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A thorough understanding of the role of lncRNA in prostate cancer pathogenesis; Current knowledge and future research directions

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ABSTRACT

In the entire world, prostate cancer (PCa) is one of the most common and deadly cancers. Treatment failure is still common among patients, despite PCa diagnosis and treatment improvements. Inadequate early diagnostic markers and the emergence of resistance to conventional therapeutic approaches, particularly androgen-deprivation therapy, are the causes of this. Long non-coding RNAs (lncRNAs), as an essential group of regulatory molecules, have been reported to be dysregulated through prostate tumorigenesis and hold great promise as diagnostic targets. Besides, lncRNAs regulate the malignant features of PCa cells, such as proliferation, invasion, metastasis, and drug resistance. These multifunctional RNA molecules interact with other molecular effectors like miRNAs and transcription factors to modulate various signaling pathways, including AR signaling. This study aimed to compile new knowledge regarding the role of lncRNA through prostate tumorigenesis in terms of their

Abbreviations: PC, prostate cancer; RT, radiotherapy; ADT, androgen-deprivation therapy; lncRNAs, long non-coding RNAs; miRNA, microRNA; ORF, open reading frame; lincRNAs, long intergenic non-coding RNAs; TSS, transcription start site; TFs, transcription factors; ceRNA, competitive endogenous RNA; CCAT1, colon cancer-associated transcript 1; AR, androgen receptor; DDX5, DEAD-box helicase 5; SND1, staphylococcal nuclease and tudor domain containing 1; SNHG, small nucleolar RNA host gene; TGF-β-R2, transforming growth factor-beta receptor type 2; SMAD, suppressor of Mothers against Decapentaplegic; TRIM25, tripartite motif 25; EMT, epithelial–mesenchymal transition; PTP4A3, protein-tyrosine Phosphatase 4 A3; WT, wild type; CHI3L1, chitinase-3-like protein 1; MALAT1, metastasis associated in lung adenocarcinoma transcript 1; DTX, docetaxel; ACSL4, Acyl-CoA synthetase long-chain family member 4; NEAT1, Nuclear Enriched Abundant Transcript 1; HMGA1, high mobility group box A1; UCA1, urothelial carcinoma associated 1; CXCR4, C-X-C motif chemokine receptor 4; SIRT1, Sirtuin 1; ATF2, activating transcription factor-2; Myo6, myosin VI; PCA3, prostate cancer gene 3; PDK3, protein kinase D3; Xist, X-inactive-specific transcript; RKIP, Raf Kinase Inhibitory Protein; CK1, Casein kinase 1; YAP, Yes-associated protein; βTrCP, β-transduction repeat-containing protein; CCND1, Cyclin D1; MDM2, Murine double minute 2; ZEB1, Zinc finger E-box binding homeobox 1; PAINT, prostate cancer-associated intergenic non-coding transcript; ERK1, extracellular signal-regulated kinases 1; PI3K, phosphatidylinositol-3-kinase; AKT, protein kinase B; PCNA, proliferating cell nuclear antigen; GAS5, Growth Arrest-Specific 5; SOCS2-AS1, suppressor of cytokine signaling 2-antisense transcript 1; TNFSF10, tumor necrosis factor superfamily member 10; PPARγ, peroxisome proliferator-activated receptor γ; HOTAIRM1, HOXA Transcript Antisense RNA, Myeloid-Specific 1; TLR3, toll-like receptor 3; mTOR, Mammalian target of rapamycin; AMPK, AMP-activated protein kinase; mTORC1, Mammalian target of rapamycin complex 1; UHRF1, Ubiquitin-like with plant homeodomain and ring finger domains 1; PLK1, Polo like kinase 1; CDC25C, C ell division cycle 25C; AURKA, Aurora kinase A; FOXM1, Forkhead Box M1; UBE2C, Ubiquitin-conjugating enzyme E2C; EGFR, epidermal growth factor receptor; CRPC, Castration-resistant PC; NEPC, Neuroendocrine prostate cancer; NED, neuroendocrine differentiation; EZH2, enhancer of zeste homolog 2; PHLPP, PH domain and Leucine-rich repeats Protein Phosphatases; FKBP51, FK506-binding protein 51; IKKα, inhibitor of nuclear factor kappa B; NF-κB, nuclear factor kappa B; ASOs, antisense oligonucleotides; CRISPRa, CRISPR activation; AAVs, Adeno-associated viruses.

