



Current Trends in Prevalence and Role of Long Noncoding RNA and Gene Fusion in Prostate Cancer: An Overview

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Ann Natl Acad Med Sci (India) 2021;57:93–101.

Abstract

Objectives The aim of this study is to analyze the current scenario in the diagnostic modalities for prostate cancer.

Materials and Methods We searched PubMed, Google Scholar, and ResearchGate for relevant data. Articles published in the last 10 years were taken into consideration. The role of long noncoding RNA and gene fusion products in the context of prostate cancer was reviewed, which included their roles in diagnosis, prognosis, and assessment of response to therapy.

Results Several long noncoding RNAs (lncRNA) have been isolated and have been shown to be useful in diagnosing and prognosticating prostate cancer. We have also looked into the role of *TMPRSS2:ERG* gene fusion in prostate carcinoma diagnosis. These molecular parameters have been looked into due to the fact that the current parameters in use such as prostate-specific antigen have several drawbacks that limit their potential.

Keywords

- ▶ long noncoding RNA
- ▶ gene fusion products
- ▶ prostate-specific antigen
- ▶ miRNA
- ▶ *TMPRSS2:ERG*

Introduction

Prostate cancer is a malignancy found commonly in elderly males. It is the second most common and overall sixth leading reason of mortality in men all over the world. In 2018, approximately 1.3 million new cases were reported. This accounted for 9.5% of total cancer burden.¹ If the incidence of prostate cancer cases grew at this rate, it is likely that we will have 1.7 million new cases by 2030, along with approximately 5 million new deaths. The main reason is the increase in aging population in the world.² The epidemiological differences between Asian and Western countries in disease incidence and mortality rates are well documented.² Countries in Oceania, Northern America, Northwestern Europe, and the Caribbean Island have the highest prostate cancer incidence in the world.^{3,4} In the United States, the estimated

deaths from prostate cancer were found to be 4.9% of all cancer deaths.¹ In comparison, African countries have been found to have lower incidence and mortality rates.³ Recent trends in the West suggest that prostate cancer mortality rates have been decreasing.^{3,5} Jemal et al postulated that this may be due to early detection and improved treatment in the West.⁶ There are limited data about incidence and mortality due to prostate cancer in Asian countries, and their authenticity is debatable. There may be many reasons for the increase. One possible explanation could be a change in lifestyles due to more westernized diets.⁵ Also, the implementation of early detection systems and national cancer registration systems has become widespread, though such national cancer registries are still nascent in most Asian countries. Earlier it was believed that prevalence of prostate cancer in India is much lower in comparison to developed countries. However, with

published online
May 27, 2021

DOI <https://doi.org/10.1055/s-0041-1729780>
ISSN 0379-038X

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rapid urbanization, there has been an increased migration of people from rural areas; life styles changes, increased awareness, and easier accessibility to medical facilities have led to more cases of prostate cancer being reported. The current population-based cancer registries (PBCRs) 2009–2011 for prostate cancer showed that the prevalence of prostate cancer is more in the metropolitan cities and the trend is increasing.⁷ In India data regarding the true incidence of prostate cancer are limited. This is mainly due to the fact that prostate cancer is not a notifiable disease and PBCRs and community-based cancer registries in India are limited. One of the major drawbacks of these cancer registry-based studies is that these are mainly urban-based and there are scarce data available from the rural population. However, since the last decade, there has been an increasing trend of cases observed.^{8,9}

Diagnostic Modalities for Prostate Cancer: Current Scenario

The characteristic of an ideal biomarker is its high diagnostic accuracy, simplicity in measurement, lower cost, and test repeatability that could be performed via easily available body fluids such as serum, urine, or prostatic fluid. Currently, the diagnosis of prostate cancer is based on clinical history of urinary obstruction in elderly males, followed by a digital rectal examination (DRE) and serial measurements of prostate-specific antigen (PSA). It is believed that DRE is positive only in 20 to 30% of cases.¹⁰ Therefore, currently both PSA and DRE are the main tools used for diagnosis as well as for assessing the response to therapy.⁸

PSA is limited in its ability to diagnose prostate cancer as it is only prostate tissue-specific and can be elevated even in benign prostate disorders. The results of the Prostate Cancer Prevention Trial showed the presence of prostate cancer over all the ranges of PSA.¹⁰ The American Cancer Society recommends an annual screening of patients aged 50 years or older in the lower risk group and of patients aged 45 years or older in the higher risk group. Several alternate approaches have been put forward, such as having age-specific cutoff rates, lowering upper reference limit, and measurement of PSA density. The most successful approach has been to use the molecular form of PSA and free PSA. The percentage of free PSA ($[\text{free PSA}/\text{total PSA}] \times 100$) has been used to improve the clinical sensitivity and specificity in diagnosing prostate cancer, especially in the gray zone of PSA (4–10 µg/L). Men with prostate cancer have lower circulating free PSA and more bound PSA. Greater utility of PSA has been seen in staging the disease and monitoring the response to therapy.¹⁰ There are several scoring systems evaluated, such as the Cancer of the Prostate Risk Assessment (CAPRA), but they lack sensitivity and specificity.¹¹

Prostate Cancer Diagnosis: Advances and Future Prospects

Long Noncoding RNA (lncRNA)

Noncoding RNAs (ncRNA) are RNA transcripts that are not involved in protein coding. They are classified into: (1) small ncRNAs (18 to 200 nucleotide in length) and (2) long

noncoding RNAs (lncRNAs) (longer than 200 nucleotides in length). It is now known that lncRNAs fold into secondary and tertiary structures and carry out their function—unlike miRNA, which do not have this property.¹² lncRNAs have been shown as modulators of important cellular processes not only under normal circumstances, but also in diseases such as cancer.^{12–17} Abnormally expressed lncRNAs can be used to indicate different stages of cancer progression, enable early prediction of disease progression, or give information regarding efficiently sustained tumor-linked signaling pathways.^{12,17} From this discussion, it can be safely concluded that lncRNAs have all the necessary characteristics to be a useful marker for the diagnosis of prostate cancer, and being a potential marker that can be used in the choice of therapy and importantly act as therapeutic target for prostate cancer therapy.¹² Depending on their role in disease pathogenesis or their site of action, several lncRNAs have been implicated. **Fig. 1** indicates the various mechanisms by which lncRNA plays a role in regulation of gene expression.

lncRNAs Implicated in the Pathogenesis of Prostate Cancer

Prostate Cancer Antigen 3 (PCA3)

