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Long Non-coding RNAs in Castration-resistant and Neuroendocrine Prostate Cancer: Potential Role and Therapeutic Impact

Kumari S. Prajapati[1], Atul K. Singh[1], Mohd Shuaib[1], Prem P. Kushwaha[1], Shashank Kumar[1], Sanjay Gupta[2, 3, 4, 5, 6]

Abstract

Prostate cancer is the most commonly diagnosed malignancy and leading cause of cancer-related deaths in men worldwide. The disease is heterogeneous in nature exhibiting various clinical subtypes and genetic/transcriptomic features. Long non-coding RNAs (lncRNAs) are transcripts of more than 200 nucleotides that does not encode any protein and play important role in several biological processes as well as pathologic states. Deregulation of lncRNAs has been associated with human diseases. In prostate cancer, numerous key lncRNAs have been identified as novel players that contribute to the pathophysiology of the disease primarily regulated by androgen and its cognate receptor. The present review attempts to summarize the potential role of lncRNA and their mechanisms of action in prostate cancer with particular focus on lncRNAs regulated by androgen receptor expressed in castration-resistant and neuroendocrine differentiated subtypes. We also emphasize the potential of these lncRNAs for their development as therapeutic targets in prostate cancer.

Key words long non-coding RNA, castration-resistant prostate cancer, neuroendocrine prostate cancer, androgen signaling

1. Molecular Signaling & Drug Discovery Laboratory, Department of Biochemistry, Central University of Punjab, Bathinda 151401, India.
2. Department of Urology, Case Western Reserve University, Cleveland, Ohio 44106, USA.
3. The Urology Institute, University Hospitals Cleveland Medical Center, Cleveland, OH 44106, USA.
4. Department of Urology, Louis Stokes Cleveland Veterans Affairs Medical Center, Cleveland, OH 44106, USA.
5. Department of Nutrition, Case Western Reserve University, Cleveland, OH 44106, USA.
6. Division of General Medical Sciences, Case Comprehensive Cancer Center, Cleveland, OH 44106, USA.
Correspondence: Sanjay Gupta (Department of Urology, The James and Eilleen Dicke Research Laboratory, Case Western Reserve University, 10900 Euclid Avenue, Cleveland, Ohio 44106 USA; Email: sanjay.gupta@case.edu).

Introduction

Prostate cancer is the second-leading and most common cause of cancer-related death in the male population worldwide [1]. Prostate cancer progression occurs from androgen-dependent to androgen-independent stage and acquires metastatic capabilities at the advanced-stage malignancy. Treatment of prostate cancer differs at various stages of progression. Hormone-sensitive prostate tumors that are organ-confined are treated by surgery or radiotherapy whereas non-organ-confined tumors are subjected to hormonal therapies targeting the androgen receptor (AR) axis. Majority of patients experience tumor remission on androgen deprivation therapy (ADT), however, ~30% of these tumors reemerge and are clinically defined as castration-resistant prostate cancer (CRPC). A study reported that within 5 years, 10% to 20% of prostate cancer patients develop CRPC on ADT treatment [2]. Clinical use of second-generation drugs which target AR axis including enzalutamide and abiraterone acetate results in the development of CRPC phenotype. The ineffectiveness of ADT as a result of chemoresistance results in the activation of AR and its downstream pathways in CRPC tumors. Other key factors responsible for the CRPC transition include intratumoral androgen production, AR ligand-binding domain activation, AR amplification, AR splice variants formation, overexpression of feedback pathways [3]. In addition to the change in CRPC features, the dynamics of cellular plasticity alters during cancer progression, where tumor cells transition to AR-independence attaining neuroendocrine characteristics [4]. Neuroendocrine prostate cancer (NEPC) is the most lethal and aggressive form possessing an unusual phenotype. The median survival of NEPC patients is < 7 months and platinum-based chemotherapy remains the solitary treatment option [5]. It is still unclear whether NEPC tumors develop either de novo or as an adaptive response to ADT possessing aggressive pathological appearance with poor clinical outcome and overall low survival [6, 7].

Numerous reports suggest that AR and its downstream signaling are fundamental for the development and progression of both localized and advanced-stage prostate cancer. AR is a ligand-dependent transcriptional factor and a member of the steroid hormone nuclear receptor family. AR shares structural and functional homology with progesterone, estrogen, mineralocorticoid, and glucocorticoid receptors [8, 9]. The human AR is located on chromosome X (Xq11-12) and consists of eight exons and seven introns [10]. AR is a 90-kb gene encoding 110-kDa molecular weight protein containing 919 amino acids. AR is organized into four distinct functional domains including the Ligand-binding domain (LBD), DNA-binding domain (DBD), Hinge domain, and amino-terminal domain (NTD) [11]. Upon binding of ligands, androgens such as dihydrotestosterone and testosterone change the AR conformation to an active state. AR is normally present in an inactive state bound with heat shock proteins (HSP70 and HSP90) and with chaperone proteins in the cytosol. The binding of androgens triggers the release of HSP from the AR necessary for dimerization, translocation into the nucleus and binding to specific androgen response elements (AREs), regulating target gene transcription and expression. AR transcript expression is also mediated with the support of other coactivators and co-suppressor proteins [12]. Identification of AR downstream molecules and novel regulators for AR activation are important in understanding the mechanism(s) of CRPC and NEPC and to improve the treatment of advanced prostate cancer.

The recent development of high-throughput technology has led to the identification of noncoding transcripts, such as long noncoding RNAs (lncRNAs). Aberrant expression of lncRNA has been noted in a variety of human diseases including cancer, contributing to the pathogenesis or maintaining diseased conditions. The present review summarizes the current knowledge of lncRNAs expression patterns in advance-stage prostate cancer including its role during malignant progression, tumor suppression, and towards the development of chemo-resistance.