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effects on the various malignant characteristics of PCa cells; in light of these characteristics and the significant potential of lncRNAs as diagnostic and therapeutic targets for PCa.
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1. Introduction

According to the GLOBOCAN estimating cancer prevalence, prostate cancer is considered the top male cancer in Western countries and the second most commonly occurring malignancy in males globally, with an estimated 1414,000 new malignancy cases and 375,304 mortality in 2020 [98,105]. The risk of PCa is predicted to elevate due to population aging and economic growth [105]. Diverse designed therapeutic methods, including surgical and non-surgical treatments such as radiotherapy (RT), androgen-deprivation therapy (ADT), prostatectomy, chemotherapy, ablative therapies, and immune-based therapies contribute to creating a suitable condition for remedying PCa patients [27]. Despite significant PC prognosis and treatment advancements, this malignancy still challenges the global healthcare system. Accumulating studies indicate solid attention to lncRNAs, as potential and novel diagnostic/therapeutic targets involved in developing and progressing different cancers [140].

Long non-coding RNAs (lncRNAs) are known as genetic material with more than 200 nucleotides that are transcribed without protein products but indicate diverse regulatory biological functions [85]. LncRNAs interact mainly with DNA, mRNA, miRNA, and protein, subsequently modulating the gene expression at the transcriptional, post-transcriptional, translational, and post-translational levels by different mechanisms [145]. Also, several lncRNAs have been functionally related to human diseases, especially many types of cancer. Dysregulated lncRNAs have been implicated in breast, glioblastoma, liver, colorectal, and leukemia. Generally, dysregulated lncRNAs act on cellular processes such as cellular proliferation, angiogenesis, metastasis ability, and immune evasion [30]. Therefore, the specific expression patterns of lncRNAs can be considered potential cancer biomarkers and highlight approaches for cancer treatment.

2. Characteristics and functions of lncRNAs

LncRNAs are well-known as heterogeneous non-coding RNAs (ncRNAs) with lengths more than 200 nt. This distinction helps to separate lncRNAs from miRNAs and other sRNAs [30]. LncRNAs lack protein-coding activity, but it is found that several lncRNAs include Open reading frames (ORFs) or short open reading frames, which can encode some small proteins [42]. Like mRNA, canonical lncRNA transcription or biogenesis requires RNA polymerase II (Pol II) [21] and undergoes post-transcriptional modifications, such as alternative splicing, 5′ capping, poly-A tail addition, and RNA editing. Some lncRNAs may also carry single nucleotide polymorphisms (SNPs) that regulate their expression and activity. Only 11–29% of lncRNAs in all tissues show expression patterns at the very minutest levels compared with protein-coding mRNAs [18].

From different genomic locations, various types of lncRNAs are transcribed; based on their transcriptional-derived site, lncRNAs are divided into four groups [16]. The largest group of lncRNAs is the long intergenic non-coding RNAs (lincRNAs) that indicate not overlapping or lying near protein-coding genes [39]. Antisense lncRNA, the second most widespread type of lncRNA, is transcribed from the opposing DNA or the antisense strand, indicating overlap with the coding strand [28]. The third type of lncRNAs includes the sense lncRNA transcripts and sense overlapping or sense intronic lncRNAs. These transcripts are located on the same strand as protein protein-coding genes and transcribed in the same direction. Bidirectional lncRNAs or divergent lncRNAs are the fourth type of lncRNAs. The mentioned transcripts are placed on the antisense strand and contain a transcription start site (TSS) adjacent to the TSS of the protein-coding gene with a transcription in the reverse direction [10]. Also, lncRNAs contain few but longer exons than protein-coding RNAs [41]. Some lncRNAs include vital conserved promoter regions between vertebrates, poorly conserved lncRNA exons between species, distinctive DNA-binding motifs in their promoters, and preferred transcription factors (TFs) [96]. LncRNAs also display cell or tissue type-specific expression and a different localization in subcellular patterns, numerous being mainly nuclear [11]. The subcellular distribution of lncRNAs is a determinative factor for their regulatory and biological activities. According to obtained data, there are nuclear, cytoplasmic, and mixed localization patterns of lncRNAs. A deep understanding of the localization of lncRNA can help choose effective methods for manipulating lncRNA levels in lncRNA-based therapeutic strategies [7]. Overall, the regulatory role of nuclear lncRNAs is related to the modulation of gene expression at the epigenetic and transcriptional level in *cis* or *trans* by different molecular mechanisms, counting signals, guides, decoys, scaffolds, and enhancers [76].

