

Long non-coding RNAs in prostate tumorigenesis and therapy (Review)

GANGGANG JIANG^{1,2*}, ZHENGMING SU^{1,2*}, XUE LIANG²,
YIQIAO HUANG¹, ZIQUAN LAN¹ and XIANHAN JIANG^{1,2}

Departments of ¹Urology and ²Center Laboratory, The Fifth Affiliated Hospital of Guangzhou Medical University, Guangzhou, Guangdong 510700, P.R. China

Received April 14, 2019; Accepted June 18, 2020

DOI: 10.3892/mco.2020.2146

Abstract. Prostate cancer (PCa) is one of the most frequently diagnosed malignancy. Although there have been many advances in PCa diagnosis and therapy, the concrete mechanism remains unknown. Long non-coding RNAs (lncRNAs) are novel biomarkers associated with PCa, and their dysregulated expression is closely associated with risk stratification, diagnosis and carcinogenesis. Accumulating evidence has suggested that lncRNAs play important roles in prostate tumorigenesis through relevant pathways, such as androgen receptor interaction and PI3K/Akt. The present review systematically summarized the potential clinical utility of lncRNAs and provided a novel guide for their function in PCa.

Contents

1. Introduction
2. Key pathways dysregulated in prostate cancer by lncRNAs
3. Therapeutic potential of lncRNAs in patients with cancer
4. Conclusions

1. Introduction

Prostate cancer (PCa) is the second most common malignancy in Western countries and accounts for 10% of cancer-related deaths (1). Approximately 26,730 deaths occurred in 2017 due to PCa in the United States. The causes of this disease

include age, functional testicles, and family heredity. Most cases of PCa undergo a series of processes from androgen sensitivity neoplasia to metastatic castration-resistant PCa (mCRPC), which is presently incurable. Currently available means for diagnosis depend on prostate specific antigen (PSA) and pathological biopsy. Since PSA testing was introduced, the incidence of localized PCa has increased significantly; PSA testing can predict cancer risk and treatment outcome (2). According to the literature, almost 240,000 individuals developed PCa in the United States yearly; however, <15% of these patients eventually died; mortality is largely dependent upon PSA testing and reasonable treatment of PCa at an early stage (3-6). However, serum PSA is not particular to PCa, and levels can be enhanced in benign prostatic hyperplasia (BPH) (7) and prostatitis (8) even after a digital rectal examination. Therefore, the lack of specificity limits its further development. Low specificity has caused unnecessary biopsies, thereby leading to the overtreatment of indolent cancers. Pathological biopsy is the standard in diagnosing PCa, but it is an invasive examination, which will cause hemorrhage, infection, and even blood poisoning. Hence, a novel biomarker for PCa diagnosis and therapy should be urgently needed.

RNA plays a crucial part in the regulation of gene expression and genome organization (9,10). RNA serves as a template for protein synthesis and exerts many functions (11). The current research has concluded that only 10% of the genome is made up of protein-coding genes. A large part of the genome (~70%) is actively transcribed, which indicates that noncoding RNAs (ncRNAs) account for an overwhelming percentage of the human transcriptome (Fig. 1). At the start, ncRNAs, which is viewed as 'noisy RNAs,' have no transcriptional function and account for almost 90% RNAs in humans (12). ncRNAs can be divided into two major groups according to their sizes, as follows: Long (lncRNA, >200 bp) and small ncRNAs (<200 bp) (13). Small ncRNAs include terminus-associated short, transcription initiation, splice site, and antisense terminus-associated short RNAs (14). Most lncRNAs are generated similar to other mRNAs, as emphasized by RNA polymerase II activity and histone modifications associated with transcription initiation and elongation (15). lncRNAs can be divided into intragenic and intergenic lncRNAs according to their locations in the genome relative to protein coding

Correspondence to: Professor Xianhan Jiang, Department of Urology, The Fifth Affiliated Hospital of Guangzhou Medical University, 621 Gangwan Road, Guangzhou, Guangdong 510700, P.R. China
E-mail: jiangxianhangz@126.com

*Contributed equally

Key words: long non-coding RNAs, androgen receptor, prostate cancer, PI3K/Akt pathway

genes (16). lncRNAs also play a role as decoys for transcription factors (17) and regulate protein activity (18,19). lncRNAs are aberrantly expressed in a several human diseases, including kidney cancer (20), colorectal cancer (21), endometrial cancer (22), testicular cancer (23,24), breast cancer (25), and hematological cancers (26,27). Bussemakers (28) first found DD3^{PCA3}, which is a lncRNA and is a potential diagnostic biomarker for PCa in 1999. This discovery started the research on the involvement of lncRNAs in PCa. We summarized the viewpoints, as follows (Fig. 1).