Androgen-receptor signaling during CRPC and NEPC progression

Recent advancement and improvements in the therapeutic strategy to suppress metastatic CRPC with second-generation AR-targeting agents with enzalutamide and abiraterone acetate increases patient survival by approximately 4.8 months [13]. Studies suggest that alteration of AR-signaling pathways and AR-signaling bypass mechanisms leads to the development of CRPC whereas the mechanism(s) of AR-independent clonal evolution promotes the emergence of NEPC tumors [14]. Some of the AR bypass mechanisms include glucocorticoid receptor, PI3K-AKT-mTOR pathway, and stress signaling [15]. Increasing evidence demonstrates a positive association between CRPC and NEPC tumors [16-18]. Clinical data suggested that following the first and second-line therapy targeting AR-axis, NEPC is found to be present in 30-40% of patients with metastatic CRPC [19]. Recent studies corroborated that continuous exposure and selective pressure of ADT induces neuroendocrine trans-differentiation, resulting in the emergence of NEPC tumors [14].

CRPC and NEPC share similar genomics but different transcriptomics [20]. Mu et al. (2017) reported that selection pressure mediated by AR-axis inhibitors stimulates NEPC formation in prostate cancer cells along with the loss of TP53 and RB1 expression [21]. Inactivation of RB1and TP53 induces the expression of the SOX2 transcription factor to entrap on lineage plasticity in prostate cancer cells and reprogramming of fibroblasts to induce-pluripotent stem cells [21]. Another important protein overexpressed under the influence of TP53 and RB1 inactivation is Enhancer of zeste homolog 2 (EZH2) [22]. EZH2, the master regulator of neuroendocrine lineage plasticity was observed to be upregulated in NEPC patients where EZH2 inhibitors are able to restore AR sensitivity [22]. Another study investigated that overexpression of N-Myc with upregulated AKT drives the formation of NEPC in mice models [23, 24]. Dardenne et al. (2016) reported that activated Aurora A kinase (AURKA) increases cell proliferation in NEPC in the absence of AR and amplification of MYCN collaborate with EZH2 to reduces AR transactivation, and promote neuroendocrine differentiation [23]. The study also reported that 40% of NEPC cells have upregulated AURKA and amplified MYCN [25]. One of the transcription factors, repressor element 1 (RE-1) silencing transcription factor (REST) particularly known as a negative master regulator of neuronal differentiation plays a critical role in cell differentiation fate [26]. REST is highly expressed in prostate adenocarcinoma and found to be downregulated in NEPC patients [27, 28]. Downregulation of REST leads to the repression of the neuronal-differentiation-related genes which ultimately leads to NEPC development. AR-axis inhibitors regulate REST both at the mRNA and protein level. REST is also regulated by SRRM4, β-TRCP and HAUSP to maintain it in an inactive form. Downregulation of REST through AR-axis inhibition via the upregulation of SRRM4 and β-TRCP induces neuroendocrine-specific differentiation among prostate cancer cells [14]. Studies also demonstrate the involvement of placental genes such as PEG10, FOXA1, and BRN2 to promote and activate neuroendocrine differentiation in prostate cancer cells [29]. HIF1A is reported to regulate the neuroendocrine characteristics in prostate cancer cells. HIF1A in cooperation with the transcription factor FOXA2 induces several HIF1A target genes essential for promoting hypoxia-induced metastasis and neuroendocrine phenotype in prostate cancer [30-32].
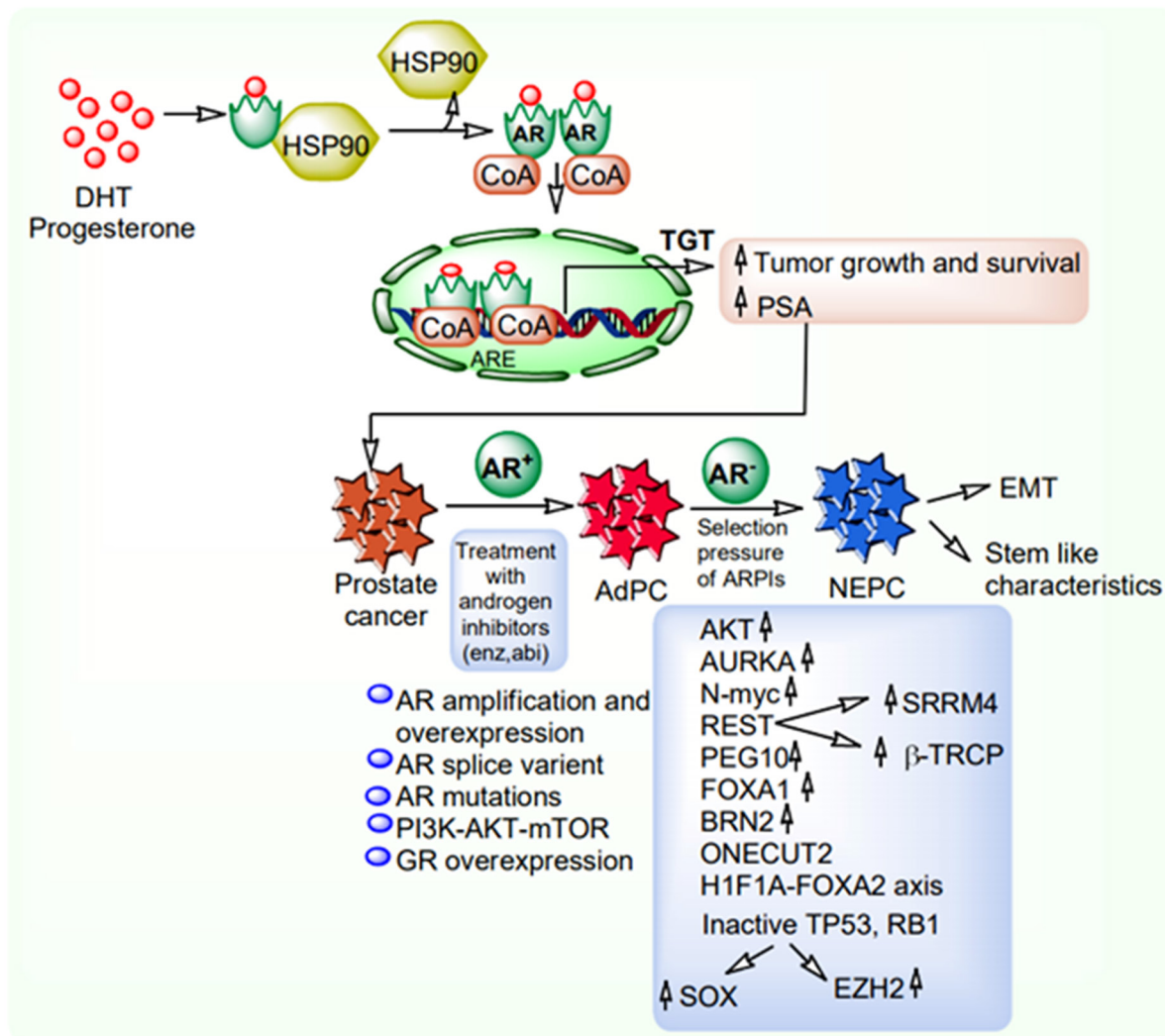
Figure 1. Molecular signaling of prostate cancer, castration resistant prostate cancer (CRPC) and neuroendocrine prostate cancer (NEPC) progression. DHT: Dihydrotestosterone; HSP90: Heat shock protein 90; AR: Androgen receptor; CoA: Coenzyme A; TGT: Target gene transcription; ARE: Androgen response element; PSA: Prostate serum antigen; Enz: Enzalutamide; Abi: Abiraterone acetate; AdPC: Adenocarcinoma prostate cancer; ARPI: Androgen receptor pathway inhibitor; NEPC: Neuroendocrine prostate cancer; EMT: Epithelial mesenchymal transition; AKT: Protein kinase B; AURKA: Aurora kinase A; REST: RE1-Silencing transcription factor; PEG10: Paternally expressed 10; FOXA1: Forkhead Box1; HIF1A: Hypoxia inducing factor 1A; TP53: Tumor suppressor protein 53; RB1: Retinoblastoma1; SOX: SRY-related HMG-box; EZH2: Enhancer of zeste homolog 2; PI3K: Phosphoinositide 3-kinase; mTOR: Mammalian target of rapamycin; SRRM4: Serine/arginine repetitive matrix 4; β-TRCP: Beta transducing repeats-containing proteins.

