Review Article

PCA3 and *TMPRSS2-ERG* gene fusions as diagnostic biomarkers for prostate cancer

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Abstract: The incidence of prostate cancer (PCa) is rising steadily among males in many countries. Serum prostate-specific antigen (PSA) is widely applied to clinical diagnosis and screening of PCa. However, the so-called grey area of PSA levels 4.0–10.0 ng/mL has a low specificity of 25–40% resulting in a high rate of negative biopsy and overtreatment. So in order to treat PCa patients in early stage, there is an urgent need for new biomarkers in PCa diagnosis. The *PCA3* gene, a non-coding RNA (ncRNA) that is highly expressed in prostate cancer (PCa) cells, has been identified as a molecular biomarkers to detect PCa, of which PCA3 has already under clinical application. PCA3 is strongly overexpressed in malignant prostate tissue compared to benign or normal adjacent one. Newly, PCA3 is considered to be a promising biomarker in clinical diagnosis and targeted therapy. The diagnostic significance of PCA3, however, is awaiting further researches. Moreover, it has been demonstrated recently that *TMPRSS2-ERG* gene fusion is identified as the predominant genetic change in patients diagnosed with PCa. Recent study revealed that combination of the *PCA3* and *TMPRSS2-ERG* gene fusion test optimizes PCa detection compared with that of single biomarker, which would lead to a considerable reduction of the number of prostate biopsies. In this review, we focused on the potential use of *PCA3* and *TMPRSS2-ERG* gene fusion detection in the diagnosis of PCa.

Keywords: Prostate; prostate cancer antigen 3 (PCA3); *TMPRSS2-ERG* gene fusion; prostate cancer (PCa); biomarker

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Introduction

Prostate cancer (PCa) has become as a leading causes of cancer death in many countries among males (1). In recent year, the incidence of PCa have showed an obvious growth trend in China. PCa is becoming urinary tract malignant tumor that impacts Chinese men's health seriously.

As an invasive testing method, the histopathologic evaluation of prostate biopsies is served as the golden standard for the diagnosis of PCa. At the early stage, PCa does not present with patent clinical manifestation. The decision of prostate biopsies implement relies largely on serum prostate-specific antigen (PSA) testing and digital rectal examination (DRE) (2). The limitations of PSA as PCa early detection biomarker are sound discussed, and the controversy of its use in the screening setting were highlighted recently (3). The so-called grey area of PSA levels 4.0–10.0 ng/mL has a low specificity of 25–40% resulting in a high rate of negative biopsy (4). In addition, DRE is very subjective leading to numerous false positive results and many unnecessary biopsies. Thus, there is an urgent need for new biomarkers in the diagnosis of PCa.

With significant advances in genetics and cell biology, numerous PCa biomarkers have been found recently. Increasing evidence has shown that long non-coding RNAs, such as prostate cancer antigen 3 (PCA3) might be served

as promising biomarkers in the diagnosis of PCa. PCA3 was initially known as DD3, located on chromosome 9q21-22. The *PCA3* gene, widely studied in recent years, is probably one of the first biomarkers which already under clinical application. Highly overexpression of PCA3 in PCa tissue was found to be a potential non-invasively prediction of prostate biopsy which might be a promising biomarker in clinical diagnosis (5). The Clinical has focused mainly on an assay about transcription-mediated amplification (TMA, Progensa PCA3 test). Authoritatively, the assay has been approved by the US Food and Drug Administration (FDA) and is Community European (CE) marked for assessing the risk of PCa in men who has a previous negative biopsy (6).

One of the earliest genetic variation, ERG oncogene, identified as a transcription factor of ETS family, located on chromosomal band 21q22 is overexpressed in over 50% of PCa (7). Transmembrane protease, serine 2 (TMPRSS2), a prostate-specific and androgen regulated gene, locates very closer to ERG on the same chromosome. It has been identified that the overexpression of ERG in major PCa was driven by fusing with TMPRSS2 (8). In recent studies, *TMPRSS2-ERG* gene fusion is the pervasive variant in about 40% to 70% PCa (9). Due to various detecting method, it is expected that *TMPRSS2-ERG* gene fusion might be a promising biomarker of PCa.