LncRNAs may function as effectors of signaling pathways that modulate transcriptional processes or the expression of various genes. Also, lncRNAs as decoys bind to regulatory proteins or transcription factors and translocate these molecules to DNA binding sites. Some lncRNA has a guiding role and employs or delocalizes modulation factors to stimulate or inhibit the expression of genes through either cis or trans mechanisms. Also, as scaffolds to other components, lncRNAs may be adaptors that transport binding partner proteins inside near other elements to help develop ribonucleoprotein complexes that contribute to maintaining genomic stability [84]. On the other hand, lncRNAs stabilize mRNA expression and translation in the cytoplasm. One of the main methods by which lncRNAs perform this activity is functioning as a competitive endogenous RNA (ceRNA) [115], which can lead to microRNA (miRNA) dysfunction via sequestration, thus suppressing the inhibitory effect of miRNAs and their mRNA targets [91] and modulating broad-ranging biological activities [71].

3. Correlation between lncRNAs and their counterpart miRNAs involved in PC tumorigenesis

miRNAs, as short non-coding RNAs, can modulate the expression of different genes primarily through binding to 3/-UTR at mRNA and protein levels [49]. In addition to the regulatory role of miRNAs, some upstream regulators also regulate the expression and activity of miRNAs via sponging and subsequently modulating the expression of their target mRNAs [156]. Growing evidence illustrated the deregulated expression of miRNA in PCa and its connection with malignant features of tumor cells. Tumor-promoting lncRNAs and tumor-suppressor lncRNAs also modulate miRNA expression through PCa initiation and development [78]. Then, in the following sections, we will characterize some of these interactions considering their oncogenic and tumor-suppressive function through PCa development and progression.

3.1. Oncogenic lncRNAs modulate the expression of miRNAs

As a tumor-promoting factor, lncRNA CCAT1 (colon cancer-associated transcript 1) has a critical role in many types of cancer. CCAT1 induces endometrial cancer proliferation, whereas it decreases the estrogen receptor-alpha (ERα) expression levels and the activity of its downstream molecular signaling [101]. Also, the regulatory effect of lncRNA CCAT1 on the expression of miRNAs in diverse malignancies has been illustrated [92]. For example, CCAT1 upregulation is correlated with the high mortality rate of castration-resistant patients to stimulate

PCa proliferation and progression. So, CCAT1 interacts with miRNA-28–5p tumor-suppressor in the cytoplasm and facilitates PCa progression in vitro and in vivo. Besides, it functions as a scaffold that promotes the formation of DEAD-box helicase 5 (DDX5) and androgen receptor (AR) transcriptional complex, modulating the expression of their target genes. AR signaling is a driver signaling pathway involved in the growth and metastasis of nearly all PCa cells. Subsequently, therapeutic approaches targeting this pathway, such as ADT, are widely used for PCa [133].

lncRNA LINC00665 is another emerging tumor-promoting factor in human cancers, indicating a crucial function in modulating numerous molecular pathways and responsible for reduced overall survival of PCa patients [25]. LINC00665 holds great promise as a target for diagnosing and treating PCa. A previous study indicated that LINC00665 increased the proliferation and metastasis of PCa cells by sponging miRNA-1224–5p and following overexpression of the Staphylococcal nuclease and tudor domain containing 1 (SND1) oncogene. The upregulated SND1 contributes to PCa progression, and miRNA-1224–5p, as a tumor-suppressor, suppresses SND1 expression [13]. Besides, the upregulated lncRNA small nucleolar RNA host gene 16 (SNHG16) has an important function in the proliferation, migration, and invasion of PCa cells. SNHG16 exerts its oncogenic effects by targeting miR-373–3p. The suppression of miR-373–3p could rescue the inhibition of cellular activities of SNHG16 knockdown through stimulating transforming growth factor-beta receptor type 2 (TGF-β-R2)/ (Suppressor of Mothers against Decapentaplegic) SMAD signaling. Also, TGF-β-R2 was illustrated to be targeted via miR-373–3p, leading to repression of cellular proliferation and migration ability. In other words, SNHG16 stimulates the cellular proliferation and migration ability of PCa cells by modulating the miR 373 3p/TGF β R2/SMAD axis [114]. Another tumor-promoting lncRNA involved in PCa progression is SNHG3 showing a correlation with poor prognosis of patients. Following SNHG3 suppression, cellular proliferation, migration, and invasion were considerably repressed in vitro in PCa cells. miR-1827, as downstream target of SNHG3, has the direct interaction with SNHG3. It is indicated that transfection with miR-1827 inhibitor overturned the effects of SNHG3 suppression on cell proliferation, invasion, and migration. Therefore, SNHG3 was suggested to promote PCa progression by sponging miR-1827, demonstrating SNHG3's potential as a diagnostic and therapeutic target for PCa [50]. Also, SNHG3 blocks miR-487a-3p, which leads to increased cellular viability, migration, and invasion, aligned with Snail and N-cadherin upregulation, and prevented E-cadherin expression in LNCaP cells.