Recent studies reported the role of ONECUT2 overexpression in inhibiting AR signaling and promoting neuroendocrine phenotype under hypoxic conditions [31, 33]. ONECUT2 plays an important role in contributing to angiogenic phenotype in NEPC. It is also demonstrated that NEPC tumors exhibit various developmental programs related to epithelial-to-mesenchymal (EMT) induction and stem-like characteristics. Dicken et al. (2018) demonstrated that the signaling interaction between AR axis and TGF-β mechanistic network influences the EMT phenotypic transformations creating the critical environment for epithelial-derived tumors to become more invasive to adopt neuroendocrine features [34]. The involvement of causal pathways facilitating CRPC and NEPC initiation and development is shown in **Figure 1**.

Role of lncRNAs in CRPC and NEPC progression

The lncRNAs are classified as >200 nucleotides in length which are transcribed by RNA pol II through regulatory regions and upstream of promoter elements ranging up to several kilobases (kb) constituting heterogeneous genomic origin and function. lncRNAs play a vital role in maintaining and regulating various biological processes including development, differentiation, proliferation, apoptosis, and invasion in various solid tumors [35]. lncRNAs also play an important role in regulating malignant progression [36]. lncRNAs fold themselves into structures that interact with DNA, RNA and proteins to regulate chromatin dynamics, transcription, protein chromatin assembly, splicing and telomere biology [37]. Some lncRNAs including nuclear-encoded lncRNA are transcribed from mtDNA after their uptake by mitochondria. lncRNAs are classified based on their genomic organization such as (i) Intergenic lncRNAs (lincRNAs)- transcribed between two protein-coding genes, (ii) Intronic lncRNAs- transcribed from introns of protein-coding genes, (iii) Overlapping lncRNAs-
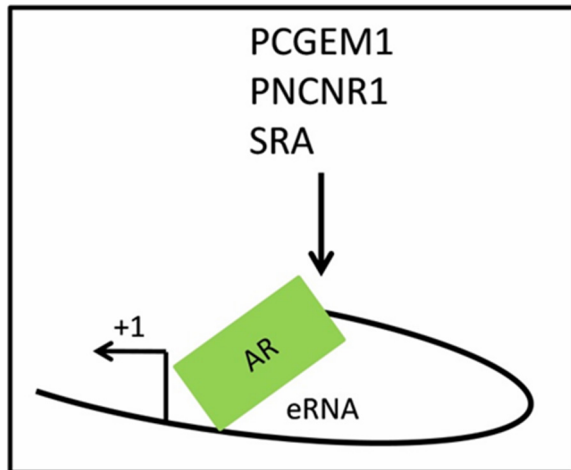
Figure 2. Regulation of AR expression by lncRNAs via promoter/ enhancer loop formation. Several lncRNAs such as PCGEM1, PNCNR1, and SRA promote the promoter/enhancer loop formation on AR regulated genes and facilitate the AR regulated gene expression. PCGEM1: Prostate cancer gene expression marker 1; PNCNR1: Prostate cancer noncoding RNA 1; SRA: Steroid receptor RNA activator; AR: Androgen receptor protein; eRNA: Enhancer-templated non-coding RNA.

transcripts constitute to overlap with known protein-coding genes, (iv) antisense lncRNAs- transcribed in the opposite direction to that of the protein-coding gene [38]. Some other parameters such as biogenesis pathway, subcellular localization, and length of the lncRNAs are used to classify lncRNAs [39]. lncRNAs show chromatin marks that are regulated by transcription factors binding to the promoter region of coding genes such as H3K4me3 and

H3K36me3 for transcription initiation and elongation [40]. Besides alteration in signaling molecules, lncRNA dysregulation provides an additional mechanism(s) for gene expression alterations that occur during CRPC and NEPC progression.