Probably, urine and venous blood specimens after prostate massage is the most easily obtained specimen for biomarkers detection. It could be collected non-invasively and is available in large amount. Urine markers are especially attractive when the prostate in the early stage disease and setting of screening (10). We have searched the literatures by using the key words PCA3, TMPRSS2, ERG, and PCa, and reviewed all the published papers. We focus on the potential value of the *PCA3* and *TMPRSS2-ERG* gene fusion, especially for their ability to calculate patient risk with ever negative biopsy for the occult cancer.

PCA3: molecular science and clinical use

PCA3, named as differential display clone 3 (DD3) initially, found by Bussemakers *et al.* in 1999, was specifically expressed in PCa tissue from 10- to 100-fold in relation to non-neoplastic prostatic surrounding tissue in 53 of 56 patients treated with radical prostatectomy (11). PCA3 is a non-coding RNA located on chromosome 9q21-22, contains a high density of stop codons, whose biological function is not well-known. Recent study suggested that PCA3 modulated the transcriptional activity of androgen receptor target genes which might play a role in the control of PCa cell survival (12).

Since PCA3 was discovered by Bussemakers *et al.*, various methods of the measurement has developed, such as Progensa TM PCA3 test, which promote the clinical applicability of PCA3 in the diagnosis of PCA. To evaluate the potential usefulness of PCA3 as a diagnostic marker for PCa, a time-resolved fluoresce-based quantitative RT-PCR assay has been developed. Urine specimens were collected after prostate massage. It has been reported that compared with normal prostate tissue, PCA3 overexpression is 66-fold up-regulated in PCa tissue (13). It also suggested that an average 11-fold up-regulation in prostate tissue specimens containing fewer than 10% PCa cells (13), which means that polymerase chain reaction assay can detected a few cancer cells in a background of normal cells, prompted the potential assay of PCA3 in urine.

In the study accompanying this review, Merola *et al.* report on PCA3 in PCa and tumor aggressiveness detection on 407 high-risk patients (3). The PCA3 test showed the best diagnostic function when compared with tPSA and f/tPSA, promoting the choice of high-risk patients that may benefit from the operation of a traumatic prostatic biopsy. In addition, the PCA3 test could show a prognostic value, which higher PCA3 score values would relate to greater tumor aggressiveness.

PCA3 guides the decision making of prostate biopsy

The golden standard for the diagnosis of PCa is the histopathologic evaluation of prostate biopsy, which is an invasive testing method. The decision of implementing prostate biopsy relies on PSA testing and DRE. Although raised levels of serum PSA are suggestive of PCa, yet, diagnostic confirmation requires a transrectal prostatic needle biopsy, which is an invasive procedure. Still there is the so-called grey area of PSA levels 4.0–10.0 ng/mL has a low specificity of 25–40% resulting in a high rate of negative biopsy (4). Among those previous negative prostate biopsy, 10–35% can be indentified cancer by a systematic repeat prostate biopsy, which result in a high proportion of unnecessary biopsies (14,15). While making a decision of initial or repeat prostate biopsy, the risk of unnecessary biopsy which leads to complication and patient discomfort, pain, anxiety, waste cost have to be taken into consideration.

The PCA3 score is the ratio of PCA3 mRNA to PSA mRNA multiplied by 1,000. Many large-scale multicenter

clinical studies have confirmed that the PCA3 score can overcome the disadvantages of the low specificity of the traditional PSA test. Recent data suggested that PCA score is correlated with the positive rate of prostate biopsy (16). It showed that when a PCA3 cutoff score of 35 was used during the first prostate biopsy, the sensitivity and specificity increased to 82.3% and 89.0% respectively. Compared to using PSA, the best PSA cutoff value of sensitivity and specificity showed only 57.4% and 53.8%, the priority of PCA score is obvious (17-20). An European study suggested that the area under the curve (AUC) of PCA3 was 0.761 and 0.65 in initial and repeat prostate biopsy respectively (16). The synthesis of these finding demonstrated that using PCA3 score at guiding both initial and repeat biopsy has priority over PSA testing.

Some research suggested that PCA3 has a higher diagnostic accuracy, but strength of evidence was insufficient to conclude that PCA3 testing leads to improve health outcome (21).