PCA3 is one of the earliest and most prolific biomarkers to be discovered in prostate cancer. In 1999, PCA3 was first isolated by differential display analysis of prostate tissues by Bussemakers et al.¹⁸ It was first named DD3. It is considered to be one of the most specific parameters for prostate cancer identification.¹² PCA3 has been shown to be expressed in more than 95% of prostate tumors in comparison to non-cancerous tissues. Ideally, it was shown that other malignancies did not express high levels of PCA3, thus enhancing its specificity. PCA3 knockdown inhibits androgen receptor (AR) signaling, cell growth, and viability. This suggests that overexpression of PCA3 may modulate AR signaling in tumor cells.¹² Also, it was seen that knockdown of PCA3 led to not complete but partial activation of epithelial markers, e.g., E-cadherin, claudin-3, and cytokeratin 18. Also, a downregulation of the mesenchymal marker such as vimentin was noted. These proteins have a well-documented role in cancer metastasis and cellular invasion and potential as prognostic markers, especially cytokeratin 18. PCA3 has also been found to regulate apoptosis, angiogenesis, and signal transduction-related cancer cell gene expression. Additionally, in a working model of PCA3, it has been shown that PCA3 acts as an unrecognized prune homolog 2 (PRUNE2) downregulating oncogene. PRUNE2 is a human homolog of the *Drosophila* prune gene. This downregulation is through RNA editing by the formation of PRUNE2/PCA3 double-stranded RNA.^{12,18–20} This gene has been proposed to act like a tumor suppressor in prostate cancer. Its downregulation can lead to increased risk of oncogenesis. This lncRNA is a classic example of a lncRNA showing epigenetic effect on tumor cell.¹⁸ Currently, apart from blood, urine as a specimen to detect PCA3 has also been looked into.

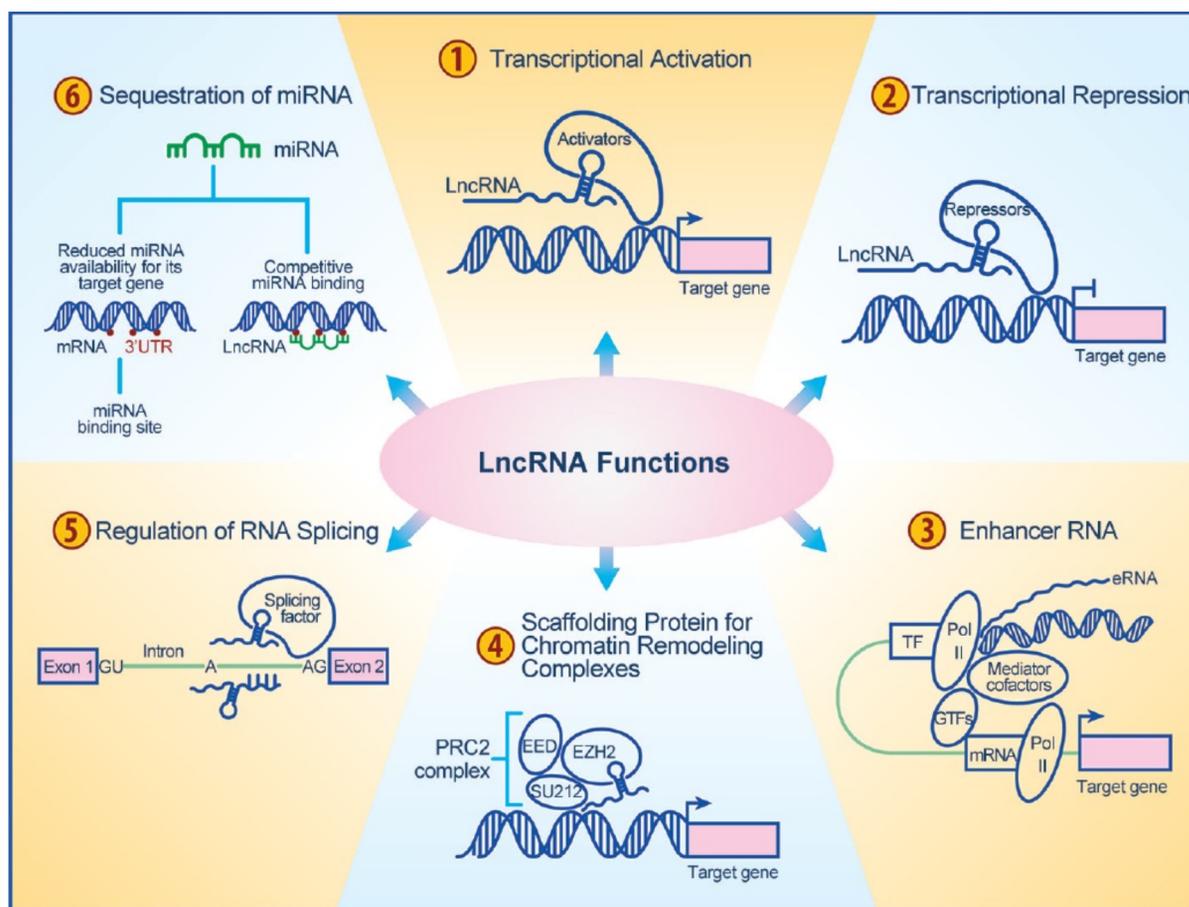


Fig. 1 Functions of long noncoding RNA.¹⁹

Second Chromosome Locus Associated with Prostate-1 (SchLAP1)

Second chromosome locus associated with prostate-1 (SchLAP1) is highly expressed in lncRNA (20–25%) in prostate cancer. Prostate cancer patients showing expression of SchLAP1 are at a higher risk of metastatic cancer. High expression of this lncRNA is common in castration-resistant prostate cancer (CRPC). It is positively associated with increased risk of disease progression, metastasis, and recurrence, leading to mortality. SchLAP1 interacts with SWI/SNF (Switch-Sucrose Non-Fermentable) complex, thus negating the tumor-suppressor effects of SWI/SNF. Expression analysis of SchLAP1 by in situ hybridization showed that this lncRNA is an independent predictor of disease recurrence after radical prostatectomy. SchLAP1 expression has been shown to correlate with cancer progression, making this lncRNA a useful tissue-based biomarker for identifying prostate cancer patients at higher risk of cancer progression.^{12,21–24}

SPRY4 Intronic Transcript 1 (SPRY4-IT1)

SPRY4 intronic transcript 1 (SPRY4-IT1), also known as *SPRIGHLY*, is a gene that produces several lncRNAs that are implicated in several malignancies including prostate cancer. It is located on 5q31.3. The gene product plays a role in cellular proliferation, apoptosis, and growth. It has been found that this lncRNA is highly upregulated in prostate

cancer cells in comparison to normal prostate epithelia. Using siRNA, SPRY4-IT1 knockdown was found to inhibit cell proliferation and enhanced tissue invasiveness and apoptosis. SPRY4-IT1 could easily be detected in majority of prostate cancer samples by using an RNA chromogenic in situ hybridization assay. Specificity of expression in prostate cancer tissue and easy detection with standard staining of tissue samples make this lncRNA useful in diagnosis.²⁵

