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Review Article

Long non-coding RNA in prostate cancer

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Abstract: Prostate cancer is the most frequently diagnosed cancer in males and its development and progression remains an important area of study. Recently, long non-coding RNAs (lncRNAs) have been evidenced as key players in cancer pathogenesis. Specifically, dysregulation of long non-coding RNA (lncRNA) expression has shown to affect tumor proliferation and metastasis, acting as either tumor suppressors or oncogenes. However, its specific mechanisms and functions in prostate cancer remain unclear. This review provides an overview of currently available information on prostate cancer-related lncRNAs, including *GAS5, GAS-007, MEG3, PCA3, PCAT14, PCAT1, PVT1, UCA1, SChLAP1, MALAT1, HOTAIR,* and *NEAT1*. Notable tumor growth inhibitors include GAS5 and MEG3. GAS5 is evidenced to interfere with the AKT/MTOR signaling pathway through targeting microRNA mir-103. MEG3, however, is proposed to inhibit the cycle, sponge miR-9-5p, and induce gene silencing. PCAT1, PVT1, and UCA1 are important tumor growth promoters. PCAT1 is indicated to be a transcriptional repressor, a mir-145-5P sponge, and a P13K/AKT pathway activator. Studies suggest that PVT1 acts via microRNA targeting and regulating proliferating cell nuclear antigen. UCA1 may sponge miR-204 and miR-331-3p as well as regulate myosin VI. Thorough understanding of these lncRNAs may elucidate new aspects of prostate cancer pathology and serve a pivotal role in developing novel diagnostic and prognostic techniques.

Keywords: Prostate cancer, *lncRNA*, *GAS5*, *GAS-007*, *MEG3*, *PCA3*, *PCAT14*, *PCAT1*, *PVT1*, *UCA1*, *SChLAP1*, *MALAT1*, *HOTAIR*, *NEAT1*

Introduction

Prostate cancer (PCa) is the most commonly diagnosed cancer in men, and the second most common cause of death for men in the U.S. The American Cancer Society reports that in 2021 there will have been an estimated 238,530 new cases and 34,130 deaths from prostate cancer [1]. This is a significant increase from 2019 estimates of 174,650 new cases and 31,620 deaths [2]. Such statistics indicate an imperative and urgent need to develop improved methods to diagnose, treat, and reduce the mortality rates of PCa.

Multiple risk factors for PCa have been identified with the most prevalent of which are age, race, and geography. PCa incidence increases significantly with age, as more than 75% of cases are diagnosed after the age of 65 [3, 4]. In the United States, African American males were found to have 58% greater incidence and 144% greater mortality compared to those of European descent [3]. Incidence and mortality further varies across different countries, with Asian populations exhibiting the lowest rates of PCa [3]. Genetics are another prevalent risk factor as relative risk of prostate cancer increases in men with a first-degree relative affected by PCa. Multiple susceptibility genes, including BRCA2, CHEK2, HOXB13, NBS1, RNASEL, ELAC2, MSR1, OGG1, PON1, and GDF15, and single nucleotide polymorphisms (SNPs) have been associated with higher relative risk [3, 4]. Infections leading to inflammation, namely urinary tract infections, sexually transmitted infections, and prostatitis, are hypothesized to promote the development of malignancies by inciting inflammation in the prostate [3]. Androgens and other hormones have been suggested to contribute as well via the improper development and maintenance of the prostate and luminal epithelium [3]. However, the re-

search surrounding inflammatory and hormonal influences remain unclear [3, 4].

Studies on immigrants have evidenced significant changes in incidence after moving which suggests a role of external risk factors [3, 4]. Smoking and components of diet such as fats, red meats, and vitamin D have been associated with increased risk to varying degrees [3, 4]. Diet may affect PCa susceptibility by altering levels of inflammatory factors released in response to oxidative stress, introducing carcinogens, and interrupting the cell growth cycle [3]. Other lifestyle factors such as physical activity, alcohol consumption, and sexual activity are still being investigated [3, 4].

In 1986, the prostate-specific antigen (PSA) was formally introduced as a diagnostic biomarker and risk indicator, due to its increased serum levels in PCa patients compared to those of disease-free patients [5]. It has since greatly improved PCa screening efforts, allowing for the detection of tumors in earlier stages. However, clinical data has shown that PSA testing can be inconsistent and occasionally yield inaccurate results. Aside from a malignancy in the prostate, elevated PSA expression levels can also be caused by benign prostate conditions such as prostatitis, hyperplasia, and other infections [5]. This false positivity leads to substantial over diagnosis and a decrease in PSA test specificity - a study of the PSA test showed a prediction accuracy of around 25% [6]. Ilic et. al. has also suggested that PSA-based screening does not improve the survival rate of PCa patients, while advances in cancer detection and treatment methods have contributed to the decline of mortality rates in several parts of the world [7, 8]. Therefore, the inconsistency of PSA testing demands more reliable markers for PCa detection, encouraging research into other potential PCa biomarkers such as long non-coding RNAs.

Long non-coding RNAs (lncRNA) are noncoding transcripts containing 200 or more nucleotides. While these transcripts are not functional for coding proteins, they participate in almost all biological processes, including gene expression, cell cycle regulation, protein synthesis, and cellular transportation [9]. Only recently have lncRNA SNPs been linked to cancer and they may serve as another risk factor for PCa [10]. Several lncRNAs have been shown to promote metastasis and proliferation of various types of cancer, while others have been demonstrated to act as tumor suppressants. These characteristics of lncRNA indicate that it may serve as a promising biomarker of PCa, as well as a target for subsequent therapeutic treatment.