The inhibitory impacts of miR-487a-3p mimic on invasion, migration, and EMT of LNCaP cells were inverted via either SNHG3 or tripartite motif 25 (TRIM25) plasmids. Also, the effect of miR-487a-3p inhibitor was inversed by TRIM25 siRNA and SNHG3 siRNA in PC-3 cells. Then, SNHG3 modulates PCa progression through sponging miR-487a-3p and following upregulation of TRIM25 [134]. LncRNA KCNQ1OT1, as another oncogenic lncRNA, has been shown to possess a binding site for miR-15a tumor-suppressor. Then, KCNQ1OT1 was suggested to sponge miR-15a and rescue the suppressive effect of miR-15a on PD-L1. The highly expressed level of PD-L1 stimulates proliferation, EMT, invasion, angiogenesis, and tumor stemness in PCa. Subsequently, lncRNA KCNQ1OT1 overexpression promoted immune evasion and malignant features of PCa cells through overexpressing PD-L1 immune checkpoint [12]. Also, another study evidenced that the suppression of KCNQ1OT1 blocked cellular invasion and migration and led to changes in levels of epithelial–mesenchymal transition (EMT) markers and essential modulators of TGF-β signaling, which all were reestablished via transfection of PCa cells using Protein-tyrosine Phosphatase 4A3 (PTP4A3)-wild type (WT) plasmid or anti-miR-137–3p. PTP4A3 could induce EMT by TGF-β signaling cascade through prostate tumorigenesis. Hence, it was illustrated that migratory and invasive features of PCa cells are promoted via the KCNQ1OT1/-miR-137–3p/PTP4A3 axis [111]. Also, miR-211–5p is another tumor-suppressor miRNA targeted by KCNQ1OT1, which binds to Chitinase-3-like protein 1 (CHI3L1) 3′-UTR and suppresses its expression. In PCa patients, the expression of miR-211–5p was shown to be low-expressed, while CHI3L1 (YKL-40) was highly expressed. The suppressed YKL-40 is induced via the deactivation of KCNQ1OT1 expression that may be offset via miR-211–5p inhibitor transfection in PCa cells. Consequently, KCNQ1OT1 lncRNA, as a ceRNA, increased the expression of CHI3L1 and PCa progression via competitive binding to miR-211–5p [40]. Another example is related to lncRNA PlncRNA-1, which is overexpressed in PCa and modulated via AR. The upregulation of PlncRNA-1 promotes PCa cellular proliferation and EMT and inhibits cell apoptosis [55]. Mechanically, PlncRNA-1 acts as ceRNA to sponge AR-modulating miRNAs, including miR-297 and miR-34c, in vitro and in vivo [31].

In PCa, lncRNA MALAT1 also displays overexpressed levels during cancer development, positively correlated with higher prostate-specific antigen, tumor stage, and Gleason score [90]. The suppressed MALAT1 dampened cell proliferation, EMT, migration, and invasion and stimulated cellular apoptosis, even in xenografts models in PCa [83]. Also, the overexpression of metastasis-associated with lung adenocarcinoma transcript 1 (MALAT1) is reported in Docetaxel (DTX)-resistant PCa patient tumors and (DTX)-resistant AR-negative DU-145 and PC3 cells. Functionally, MALAT1 was indicated to sponge miR-145–5p and consequently increase AKAP12 expression, a direct target of miR-145–5p. The upregulated miR-145–5p and silenced AKAP12 suppressed the oncogenic effects of MALAT1 on tumorigenesis and DTX resistance in PCa cells [125]. The expression level of another lncRNA with tumor-promoting activity, Nuclear Enriched Abundant Transcript 1 (NEAT1), was also reported to increase cell proliferation, migration, and invasion, inhibit cellular apoptosis, and arrest cell cycle progression. NEAT1 downregulates miR-766–5p expression through ceRNA activity leading to malignant features in PCa cells, whereas the overexpressed miRNA-766–5p hampers the malignant features of PCa cells. miRNA-766–5p was also illustrated to target E2F3 directly and to be modulated by NEAT1 expression. Then, NEAT1 contributes to PCa progression by modulating miRNA-766–5p and E2F3 expression [149]. Also, NEAT1 was reported to be considerably enhanced in PCa tumor and DTX-resistant cells. Increased drug resistance associated with NEAT1 is a consequence of the upregulation of Acyl-CoA synthetase long-chain family member 4 (ACSL4), high mobility group A1 (HMGA1), and RET through binding to associated miRNAs, including miR-34a-5p, miR-98–5p, and miR-204–5p [38,53].

