that are significantly different from those of prostatic adenocarcinoma, which accounts for the vast majority of prostate cancers.^{1–3} Most prostatic adenocarcinomas are asymptomatic and are identified by an increase of serum prostate-specific antigen (PSA). The disease progresses slowly and metastasis usually occurs at an advanced stage with a predilection for the bone. Prostatic adenocarcinoma generally responds well to androgen ablation. Most patients are able to achieve long life expectancy. In contrast, most prostatic SCC patients present with symptoms, such as urinary outflow obstruction, hematuria, bone pain, and renal failure, yet their PSA levels are not usually increased. The disease progresses rapidly and metastasis often develops at an early stage with a predilection for visceral organs such as the liver and lungs. Due to the lack of androgen receptor, SCC is often resistant to androgen ablation. Most prostatic SCC patients die of disease within 1 year.³

SCC can arise in various organs with the lung being the most common origin. Because lung SCC is far more common than prostatic SCC, metastasis from a primary lung SCC should be always considered when SCC is observed in the prostate. Such distinction may be difficult, because SCCs of various origins share similar histologic, immunohistochemical and ultrastructural features.^{4–6} Furthermore, most prostatic SCC lose the prostate-specific immunohistochemical markers, such as prostatic acid phosphatase, PSA, prostate-specific membrane antigen, and prostein.⁵ Therefore, a specific molecular marker is needed to help establish the prostatic origin of SCC.

Recent studies have revealed a unique gene fusion in the majority of prostate cancers.^{7–12} This gene fusion is characterized by the translocation of the 5' transmembrane protease serine 2 (*TMPRSS2*) gene to the *ETS*-related gene (*ERG*) gene.⁷ The *TMPRSS2* gene is regulated by androgen in the prostate, and the *ERG* gene, a transcriptional factor, functions as an oncogene. The fusion of *TMPRSS2-ERG* leads to an aberrant function of the *ERG* oncogene in the prostate, which is believed to contribute to the oncogenesis of prostate cancer. Several other *ETS* members, such as *ETV1*, *ETV4*, and *ETV5*, have also been found to be fused to the *TMPRSS2* gene in prostate cancer.^{7,8,12} However, *ERG* is far more common than the other *ETS* members, accounting for over 80% of the *TMPRSS2-ETS* gene fusions in prostate cancer. To understand the role of the *TMPRSS2-ERG* gene fusion in prostatic SCC, we evaluated the *TMPRSS2-ERG* gene fusion in prostatic SCC in comparison with SCC of non-prostatic origins, and we also investigated the *TMPRSS2-ERG* gene fusion in mouse xenografts derived from prostatic SCC carrying the *TMPRSS2-ERG* gene fusion.

Materials and methods

Case Selection

Twelve cases of prostatic SCC were obtained from the pathology files at The University of Texas M. D. Anderson Cancer Center (Houston, TX, USA). The specimens included

prostate biopsies (n=6), radical prostatectomies (n=5), and lymph node biopsy (n=1). In addition, 12 cases of SCC of the urinary bladder and 11 cases of SCC of the lung were also obtained for comparison. The histologic slides were reviewed for pathological analysis. Clinical and follow-up information was obtained from the medical records.

Immunohistochemistry

Four micrometer thick sections were cut from formalin-fixed paraffin-embedded tissue blocks and immunostaining was performed in a DAKO Auto Stainer (Carpinteria, CA, USA) using EnVision polymer (DAKO). The following primary antibodies were used: prostate-specific antigen (PSA) (1:8000, Dako), synaptophysin (1:600, Novocastra, UK), chromogranin A (1:4000, Millipore, USA), CD56 (1:50, Invitrogen, USA). To enhance immunostaining, a heat-induced epitope retrieval procedure was performed using a Black and Decker vegetable steamer (Shelton, CT, USA). The antigen antibody immunoreaction was visualized using diaminobenzidine (DAB) as a chromogen. The slides were counterstained with Mayer's hematoxylin.