Along with early detection, novel techniques for PCA treatment are necessary to improve prognosis and quality of life of PCa patients. Current methods of treatment include surgery, hormonal therapy, radiation therapy, and chemotherapy, with androgen deprivation therapy (ADT) as the standard for PCa. As the name states, it prevents the proliferation of PCa cells by preventing access of androgen receptors (ARs) to vital hormones such as testosterone. However, while ADT may be effective initially, patients will often progress to castration resistant prostate cancer (CRPC) and become resistant to the treatment [11, 12]. Radical prostatectomy and radiation therapy are common treatment options for localized prostate cancer but can have adverse side effects such as incontinence, erectile dysfunction, and bowel problems [13]. Cryotherapy, usually used to treat localized cancer or cancer recurrence after radiation therapy, poses the same risks [13]. Chemotherapy is often introduced for metastatic PCa, but it is an aggressive treatment that often indiscriminately affects healthy cells.

Prostate cancer and lncRNA

Human cancer is a comprehensive syndrome in which various genetic mutations and altered gene expression profiles produce a variety of macromolecules that can be used in cancer diagnosis and treatment. LncRNAs have displayed a wide variety of functions ranging from regulating cell proliferation, metastasis, and cancer progression [14]. They have been used as biomarkers for earlier diagnosis and treatment; and have displayed regulatory functions in the tumor growth. Several lines of lncRNA have been found to play important roles in the function of PCa [14].

In this short review, we will discuss the up-to-date findings of cancer-related lncRNAs including *GAS5, GAS-007, MEG3, PCA3, PCAT14, PCAT1, PVT1, UCA1, SChLAP1, MALAT1, HOTAIR,* and *NEAT1.* The functions of lncRNA in cancer are primarily categorized into two

Table 1. A compilation of various lncRNA that have been observed to affect PCa. Columns are separated by the lncRNA's location, effect on PCa, and clinical applications

lncRNA	Location	Effect on PCa	Clinical Application	References
GAS5	Tissue	Downregulation	Prognosis	[15-18]
GAS5-007	Tissue	Downregulation	Prognosis, Therapeutic Target	[19]
MEG3	Tissue	Downregulation	Therapeutic Uses	[20-25]
PCAT14	Tissue	Downregulation	Early Detection	[26-28]
PCA3	Tissue	Upregulation	Early Detection	[29-33]
PCAT1	Tissue	Upregulation	Prognosis	[30-37]
PVT1	Tissue	Upregulation	Prognosis	[38-44]
UCA1	Bladder	Upregulation	Prognosis, Therapeutic Target	[45-48]
ScHLAP1	Tissue	Upregulation	Prognosis	[49, 50]
MALAT1	Tissues, Urine	Upregulation	Therapeutic Target	[51-55]
HOTAIR	Lymphocytes	Upregulation	Therapeutic Target	[56]
NEAT1	Endocrine Glands	Upregulation	Prognosis, Therapeutic Target	[57-59]

groups: Those that promote the progression of cancer, through regulating suppressing agent, and those that inhibit cancer, by reducing the expression of oncogenic proteins. Preclinical studies have shown the potential of these lncRNAs for future PCa diagnosis and treatment. **Table 1** briefly summarizes the lncRNA that will be discussed in this paper.

LncRNA as PCa growth inhibitors

GAS5: Growth arrest-specific transcript 5, or GAS5 is an androgen-responsive lncRNA that plays an important role in the tumorigenesis and progression of PCa. It is reported to act as a tumor suppressor and promote PCa cell apoptosis [15]. Xue et al. observed GAS5 to be downregulated in PCa tissues and cell lines compared to normal prostate tissues and cells, which corroborates its role as an inhibitor [16]. They delved further into the underlying mechanisms of inhibition and evidenced GAS5 as an inhibitor of the AKT/mTOR pathway, an intracellular signaling pathway crucial in the progression of the cell cycle [16]. Overexpression of mir-103 rescued GAS5 effects on the AKT/mTOR signaling pathway, indicating that GAS5 may be exerting its effects via the targeting of mir-103 [16].

A GAS5 polymorphism has been recently studied as a possible correlator to certain characteristics of PCa such as lymph node metastasis as well [17].

Glucocorticoids such as prednisone and dexamethasone are often used to treat CPRC and to counter side effects of ADT. GAS5 was found to be an important regulator in dexamethasone treatment as it exerted proliferation-inhibition in AR-negative PCa cell lines but not in AR-positive PCa cell lines [18]. In AR-positive cell lines, GAS5 was found bound to AR instead and unable to translocate to the nucleus [18].

GAS5-007 is a special transcript isoform of GAS5. According to a study conducted by Zhang et. al., who examined GAS5-007 in PCa, the expression of GAS5-007 was reduced when exposed to androgen treatment and inhibited by AR [19]. Knockdown of GAS5-007 led to the inhibition of proliferation, and cell cycle, as well as promoted cell apoptosis [19]. In addition, GAS5-007 has also been shown to be involved in translational elongation, protein biosynthesis, and transcription [19].

These findings suggesting GAS5-007 as a cancer promoter are inconsistent with previous studies that evidenced GAS5 as a tumor suppressor. The possibility that different transcripts of a single lncRNA have different regulatory functions makes the role of lncRNAs more nuanced and requires further examination.