Metastasis-Associated Lung Adenocarcinoma Transcript 1 (MALAT1)

Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is a lncRNA that was originally found to be overexpressed in metastatic non-small cell lung cancer tissues. It is derived from the gene present on chromosome 11q13.1. The gene product undergoes modification by RNase P to form a tRNA like lncRNA at its 3' end called MALAT1. Recent studies have showed MALAT1 overexpression in other human cancers, such as breast and pancreas. In prostate cancer, MALAT1 overexpression is linked with factors indicating poor prognosis such as high Gleason score, tumor metastasis, and a serum PSA value greater than 20 ng/mL. It was also observed that the expressions were much higher in CRPC. In a study that compared the expression of MALAT1 in urinary samples of biopsy-proven and normal-biopsy cancer patients, it could be safely concluded that MALAT1 was

higher in biopsy-positive samples. From this, it could be inferred that urinary MALAT1 could be used as a promising diagnostic biomarker.²⁶⁻³²

Transient Receptor Potential Cation Channel, Subfamily M, Member 2-Antisense Transcript (TRPM2-AS)

Transient receptor potential melastatin 2 (Trpm2) are non-voltage-activated channels which are permeable to both divalent and multivalent cations. They are extensively expressed in heart, kidney, and brain. It has been found to be elevated in bladder, colon, brain, and prostate cancers. They induce cellular injury due to calcium overload in the cell. The human Trpm2 (previously LTrpc2) gene is located in chromosome 21q22.3.³³ TRPM2-AS is an antisense lncRNA. It is transcribed from the antisense strand of the TRPM2 gene. Elevated levels of TRPM2-AS were indicative of poor prognosis. In vitro knockdown of TRPM2-AS caused apoptosis in prostate cancer cells. Microarray analysis showed that TRPM2-AS regulates the expression of genes involved in cell survival control, response to unfolded protein, and cell cycle in prostate cancer cells.³³⁻³⁵

Nuclear Enriched Abundant 1 (NEAT1)

NEAT1 is a key constituent of paraspeckles (nuclear substructures, located in the nucleus and have a role in regulation of gene expression). NEAT1 exists as two isoforms, named long and short, respectively, depending on the distinct termination sites. It has been shown that NEAT1 short has a distinct poly(A) tail, which is lacked in NEAT1 long. NEAT1 has a role in the formation of paraspeckles, but despite this, the expression of NEAT1 is very less in normal tissues. Using endogenous RNA purification methods, West et al showed that NEAT1 attaches near the active transcription sites in the genome and functions in association with another lncRNA MALAT1.³⁶ NEAT1 acts via competing with miR-107, which is a tumor suppressor miR. CDK6 has been found to be one of the targets of miR-107. Suppression of miR-107 can lead to enhanced G1/S transition and hence increased tumorigenesis. NEAT1 has also been shown to inhibit miR-377, which is again a tumor suppressor miR. It acts via inhibiting E2F3 and MAP3K7. MAP3K7 is a serine/threonine kinase having a potential role in several malignancies.³⁶ In a study combining chromatin immunoprecipitation sequencing with RNA sequencing techniques in prostate cancer cells, NEAT1 was the most significantly overexpressed lncRNA. NEAT1 expression was associated with cancer progression, and cells expressing high levels of NEAT1 were found to be resistant to decreased androgen levels and therapy with AR antagonists. NEAT1 has been shown to recognize the promoter regions of the target genes and modifies them epigenetically to favor transcription and enhance oncogenic growth.³⁶⁻³⁸

lncRNAs Related with AR Signaling

Prostate Cancer Gene Expression Marker 1 (PCGEM1)

PCGEM1 is a highly prostate-specific lncRNA and has a role in cell proliferation. It is an androgen-regulated lncRNA. The chromosomal location for the gene coding this lncRNA

is 2q32.2. This lncRNA has been proposed to have an antiapoptotic effect along with influencing the AR and the Myc. Apart from prostate cancer, this RNA has also been implicated in osteoarthritis.^{39,40} The myocyte enhancer factor 2 (MEF2) has a role in cell differentiation, proliferation, and metastasis. It has been demonstrated that the expression of PCGEM1 is regulated by MEF2. Increased expression of MEF2 was shown to enhance the expression of PCGEM1 via its positive effect in its promoter. Gene expression analysis showed that MEF2 was differentially expressed under the influence of androgens.⁴¹ Expression of PCGEM1 has been found in approximately 50% of prostate tumors, with functional analysis supporting the fact that this RNA has a role in cell proliferation promotion and colony formation. It was shown that cell proliferation regulation by PCGEM1 was via the regulation of c-Myc.⁴¹⁻⁴³

PCAT (Prostate Cancer Associated Transcript 1) Family

PCAT1 is a lncRNA expressed with great specificity in prostate tissue. It is upregulated in high-grade metastatic prostate cancer. It was discovered by Prensner and Chinnaiyan in 2011. PCAT1 gene is located on chromosome 8q24 and is 725 kb upstream of the c-Myc oncogene. PCAT1 has been found to induce in vitro cell proliferation. Apart from cellular proliferation, PCAT1 has been found to have repressive effects on other genes, including BRCA2. PCAT1 promotes cell proliferation by interacting with c-Myc. It plays the role of a dummy for c-Myc-targeting miRNAs. Apart from having a role in cell proliferation, tumor metastasis, and invasion, PCAT1 has also been implicated in epithelial mesenchymal transition via the Wnt/ β catenin pathway.⁴⁴ Other PCAT family members, namely, PCAT6, PCAT7, and PCAT18, have been found to have predictive role in assessment of tumor progression by regulating AR signaling. Expressions of PCAT6 and PCAT7 were found to be higher in primary and metastatic prostate cancer. Knockdown of PCAT6 and PCAT7 using RNA silencing reduced cell growth. PCAT18, a highly prostate-specific lncRNA, was found to be increasingly expressed in metastatic prostate cancer tissues. Expression level of PCAT18 is also regulated by AR signaling. Knockdown of PCAT18 decreased cell growth.⁴⁵⁻⁵⁰ PCAT29 is functionally a tumor suppressor RNA and was identified as an AR-regulated lncRNA. Interestingly, it was noted that PCAT29 downregulation significantly increased cellular proliferation and migration, whereas PCAT29 overexpression did the reverse. In specimens taken from prostate cancer patients, low PCAT29 expression was linked with poor prognosis, suggesting that decreased expression of this lncRNA may help us identify those patients who are at a higher risk for disease recurrence.⁵¹⁻⁵³

Prostate Cancer Noncoding RNA-1 (PRNCR1)