Various lncRNAs are known to play major roles in CRPC progression. These lncRNAs regulate key cellular processes in CRPC cells such as cell proliferation, invasion, metastasis, angiogenesis, and resistance to apoptosis [41]. Genome-wide association studies have revealed a high proportion of genetic alterations in prostate cancer-associated with lncRNAs coding region of the genome, suggesting the important role of lncRNAs in cancer progression [42, 43]. The intergenic region 8q24 is a gene desert located near the MYC proto-oncogene is reported to be involved in carcinogenesis [44]. In prostate cancer, 8q24 is a major susceptibility region that transcribes various single nucleotide polymorphism containing RNAs that are involved in the promotion of hormone-dependent prostate cancer to CRPC [45]. lncRNAs such as prostate-specific transcript 1 (PCGEM1), prostate cancer-associated non-coding RNA 1 (PRNCR1), and steroid receptor RNA activator (SRA) are reported to enhance AR-mediated transcription of target genes via a chromatin loop formation. These lncRNAs bind to the enhancer region of AR target genes and recruit DOT1L methyltransferase which promotes AR methylation on K349. Methylation of AR on K349 results in the recruitment of pygo 2 which further enhances loop formation between enhancer and promoter resulting in elevated transcription of the target genes. Furthermore, lncRNAs mediated loop formation promotes prostate cancer progression via both ligand-dependent and ligand-independent manner [46]. Apart from prostate cancer progression by PCGEM1 via loop formation mechanism, it also promotes cancer progression via upregulation of metabolism [47]. PCGEM1 promotes CRPC metabolically through the upregulation of aerobic glycolysis, pentose phosphate pathway, lipid and glutamine metabolism. Regulation of metabolism by PCGEM1 is independent of the presence of AR and androgen and it is mediated by MYC activation [47] (**Figure 2**). Another lncRNAs reported to associate with tumor metabolism
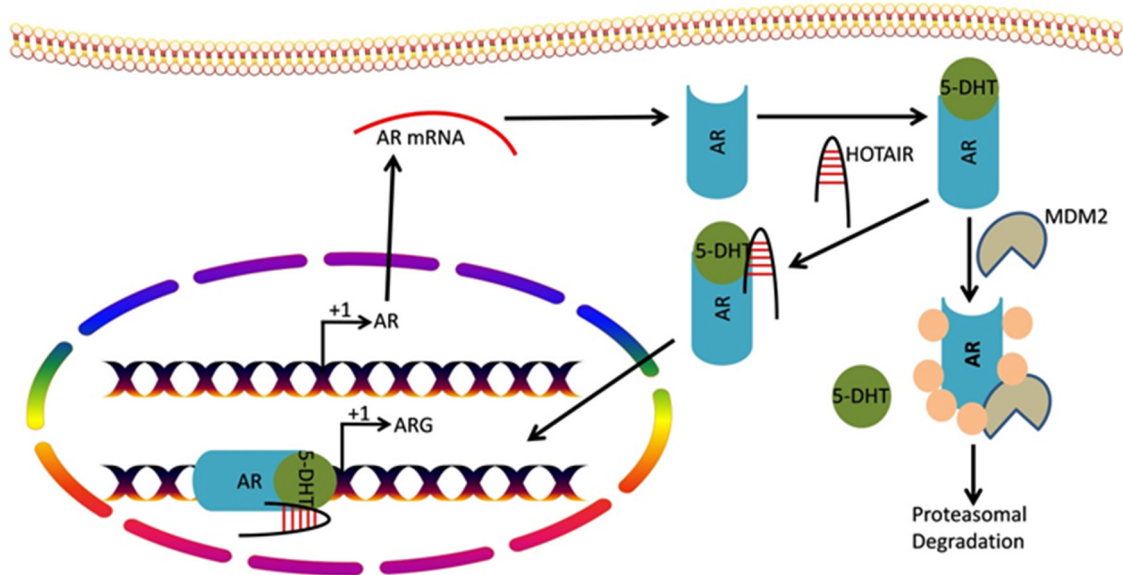
Figure 3. Inhibition of AR protein degradation by HOTAIR. E3 ubiquitin ligase MDM2 binds with AR protein and promotes its proteasomal degradation. lncRNA HOTAIR binds with AR protein and prevents the binding of MDM2 and thereby promotes the AR mediated gene expression. AR: Androgen receptor protein; 5-DHT: Dihydrotestosterone; ARG: AR responsive genes; HOTAIR: HOX transcript antisense RNA; MDM2: Mouse double minute 2 homolog.

is lincRNA-p21. Under the hypoxic condition, hypoxia-inducible factor α (HIF-α) induces the expression of lincRNAp21. Isin et al. (2015) reported the elevated expression of lincRNA-p21 in prostate cancer suggests lincRNA-p21 could be an important player in the regulation of CRPC metabolism [48].

The lncRNA HOX transcript antisense RNA (HOTAIR) is reported to facilitate AR-mediated transcriptional response and promote CRPC [49]. Another mechanism by which HOTAIR regulates CRPC progression is by reciprocal regulation of EZH2 and DNMT1 which results in the polyphylline-1 inhibited progression of CRPC [50]. HOTAIR protects AR from E3 ubiquitin ligase MDM2-mediated protein degradation through direct interaction with AR. Therefore, overexpression of HOTAIR contributes to upregulates AR target gene expression in an androgen-independent mode and thus promotes CRPC progression [49] (**Figure 3**). The lncRNA suppressor of cytokine signaling 2-antisense transcript 1 (SOCS2-AS1) also facilitates AR-mediated transcriptional response. SOCS2-AS1 associated with AR protein promotes transcriptional repression of tumor suppressor gene

TNFSF10 [51] (**Figure 4**).