MEG3: MEG3 is a transcript that has been identified to cause suppression of multiple types of cancer [20-22]. Studies have shown that MEG3 decreased significantly in prostate cancer tissues relative to adjacent normal tissues [23]. MEG3 inhibited intrinsic cell survival pathway *in vitro* and *in vivo* by reducing the protein expression of Bcl-2, enhancing Bax and activating caspase 3 [23]. It was further demonstrat-

ed that MEG3 inhibited the expression of cell cycle regulatory protein Cyclin D1 and induced cell cycle arrest in G0/G1 phase. As a result, MEG3 shows anti-cancer effect through inhibiting cell proliferation, and inducing apoptosis in PCa [23].

A study by Wu et al. showed that MEG3 was downregulated in prostate cancer tissues and cells and suggested a potential mechanism via sponging microRNA miR-9-5p which normally downregulates Quaking protein QKI-5 [24]. Overexpression of both MEG3 and QKI-5 inhibited PCa progression while overexpression of miR-9-5p had the opposite effect [24].

Zhou et al. investigated another potential mechanism of MEG3 in which it binds to EZH2, a histone methyltransferase that catalyzes histone H3 lysine 27 trimethylation and leads to gene silencing, suppressing development of PCa [25].

PCAT14: This prostate cancer specific lncRNA PCAT14 has garnered much attention due to its uses in the identification of PCa as well as its viability in PCa prognosis. From analysis of a RNA-seq dataset including a total number of 585 benign prostate tissue, localized and metastatic PCa samples, it's found that PCAT14 highly expressed in well differentiated PCa tumors [26]. A reduced expression of PCAT14 in prostate cancer was related to T stage, N stage, primary therapy outcome, residual tumor, Gleason score, and age. The expression of PCAT14 was independently associated with the progression-free interval in prostate cancer patients [27]. In addition, a meta-analysis summarized 18 studies including 18 on prognosis and 9 on clinicopathological features. The results also indicate that PCAT14 is associated with overall survival and metastasis-free survival of PCa [28].

LncRNA as PCa growth promoters

PCA3: PCA3 is a type of lncRNA that is a specific marker of prostate cancer, and also regulates the human prostate cancer suppressor PRUNE2 [29]. PRUNE2 is a protein-coding gene variant which harbors the PCA3 locus, thereby classifying PCA3 as an antisense intronic long noncoding RNA [29]. PCA3 controls PRUNE2 levels via a unique regulatory mechanism, by which the PRUNE2/PCA3 double-stranded RNA undergoes RNA-dependent adenosine-to-inosine RNA editing [29]. A recent study shows that the score of the PCA/PSA RNA was a reliable signature for PCa diagnosis-PCA3 RNA/PSA RNA score is elevated and correlated as prostate cancer biomarker [30]. Consistently, an exploratory analysis from 12,076 patients shows that decreased PCA3 is a marker for poorly differentiated prostate tumors [31].

Multiple studies have evidenced that PCA3 knockdown reduces tumor growth and viability and that it does so via regulating AR signaling pathways. Cells treated with dihydrotestosterone (DHT), an AR agonist, significantly upregulated PCA3 expression and PCA3 silencing reversed the effects of DHT on other genes [32]. PCA3 also has been evidenced to modulate a variety of genes as well as microRNAs, that involving cell adhesion, invasion, DNA damage repair, angiogenesis, tumor suppression, and apoptosis [32, 33]. Its involvement in multiple avenues relating to PCa make it an attractive biomarker for further investigation.

PCAT1: Prostate cancer-associated transcript 1 (PCAT1) was originally discovered in prostate cancer. It may be a biomarker for various forms of cancer. It's been used in esophageal squamous carcinoma, and human urothelial carcinoma [34-36]. A prostate cancer transcriptome sequencing study discovers 121 unannotated prostate cancer-associated ncRNA transcripts (PCATs) by employing RNA-Seq on a cohort of 102 prostate tissues and cells lines [37]. The findings indicate that PCAT-1 as a transcriptional repressor implicated in subset of prostate cancer patients [37]. Further study reveals PCAT-1 mediated prostate cancer cell proliferation is dependent on c-Myc protein stabilization [38]. Plus, PCAT-1 can also act as a miR-145-5p sponge to modulate FSCN1 expression, subsequently contributes to PCa tumorigenesis [39].

Yuan et al. demonstrated PCAT1 as a promoter of cell proliferation and inhibitor of apoptosis [40]. Additionally, its genetic variant rs1902432 was found to be significantly associated with increased risk of PCa [40].

PCAT1 may be promoting PCa progression by activating the phosphatidylinositol 3-kianse (P13K)/AKT pathway [41]. PH and leucine-rich repeat protein phosphatase (PHLPP) is an

antagonist of the pathway and PCAT was evidenced to bind and displace PHLPP, restoring AKT signaling [41].

PVT1: PVT1 is located in the well-known cancer-related region, 8q24 and has been implicated in a variety of human cancers including prostate cancer. Mechanical analysis shows the involvement of miR-146a in PVT1 mediated prostate cancer growth [42]. Functional study shows that knockdown of PVT1 induces apoptosis of PCa through cleavage of Caspase 3 and downregulation of c-Myc [43]. Additionally, a significant association was found between PVT1 expression and tumor stage [43].