2. Key pathways dysregulated in prostate cancer by lncRNAs

Androgen receptor (AR) interaction. The AR, as a protein coding gene, is situated on the X chromosome, is approximately 110 kD and made up of four functional regions, namely, (1) the hinge region, (2) ligand-binding domain, (3) N-terminal transactivation domain, and (4) DNA-binding domain (29-31). The AR is a nuclear transcription factor required for normal prostate development and PCa; thus, it plays key roles in PCa initiation and progression (32,33). PCa undergoes progression from androgen-sensitive to resistance to castration. Androgen deprivation therapy (ADT) is the frontline treatment for PCa at the late stages. However, after 12 to 24 months of androgen deprivation, PCa will eventually progress to the lethal form of the disease known as castration-resistant PCa (CRPC), which is eventually fatal for patients with PCa. The reactivation of the AR is central to the progression of CRPC, and treatment mechanisms may also be mediated by the AR signaling axis. AR-dependent resistance mechanisms include AR enhancement, AR single-base substitution, changed intratumoral androgen biosynthesis, and the expression of constitutively active AR splice variants (34-37). lncRNAs can function as oncogenic and tumor suppressor in PCa through AR signaling axis (Table I).

PCGEM1. PCGEM1, as the earliest prostate-specific lncRNA, is located on chromosome 2q32 and overexpressed in nearly 84% of patients with PCa. Recent studies revealed the PRNCR1 binding site to AR 549-623 location and the PCGEM1 combining site to the N-terminal location of AR. PCGEM1 and PRNCR1 interact with AR (38) in a recently published report. In various PCa cells, lncRNA cannot be detected in AR-null cell lines, such as DU145 and PC3 (39,40). The coalition of PRNCR1 and AR leads to enrollment of DOT1L methyltransferase methylating AR and allows the subsequent interaction of PCGEM1 with the methylated AR. In turn, PCGEM1 recruits PYGO2 (Pygopus 2), thereby allowing the binding of AR to H3K4me3 chromatin marks to the promoter regions of AR-regulated genes and leading to their activation (38).

A positive correlation of PCGEM1 with AR3, which is one of the most important splice variants that play a key role in castration resistance, was observed (41-43). This AD-PCGEM1-AR3 axis can explain several reasons why the effectiveness of ADT can only be sustained for a short time. Heterogeneous nuclear ribonucleoprotein A1 (hnRNP A1) and U2AF65, as splicing factors, play key roles in AR3 expression. When hnRNP A1 combines with PCGEM1, the coalition

activity of hnRNP A1 to AR pre-mRNA is weakened. By contrast, the binding activity of U2AF65 to AR pre-mRNA is enhanced. A specific molecular mechanism does not explain why interaction between U2AF65 and PCGEM1 is dominant. The binding of PCGEM1 to U2AF65 is more competitive than that of hnRNP A1 to AR pre-mRNA (44).

HOX transcript antisense RNA (HOTAIR). HOTAIR lncRNA is a 2.2 kb-long transcript and overexpressed in a variety of cancer types, such as breast cancer, colorectal cancer, lung cancer, and pancreatic cancer (45-48). HOTAIR is sensitive to androgen and inhibited by androgen severely, and its expression inhibits AR ubiquitination and avoids AR protein degradation (49). HOTAIR lncRNA is entirely abolished after AR target gene is knocked down via RNA interference (49). Zhang *et al* (49) concluded that HOTAIR overexpression enhances aggressivity in PCa and upregulates in enzalutamide-resistant PCa cells. Therefore, attention should be paid to HOTAIR as a potential therapy target in enzalutamide-resistant patients with PCa in the future.

C-Terminal binding protein 1 antisense (CTBP1-AS) CTBP1-AS, which is situated in the AS region of C-terminal binding protein 1 (CTBP1), is related to AR signaling pathway and is overexpressed in both local PCa patients and metastatic PCa patients, but not in Benign Prostatic Hyperplasia (BPH). It is recruited to AR-binding sites. The CTBP1-AS lncRNA directly inhibited the expression of CTBP1 (50), which acted as the corepressor of AR by recruiting the RNA binding transcriptional repressor PTB-associated splicing factor and histone deacetylases. Thus, CTBP1-AS can enhance AR transcriptional activity. Takayama *et al* (51) have reported that upregulation of CTBP1-AS and downregulation of CTBP1 in PCa. CTBP1-AS knockdown inhibited cell proliferation in hormone-depleted condition in both cell lines; in contrast, CTBP1-AS overexpression induced tumor growth after castration (51).