Determination of *TMPRSS2-ERG* Gene Fusion

TMPRSS2-ERG gene fusion was evaluated by fluorescence *in situ* hybridization (FISH) using break-apart probes of the *ERG* gene, as previously described.¹³ The probes, consisting of a rhodamine-labeled 5'-*ERG* probe (*BAC RP11-95I21*) and a fluorescein isothiocyanate-labeled 3'-*ERG* probe (*BAC RP11-476D17*), were obtained from Children's Hospital of Oakland Research Institute (Oakland, CA, USA). Tissue pretreatment was performed using Paraffin Pretreatment Kit I (Vysis, Des Plaines, IL, USA), and hybridization and washing were performed using Vysis hybridization reagents, following the manufacturer's protocols. In cells with no *ERG* rearrangement, 2 pairs of co-localized green and red signals were present. In cells with *ERG* rearrangement, only 1 pair of co-localized green and red signals was maintained, the other pair either broke into 1 green signal and 1 red signal or lost the red signal. A mean of 100 cells was evaluated per tumor focus. A cutoff level of 10% was set for the FISH analysis, i.e., a positive signal required at least 10% of the evaluated nuclei showing rearrangement of the *ERG* gene.

Mouse Xenograft Models

With the approval of the Institutional Review Board of The University of Texas M. D. Anderson Medical Center, fresh tumor specimens from two patients (Case No. 3 and 9, Table 1) were collected. The specimens were cut into pieces of approximately 1 mm³ and trypsinized. The disaggregated cells were washed, counted and resuspended at 4–5 × 10⁶ cells/100 µl of growth medium. About 2 × 10⁶ cells were injected into subcutaneous pockets of 6- to 8-week-old male CB17 SCID mice (Charles River Laboratories, Wilmington, MA, USA) as previously described.¹⁴ The xenograft tumors were excised 8–10 weeks after the injection. A portion of each xenograft tumor was used for RNA extraction, and the rest of the tumor was fixed in 10% formalin overnight. Serial 5-µm tissue sections were cut from each sample; one section was stained with H&E, and adjacent sections were used for immunohistochemical staining or FISH analysis as described above. All animal experiments were conducted in accordance with accepted standards of animal care and were approved by our Institutional Animal Care and Use Committee.

RT-PCR and DNA Sequencing

RNA was extracted using a Picopure RNA isolation kit (Arcturus Engineering, Mountain View, CA, USA). For cDNA preparation, the RNA was first treated with DNase I (Invitrogen), and reverse transcription was done using Superscript II (Invitrogen) according to the manufacturer's protocol. Reverse transcription reactions were amplified by PCR using gene-specific primers under standard reaction conditions. The forward primer, TAGGCGCGAGCTAAGCAGGAG, matched exon 1 of the *TMPRSS2* gene, and the reverse primer, CAACGGTGTCTGGGCTGCCCACC, matched exon 5 of the *ERG* gene. All products were resolved on 2% agarose gels and visualized by ethidium bromide. DNA elution was performed to extract discrete PCR products from the gel, and direct PCR sequencing was performed on the purified PCR products.

Results

Twelve patients with prostatic SCC were selected for this study (Table 1). The mean age of patients at the diagnosis of prostatic SCC was 68 years (range, 44–77 years). Three patients had *de novo* prostatic SCC, and nine patients had a history of preexisting prostatic adenocarcinoma. In the latter, the mean interval between the initial diagnosis of prostatic adenocarcinoma and the diagnosis of SCC was 60 months (range, 8–144 months). The SCCs were composed of sheets of small cells with scant cytoplasm, dense nuclei, and inconspicuous nucleoli (Figure 1A). In 11 cases, the neuroendocrine differentiation of the SCCs was supported by positive immunohistochemical staining for synaptophysin (Figure 1B), chromogranin, and CD56. In the remaining one case, immunostaining was not performed.