Among at least 12 PVT1 exons, exon 9 was found elevated in aggressive PCa cell lines derived from males of African ancestry (MoAA), indicating its potential as an indicator for advanced PCa [42, 44]. A study specifically focused on exon 9 demonstrated that it was significantly expressed in PCa tissue and induced migration, proliferation, and castration resistance [45]. Most notably, mice implanted with PVT1 overexpressing exon 9 developed malignant tumors [45]. PVT1's effects may be exerted via regulation of proliferating cell nuclear antigen (PCNA) expression [45]. PCNA is overexpressed in cell lines that overexpressed exon 9, while PCNA expression decreased with exon 9 silencing [45].

PVT1 has been suggested to have multiple mechanisms that affect PCa. One study investigating the interactions between PVT1 and NOP2, a potential biomarker for cancer aggressiveness, found that PVT1 targets miRNAs to upregulate NOP2 mRNA [46]. PVT1 was also found to target microRNA-15a-5p (miR-15a-5p), which binds to kinesin family member 23 (KIF23) [47]. miR-15a-5p is a potential tumor suppressor while KIF23 has been studied as a therapeutic target for other types of cancer and its knockdown has been shown to have PCa-inhibitory effects [47]. Videira et al. demonstrated that PVT1 represses a gene set that has tumor suppressing properties, potentially explaining the aggressiveness of tumors expressing high levels of this lncRNA [48].

UCA1: UCA1 has been found to be an oncogene under certain conditions, but its effects on PCa were unclear. UCA1 was significantly upregulated in PCa cell lines and tissue samples compared to benign tissue samples [49]. High UCA1 expression was positively associated with high Gleason score, advanced TNM stage and shorter overall survival of PCa patients [49]. Inhibition of UCA1 suppressed PCa cells proliferation, migration and invasion in vitro, and depletion UCA1 inhibited the growth of PCa cells in vivo [49].

UCA1 has shown to have many interactions with microRNAs. One study explored its function as a sponge of miR-204, a known tumor suppressor [50]. Yu et al. proposed UCA1 to promote PCa progression by sponging miR143 and regulating miR143's target myosin VI, a motor protein implicated in promoting PCa cell growth and migration [51]. Repressed UCA1 was shown to promote miR-143 expression, which in turn downregulated expression myosin VI [51]. Another study suggested a similar dynamic in which UCA1 sponges miR-331-3p, which regulates eukaryotic translation initiation factor 4 gamma 1 (E1F4G1), often overexpressed in multiple forms of malignancies [52]. The relationship between UCA1 and multiple miRNAs with further downstream effects make it an attractive biomarker and therapeutic target.

SChLAP1: SChLAP1 is shown to aid in the discrimination of aggressive tumors from indolent forms of cancer. SChLAP1 coordinates metastasis of PCa [53]. It antagonizes the SWI/SNF chromatin-modifying complex, which has tumor suppressive functions [53]. The expression of SChLAP1 characterizes an aggressive case of PCa. SChLAP1 coordinates cancer cell invasion in vitro and metastatic seeding in vivo [53]. Another large cohort study also showed that high expression of SCHLAP1 was significantly associated with adverse clinicopathological characteristics, including Gleason grade (Grade Group), cribriform growth/intraductal carcinoma, and high pathology stage [54]. High expression of SCHLAP1 was also shown to be a predictor of biochemical recurrence [54].

MALAT1: MALAT1 is overexpressed in the progressed PCa and promotes the expression of the androgen receptor variant AR-V7 [55]. It is regulated by estrogen and is involved in androgen receptor signaling [55].

Dai et al. demonstrated that MALAT1 knockdown reduced prostate cancer tumorigenesis

in mice and further suggests that MALAT1 inactivates AR signaling via sponging miR-320b [56, 57]. Another study evidences MALAT1 as a miR-140 sponge, as MALAT1 silencing reduced mRNA of Baculoviral IAP repeat containing 6 (BIRC6), an inhibitor of apoptosis [58]. Introduction of miR-140 sponge inhibitor attenuated these effects, suggesting MALAT1 sponging of miR-140 allowed for upregulation of BIRC6 [58].

MALAT1, like MEG3, may also bind with EZH2 and regulate expression of EZH2 activated genes [59]. It was shown to enhance target genes of EZH2 as well as EZH2-mediated invasion and migration [59]. Knockdown of this lncRNA even derepressed EZH2 repressed genes [59]. This suggests MALAT1 may play a vital role in EZH2 interactions, which is especially noteworthy as EZH2 is often overexpressed in CRPC [59].

HOTAIR: HOTAIR has been demonstrated to promote PCa metastasis by targeting hepatocellular adhesion molecule (hepaCAM), a protein involved in cell adhesion and migration [60]. Lack of hepaCAM allows for tumor detachment and subsequent migration and distal metastasis [60]. Li et al. found that HOTAIR levels was inversely correlated with hepaCam by recruiting polycomb recessive complex 2 (PRC2) to enhance EZH2 activity and effectively silencing hepaCAM genes with an abnormally activated MAPK pathway [60]. It suggested that the HOTAIR/hepaCAM/MAPK axis may provide a new avenue towards therapeutic strategies and prognostic indicators for advanced prostate cancer.

NEAT1: The lncRNA NEAT1 functions as a transcriptional regulator and contributes to a cancer-favorable transcriptome, thereby promoting tumorigenesis in experimental animal models [61]. NEAT1 is recruited to the chromatin of well-characterized prostate cancer genes and contributes to an epigenetic 'on' state [61]. It was found as a potential biomarker for estrogen receptor Er(alpha), which is expressed in prostate cancer and potentially serves as an alternative signaling pathway for PCa regulation [61].