PCa gene 3 (PCA3). PCA3 is a lncRNA that was initially named as DD3 and is located on chromosome 9q21-22 in antisense direction within the intron 6 of the Prune homolog 2 gene (PRUNE2 or BMCC1) (52). PCA3 is overexpressed in PCa cell lines (53,54) and modulates PCa cell survival partly according to the AR pathway, which is involved in the oncogenesis of PCa. Meanwhile, the positive rates of its sensitivity and specificity are 82.3 and 89.0%, respectively, compared with PSA, which showed only 57.4 and 53.8% (55). Lemos *et al* (56) reported that PCA3 may regulate AR signal pathway through AR cofactors (57), such as ARA 54, ARA 70, CBP, and P300, when PCA3 and ERK are silenced, and Akt protein phosphorylation levels stayed the same. Thus, the preferred method should be activate AR. Both AR cofactors, including coactivators and corepressors, were upregulated, which indicated that PCA3 may be a negative modulator to AR and aberrant cofactor activity because altered or changed expression levels may be factors to the progression to mCRPC. A future potential therapy for PCa patients, especially mCRPC, is the application of PCA3.

Phosphatidylinositol 3-kinase (PI3K)/Akt pathway. PI3K/Akt pathway is one of the key signal transduction pathways regulating

Table I. lncRNAs in prostate cancer.

lncRNA	Location	Expression	Pathway	(Refs.)
PCGEM1	2q32	↑	AR interaction	(39,40)
HOTAIR	12q13.13	↑	AR interaction	(49)
CTBP1-AS	4p16.3	↑	AR interaction	(51)
PCA3	9q21-22	↑	AR interaction	(56)
UCA1	19p13.12	↑	PI3K/Akt pathway	(67)
LINC01296	14q11.2	↑	PI3K/Akt pathway	(68)
PCAT-1	8q24.21	↑	by C-MYC protein	(72)
SChLAP1	2q31.1	↑	Interfering with SWI/SNF tumor-inhibiting complex	(75)
H19	11p15.5	↓	Down-regulation of TGFBI	(86)
TODRA	15q15.1	↑	Causing DSB repair by HR	(88)

lncRNA, long non-coding RNA.

cell proliferation. PI3K/AKT/mTOR signaling, PTEN/PI3K/AKT pathway, and PI3K/AKT/NF- κ B/BMP-2-Smad axis play important roles in cancer progression and development (58). PI3K enzymes regulate cellular signal transduction. The PI3K/Akt pathway mainly includes PI3K activation, recruiting pleckstrin homology (PH) domain-containing proteins, phosphorylation, activating AKT, and activating necessary downstream targets (59). PI3K/AKT/mTOR is overexpressed in 30-50% of all prostate cancers (60), and its signal is regulated in PCa cellular proliferation (61), apoptosis (62), invasion, and migration (63).

lncRNA-ATB. lncRNA-ATB is first identified in hepatocellular carcinoma (64). Xu *et al* (65) reported that lncRNA-ATB is overexpressed in PCa tissues compared with normal tissues, and it is related to high PSA level, high Gleason score, and biochemical recurrence when the knockdown of lncRNA-ATB and PI3K/Akt signaling pathways is inhibited. Meanwhile, the roles of lncRNA-ATB in the invasion, migration, and tumor growth remain unclear.

Urothelial carcinoma associated 1 (UCA1). UCA1 is a lncRNA that is related to various cancer types (66). Ghiam *et al* (67) revealed that UCA1 expression is high in PCa cells when UCA1 knockdown enhances radiosensitivity in classic PCa cell lines and irradiation-resistant PCa cells due to PI3K/Akt pathway downregulation.

LINC01296. LINC01296 is located at chromosome 14q11.2. Wu *et al* (68) found that LINC01296 is upregulated in LNCaP cell lines but not in normal cell lines. Meanwhile, when silencing LINC01296, the protein expression level of PI3K-Akt-mTOR signaling pathway significantly decreased compared with that of normal cell. Therefore, the lncRNA LOC400891 regulates cell proliferation through the PI3K-Akt-mTOR signaling pathway (69).

Act as a tumorigenesis or a tumor-inhibiting gene. Genome instability is the main factor in the promotion of cancer. The

aberrant expression of lncRNAs is related to the development and progression of PCa and plays an important role in tumorigenesis or tumor-inhibiting in patients with PCa. Several lncRNAs are upregulated as oncogenes, whereas others are downregulated in cancer.