PCA3 and Gleason score

Histologic differentiation of PCa is closely related to the prognosis, biologic behavior, treatments option and patient outcome. Gleason grading system is used to evaluate the prognosis of PCa based on its microscopic appearance (22). The present results indicated a correlation between PCA3 and Gleason score (23). However, some data suggested that there was no difference between the migrated Gleason score tumor group and the group of confirmed Gleason score tumors, thus the ability of PCA3 to predict final Gleason score was limited. In addition, a PCA3 score >35 did not appear in a multivariate analysis as an independent factor of a Gleason score >7. Consequently, it is blurred of the clinical impact of PCA3 and Gleason score correlation is ambiguous (24).

Although there are some limitations of PCA3 application, it is still considered as a useful clinical tool in the diagnosis of PCa, especially when the viewpoint of combining PCA3 assay with other markers has been raised up, such as *TMPRSS2-ERG* gene fusion, another biomarker of PCa (25).

TMPRSS2-ERG gene fusion in PCa

ERG gene was identified as a transcription factor of ETS family (26,27), which involved in chromosome translocations in Ewing family of tumors as well as in leukemias. In 2005, frequent overexpression of ERG in PCa was observed (28). Later that year, it was discovered that the mechanism underlying this overexpression was the recurrent genomic rearrangement between the first exon(s) of TMPRSS2 and the ERG oncogenes (29). It had been confirmed that The fusion of *TMPRSS2* and *ERG* genes appeared in nearly 50% of PCa patients (30,31). TMPRSS2 is an androgen-regulated gene that is preferentially expressed in the prostate (32). TMPRSS2 is located on chromosomal band 21q22. ERG maps also 21q22 in the same orientation, at a distance of approximately 3 Mb. The fusion of the androgen- and prostate-specific regulating sequences and first exon(s) of TMPRSS2 to the coding sequences of ERG resulted in the androgen-regulated overexpression of ERG.

TMPRSS2-ERG gene fusion in the activation of transforming growth factor beta/smads signaling pathway

Although the specific role of TMPRSS2-ERG fusion in PCa is not well understood, yet ERG-positive patients have a low rate of high Gleason grade, poor differentiation compared to ERG-negative patients (33,34). *TMPRSS2-ERG* gene fusions may be cancer-initiating, and expressed at both RNA and protein levels in PCa stem cells (34,35). It also has been shown that an anti-epileptic drug targets ERG-positive PCa cells through the activation of tumor suppressors and nuclear receptors (36).

Recent studies found that it might play an important role in the acitivation of Transforming Growth Factor Beta/Smads Signaling Pathway (37). It is well known that TGF-β signaling pathway involved in cell proliferation, differentiation, migration, adhesion, apoptosis, embryonic development, and is even related to human diseases including cardiovascular, fibrosis, reproductive, wounded healing disorders and cancer (38,39). After TGF-β ligand binding to its receptor, R-Smads (receptor-regulated Smads) including Smad2 and Smad3 protein are phosphorylated, and then form a complex by interacted with Smad4. The complex then translocate into nucleus and bind to target genes.

It is common to find genetic alteration and recurrent gene fusion between ERG and TMPRSS2 on chromosome 21 in prostate. In these PCa cases, *ERG* gene expression is significantly upregulated by the androgen-responsive promoter of TMPRSS2. Although the role of *TMPRSS2-ERG* gene fusion protein in PCa is not well understood, recent

results found that over-expression of ERG may be a useful biomarker of PCa diagnosis.

TMPRSS2-ERG gene fusion in small cell carcinoma (SCC) of PCa

SCC, accounts for less than 2.0% of de novo PCa, is a rare variant neuroendocrine tumor of the prostate (40). Compared with prostatic adenocarcinoma, which accounts for most PCas, prostatic SCC shows obvious difference in clinicopathologic features. Most prostatic adenocarcinomas hardly have clinical manifestation and can be identified by an increase of PSA. The process of prostatic adenocarcinomas is slow and the metastasis often occurs at advanced stage. Responding well to androgen ablation treatment, patients with prostatic adenocarcinomas can achieve long life expectancy (41).