This lncRNA was first identified by Chung et al in 2011.⁵² The transcript was found to be 13-kb long and is polyadenylated. PRNCR1 was initially identified as a novel lncRNA transcribed from 8q24. 8q24 genomic locus is an important gene locus greatly associated with prostate cancer susceptibility and has presence of another lncRNA, namely, PCAT1. Knockdown of PRNCR1 by RNA silencing reduced prostate

cancer cell viability and AR activation activity. This indicated that PRNCR1 could be implicated in prostate cancer possibly through AR. In another study, it was found that PRNCR1 and PCGEM1 can successively bind to AR and strongly increase gene activation and proliferation in prostate cancer cells by using AR. However, further studies showed that neither PCGEM1 nor PRNCR1 interacts with AR and that neither gene was of any prognostic importance for prostate cancer.⁵²⁻⁵⁴

C-Terminal Binding Protein 1 (CTBP1)

The cytogenetic location of CTBP1 is 4p16.3. This gene encodes transcriptional regulators that interact with chromatin-modifying enzymes to regulate cellular pathways. CTBP1 is mainly a repressor acting via histone acetylases and deacetylases.⁵⁵ A lncRNA located at the antisense region of the CTBP1 gene, i.e., CTBP1-AS, was demonstrated to promote tumor growth of both hormone-sensitive and hormone-resistant prostate cancer models epigenetically.^{56,57} These studies underlined the importance of the role played by an androgen-regulated lncRNAs in cancer progression.

HOX Transcript Antisense RNA (HOTAIR)

This gene is located in the HOMEBOX C gene cluster present on chromosome 12. HOTAIR and its variants have been implicated in many malignancies. It has been shown that aberrant HOTAIR expression can result in chemoresistance in malignancies, and knockdown of HOTAIR has been found to cause tumor invasion and metastasis.⁵⁸ In prostate cancer, HOTAIR was reported as a lncRNA that were suppressed by androgens. HOTAIR was thought to bind with AR protein and subsequently block its interaction with E3 ubiquitin ligase, thus preventing the receptor ubiquitination and degradation. Increased expression of HOTAIR was associated with increased prostate cancer cell growth and invasion.⁵⁹⁻⁶⁷

Suppressor of Cytokine Signaling 2-Antisense Transcript 1 (SOCS2-AS1)

SOCS2-AS1 is an androgen-regulated lncRNA. It is located at the antisense strand of SOCS2. SOCS2 belongs to a family of eight genes whose function is via the JAK/STAT pathway. The expressions of SOCS2-AS1 and SOCS2 were thought to be in an androgen-dependent manner. RNA silencing-induced SOCS2-AS1 and SOCS2 downregulation reduced the cellular proliferation in prostate cancer cells. It has been documented that SOCS2-AS1 has been expressed in CRPC model cells and that they have a role in promotion of growth in both androgen-resistant and androgen-dependent cells, and it also inhibited apoptosis. Furthermore, through epigenetic modification, SOCS2-AS1 promoted androgen signaling for the target genes of AR, including TNFSF10 (tumor necrosis factor superfamily member 10). This suggested that SOCS2-AS1 had an important role in CRPC development by repressing apoptosis.⁶⁸

POTEF-Antisense Transcript-1 (POTEF-AS1)

Prostate, ovary, testis expressed protein family member-F gene (POTEF) antisense transcript 1 is a lncRNA transcribed

from the antisense strand of prostate, ovary, testis expressed protein family member-F gene (POTEF). This gene is located on chromosome 2q21.1. POTEF is one of main proteins that is encoded by the POTE family genes, and is mainly expressed in the tissues of prostate, ovary, testis, and placenta. POTEF-AS1, which is coded from the antisense strand of POTEF, was demonstrated to promote cell growth and inhibit apoptosis. It was shown to repressed genes related to toll-like receptor signaling pathways.^{69,70}

lncRNAs as Tumor Suppressors

Growth Arrest-Specific 5 (GAS5)

GAS5 is a tumor-suppressive lncRNA that promotes apoptosis and decreases AR action. It was found to isolate androgen/AR complexes and prevent their binding to target genes. It was noted that there was a decrease in the expression levels of GAS5 when prostate cancer cells acquire androgen resistance. In a recent study, mTOR inhibitor was found to regulate GAS5 expression in prostate cancer cells. In AR-positive prostate cancer cell lines, such as LNCaP and 22Rv1, mTOR inhibitors have shown to increase expression levels of cellular GAS5 and also inhibited cell growth. GAS5 silencing cells resulted in reduced sensitivity to mTOR inhibitors. In early-stage prostate cancer, these mTOR inhibitors may be used to increase GAS5 levels and hence increase cellular apoptosis, which may be a useful therapeutic target.⁷¹⁻⁷³

Focally Amplified lncRNA Onchromosome1 (FALEC)

It is an oncogenic lncRNA having a chromosomal location of 1q21.2. It has been shown that FALEC acted via binding to polycomb repressive complex 1 (PRC1) and BMI1 proto-oncogene to alter the levels of H2AK119. Histone H2AK119 monoubiquitination is necessary for binding and subsequent suppression of PRC1. Altered expression of PRC1 complex can result in suppression of CDKN1A, p21, TP53I3 targets, which allow proliferation of tumor cells. A study conducted by Zhao et al using real-time polymerase chain reaction (RT-PCR) analysis showed that there was an increased expression of FALEC in prostate cancer cells in comparison to normal epithelial cells. Higher expression of FALEC was associated with high-grade tumor with increased tissue invasiveness and high Gleason score. The elevated expression correlated with poor prognosis.⁷⁴

Antisense Noncoding RNA in the INK4 Locus (ANRIL)

It is an antisense lncRNA found at the gene locus of CDKN2A/B. This gene locus is associated with many metabolic and malignant diseases. ANRIL is a complex gene containing 21 exons. In malignancies, a gain-of-function mutation in ANRIL is associated with increased cellular proliferation, metastasis, increased cell survival via the PI3K/AKT pathway, and epithelial-to-mesenchymal cell transition by activating the ATM-E2F1 signaling pathway. Zhao et al illustrated the role of ANRIL in cell proliferation and migration in prostate cancer cells using the CCK8 assay and RT-PCT.⁷⁵ Their result showed that ANRIL expression was significantly elevated in prostate cancer tissues. Knockdown of ANRIL inhibited the

proliferation and migration of prostate cancer cells and significantly decreased the levels of TGF- β 1 and p-Smad2, which are involved in cellular proliferation. In prostate cancer, the rs4977574, rs1333048, and rs10757278 polymorphisms of lncRNA ANRIL were associated with benign prostate hyperplasia.⁷⁵⁻⁷⁷

► **Table 1** enlists the various lncRNA discussed and their possible role in prostate cancer therapy.