FISH analysis demonstrated rearrangement of the *ERG* gene, an indication of the *TMPRSS2-ERG* gene fusion, in 8 of the 12 cases (67%) of prostatic SCC. In the 8 cases with the *TMPRSS2-ERG* gene fusion, 65% to 90% of the evaluated nuclei showed positive *ERG* gene rearrangement signals (Table 1). In 7 cases, the rearrangement was associated with a deletion of the 5' end of the *ERG* gene (Figure 1C). In the remaining one case, the rearrangement was not associated with the deletion (Figure 1D). Rearrangement of the *ERG* gene was not observed in any SCC of the urinary bladder (Figures 2A and 2B) or the lung.

Mouse xenografts from 2 patients (No. 3 and 9 in Table 1) were established by subcutaneous implant of prostatic SCC. The xenograft tumors showed typical features of prostatic SCC (Figure 3A). On immunostains, the tumor cells were negative for PSA but positive for synaptophysin (Figure 3B) and chromogranin (Figure 3C). On FISH analysis, rearrangement of the *ERG* gene was present in both xenografts (Figure 3D). RT-PCR analysis yielded two discrete fusion transcripts (Figure 3E). DNA sequencing demonstrated that one product was a fusion of exon 1 of *TMPRSS2* and exon 4 of *ERG* and the other product was a fusion of exon 1 of *TMPRSS2* and exon 5 of *ERG* (Figure 3F).

Clinical follow-up was available for all patients (Table 1). The patients had received chemotherapy ($n = 12$), hormonal therapy ($n = 10$), radiation therapy ($n = 8$), and radical prostatectomy ($n = 5$). All patients developed metastasis and died at an average of 10 months (range, 1–23 months) after the diagnosis of SCC.

Discussion

Although the origin of SCC in the prostate remains uncertain, several hypotheses have been proposed. Because the majority of prostatic SCCs express neuroendocrine proteins, such as synaptophysin, chromogranin, and CD56, it is suggested that prostatic SCC may be derived from malignant transformation of neuroendocrine cells, a normal component in the prostatic glands.¹⁵ Similarly, some prostatic SCCs still express prostatic epithelial markers, such as PSA, prostate-specific membrane antigen, prostatic acid phosphatase, and prostein, it is also postulated that prostatic SCC may represent a dedifferentiation of the conventional prostatic adenocarcinoma during the progression of disease.¹⁶ Recently, it has been suggested that prostatic SCC may arise from the pluripotent stem cells in the prostate, as some prostatic SCCs demonstrate an extremely active proliferation.¹⁷ In this study, we found the *TMPRSS2-ERG* gene fusion in the majority of prostatic SCC including *de novo* and those with previous history of prostatic adenocarcinoma, which would favor the opinion that prostatic SCC may evolve from conventional prostatic adenocarcinoma.

As SCCs of various origins share similar morphologic and immunohistochemical features, it may be difficult to determine the origin of SCC, especially after metastasis. Although prostatic markers such as prostatic acid phosphatase, PSA, prostate-specific membrane antigen, and prostein may be helpful in establishing the prostatic origin, the majority of prostatic SCCs are negative for these markers.⁵ Prostatic SCC was initially reported to be negative for thyroid transcription factor-1,¹⁸ nonetheless subsequent studies have found that most prostatic SCCs express TTF-1.⁶ A recent study found that CD44 may be a unique feature of prostatic SCC, but a substantial number of lung SCCs are also positive for CD44.¹⁹ In the current study, we found that the majority of prostatic SCCs carried the *TMPRSS2-ERG* gene fusion, while all SCCs of non-prostatic origins, including the lung and urinary bladder, lacked this gene fusion. Thus the specific expression of *TMPRSS2-ERG* gene fusion in prostatic SCCs suggests that the *TMPRSS2-ERG* gene fusion may be useful in establishing the prostatic origin of SCC.

Although prostatic SCC carries a unique molecular signature, the *TMPRSS2-ERG* gene fusion, it shares similar clinical features with non-prostatic SCC.²⁻⁴ Regardless of the site of origin, all SCCs progress rapidly and have a dismal prognosis. Like non-prostatic SCC, prostatic SCC shows a favorable response to systemic chemotherapy composed of etoposide and cisplatin.²⁻³ Although lung SCC is far more common than prostatic SCC, in the absence of a lung primary, the presence of SCC in a prostate specimen is most likely to be a prostatic primary.⁵ The involvement of prostate by lung SCC is rare and only occurs in the setting of widespread metastases. Hence, the distinction of prostatic SCC from non-prostatic origin has limited value in the prognosis and treatment of SCC patients.