PCa-associated lncRNA transcripts 1 (PCAT-1). PCAT-1, which is located in the 8q24.21 gene desert with nearly 725 kb upstream of the c-MYC oncogene (70), is overexpressed in patients with PCa (71). C-MYC protein is upregulated by PCAT-1, thereby resulting in specific gene expression programs and cell proliferation (72). When PCAT-1 is knocked down in LNCaP cells, cellular proliferation is diminished, thereby indicating that it is a potential novel biomarker for colorectal cancer metastasis.

Second chromosome locus associated with prostate-1 (SChLAP1). SChLAP1 is a novel biomarker that is highly upregulated in PCa (73-75) and associated with a high risk of CRPC, thereby leading to tumor cell invasion and metastasis. SChLAP1 can interfere with the SWI/SNF tumor-inhibiting complex (76) to promote tumor metastasis. SChLAP1 damages genomic binding and SNF5-mediated gene expression regulation. Similarly, Mehra *et al* (75) found that knocking down SChLAP1 can inhibit cell proliferation and migration in bladder cancer cell lines.

Noncoding nuclear-enriched abundant transcript2 (NEAT2). The lncRNA NEAT2 is 7 kb long and is also known as MALAT1. NEAT2 is highly overexpressed in a series of cancers, including prostate cancer (77), osteosarcoma (78), pancreatic cancer (79), breast cancer (80), bladder cancer (81), and esophageal cancer (82,83). When NEAT2 is knocked down, cell hyperproliferation and metastasis are inhibited in a PCa cell, thereby leading to cell cycle block in the G₀/G₁ phases (77). NEAT2 promotes the activation of PRC2 by connecting to the polycomb protein enhancer of zeste homolog 2 (EZH2) and enhances the EZH2-mediated inhibition of polycomb-dependent target gene E-cadherin in clear renal

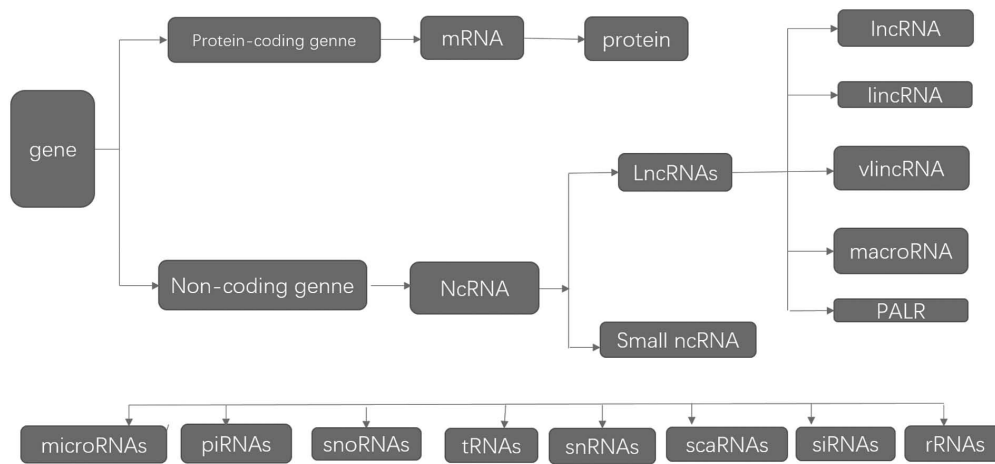


Figure 1. The construction of human genome. Human genome is mainly classified into protein-coding sequences and noncoding sequences. The ncRNAs are composed of lncRNAs and small ncRNAs, depending on the size. Small ncRNAs consist of piRNAs, miRNAs, snoRNAs, tRNAs, snRNAs, scaRNAs, siRNAs and rRNAs. lncRNAs are including lncRNA, macroRNA, lincRNA, PALR and vlinRNA. Adapted from St Laurent *et al* (95). ncRNA, non-coding RNA; lncRNA, long non-coding RNA; piRNA, piwi-interacting RNA; miRNA, microRNA; snoRNA, small nucleolar RNA; tRNA, transfer RNA; snRNA, small nuclear RNA; scaRNA, small Cajal body-specific RNA; siRNA, small interfering RNA; rRNA, ribosomal RNA; lincRNA, long-intergenic non-coding RNA; PALR, promoter-associated long RNA; vlinRNA, very long intergenic non-coding RNA.

cancer (84). Meanwhile, NEAT2 controls cell cycle progression by regulating the oncogenic transcription factor B-MYB (Mybl2) (85).