On the contrary, patients with prostatic SCC show no increase in PSA. And the disease progresses rapidly with metastasis at very early stage. For the lack of androgen receptor, prostatic SCC shows resistance to androgen ablation (42). SCC can originate in various organs, such as lung, cervix, prostate, urinary bladder, etc., with the lung being the most common origin. As SCCs arising from different organs share similar histologic, immunohistochemical, and ultrastructural features (43-45), it may be difficult to deduce the origin when SCC is observed in the prostate especially after its metastasis. Besides it, most prostatic SCCs lose the prostate-specific immunohistochemical markers, such as prostatic acid phosphatase, PSA, prostate-specific membrane antigen, and protein (44). Therefore, a specific molecular marker to distinguish the prostatic origin of SCC may be clinically useful.

Despite the frequent occurrence of *ERG* gene rearrangements in adenocarcinoma, the incidence of these rearrangements in prostatic SCC is unclear. Recent study found that the presence of ERG rearrangements in nearly half of the prostatic SCCs is a similar rate of rearrangement that found in prostatic acinar carcinomas. Furthermore, the high concordance rate of ERG rearrangement between the SCC and adenocarcinoma components in a given patient supports a common origin for these two subtypes of PCa. The absence of *TMPRSS2-ERG* gene fusion in bladder or lung SCCs highlighted the utility of detecting *TMPRSS2-ERG* gene fusion in SCCs of unknown primary for establishing prostatic origin and identified a promising molecular marker for establishing prostatic origin in SCCs of unknown primary (46).

Evaluation of PCA3 and TMPRSS2-ERG gene fusions as diagnostic biomarkers for PCa

The gold standard for the diagnosis of (PCa) is based on the histopathologic evaluation of prostate biopsies, an invasive procedure associated with patients' discomfort, anxiety and severe complications. Because localized PCa often does not present with symptoms, the selection of men qualifying for prostate biopsies relies on serum PSA testing and digital rectal examination (DRE). However, PSA has a low specificity resulting in a high negative biopsy rate (47). And DRE is very subjective. A specific biomarker of PCA is required for clinical diagnosis.

In 2006, the *TMPRSS2-ERG* gene fusion transcripts were successfully detected in urine samples (48). This urine test had a sensitivity of 37% and a specificity of 93% for the prediction of PCa on prostate biopsy (7). TMPRSS2-ERG had great predictive value to PCA3 and the European Randomised study of Screening for Prostate Cancer (ERSPC) risk calculator parameters for predicting PCa (6).

Recent study shown that both PCA3 and TMPRSS2-ERG fusion had independent additional predictive value for predicting PCa. Recent study suggested that applying this biomarker panel of PCA3 combine with TMPRSS2-ERG fusion to clinical diagnosis could avoid 35% negative prostate biopsies, missing only 10% of the men with PCa with a Gleason score-7 (7). Implementing the novel biomarker panel PCA3 and TMPRSS2-ERG into clinical practice would lead to a considerable reduction of prostate biopsies.

However, some cohort studies and meta-analysis revealed that TMPRSS2-ERG fusion status was not a strong predictor of PCa recurrence or cancer-specific mortality. The role of TMPRSS2-ERG in PCa pathogenesis and progression is only starting to emerge (49). Recent study proposed prostate health index (PHI) calculated by a mathematical formula combining PSA molecular forms, which also can offer a reduction in unnecessary biopsy (50).

Conclusions

Formerly, PCa candidates biopsy selection relies largely on serum PSA testing and digital rectal examination (DRE). However, due to the lack of specificity, new biomarkers of PCa is needed urgently. Unfortunately, PCA3 test also has limitations. For instance, patients with indolent tumors present a low PCA3 score which PCA3 test cannot exclude.

Since *TMPRSS2-ERG* gene fusions has been detected

in a significant portion of PCa, it is identified as a potential diagnostic and therapeutic target of PCa, especially in SCC. And recent study showed a great ascendance of biomarker panel combining PCA3 and TMPRSS2-ERG in PCa diagnosis, which may prevail in clinical practice. Therefore, in order to optimize the PCa detection, combining the *PCA3* and *TMPRSS2-ERG* gene fusion test might have applicable diagnostic.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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