Both *TMPRSS2* and *ERG* genes are located on the long arm of chromosome 21. The *TMPRSS2-ERG* gene fusion results from deleting the interval DNA, which includes the majority of the *TMPRSS2* gene and a small portion of the 5'-*ERG* gene.⁷ On FISH analysis using the *ERG* break-apart probes, the interval DNA may be completely lost, which is characterized by rearrangement of the *ERG* gene with a deletion of the 5' *ERG* gene, or the internal DNA is translocated to another chromosome, which is characterized by

rearrangement of the *ERG* gene with no deletion. Several studies have suggested that the *TMPRSS2-ERG* gene fusion, particularly those associated with deletion of the 5'-*ERG* gene, is linked to an aggressive phenotype of prostate cancer.^{10,20–22} However, Gopalan *et al* found that the *TMPRSS2-ERG* gene fusion was not associated with recurrence, metastasis, or patient survival in a large scale study of more than 500 patients.²³ Several factors, such as cohort selection, method of gene fusion detection, and clinical end point, may contribute to this inconsistency.

There have been limited studies of the *TMPRSS2-ERG* gene fusion in prostatic SCC. A recent study by Han *et al* showed that 5 of the 7 cases (71%) of prostatic SCC carried the *TMPRSS2-ERG* gene fusion, which were all associated with deletion of the 5'-*ERG*.²⁴ In the current study, we found that 8 of the 12 cases (67%) of prostatic SCC expressed the *TMPRSS2-ERG* gene fusion and the rearrangement was associated with deletion of the 5'-*ERG* gene in 7 cases. Thus the high prevalence of *TMPRSS2-ERG* gene fusion in both prostatic SCC and adenocarcinoma suggests a close relationship between SCC and adenocarcinoma in the prostate. Furthermore, the presence of *TMPRSS2-ERG* gene fusion in *de novo* prostatic SCC suggests that SCC may share a common pathogenetic pathway with adenocarcinoma in the prostate.

Mouse xenograft is a valuable model to study the regulatory mechanism of prostate cancer and to test new therapeutic modalities.²⁵ Several mouse xenografts of metastatic prostate cancer have been established in our institution,²⁶ and two of them were derived from metastatic prostatic SCC carrying the *TMPRSS2-ERG* gene fusion. The histologic and immunohistochemical features of prostatic SCC xenografts showed a striking resemblance to those observed in the patient's original specimens. Furthermore, these two prostatic SCC xenografts also carried the *TMPRSS2-ERG* gene fusion. Our results suggest that mouse xenografts of prostatic SCC maintain the histologic, immunohistochemical and genetic features of the human original specimens.

Previous studies have shown that the *TMPRSS2-ERG* fusion gene expresses a variety of mRNA transcripts due to alternative splicing.^{9,11} In this study, we found that prostatic SCC expressed two different *TMPRSS2-ERG* transcripts, which were composed of fusion of exon 1 of *TMPRSS2* to exon 4 or 5 of the *ERG* gene. Compared with the eight types of *TMPRSS2-ERG* gene fusion products in prostate cancer previously described by Wang *et al*,⁹ the transcripts in our prostatic SCCs represent types III and IV described in their study. Among the *TMPRSS2-ERG* transcripts reported in prostate cancer, type III is the most common form while type IV is the least common form.⁹ Interestingly, a previous study demonstrated similar findings in NCI-H660, a cell line originating from prostatic SCC.²⁷ The *TMPRSS2-ERG* gene fusion in NCI-H660 involved the deletion of 5'-*ERG* and expressed two discrete transcript products, which were composed of the fusion of exon 1 of *TMPRSS2* to exon 4 or 5 of the *ERG* gene. Although additional studies are needed, our limited studies suggest that prostate cancer carrying these two transcripts may have a predilection for the transformation to prostatic SCC.