Prostate-specific lncRNA prostate cancer-associated transcript 1 (PCAT1) is involved in the regulation of stress response and DNA repair processes. Uncontrolled cell division of cancer cells results in the accumulation of many types of aberrations in the DNA of cancer cells which leads to genomic instability. PCAT1 was reported to be upregulated in CRPC and it activates AKT and NF-κB signaling pathways by regulating PHLPP/FKBP51/ IKKα complex [52]. Prensner et al. (2014) reported that PCAT1 downregulates tumor suppressor gene BRCA1 results in aberrant homologous recombination and DNA repair [53]. PCAT1 is associated with PRC2 subunit, suppressor of zeste 12 homolog (SUZ12), and functions as a transcriptional repressor [54].

Other lncRNAs involve in the progression of CRPC are Nuclear enriched abundant transcript 1 (NEAT1) and Prostate cancer-associated transcript 5 (PCAT5). NEAT1 regulates the expression level of specific prostate cancer-associated genes along with the modulation of expression of TMPRSS2-ERG fusion transcripts [55]. PCAT5 is overexpressed in ERG positive CRPCs. PCAT5 promotes proliferation, invasion and resistance to apoptosis in
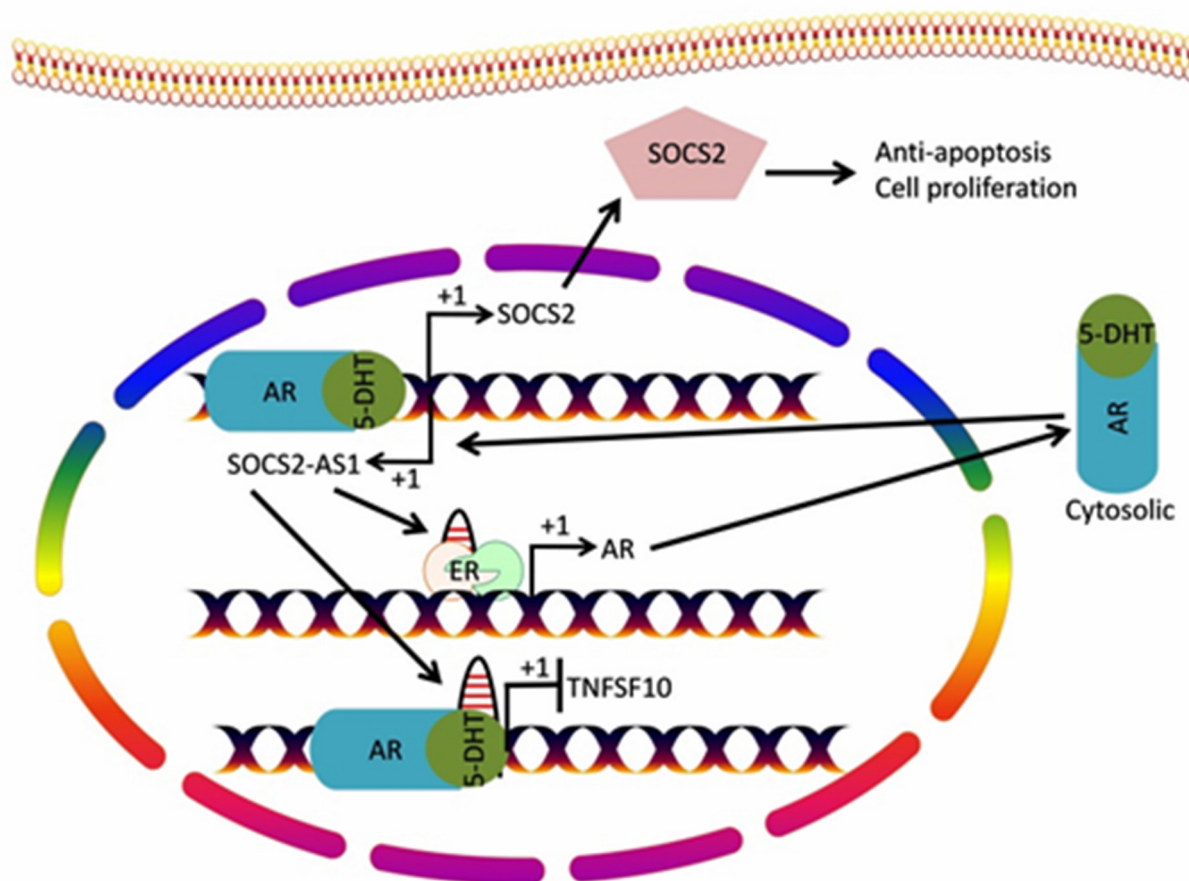

Figure 4. Interaction of SOCS2-AS1 lncRNA with AR. Cytosolic AR protein translocates into the nucleus and facilitates transcription of SOCS2 gene. Transcription of sense strand results in the production of SOCS2 protein which promotes carcinogenesis of prostate cancer via promoting cell proliferation and anti-apoptosis. Transcription of antisense strand produces lncRNA SOCS2-AS1 which binds to AR protein and promotes gene regulation such as transcriptional inhibition of tumor suppressor gene TNFSF10. Furthermore SOCS2-AS1 also promotes expression of AR protein by directly binding to its promoter and recruiting epigenetic regulators on AR promoter. AR: Androgen receptor protein; 5-DHT: Dihydrotestosterone; ER: Epigenetic regulators; SOCS2: Suppressor of Cytokine Signaling 2; SOCS2-AS1: Suppressor of cytokine signaling 2-antisense transcript 1; TNFS10: TNF Superfamily Member 10.