TMPRSS2:ERG Gene Fusion

Genomic rearrangements have long been implicated as initial events in oncogenesis. There are many malignancies that have gene fusion in their pathogenesis, e.g., the Philadelphia chromosome, which has been implicated in many hematological malignancies such as chronic myeloid leukemia and acute myeloid leukemia. In the case of prostate cancer, gene fusion transcripts of ERG (also known as *TMPRSS2:ERG*, or T2E), which is a member of the ETS family (erythroblast transformation-specific) of oncogenes-transcription factors has been implicated. ERG gene produces ERG protein, which has a role in embryonal development, angiogenesis, cell proliferation, and differentiation. This gene fusion product has been identified as promising urinary novel

biomarkers.⁷⁸ Laxman et al were the first to show the presence of mRNA products of the *TMPRSS2:ERG* fusion gene in the urine samples from prostate cancer patients.⁷⁹ In 2005, Tomlins et al identified gene members of the ETS family of oncogenes in 55% of prostate cancer patients,⁷⁹ similar to the results of an earlier study in which ERG overexpression was found in 72% of prostate cancer cases. More so by performing the assays in combination, they were able to detect fusion of these ETS family genes with the 5' untranslated region of the *TMPRSS2* gene in more than 90% of cases, resulting in overexpression of ERG or its variant gene (ETV) 1. *TMPRSS2* gene is highly prostate-specific and an androgen-regulated gene. From this, they concluded that overexpression is most probably caused by the gene fusion.^{79,80} Of all the fusion gene-associated overexpression, *TMPRSS2:ERG* fusion was found to be the most common. However, some rarer variants of the ETS superfamily were also reported, such as ETV4 and ETV5, in prostate cancer.⁸¹⁻⁸³

Salami et al looked into the urinary *TMPRSS2:ERG* and PCA3 and correlated it with serum PSA values post DRE to predict prostate cancer in subsequent biopsy. *TMPRSS2* is an androgen-responsive gene. The result showed that post DRE, *TMPRSS2:ERG* in urine was associated with prostate

Table 1 Summary of all long noncoding RNAs and their utility

S. no.	Name of the long noncoding RNA	Clinical utility	References
1	<i>Prostate cancer antigen 3 (PCA3)</i>	Role in diagnosis as well as in prognosis	13,18,20,21
2	Second chromosome locus associated with prostate-1 (SChLAP1)	Role is predicting severity of disease and potent marker for disease recurrence	13,22-25
3.	<i>SPRY4 intronic transcript 1 (SPRY4-IT1)</i>	Diagnostic marker	26
4.	<i>Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1)</i>	Prognosis assessment	28-33
5.	<i>Transient receptor potential cation channel, subfamily M, member 2-antisense transcript (TRPM2-AS)</i>	Prognosis assessment	34-36
6.	<i>Nuclear enriched abundant 1 (NEAT1)</i>	Disease progression and resistance to androgen therapy	37-39
7.	<i>Prostate cancer gene expression marker 1 (PCGEM1)</i>	Disease progression	40-44
8.	Prostate cancer associated transcript 1 (PCAT) family	Disease progression and recurrence	46-54
9.	Prostate cancer noncoding RNA-1 (PRNCR1)	Prognostic marker	53-55
10.	C-terminal binding protein 1 (CTBP1)	Disease progression	56-58
11.	HOX transcript antisense RNA (HOTAIR)	Disease progression	60-68
12.	Suppressor of cytokine signaling 2-antisense transcript 1 (SOCS2-AS1)	Role in development of CRPC	69
13.	POTEF-antisense transcript-1 (POTEF-AS1)	Disease progression	70,71
14.	Growth arrest-specific 5 (GAS5)	Prospective therapeutic target	72-74
15.	Focally amplified lncRNA on chromosome 1 (FALEC)	Prognostic marker	76
16	Antisense noncoding RNA in the INK4 locus (ANRIL)	Diagnosis and disease progression. Gene polymorphism caused expression in benign disease	75,77,78

cancer (odds ratio, 12.02; $p = 0.001$). PCA3 had the maximum sensitivity in diagnosing prostate cancer (93%), whereas *TMPRSS2:ERG* was found to have the highest specificity (87%). Moreover, *TMPRSS2:ERG* was found to be the best in differentiating prostate cancer (area under the curve [AUC], 0.77 vs. 0.65 for PCA3 and 0.72) from serum PSA taken on its own. Combining serum PSA, PCA3, and *TMPRSS2:ERG* in a combined stepwise manner could increase clinical utility and enhance cancer prediction (AUC, 0.88; specificity 90% at 80% sensitivity).⁸⁴ Similar work was done on in vitro and in vivo models by Tomlins et al; they also concluded that *TMPRSS2:ERG* fusion gene product increased the invasiveness of prostate cancer.⁸⁵ Hägglöf et al demonstrated that *TMPRSS2:ERG* gene fusion product also correlated with clinical markers such as high-grade tumor, elevated Gleason score, presence of metastasis, and presence of elevated levels of markers such as Ki67, pEGFR, and pAkt, which are cellular tumor makers.⁸⁶ The role of *TMPRSS2:ERG* as a predictor of prognosis for prostate cancer has been evaluated with a lot of inconsistency in results. However, it is evident now that in patients treated with radical prostatectomy, *TMPRSS2:ERG* fusion does not impact patient outcome.⁸⁷ Various methods can be used to detect *TMPRSS2:ERG* fusion. ERG protein overexpression in nuclei by immune histochemistry, which is the most commonly used method and is easy to perform and inexpensive.⁸⁸

Conclusion

Currently, lncRNAs are one of the most analyzed entities. Several studies are simultaneously going on to check their role in various cancers, including breast cancer. There are several advantages and disadvantages with the use of lncRNA in the diagnosis and treatment of prostate cancer patients. lncRNAs as biomarkers can be useful if they can be easily detected in biological fluids. Since lncRNA is itself a functional molecule, its expression patterns may give clinician precise and basic information on tumors' biological behavior and aggressiveness. This can potentially lead to the possibility of designing personalized strategies for a single prostate cancer patient. Currently, PCA3 is the main lnc that is used for diagnostic purpose in prostate cancer. Among the main disadvantages, the aggressive nature of the tumor is the result of a complex process that involves, apart from lncRNA, a variety of other driver genes. Therefore, for more conclusive outcomes, uropathologists have to test and validate not a single driver gene, but a panel of genes. This will entail a lot of costs and trained manpower.⁴⁶ Apart from this, there are some other unanswered questions, such as the stability of circulating lncRNA in the specimens and also regarding the alteration in stability due to disease condition. The potential of lncRNA as therapeutic targets is currently being explored. There are several angles that are under investigation, such as silencing of lnc, structural disruption, or even a functional blockade. However, all these studies are still in nascent stage.⁸⁹ Lee et al have reported a urine-based assay using PCA3 for diagnosis of prostate cancer⁹⁰ but it has not found use in the routine clinical practice to the best of our knowledge.