H19. The H19 gene, which is transcribed from H19/Igf2 gene cluster, is located on human chromosome 11p15.5. H19 can act as a tumor suppressor gene. Zhu *et al* (86) found that the decreased H19 expression is significant in metastatic prostate cell compared with local prostate epithelial cell. Hence, H19/miR-675 axis inhibits PCa metastasis according to TGFBI downregulation.

Other genes. Double-strand DNA breaks (DSBs) are potentially lethal DNA lesions. Homologous recombination (HR) is an effective pathway for eliminating DSBs and repairing injured DNA replication forks. RAD51 is the core recombinase involved in HR, and increased RAD51 levels may cause tumorigenesis. Prensner *et al* (87) found that lncRNA PCAT1 is involved in the DSB repair process in PCa. TODRA is a novel lncRNA that is also known as RAD51 antisense RNA 1 and is located on 15q15.1. TODRA plays a role in RAD51 regulation. Gazy *et al* (88) reported that the overexpression of TODRA causes DSB repair by HR and also enhances the fraction of RAD51 foci formed after DNA damage.

Recent studies indicated that lncRNAs can recognize miRNA elements that can be targeted by miRNAs (89). A Zebrafish model where miR-125b regulates 7sl lncRNA expression is a typical example of the miRNA-lncRNA interaction (90). Meanwhile, HOTAIR downregulation is targeted by the tumor suppressor miR-34a, thereby inhibiting CRPC cell growth (91).

3. Therapeutic potential of lncRNAs in patients with cancer

lncRNAs has multiple functions and high cell-type specificity. Thus, lncRNAs can provide an avenue for PCa diagnosis, prognosis, and therapy. Currently, the use of lncRNA for PCa patients is being explored.

lncRNA targeting strategy. The RNAi technology, which interferes with RNA expression through antisense technologies, can be widely used for the weak expression levels of lncRNAs with oncology potential (92). The key cancer-associated genes with therapeutic siRNAs have been suppressed in clinical trials.

Another method for inhibiting cancer-associated RNA is by using catalytic nucleic acids, including antisense oligonucleotides (ASOs) or by using small molecule inhibitors that can also be used to modulate lncRNAs. The small molecule inhibitors prevent the interaction of HOTAIR with LSD1 or PRC2 complexes, thereby restricting the metastatic potential of breast cancer (93).

Targeting lncRNAs through the CRISPER/Cas system. Currently, CRISPER/Cas (clustered regularly interspaced short palindromic repeats/CRISPER-associated system) take advantage of knocking out targeting gene for treating PCa patients. Meanwhile, Shechner *et al* (94) have ever reported of using CRISPER/Cas system successfully.

4. Conclusions

lncRNAs are potential novel biomarkers as therapeutic targets for patients with PCa. Considering the multiple and varied processes of PCa, its treatment should be planned precisely for each patient. At the same time, when modern technology is used to kill tumors, the safety of normal tissues should be ensured. However, in spite of its advantage over other therapeutic options, many questions need to be addressed.

The biggest challenge is that further research and large-scale validation studies are imperative before the successful application to clinical trials, because the molecular mechanisms of lncRNAs and pathogenesis of PCa have not been thoroughly understood. Nevertheless, the clearer the lncRNA functions are, the better their field of therapeutic usage will be. The next challenge is that the current lncRNA marker candidates are mostly based on a small sample, and the

lack of validity limits further development. Thus, the effectiveness of lncRNA markers have to be prospectively verified in large and varied datasets. Research in animal models and clinical trials is needed to evaluate the potential side effects, including toxicity, body distribution, pharmacokinetics, and pharmacodynamics data.

Hence, lncRNAs are intriguing targets in treating patients with PCa, and their potential in therapy can be remarkable.

Acknowledgements

The authors would like to thank Miss Chen Gao (Department of Surgery, Peking University Shenzhen Hospital, Shenzhen, Guangdong, China) for assistance.

Funding

The present study was supported by funding from Science and Technology Plan Project of Guangzhou of China (grant no. 201510010177), Medical Science and Technology Program of Guangzhou of China (grant nos. 20171A011329 and 20171A010325), Youth Scientific Research Project of Guangzhou Medical University of China (grant no. 2015A14) and Medical Research Foundation of Guangdong Province of China (grant no. A2018093).

Availability of data and materials

All data generated or analyzed during the present study are included in this article.

Authors' contributions

GJ, ZS, XL, YH, ZL and XJ conceived and designed the study. GJ and ZS wrote the manuscript. GJ, ZS, XL, YH, ZL and XJ collected the data. ZS and XJ reviewed and edited the manuscript. All authors read and approved the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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