CRPC cells [56]. SChLAP1 is another lncRNA overexpressed in CRPC. SWI/SNF Complex antagonist associated with prostate cancer 1 (SChLAP1) promotes invasion and migration of CRPC cells by regulating the SWItch/Sucrose Non-Fermentable-complex and inhibiting its gene expression regulatory function [57].

Metastasis associated lung adenocarcinoma transcript 1 (MALAT1) lncRNA is reported to be involved with pathological complications of organs that have a strong association with sex hormones. MALAT1 is one of the 10 most upregulated transcripts in CRPC and its upregulation is associated with the CRPC progression [58, 59]. Wang et al. (2015) reported that MALAT1 regulates the activity of EZH2 in CRPC via facilitating promoter activity and H3K27me3 activity of EZH2 [60]. MALAT1 cooperates with EZH2 playing a crucial role in EZH2-mediated migration and invasion in CRPC cell lines [60]. Studies reported the high expression of MALAT1 in CRPC whose knockdown reduces cell growth and invasion which are also repressed by androgen treatment.

Growth arrest-specific 5 (GAS5) lncRNA is reported to be downregulated in mCRPC and the result of which shows reduced chemotherapy-induced cellular apoptosis [61]. It is apparent that low-level GAS5 makes mTOR inhibitors insensitive to CRPC cells [62].

It has been demonstrated that lncRNAs function as a decoy or molecular sponge for the miRNAs targeting protein-coding mRNA. Zhu et al. (2014) demonstrated the significant downregulation of H19 and H19-derived miR-675 in metastatic prostate cancer cells as compared to non-metastatic prostate cancer cells [63]. However, the upregulation of H19 increases miR-675 expression inhibiting prostate cancer cell migration. Additionally, miR-675 targets RB and CDC6, residing within the first exonic region of H19 [64, 65]. H19 and miR-675 are significantly downregulated that increases the expression of TGF-β1 thus promoting cell migration. Binding of miR-675 at the 3' UTR of TGF-β1 mRNA inhibits its translation, thereby H19-miR-675 axis considered as a suppressor of metastatic prostate cancer [63]. Upregulated lncRNA MIR221HG which is transcribed in the promoter region of miR-221/222 is reported to promote cell growth in an androgen-independent manner. Upregulation of MIR221HG inhibits the expression of CRPC markers including TMPRSS2, KLK3, and FKBP5 produced on AR induction. Clinically, a high expression level of MIR222HG is reported with prostate cancer progression and development to CRPC [66].

PTENP1, a pseudogene of the tumor suppressor gene PTEN containing MREs transcript similar to PTEN targeting miRNAs including miR-21, miR-124, miR-17, miR-26a, and miR-19 families [67]. Furthermore, PTEN loss is greatly associated with the development of CRPC and with poor clinical outcomes in CRPC patients [68]. PTENP1 and PTEN are positively correlated to each other in prostate cancer progression. PTENP1 and PTEN compete with each other for binding to their common miRNAs. Overexpression of 3' UTR PTENP1 diminished the proliferation rate of DU145 cells through the upregulation of PTEN both at the mRNA a protein levels [69]. Therefore, PTENP1 acts as a decoy through altering anti-PTEN miRNA away from PTEN and the result of which increases tumor suppressor activity of PTEN [67]. Clinical data suggest that NEPC arise de novo in prostate cancer patients with 0.5% to 2% frequency. Ramnarine et al. (2018) developed a first-in-field patient-derived xenograft (PDX) model of NEPC to study the clinical implications of the landscape of lncRNA in NEPC [70]. Longitudinal deep transcriptomic profiling of PDX of androgen deprivation enables to observe dynamic transcriptional changes during neuroendocrine differentiation. The group identified 122 lncRNAs that strongly distinguish the existence of NEPC different from adenocarcinoma tumor patients and the top identified lncRNAs are H19, LINC00617, FENDRR,

LINC00514, and SSTR5-AS1 [70].

Transcription factor binding site (TFBS) analysis identified NEPC-associated TF motifs that are present within the NEtD lncRNA sequences which indicates the functional role of identified lncRNAs in NEPC pathogenesis [70]. FOXF1 adjacent non-coding developmentary regulatory RNA (FENDRR) is the most deregulated lncRNA in NEPC [71]. FENDRR is reported to interact with PRC2 which is a key player in prostate tumor progression. FENDRR is reported to reduce tumor invasion by targeting CSNK1E in PC-3 cells [72].

LINC00514 is a highly expressed lncRNA NEPC which is predicted to bind with TADA3 and lowers its activity [70]. TADA3 is an important regulator of cell proliferation through the stabilization and regulation of p53 activity [73]. The interaction between TADA3 and p53 could be one of the reasons for the loss of p53 in NEPC.

SSTR5 antisense RNA 1 (SSTR5-AS1) lncRNA was reported to be highly expressed in NEPC. SSTR5-AS1 is an antisense transcript of SSTR5 which belongs to the family of somatostatin receptor family [70]. Somatostatins are reported to regulate important cellular processes such as cell proliferation neurotransmission, and endocrine signaling [74]. Another lncRNA involved in the progression of NEPC is NEAR1. NEAR1 is reported to promote the proliferation and survival of NEPC cells [75].

Long intergenic non-coding protein-coding RNA 8 (H19) is an imprinted maternally expressed untranslated mRNA mainly located in the region of chromosome 11 (11p15.5) near the insulin-growth factor 2 (IGF2) gene [76]. In the case of metastatic prostate cancer, H19 plays a tumor-suppressive role by suppressing transforming growth factor-β1 (TGF-β1) effects [63]. Downregulation of H19 inhibited glucose metabolism, lactic acid production, cell growth, and proliferation in AR-negative prostate cancer cells [77].