As far as gene fusion products go, there have been studies that show promise in the use of gene fusion products; however, the overall picture is still obscure. There are various methods that can be used to detect gene fusion, such as FISH, gene sequencing, and gene chip, which are complex procedures requiring highly skilled manpower, high costs, and stringent sample requirement.⁸⁸ This article is an attempt to present an overview of the potential of lncRNA and gene fusion products in the field of prostate cancer, and has not gone into too much details about each lncRNA or gene fusion as they are very extensive on their own. There has been extensive work done with the use of microRNA and their potential in the diagnostic and prognostic area of prostate cancer, but that is beyond the scope of this article.

Although prostate cancer is one of the most common malignancies in males, still there is no ideal marker for its diagnosis and for assessment of response to treatment. With the advancement in molecular diagnostic techniques, more emphasis should be laid on molecular markers as they may be more sensitive and specific. However, the issues of assay standardization, higher costs of sample processing, and requirement of highly trained personnel for assay performance limit their current use.

Conflict of Interest

None declared.

References

- 1 National Cancer Institute. Cancer stat facts: prostate cancer. Available at: <https://seer.cancer.gov/statfacts/html/prost.html>
- 2 Center MM, Jemal A, Lortet-Tieulent J, et al. International variation in prostate cancer incidence and mortality rates. *Eur Urol* 2012;61(6):1079–1092
- 3 Taitt HE. Global trends and prostate cancer: a review of incidence, detection, and mortality as influenced by race, ethnicity, and geographic location. *Am J Men Health* 2018;12(6):1807–1823
- 4 Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin* 2015;65(2):87–108
- 5 Baade PD, Youlten DR, Krnjacki LJ. International epidemiology of prostate cancer: geographical distribution and secular trends. *Mol Nutr Food Res* 2009;53(2):171–184
- 6 Jemal A, Center MM, DeSantis C, Ward EM. Global patterns of cancer incidence and mortality rates and trends. *Cancer Epidemiol Biomarkers Prev* 2010;19(8):1893–1907
- 7 Jain S, Saxena S, Kumar A. Epidemiology of prostate cancer in India. *Meta Gene* 2014;2:596–605
- 8 Scher HI, Eastham JA. Benign and Malignant Diseases of the Prostate. In: Jameson JL, Fauci A, Kasper D, et al., eds. *Harrison's Principles and Practice of Internal Medicine*. 19th ed. New York, NY: McGraw-Hill Education; 2017:579–580
- 9 National Cancer Registry Programme (NCRP), Time Trends in Cancer Incidence Rates 1982–2005. Bengaluru, Karnataka: Indian Council of Medical Research; 2009
- 10 Lori SJ, Rai AJ. Tumor markers. In: Burtis C, Ashwood E, Bruns D, eds. *Tietz Textbook of Clinical Chemistry and Molecular Diagnostics*. 5th ed. Philadelphia, PA: Elsevier Saunders; 2012:628–631
- 11 Shukla KK, Sanjeev M, Puneet P, Mishra V, Singhal B, Sharma P. Recent scenario of microRNA as diagnostic and