A more recent study examined the effect of N6-methyladenosine (m6A), the most prominent messenger RNA modification, on transcriptional variant NEAT1-1 [62]. Researchers identified 4 m6A sites and positively correlated m6A level with cancer progression, bone metastasis, and fatality [62]. NEAT1-1 may also bind at its m6a site with cyclin1 and CDK19 to form a complex unique to bone metastatic prostate cancer [62].

NEAT1 has also been investigated for its role in developing docetaxel-based chemotherapy resistance [63]. The lncRNA was elevated in resistant PCa samples and dysregulation of NEAT1 affected the resistance in vitro and in vivo. It was found to sponge miR-34a-5p and miR-204-5p, which in turn inhibited expression of acyl-CoA synthetase 4 (ACSL4) [63]. This suggests that NEAT1 as a potential target in overcoming docetaxel resistance.

Conclusion

While long non-coding RNAs offer little transcriptional value, scientists are beginning to uncover their critical contributions to tumor pathology and realizing their potential as cancer biomarkers. LncRNAs potentially have many important biological functions in the development of PCa. As such, the understanding of such functions may be the key to novel screening methods and treatments that are urgently needed given PCa's prominence in the male population and continued rise in disease incidence every year.

Based on the available research, lncRNAs are implicated in gene transcription as well as important regulators of a variety of signaling pathways. These roles make them possible of targets for all stages of PCa development-screening, diagnosis, prognosis, and treatment. Their roles will need to be more thoroughly understood by basic studies and solidified through clinical trials for developing effective targeting agents and screening tests with higher sensitivity and specificity.

Studies explored in this review demonstrate that lncRNAs may operate through multiple mechanisms and can participate in more than one facet of cancer pathogenesis. Given what we have yet to discover about lncRNAs and their involvement in other non-cancer related processes, lncRNAs may not be direct points of diagnosis and therapy on their own. Rather, they will likely be more effective as a tool to

guide and fine-tune risk predictions. Additionally, following lncRNA may lead to specific pathways or processes that are unique to PCa or localized to the tumor region and offer easier targets for future intervention.

Future research direction

While the potential molecular bases of lncRNA involvement in prostate cancer pathogenesis are gradually being clarified, there are many steps that need to be taken until they can be officially recognized as biomarkers and therapeutic targets. As a potential biomarker, lncRNA dysregulation may be present because of other conditions or comorbidities. Further work is required to determine what specific dysregulations are unique to PCa. As a potential therapeutic target, lncRNAs are shown to have multiple critical regulatory functions and they are certainly not localized to PCa malignancies. Its influences in all aspects of human biology must be investigated first to account for potential adverse side effects. Current studies on lncRNAs have mostly utilized cell lines and animal models. Only after lncRNA functions have been thoroughly understood can they then be assessed via *in vivo* and clinical studies of large, diverse populations.

Disclosure of conflict of interest

None.

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References

[1] Siegel RL, Miller KD, Fuchs HE and Jemal A. Cancer statistics, 2021. CA Cancer J Clin 2021; 71: 7-33.
[2] Siegel RL, Miller KD and Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019; 69: 7-34.
[3] Patel AR and Klein EA. Risk factors for prostate cancer. Nat Clin Pract Urol 2009; 6: 87-95.
[4] Cuzick J, Thorat MA, Andriole G, Brawley OW, Brown PH, Culig Z, Eeles RA, Ford LG, Hamdy FC, Holmberg L, Ilic D, Key TJ, La Vecchia C, Lilja H, Marberger M, Meyskens FL, Minasian LM, Parker C, Parnes HL, Perner S, Rittenhouse H, Schalken J, Schmid HP, Schmitz-Drager BJ, Schroder FH, Stenzl A, Tombal B, Wilt TJ and Wolk A. Prevention and early detection of prostate cancer. Lancet Oncol 2014; 15: e484-492.
[5] Carter HB and Pearson JD. PSA velocity for the diagnosis of early prostate cancer. A new concept. Urol Clin North Am 1993; 20: 665-670.
[6] Barry MJ. Clinical practice. Prostate-specific-antigen testing for early diagnosis of prostate cancer. N Engl J Med 2001; 344: 1373-1377.
[7] Ilic D, Neuberger MM, Djulbegovic M and Dahm P. Screening for prostate cancer. Cochrane Database Syst Rev 2013; 2013: CD004720.
[8] Torre LA, Siegel RL, Ward EM and Jemal A. Global cancer incidence and mortality rates and trends -- an update. Cancer Epidemiol Biomarkers Prev 2016; 25: 16-27.
[9] Pickl JM, Heckmann D, Ratz L, Klauck SM and Sultmann H. Novel RNA markers in prostate cancer: functional considerations and clinical translation. Biomed Res Int 2014; 2014: 765207.
[10] Chandra Gupta S and Nandan Tripathi Y. Potential of long non-coding RNAs in cancer patients: from biomarkers to therapeutic targets. Int J Cancer 2017; 140: 1955-1967.
[11] Lin HM, Castillo L, Mahon KL, Chiam K, Lee BY, Nguyen Q, Boyer MJ, Stockler MR, Pavlakis N, Marx G, Mallesara G, Gurney H, Clark SJ, Swarbrick A, Daly RJ and Horvath LG. Circulating microRNAs are associated with docetaxel chemotherapy outcome in castration-resistant prostate cancer. Br J Cancer 2014; 110: 2462-2471.
[12] Alatrash G, Jakher H, Stafford PD and Mittendorf EA. Cancer immunotherapies, their safety and toxicity. Expert Opin Drug Saf 2013; 12: 631-645.
[13] Punnen S, Cowan JE, Chan JM, Carroll PR and Cooperberg MR. Long-term health-related quality of life after primary treatment for localized prostate cancer: results from the CaPSURE registry. Eur Urol 2015; 68: 600-8.
[14] Ghiam AF, Vesprini D and Liu SK. Long noncoding RNAs: new frontiers for advancing personalized cancer medicine in prostate cancer. Transl Androl Urol 2017; 6: 326-330.
[15] Pickard MR, Mourtada-Maarabouni M and Williams GT. Long non-coding RNA GAS5 regulates apoptosis in prostate cancer cell lines. Biochim Biophys Acta 2013; 1832: 1613-1623.
[16] Xue D, Zhou C, Lu H, Xu R, Xu X and He X. LncRNA GAS5 inhibits proliferation and progression of prostate cancer by targeting miR-103 through AKT/mTOR signaling pathway. Tumour Biol 2016; [Epub ahead of print].
[17] Lin CY, Wang SS, Yang CK, Li JR, Chen CS, Hung SC, Chiu KY, Cheng CL, Ou YC and Yang