The lncRNA-p21 was identified to activate p21 and a p53 corepressor to stimulate and promote the PRC2 target gene expression that affects cellular epigenetic regulation [78]. Luo et al. (2019) reported high expression of lncRNA-p21 in NEPC derived xenograft tissues [79]. Chang et al. (2018) proposed HOTAIR as a REST-regulated lncRNA that drives neuroendocrine differentiation in prostate cancer cells [80]. HOTAIR is identified as a novel REST-repressed and upregulated lncRNA in NEPC cells, whose knockdown suppresses neuroendocrine differentiation. HOTAIR is reported to interact with PRC2 complex and EZH2 allowing the repressor complex to bind to AR suppressing AR activity [81]. A study reported that SChLAP1 exerts its oncogenic effect by negatively regulating miR-198 thereby affecting the MAPK1 signaling pathway [82]. SChLAP1 is reported to be regulated in both CRPC and NEPC tumors. Thus, there is a possibility of involvement of SChLAP1 and miR-198 relation in prostate cancer progression to NEPC. Similarly, MALAT1 was also found to be negatively regulated by miR-1 expression in androgen receptor-negative prostate cancer cells. MALAT1 acts as a molecular sponge of miR-1 which increases the expression level of KRAS thereby affecting cell proliferation, apoptosis, and migration [83]. Ling et al. (2017) reported HOTAIR as a direct negative target of miR-193a [84]. MiR-193a performs tumor-suppressive functions, however, was found downregulated in metastatic prostate cancer through HOTAIR mediated EZH2 expression. Therefore, HOTAIR/EZH2/miR-193a feedback loop formation paying a vital role in NEPC progression [84].

LncRNA myocardial infarction associated transcript (MIAT) interacts with polycomb genes and is highly upregulated in NEPCs. Clinical database analysis by Crea et al. (2016) suggested higher expression of lncRNA MIAT is involved in prostate cancer progression and trans-differentiation from prostatic

adenocarcinomas to NEPC [85]. LncRNA MIAT expression is confined to a small proportion of prostate cancer with recurrence in Rb mutations, high metastatic potential, and poor prognosis [85] (**Table 1**).

lncRNAs as therapeutic targets in CRPC and NEPC

The role of lncRNAs is multifunctional having high cell-type specificity in prostate cancer and thus are attractive therapeutic targets. Several studies using various anticancer drugs have demonstrated to regulate the expression of dysregulated lncRNAs. For example, enzalutamide, the most common antiandrogen used

in the treatment of CRPC which blocks AR-based signaling and reduced the expression level of H19 lncRNA [86]. GAS5 lncRNA is encoded on a prostate cancer-associated locus on chromosome 1q25 and its down expression promotes castration resistance in prostate cancer cells. Yacqub-Usman et al. (2015) demonstrated that mTOR inhibitors modulate GAS5 lncRNA expression and its cellular level is associated with induction of apoptosis and AR suppression [87]. The mTOR pathway regulates GAS5 lncRNA levels in AR stimulated prostate cancer cells and overexpression of GAS5 has been observed in the mTOR inhibitors treated cells [87]. Another study reported that downregulation of GAS5 delays apoptosis induction in response to chemotherapeutic drugs

Table 1. Represents various lncRNAs involved in CRPC and NEPC development and progression.

lncRNAs	Cancer type	Target	Functions	References
PCGEM1	CRPC	MYC	Increase aerobic glycolysis, PPP, lipid and glutamine metabolism, promotes CRPC	[47]
HOTAIR	CRPC NEPC	EZH2, DNMT REST	CRPC progression, Neuroendocrine differentiation	[50, 80]
SOCS2-AS1	CRPC	TNFSF10	Repression of tumor suppressor gene	[51]
lincRNA-p21	CRPC	HIF-α	CRPC progression	[48]
PCAT1	CRPC	AKT, NF-κB, PHLPP/FKBP51/IKKα complex, BRCA1	Genomic instability, aberrant homologues recombination and DNA repair	[52]
NEAT1	CRPC	TMPRSS2-ERG fusion transcripts	CRPC progression	[55]
PCAT5	CRPC	ERG	Promotes proliferation, invasion and resistance to apoptosis in CRPC cells	[56]
SChLAP1	CRPC	SWItch/Sucrose Non-Fermentable-complex	Promotes invasion and migration of CRPC	[57]
MALAT1	CRPC	EZH2	CRPC progression, migration and invasion in CRPC cells	[60]
GAS5	mCRPC	mTOR	Reduced chemotherapy-induced cellular apoptosis	[61, 62]
FENDRR	NEPC	PRC2	Tumor progression	[72]
LINC00514	NEPC	TADA3, p53	NEPC development	[73]
H19	NEPC	TGF-β1	Lactic acid production, cell growth, and proliferation in AR-negative prostate cancer cells	[63]
LncRNA-p21	NEPC	PRC2	Affect epigenetic regulation, NEPC formation	[78]
MIAT	NEPC	Polycomb genes	Trans-differentiation from prostatic adenocarcinomas to NEPC, high metastatic potential, and poor prognosis	[85]

CRPC: Castration resistant prostate cancer; NEPC: Neuroendocrine prostate cancer; PCGEM1: Prostate specific transcript 1; HOTAIR: HOX transcript antisense RNA; SOCS2-AS1: Suppressor of cytokine signaling 2- antisense transcript 1; PCAT1: Prostate cancer associated transcript 1; PCAT5: Prostate cancer associated transcript 5; MALAT1: Metastasis associated lung adenocarcinoma transcript 1; GAS5: Growth arrest-specific 5; FENDRR: FOXF1 adjacent non-coding developmentary regulatory RNA; MIAT: Myocardial infarction associated transcript; AKT: Protein kinase B; REST: RE1-Silencing transcription factor; HIF1A: Hypoxia inducing factor 1A; TP53: Tumor suppressor protein 53; EZH2: Enhancer of zeste homolog 2; mTOR: Mammalian target of rapamycin; PRC2: Polycomb repressive complex 2; TADA3: Transcriptional adaptor 3; DNMT: DNA methyl transferase; TGF-β1: Transforming growth factor-β1; TMPRSS2: Transmembrane protease serine 2; ERG: ETS-Related gene; NF-kb: Nuclear factor- kb; PHLPP: PH domain leucine-rich repeat protein phosphatase; FKBP5: FK506-Binding protein 51; IKKα: IκB Kinase α; BRCA1: Breast cancer type 1 susceptibility protein.

including docetaxel, nutlin-3a, and mitoxantrone, and hence decreasing the effectiveness of chemotherapeutic agents.