- prognostic biomarkers of prostate cancer. *Urol Oncol* 2017; 35(3):92–101
- 12 Misawa A, Takayama KI, Inoue S. Long non-coding RNAs and prostate cancer. *Cancer Sci* 2017;108(11):2107–2114
 - 13 Feng S, Yao J, Chen Y, et al. Expression and functional role of reprogramming-related long noncoding RNA (lincRNA-ROR) in glioma. *J Mol Neurosci* 2015;56(3):623–630
 - 14 Hu L, Wu Y, Tan D, et al. Up-regulation of long noncoding RNA MALAT1 contributes to proliferation and metastasis in esophageal squamous cell carcinoma. *J Exp Clin Cancer Res* 2015;34:7
 - 15 Kandoth C, McLellan MD, Vandin F, et al. Mutational landscape and significance across 12 major cancer types. *Nature* 2013;502(7471) :333–339
 - 16 Ciriello G, Miller ML, Aksoy BA, Senbabaoglu Y, Schultz N, Sander C. Emerging landscape of oncogenic signatures across human cancers. *Nat Genet* 2013;45(10):1127–1133
 - 17 Prensner JR, Chinnaiyan AM. The emergence of lncRNAs in cancer biology. *Cancer Discov* 2011;1(5):391–407
 - 18 Bussemakers MJ, van Bokhoven A, Verhaegh GW, et al. DD3: a new prostate-specific gene, highly overexpressed in prostate cancer. *Cancer Res* 1999;59(23):5975–5979
 - 19 Malik B, Feng FY. Long noncoding RNAs in prostate cancer: overview and clinical implications. *Asian J Androl* 2016;18(4):568–574
 - 20 Lemos AE, Ferreira LB, Batoreu NM, de Freitas PP, Bonamino MH, Gimba ER. PCA3 long noncoding RNA modulates the expression of key cancer-related genes in LNCaP prostate cancer cells. *Tumour Biol* 2016;37(8):11339–11348
 - 21 Salameh A, Lee AK, Cardó-Vila M, et al. PRUNE2 is a human prostate cancer suppressor regulated by the intronic long noncoding RNA PCA3. *Proc Natl Acad Sci U S A* 2015;112(27):8403–8408
 - 22 Prensner JR, Iyer MK, Sahu A, et al. The long noncoding RNA SchLAP1 promotes aggressive prostate cancer and antagonizes the SWI/SNF complex. *Nat Genet* 2013;45(11):1392–1398
 - 23 Prensner JR, Zhao S, Erho N, et al. RNA biomarkers associated with metastatic progression in prostate cancer: a multi-institutional high-throughput analysis of SchLAP1. *Lancet Oncol* 2014;15(13):1469–1480
 - 24 Mehra R, Shi Y, Udager AM, et al. A novel RNA in situ hybridization assay for the long noncoding RNA SchLAP1 predicts poor clinical outcome after radical prostatectomy in clinically localized prostate cancer. *Neoplasia* 2014;16(12):1121–1127
 - 25 Mehra R, Udager AM, Ahearn TU, et al. Overexpression of the long non-coding RNA SchLAP1 independently predicts lethal prostate cancer. *Eur Urol* 2016;70(4):549–552
 - 26 Lee B, Mazar J, Aftab MN, et al. Long noncoding RNAs as putative biomarkers for prostate cancer detection. *J Mol Diagn* 2014;16(6):615–626
 - 27 Ji P, Diederichs S, Wang W, et al. MALAT-1, a novel non-coding RNA, and thymosin beta4 predict metastasis and survival in early-stage non-small cell lung cancer. *Oncogene* 2003;22(39):8031–8041
 - 28 Lin R, Maeda S, Liu C, Karin M, Edgington TS. A large noncoding RNA is a marker for murine hepatocellular carcinomas and a spectrum of human carcinomas. *Oncogene* 2007;26(6):851–858
 - 29 Konishi H, Ichikawa D, Yamamoto Y, et al. Plasma level of metastasis-associated lung adenocarcinoma transcript 1 is associated with liver damage and predicts development of hepatocellular carcinoma. *Cancer Sci* 2016;107(2):149–154
 - 30 Ren S, Liu Y, Xu W, et al. Long noncoding RNA MALAT-1 is a new potential therapeutic target for castration resistant prostate cancer. *J Urol* 2013;190(6):2278–2287
 - 31 Wang F, Ren S, Chen R, et al. Development and prospective multicenter evaluation of the long noncoding RNA MALAT-1 as a diagnostic urinary biomarker for prostate cancer. *Oncotarget* 2014;5(22):11091–11102
 - 32 Wang D, Ding L, Wang L, et al. lncRNA MALAT1 enhances oncogenic activities of EZH2 in castration-resistant prostate cancer. *Oncotarget* 2015;6(38):41045–41055
 - 33 Cheung JY, Miller BA. Transient receptor potential-melastatin channel family member 2: friend or foe. *Trans Am Clin Climatol Assoc* 2017;128:308–329
 - 34 Orfanelli U, Jachetti E, Chiacchiera F, et al. Antisense transcription at the TRPM2 locus as a novel prognostic marker and therapeutic target in prostate cancer. *Oncogene* 2015;34(16):2094–2102
 - 35 Lavorgna G, Chiacchiera F, Briganti A, Montorsi F, Pasini D, Salonia A. Expression-profiling of apoptosis induced by ablation of the long ncRNA TRPM2-AS in prostate cancer cell. *Genom Data* 2014;3:4–5
 - 36 Ghafouri-Fard S, Taheri M. Nuclear enriched abundant transcript 1 (NEAT1): a long non-coding RNA with diverse functions in tumorigenesis. *Biomed Pharmacother* 2019;111:51–59
 - 37 West JA, Davis CP, Sunwoo H, et al. The long noncoding RNAs NEAT1 and MALAT1 bind active chromatin sites. *Mol Cell* 2014;55(5):791–802
 - 38 Chakravarty D, Sboner A, Nair SS, et al. The oestrogen receptor alpha-regulated lncRNA NEAT1 is a critical modulator of prostate cancer. *Nat Commun* 2014;5:5383
 - 39 Ho TT, Huang J, Zhou N, et al. Regulation of PCGEM1 by p54/nrb in prostate cancer. *Sci Rep* 2016;6:34529
 - 40 Zhao Y, Xu J. Synovial fluid-derived exosomal lncRNA PCGEM1 as biomarker for the different stages of osteoarthritis. *Int Orthop* 2018;42(12):2865–2872
 - 41 Zhang S, Li Z, Zhang L, Xu Z. MEF2-activated long non-coding RNA PCGEM1 promotes cell proliferation in hormone-refractory prostate cancer through downregulation of miR-148a. *Mol Med Rep* 2018;18(1):202–208
 - 42 Srikantan V, Zou Z, Petrovics G, et al. PCGEM1, a prostate-specific gene, is overexpressed in prostate cancer. *Proc Natl Acad Sci U S A* 2000;97(22):12216–12221
 - 43 Petrovics G, Zhang W, Makarem M, et al. Elevated expression of PCGEM1, a prostate-specific gene with cell growth-promoting function, is associated with high-risk prostate cancer patients. *Oncogene* 2004;23(2):605–611
 - 44 Xiong T, Li J, Chen F, Zhang F. PCAT-1: a novel oncogenic long non-coding RNA in human cancers. *Int J Biol Sci* 2019;15(4):847–856
 - 45 Hung CL, Wang LY, Yu YL, et al. A long noncoding RNA connects c-Myc to tumor metabolism. *Proc Natl Acad Sci U S A* 2014;111(52):18697–18702
 - 46 Prensner JR, Chen W, Iyer MK, et al. PCAT-1, a long noncoding RNA, regulates BRCA2 and controls homologous recombination in cancer. *Cancer Res* 2014;74(6):1651–1660
 - 47 Prensner JR, Chen W, Han S, et al. The long non-coding RNA PCAT-1 promotes prostate cancer cell proliferation through cMyc. *Neoplasia* 2014;16(11):900–908
 - 48 Du Z, Fei T, Verhaak RG, et al. Integrative genomic analyses reveal clinically relevant long noncoding RNAs in human cancer. *Nat Struct Mol Biol* 2013;20(7):908–913
 - 49 Rönna CG, Verhaegh GW, Luna-Velez MV, Schalken JA. Noncoding RNAs as novel biomarkers in prostate cancer. *BioMed Res Int* 2014;2014:591703
 - 50 Crea F, Watahiki A, Quagliata L, et al. Identification of a long non-coding RNA as a novel biomarker and potential therapeutic target for metastatic prostate cancer. *Oncotarget* 2014;5(3):764–774
 - 51 Malik R, Patel L, Prensner JR, et al. The lncRNA PCAT29 inhibits oncogenic phenotypes in prostate cancer. *Mol Cancer Res* 2014;12(8):1081–1087
 - 52 Chung S, Nakagawa H, Uemura M, et al. Association of a novel long non-coding RNA in 8q24 with prostate cancer susceptibility. *Cancer Sci* 2011;102(1):245–252