SF. Impact of GAS5 genetic polymorphism on prostate cancer susceptibility and clinicopathologic characteristics. Int J Med Sci 2019; 16: 1424-1429.
[18] Hu J, Deng J, Cao R, Xiong S and Guo J. LncRNA GAS5 participates in the regulation of dexamethasone on androgen receptor-negative and -positive prostate cancer cell proliferation. Mol Cell Probes 2020; 53: 101607.
[19] Zhang Y, Su X, Kong Z, Fu F, Zhang P, Wang D, Wu H, Wan X and Li Y. An androgen reduced transcript of lncRNA GAS5 promoted prostate cancer proliferation. PLoS One 2017; 12: e0182305.
[20] Liu Z, Wu C, Xie N and Wang P. Long non-coding RNA MEG3 inhibits the proliferation and metastasis of oral squamous cell carcinoma by regulating the WNT/beta-catenin signaling pathway. Oncol Lett 2017; 14: 4053-4058.
[21] Wang X, Wang Z, Wang J, Wang Y, Liu L and Xu X. LncRNA MEG3 has anti-activity effects of cervical cancer. Biomed Pharmacother 2017; 94: 636-643.
[22] Wei GH and Wang X. LncRNA MEG3 inhibit proliferation and metastasis of gastric cancer via p53 signaling pathway. Eur Rev Med Pharmacol Sci 2017; 21: 3850-3856.
[23] Luo G, Wang M, Wu X, Tao D, Xiao X, Wang L, Min F, Zeng F and Jiang G. Long non-coding RNA MEG3 inhibits cell proliferation and induces apoptosis in prostate cancer. Cell Physiol Biochem 2015; 37: 2209-2220.
[24] Wu M, Huang Y, Chen T, Wang W, Yang S, Ye Z and Xi X. LncRNA MEG3 inhibits the progression of prostate cancer by modulating miR-9-5p/QKI-5 axis. J Cell Mol Med 2019; 23: 29-38.
[25] Zhou Y, Yang H, Xia W, Cui L, Xu R, Lu H, Xue D, Tian Z, Ding T, Cao Y, Shi Q and He X. LncRNA MEG3 inhibits the progression of prostate cancer by facilitating H3K27 trimethylation of EN2 through binding to EZH2. J Biochem 2020; 167: 295-301.
[26] Shukla S, Zhang X, Niknafs YS, Xiao L, Mehra R, Cieslik M, Ross A, Schaeffer E, Malik B, Guo S, Freier SM, Bui HH, Siddiqui J, Jing X, Cao X, Dhanasekaran SM, Feng FY, Chinnaiyan AM and Malik R. Identification and validation of PCAT14 as prognostic biomarker in prostate cancer. Neoplasia 2016; 18: 489-499.
[27] Yan Y, Liu J, Xu Z, Ye M and Li J. LncRNA PCAT-14 is a diagnostic marker for prostate cancer and is associated with immune cell infiltration. Dis Markers 2021; 2021: 9494619.
[28] Ma W, Chen X, Ding L, Ma J, Jing W, Lan T, Sattar H, Wei Y, Zhou F and Yuan Y. The prognostic value of long noncoding RNAs in prostate cancer: a systematic review and meta-analysis. Oncotarget 2017; 8: 57755-57765.
[29] Salameh A, Lee AK, Cardo-Vila M, Nunes DN, Efstathiou E, Staquicini FI, Dobroff AS, Marchio S, Navone NM, Hosoya H, Lauer RC, Wen S, Salmeron CC, Hoang A, Newsham I, Lima LA, Carraro DM, Oliviero S, Kolonin MG, Sidman RL, Do KA, Troncoso P, Logothetis CJ, Brentani RR, Calin GA, Cavenee WK, Dias-Neto E, Pasqualini R and Arap W. PRUNE2 is a human prostate cancer suppressor regulated by the intronic long noncoding RNA PCA3. Proc Natl Acad Sci U S A 2015; 112: 8403-8408.
[30] Wang T, Qu X, Jiang J, Gao P, Zhao D, Lian X and Li X. Diagnostic significance of urinary long non-coding PCA3 RNA in prostate cancer. Oncotarget 2017; 8: 58577-58586.
[31] Alshalalfa M, Verhaegh GW, Gibb EA, Santiago-Jimenez M, Erho N, Jordan J, Yousefi K, Lam LLC, Kolisnik T, Chelissery J, Seiler R, Ross AE, Karnes RJ, Schaeffer EM, Lotan TT, Den RB, Freedland SJ, Davicioni E, Klein EA and Schalken JA. Low PCA3 expression is a marker of poor differentiation in localized prostate tumors: exploratory analysis from 12,076 patients. Oncotarget 2017; 8: 50804-50813.
[32] Ferreira LB, Palumbo A, de Mello KD, Sternberg C, Caetano MS, de Oliveira FL, Neves AF, Nasciutti LE, Goulart LR and Gimba ER. PCA3 noncoding RNA is involved in the control of prostate-cancer cell survival and modulates androgen receptor signaling. BMC Cancer 2012; 12: 507.
[33] Lemos AEG, Matos ADR, Ferreira LB and Gimba ERP. The long non-coding RNA PCA3: an update of its functions and clinical applications as a biomarker in prostate cancer. Oncotarget 2019; 10: 6589-6603.
[34] Prensner JR, Chen W, Iyer MK, Cao Q, Ma T, Han S, Sahu A, Malik R, Wilder-Romans K, Navone N, Logothetis CJ, Araujo JC, Pisters LL, Tewari AK, Canman CE, Knudsen KE, Kitabayashi N, Rubin MA, Demichelis F, Lawrence TS, Chinnaiyan AM and Feng FY. PCAT-1, a long noncoding RNA, regulates BRCA2 and controls homologous recombination in cancer. Cancer Res 2014; 74: 1651-1660.
[35] Liu L, Liu Y, Zhuang C, Xu W, Fu X, Lv Z, Wu H, Mou L, Zhao G, Cai Z and Huang W. Inducing cell growth arrest and apoptosis by silencing long non-coding RNA PCAT-1 in human bladder cancer. Tumour Biol 2015; 36: 7685-7689.
[36] Shi WH, Wu QQ, Li SQ, Yang TX, Liu ZH, Tong YS, Tuo L, Wang S and Cao XF. Upregulation of the long noncoding RNA PCAT-1 correlates with advanced clinical stage and poor prognosis in esophageal squamous carcinoma. Tumour Biol 2015; 36: 2501-2507.
[37] Prensner JR, Iyer MK, Balbin OA, Dhanasekaran SM, Cao Q, Brenner JC, Laxman B, Asangani IA, Grasso CS, Kominsky HD, Cao X, Jing X,