In summary, we demonstrate that most human prostatic SCCs carry the *TMPRSS2-ERG* gene fusion, confirming the involvement of this gene fusion in prostatic SCC. In addition,

mouse xenografts derived from human prostatic SCC also carry the *TMPRSS2-ERG* gene fusion. The presence of the *TMPRSS2-ERG* gene fusion in both prostatic SCC and adenocarcinoma suggests a close relation of oncogenesis between them. Furthermore, the *TMPRSS2-ERG* gene fusion is not present in SCC of non-prostatic origins, including the lung and the urinary bladder. Thus the *TMPRSS2-ERG* gene fusion may be used as a molecular marker to establish the prostatic origin of metastatic SCC.

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Figure 1.

Prostatic small cell carcinoma expresses the *TMPRSS2-ERG* gene fusion. The tumor shows solid sheets of poorly differentiated carcinoma cells with scant cytoplasm, dense nuclei and inconspicuous nucleoli (A); the tumor cells are immunoreactive for synaptophysin (B); FISH analysis demonstrates rearrangement of the *ERG* gene associated with deletion of the 5' *ERG* gene in one case (C) and without deletion in another case (D).

Figure 2. Bladder small cell carcinoma lacks the *TMPRSS2-ERG* gene fusion. The tumor cells are poorly differentiated with scant cytoplasm and dense nuclei (A); FISH analysis shows no rearrangement of the *ERG* gene (B).

Figure 3.

Mouse xenograft of prostatic small cell carcinoma expresses the *TMPRSS2-ERG* gene fusion. The xenograft tumor cells are poorly differentiated with scant cytoplasm and hyperchromatic nuclei (A); the tumor cells are immunoreactive for synaptophysin (B) and chromogranin (C); FISH analysis shows rearrangement of the *ERG* gene associated with a deletion of the 5' *ERG* gene (D); RT-PCR demonstrates two discrete transcripts of the *TMPRSS2-ERG* gene fusion in two xenografts derived from Cases # 3 (a) and # 9 (b). (E);

DNA sequencing demonstrates that the two transcripts are fusions of exon 1 of the *TMPRSS2* gene to exon 4 or 5 of the *ERG* gene (F).

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Table 1Summary of patients' clinicopathologic features and *TMPRSS2-ERG* gene fusion status

Case No.	Age (years)	Preexisting AdenoCa GS	Interval ^a (months)	SCC specimen	Gene fusion	Follow-up ^b (months)
1	72	N/A	N/A	RP	Neg.	DOD (7)
2	77	7 (3+4)	57	RP	Pos. del. (80%) ^d	DOD (3)
3 ^c	71	7 (4+3)	43	RP	Pos. del. (90%)	DOD (11)
4	62	9 (4+5)	8	PBX	Pos. del. (75%)	DOD (6)
5	48	7 (3+4)	19	PBX	Neg.	DOD (1)
6	64	9 (5+4)	27	PBX	Pos. del. (85%)	DOD (1)
7	85	6 (3+3)	117	RP	Neg.	DOD (20)
8	78	9 (5+4)	59	PBX	Pos. del. (80%)	DOD (23)
9 ^c	44	6 (3+3)	144	LNBX	Pos. del. (70%)	DOD (22)
10	77	N/A	N/A	PBX	Neg.	DOD (21)
11	72	8 (4+4)	66	RP	Pos. no del. (65%)	DOD (2)
12	69	N/A	N/A	PBX	Pos. del. (90%)	DOD (1)

AdenoCa, adenocarcinoma; del., deletion; DOD, died of disease; GS, Gleason score; N/A, not available; LNBX, lymph node biopsy; Neg., negative; PBX, prostate biopsy; Pos., positive; RP, radical prostatectomy; SCC, small cell carcinoma.

^aInterval between the initial diagnosis of prostatic adenocarcinoma and the diagnosis of SCC.

^bInterval between the diagnosis of SCC and the time of death.

^cProstatic SCC specimens from these two patients were used for mouse xenografts.

^dThe number in parenthesis indicates the percentage of nuclei with positive gene fusion signal.