- 53 Yang L, Lin C, Jin C, et al. lncRNA-dependent mechanisms of androgen-receptor-regulated gene activation programs. *Nature* 2013;500(7464):598–602
- 54 Prensner JR, Sahu A, Iyer MK, et al. The lncRNAs PCGEM1 and PRNCR1 are not implicated in castration resistant prostate cancer. *Oncotarget* 2014;5(6):1434–1438
- 55 Beck DB, Cho MT, Millan F, et al. A recurrent de novo CTBP1 mutation is associated with developmental delay, hypotonia, ataxia, and tooth enamel defects. *Neurogenetics* 2016;17(3):173–178
- 56 Parolia A, Crea F, Xue H, et al. The long non-coding RNA PCGEM1 is regulated by androgen receptor activity in vivo. *Mol Cancer* 2015;14:46
- 57 Takayama K, Horie-Inoue K, Katayama S, et al. Androgen-responsive long noncoding RNA CTBP1-AS promotes prostate cancer. *EMBO J* 2013;32(12):1665–1680
- 58 Rajagopal T, Talluri S, Akshaya RL, Dunna NR. HOTAIR lncRNA: a novel oncogenic propellant in human cancer. *Clin Chim Acta* 2020;503:1–18
- 59 Gupta RA, Shah N, Wang KC, et al. Long non-coding RNA HOTAIR reprograms chromatin state to promote cancer metastasis. *Nature* 2010;464(7291):1071–1076
- 60 Kogo R, Shimamura T, Mimori K, et al. Long noncoding RNA HOTAIR regulates polycomb-dependent chromatin modification and is associated with poor prognosis in colorectal cancers. *Cancer Res* 2011;71(20):6320–6326
- 61 Geng YJ, Xie SL, Li Q, Ma J, Wang GY. Large intervening non-coding RNA HOTAIR is associated with hepatocellular carcinoma progression. *J Int Med Res* 2011;39(6):2119–2128
- 62 Niinuma T, Suzuki H, Nojima M, et al. Upregulation of miR-196a and HOTAIR drive malignant character in gastrointestinal stromal tumors. *Cancer Res* 2012;72(5):1126–1136
- 63 Li D, Feng J, Wu T, et al. Long intergenic noncoding RNA HOTAIR is overexpressed and regulates PTEN methylation in laryngeal squamous cell carcinoma. *Am J Pathol* 2013;182(1):64–70
- 64 Kim K, Jutooru I, Chadalapaka G, et al. HOTAIR is a negative prognostic factor and exhibits pro-oncogenic activity in pancreatic cancer. *Oncogene* 2013;32(13):1616–1625
- 65 Nie Y, Liu X, Qu S, Song E, Zou H, Gong C. Long non-coding RNA HOTAIR is an independent prognostic marker for nasopharyngeal carcinoma progression and survival. *Cancer Sci* 2013;104(4):458–464
- 66 Ge XS, Ma HJ, Zheng XH, et al. HOTAIR, a prognostic factor in esophageal squamous cell carcinoma, inhibits WIF-1 expression and activates Wnt pathway. *Cancer Sci* 2013;104(12):1675–1682
- 67 Zhang A, Zhao JC, Kim J, et al. lncRNA HOTAIR enhances the androgen-receptor-mediated transcriptional program and drives castration-resistant prostate cancer. *Cell Rep* 2015;13(1):209–221
- 68 Misawa A, Takayama K, Urano T, Inoue S. Androgen-induced long noncoding rna (lncRNA) SOCS2-AS1 promotes cell growth and inhibits apoptosis in prostate cancer cells. *J Biol Chem* 2016;291(34):17861–17880
- 69 Misawa A, Takayama KI, Fujimura T, Homma Y, Suzuki Y, Inoue S. Androgen-induced lncRNA POTE-AS1 regulates apoptosis-related pathway to facilitate cell survival in prostate cancer cells. *Cancer Sci* 2017;108(3):373–379
- 70 Bera TK, Saint Fleur A, Lee Y, et al. POTE paralogs are induced and differentially expressed in many cancers. *Cancer Res* 2006;66(1):52–56
- 71 Kino T, Hurt DE, Ichijo T, Nader N, Chrousos GP. Noncoding RNA gas5 is a growth arrest- and starvation-associated repressor of the glucocorticoid receptor. *Sci Signal* 2010;3(107):ra8
- 72 Pickard MR, Mourtada-Maarabouni M, Williams GT. Long non-coding RNA GAS5 regulates apoptosis in prostate cancer cell lines. *Biochim Biophys Acta* 2013;1832(10):1613–1623
- 73 Shi XB, Tepper CG, White RW. MicroRNAs and prostate cancer. *J Cell Mol Med* 2008;12(5A):1456–1465
- 74 Zhao R, Sun F, Bei X, et al. Upregulation of the long non-coding RNA FALEC promotes proliferation and migration of prostate cancer cell lines and predicts prognosis of PCa patients. *Prostate* 2017;77(10):1107–1117
- 75 Zhao B, Lu YL, Yang Y, et al. Overexpression of lncRNA ANRIL promoted the proliferation and migration of prostate cancer cells via regulating let-7a/TGF- β 1/Smad signaling pathway. *Cancer Biomark* 2018;21(3):613–620
- 76 Kong Y, Hsieh CH, Alonso LC. ANRIL: a lncRNA at the CDKN2A/B locus with roles in cancer and metabolic disease. *Front Endocrinol (Lausanne)* 2018;9:405
- 77 Taheri M, Pouresmaeili F, Omrani MD, et al. Association of ANRIL gene polymorphisms with prostate cancer and benign prostatic hyperplasia in an Iranian population. *Biomarkers Med* 2017;11(5):413–422
- 78 Sanguedolce F, Cormio A, Brunelli M, et al. Urine TMPRSS2:ERG fusion transcript as a biomarker for prostate cancer: literature review. *Clin Genitourin Cancer* 2016;14(2):117–121
- 79 Laxman B, Tomlins SA, Mehra R, et al. Noninvasive detection of TMPRSS2:ERG fusion transcripts in the urine of men with prostate cancer. *Neoplasia* 2006;8(10):885–888
- 80 Tomlins SA, Rhodes DR, Perner S, et al. Recurrent fusion of TMPRSS2 and ETS transcription factor genes in prostate cancer. *Science* 2005;310(5748):644–648
- 81 Petrovics G, Liu A, Shaheduzzaman S, et al. Frequent overexpression of ETS-related gene-1 (ERG1) in prostate cancer transcriptome. *Oncogene* 2005;24(23):3847–3852
- 82 Tomlins SA, Mehra R, Rhodes DR, et al. TMPRSS2:ETV4 gene fusions define a third molecular subtype of prostate cancer. *Cancer Res* 2006;66(7):3396–3400
- 83 Helgeson BE, Tomlins SA, Shah N, et al. Characterization of TMPRSS2:ETV5 and SLC45A3:ETV5 gene fusions in prostate cancer. *Cancer Res* 2008;68(1):73–80
- 84 Salami SS, Schmidt F, Laxman B, et al. Combining urinary detection of TMPRSS2:ERG and PCA3 with serum PSA to predict diagnosis of prostate cancer. *Urol Oncol* 2013;31(5):566–571
- 85 Tomlins SA, Laxman B, Varambally S, et al. Role of the TMPRSS2-ERG gene fusion in prostate cancer. *Neoplasia* 2008;10(2):177–188
- 86 Hägglöf C, Hammarsten P, Strömvall K, et al. TMPRSS2-ERG expression predicts prostate cancer survival and associates with stromal biomarkers. *PLoS One* 2014;9(2):e86824
- 87 Gopalan A, Leversha MA, Satagopan JM, et al. TMPRSS2-ERG gene fusion is not associated with outcome in patients treated by prostatectomy. *Cancer Res* 2009;69(4):1400–1406
- 88 Hossain D, Bostwick DG. Significance of the TMPRSS2:ERG gene fusion in prostate cancer. *BJU Int* 2013;111(5):834–835
- 89 Vicentini C, Galuppini F, Corbo V, Fassan M. Current role of non-coding RNAs in the clinical setting. *Noncoding RNA Res* 2019;4(3):82–85
- 90 Lee GL, Dobi A, Srivastava S. Prostate cancer: diagnostic performance of the PCA3 urine test. *Nat Rev Urol* 2011;8(3):123–124