Wang X, Siddiqui J, Wei JT, Robinson D, Iyer HK, Palanisamy N, Maher CA and Chinnaiyan AM. Transcriptome sequencing across a prostate cancer cohort identifies PCAT-1, an unannotated lincRNA implicated in disease progression. Nat Biotechnol 2011; 29: 742-749.

[38] Prensner JR, Chen W, Han S, Iyer MK, Cao Q, Kothari V, Evans JR, Knudsen KE, Paulsen MT, Ljungman M, Lawrence TS, Chinnaiyan AM and Feng FY. The long non-coding RNA PCAT-1 promotes prostate cancer cell proliferation through cMyc. Neoplasia 2014; 16: 900-908.

[39] Xu W, Chang J, Du X and Hou J. Long non-coding RNA PCAT-1 contributes to tumorigenesis by regulating FSCN1 via miR-145-5p in prostate cancer. Biomed Pharmacother 2017; 95: 1112-1118.

[40] Yuan Q, Chu H, Ge Y, Ma G, Du M, Wang M, Zhang Z and Zhang W. LncRNA PCAT1 and its genetic variant rs1902432 are associated with prostate cancer risk. J Cancer 2018; 9: 1414-1420.

[41] Shang Z, Yu J, Sun L, Tian J, Zhu S, Zhang B, Dong Q, Jiang N, Flores-Morales A, Chang C and Niu Y. LncRNA PCAT1 activates AKT and NF-kappaB signaling in castration-resistant prostate cancer by regulating the PHLPP/FKBP51/IKKalpha complex. Nucleic Acids Res 2019; 47: 4211-4225.

[42] Liu HT, Fang L, Cheng YX and Sun Q. LncRNA PVT1 regulates prostate cancer cell growth by inducing the methylation of miR-146a. Cancer Med 2016; 5: 3512-3519.

[43] Yang J, Li C, Mudd A and Gu X. LncRNA PVT1 predicts prognosis and regulates tumor growth in prostate cancer. Biosci Biotechnol Biochem 2017; 81: 1-6.

[44] Ilboudo A, Chouhan J, McNeil BK, Osborne JR and Ogunwobi OO. PVT1 exon 9: a potential biomarker of aggressive prostate cancer? Int J Environ Res Public Health 2015; 13: ijerph13010012.

[45] Pal G, Huaman J, Levine F, Orunmuyi A, Olapade-Olaopa EO, Onagoruwa OT and Ogunwobi OO. Long noncoding RNA from PVT1 exon 9 is overexpressed in prostate cancer and induces malignant transformation and castration resistance in prostate epithelial cells. Genes (Basel) 2019; 10: 964.

[46] Sun F, Wu K, Yao Z, Mu X, Zheng Z, Sun M, Wang Y, Liu Z and Zhu Y. Long noncoding RNA PVT1 promotes prostate cancer metastasis by increasing NOP2 expression via targeting tumor suppressor microRNAs. Onco Targets Ther 2020; 13: 6755-6765.