High levels of HOTAIR endorses CRPC progression. Polyphyllin I is a steroidal saponin that exhibited antitumor activity and inhibits the growth of CRPC cells by reducing the level of HOTAIR [88]. Paclitaxel, a natural anticancer drug, negatively regulates the expression of highly expressed lncRNA DANCR in prostate cancer tissues and cells, and its downregulation is associated with loss of proliferation in prostate cancer [89].

Analysis of prostate cancer cell lines and clinical specimens demonstrated upregulation of lncRNA-p21 in NEPC where treatment with enzalutamide was shown to increase lncRNA-p21 activity promoting neuroendocrine differentiation. This mechanistic study corroborated that enzalutamide treatment promotes transcription of lncRNA-p21 altering AR levels and it's binding with AREs, thereby switching the function of EZH2 from histone-methyltransferase to non-histone methyltransferase. The switching mechanism of EZH2 methylates STAT3 to promote neuroendocrine differentiation [79]. Enzalutamide inhibitor GSK503 reported suppressing neuroendocrine differentiation [90]. Preclinical studies of EZH2 inhibitors such as GSK126 and DZNep reported to target AR/lncRNA-p21/EZH2/STAT3 signaling to block enzalutamide-induced neuroendocrine differentiation [79].

Studies have demonstrated that plant-derived anticancer agents modulate the lncRNAs involved in prostate tumorigenesis like HOTAIR, H19, PCGEM1, DANCR, and lncRNAs-p21 [91, 92]. Aird et al. (2018) demonstrate that plant isoflavone genistein modulates the expression of HOTAIR in prostate cancer, which consequently modulates the activity of the PI3K/AKT signaling pathway [93]. Genistein induces apoptosis in prostate cancer cells by downregulating WNT and AKT signaling pathways, which might lead to decrease expression of HOTAIR in treated cells. In another study, Liu et al. (2019) have shown that polyphenol curcumin causes modulation of HOTAIR lncRNA in prostate cancer cells [94]. Similarly, resveratrol has been shown to inhibit AR signaling pathway in prostate cancer by modulating the expression of PCGEM1 and PRNCR1 lncRNAs [92]. Another study on resveratrol demonstrates a reduction of PCAT29 lncRNA expression in prostate cancer [95]. Liu et al. (2016) reported that 1,2,6-tri-O-galloyl-beta-D-glucopyranose has the potential to modulate lncRNA levels and could be a novel approach to treat prostate cancer [96].

Conclusion and future prospects

The lncRNAs play an important role in the progression of prostate cancer from androgen-dependent to androgen-independent stages and transition to CRPC and NEPC. Dysregulation of lncRNA expression contributes to the development of primary prostate cancer as well as the disease progression to CRPC and NEPC. While several prostate cancer lncRNAs promote aggressive phenotypes in preclinical models and are associated with disease progression in clinical cohorts, the underlying mechanisms of these oncogenic lncRNAs need further exploration. Unlike protein-coding mRNAs and miRNAs, our understanding of lncRNAs is still in the initial stage with many gaps in our knowledge. First, extensive study of lncRNAs is lacking and only a small fraction of lncRNAs have been experimentally validated. It remains unclear whether abnormal expression of lncRNA is a cause or consequence of tumorigenesis. Second, there is an increase in the recognition and detection of lncRNAs, although their biological functions and mechanisms of action in cancer require further investigation. Third, the proposed role of lncRNAs remains unclear, therefore it is not possible to suggest them as biomarkers for early detection, prognostication or in chemo-resistance of cancer. In fact, the role of lncRNAs in resistance to common drugs docetaxel, paclitaxel,

gemcitabine, and cisplatin, and others is urgently needed to suggest them as potential biomarkers of resistance to systemic treatments. Regarding therapeutic problems during hormonal therapies and the development of chemoresistance, lncRNAs with cancer-specific expression would serve as promising targets for advanced prostate cancer. Furthermore, extensive investigation based on preclinical and clinical studies would enable the development of next-generation clinical strategies for prostate cancer management.

The initiation and success of new genome editing tools including clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR associated (Cas) has promptly revolutionized the field of cancer biology. Although frequently used to engineer protein-coding genes, recent studies recommend that the technology can be applied to non-coding genes including lncRNAs, and to permanently correct in vivo genetic mutations. The technology can also benefit to identify genes involved in drug resistance to understand the mechanism of drug action and the efficacy of drug combinations in malignant cells. The use of this technology will help to uncover novel lncRNAs, to better annotate known lncRNAs, as well as to assess lncRNA localization, structure and function. Additional methodologies such as RNAi, antisense oligonucleotides, or small molecule inhibitors could be employed to better understand the biology of lncRNAs. Thus, given the roles of lncRNAs in various subtypes of prostate cancer, it will be important to recognize the therapeutic impact of targeting specific lncRNAs leading to a more efficient and broader therapeutic implication in prostate cancer.

Ethical policy

Approval was taken from institutional ethical committee. The study was performed in accordance with the Declaration of Helsinki. Patients gave their informed consent for their participation.

Author contributions

SG and SK designed the study and drafted the manuscript. KSP, AKS and MS searched literature and compiled the data. KSP, AKS, and PPK prepared the figures and tables. All authors read and approved the final manuscript.

Competing interests

The authors declare no competing interests.

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