[47] Wu H, Tian X and Zhu C. Knockdown of lncRNA PVT1 inhibits prostate cancer progression in vitro and in vivo by the suppression of KIF23 through stimulating miR-15a-5p. Cancer Cell Int 2020; 20: 283.

[48] Videira A, Beckedorff FC, daSilva LF and Verjovski-Almeida S. PVT1 signals an androgen-dependent transcriptional repression program in prostate cancer cells and a set of the repressed genes predicts high-risk tumors. Cell Commun Signal 2021; 19: 5.

[49] Zhang S, Dong X, Ji T, Chen G and Shan L. Long non-coding RNA UCA1 promotes cell progression by acting as a competing endogenous RNA of ATF2 in prostate cancer. Am J Transl Res 2017; 9: 366-375.

[50] He C, Lu X, Yang F, Qin L, Guo Z, Sun Y and Wu J. LncRNA UCA1 acts as a sponge of miR-204 to up-regulate CXCR4 expression and promote prostate cancer progression. Biosci Rep 2019; 39: BSR20181465.

[51] Yu Y, Gao F, He Q, Li G and Ding G. LncRNA UCA1 functions as a ceRNA to promote prostate cancer progression via sponging miR143. Mol Ther Nucleic Acids 2020; 19: 751-758.

[52] Hu M and Yang J. Down-regulation of lncRNA UCA1 enhances radiosensitivity in prostate cancer by suppressing EIF4G1 expression via sponging miR-331-3p. Cancer Cell Int 2020; 20: 449.

[53] Prensner JR, Iyer MK, Sahu A, Asangani IA, Cao Q, Patel L, Vergara IA, Davicioni E, Erho N, Ghadessi M, Jenkins RB, Triche TJ, Malik R, Bedenis R, McGregor N, Ma T, Chen W, Han S, Jing X, Cao X, Wang X, Chandler B, Yan W, Siddiqui J, Kunju LP, Dhanasekaran SM, Pienta KJ, Feng FY and Chinnaiyan AM. The long noncoding RNA SChLAP1 promotes aggressive prostate cancer and antagonizes the SWI/SNF complex. Nat Genet 2013; 45: 1392-1398.

[54] Kidd SG, Carm KT, Bogaard M, Olsen LG, Bakken AC, Lovf M, Lothe RA, Axcrona K, Axcrona U and Skotheim RI. High expression of SCHLAP1 in primary prostate cancer is an independent predictor of biochemical recurrence, despite substantial heterogeneity. Neoplasia 2021; 23: 634-641.

[55] Aiello A, Bacci L, Re A, Ripoli C, Pierconti F, Pinto F, Masetti R, Grassi C, Gaetano C, Bassi PF, Pontecorvi A, Nanni S and Farsetti A. MALAT1 and HOTAIR long non-coding RNAs play opposite role in estrogen-mediated transcriptional regulation in prostate cancer cells. Sci Rep 2016; 6: 38414.

[56] Dai X, Liang Z, Liu L, Guo K, Xu S and Wang H. Silencing of MALAT1 inhibits migration and invasion by sponging miR13p in prostate cancer cells. Mol Med Rep 2019; 20: 3499-3508.

[57] Dai X, Liu L, Liang Z, Guo K, Xu S and Wang H. Silencing of lncRNA MALAT1 inhibits cell cycle progression via androgen receptor signaling in prostate cancer cells. Pathol Res Pract 2019; 215: 712-721.

[58] Hao T, Wang Z, Yang J, Zhang Y, Shang Y and Sun J. MALAT1 knockdown inhibits prostate

cancer progression by regulating miR-140/BIRC6 axis. Biomed Pharmacother 2020; 123: 109666.
[59] Wang D, Ding L, Wang L, Zhao Y, Sun Z, Karnes RJ, Zhang J and Huang H. LncRNA MALAT1 enhances oncogenic activities of EZH2 in castration-resistant prostate cancer. Oncotarget 2015; 6: 41045-41055.
[60] Li T, Liu N, Gao Y, Quan Z, Hao Y, Yu C, Li L, Yuan M, Niu L, Luo C and Wu X. Long noncoding RNA HOTAIR regulates the invasion and metastasis of prostate cancer by targeting hepaCAM. Br J Cancer 2021; 124: 247-258.
[61] Chakravarty D, Sboner A, Nair SS, Giannopoulou E, Li R, Hennig S, Mosquera JM, Pauwels J, Park K, Kossai M, MacDonald TY, Fontugne J, Erho N, Vergara IA, Ghadessi M, Davicioni E, Jenkins RB, Palanisamy N, Chen Z, Nakagawa S, Hirose T, Bander NH, Beltran H, Fox AH, Elemento O and Rubin MA. The oestrogen receptor alpha-regulated lncRNA NEAT1 is a critical modulator of prostate cancer. Nat Commun 2014; 5: 5383.
[62] Wen S, Wei Y, Zen C, Xiong W, Niu Y and Zhao Y. Long non-coding RNA NEAT1 promotes bone metastasis of prostate cancer through N6-methyladenosine. Mol Cancer 2020; 19: 171.
[63] Jiang X, Guo S, Zhang Y, Zhao Y, Li X, Jia Y, Xu Y and Ma B. LncRNA NEAT1 promotes docetaxel resistance in prostate cancer by regulating ACSL4 via sponging miR-34a-5p and miR-204-5p. Cell Signal 2020; 65: 109422.