Urothelial carcinoma associated 1 (UCA1), as another oncogenic lncRNA, is positively linked with advanced TNM stage, Gleason score, and PCa patients' poor survival [35,141]. LncRNA UCA1 increases oncogenic factors, including C-X-C motif chemokine receptor 4 (CXCR4), Sirtuin 1 (SIRT1), and Activating transcription factor-2 (ATF2), by sponging miR-204. The suppressed UCA1 prevented cellular proliferation, invasion, migration and increased in vivo and in vitro sensitivity to chemotherapy [44,108,141]. Besides, UCA1 sponges miR-143 as an anti-proliferative miRNA, leading to upregulating myosin VI (Myo6) expression and other oncogenes in PCa [136]. Also, UCA1 directly interacts with miR-184 and acts as a sponge for this miRNA, affecting apoptosis and metastasis in PCa cells [157]. The dysregulation of lncRNA TUG1 has been stated to exert both tumor-suppressor and oncogenic activity that depends on several factors [34]. TUG1 is another lncRNA upregulated in PCa tissues that correlate with poor patient survival and prognosis [123,129]. It is indicated that TUG1 stimulates PCa cell proliferation, EMT, invasion, and migration through sponging and downregulating miR-496 and miR-26a. The silenced TUG1 blocked tumor growth in DU145 xenograft. It boosted radio-sensitivity in vivo through the overexpression of miR-496 and blockage of the Wnt/b-catenin pathway mediated by β-catenin inhibition and down-regulation of c-myc and cyclin D1 [59,126]. Prostate cancer gene 3 (PCA3) or DD3, as PCa-highly specific lncRNA and a diagnostic biomarker of PCa, is reported to activate AR signaling, promoting PCa

cells' survival [57]. PCA3 also has a suppressive effect on miR-1261 expression through ceRNA activity. miR-1261 inactivates Protein kinase D3 (PRKD3 or PKD3) expression and inhibits PCa invasion and migration. Silencing of PCA3 promotes the expression of miRNA-1261, which in turn targets the PRKD3 gene and efficiently suppresses in vitro PCa progression by inducing autophagy [45]. It has also been recognized miR-218–5p has a binding site inside the PCA3 sequence. The silenced PCA3 increased apoptosis and prevented cellular proliferation and migration, induction of miR-218–5p expression containing malignant properties through blocking HMGB1. Thus, lncRNA PCA3 contributes to PCa progression by sponging miR-218–5p and modulating HMGB1 [139]. Table 1 represents further interactions between lncRNAs and miRNAs through prostate tumorigenesis.

3.2. Tumor-suppressors lncRNAs interact with miRNAs in prostate cancer

Growing evidence indicates that various lncRNAs act as oncogenic genes in the initiation and progression of malignancies via the modulation of miRNAs. Against the oncogenic functions of lncRNA, several lncRNAs act as tumor-suppressors to prevent viability and migration, induce apoptosis, and maintain genomic stability by modulating the activity of miRNAs [95].

It has been stated that lncRNA X-inactive-specific transcript (Xist) modulates the malignant properties of various cancers. XIST was low expressed in human PCa and was associated with poor prognosis in patients with PCa. XIST inhibited cell proliferation and metastasis in PCa both in vitro and in vivo. MiR-23a was found as a direct target of XIST. It negatively regulates the expression of miR-23a, promoting Raf Kinase Inhibitory Protein (RKIP) expression. The upregulated miR-23a strongly abolished the up-regulation of RKIP prompted via XIST, indicating that XIST positively modulates the expression of RKIP through competitively binding to miR-23a [24]. Also, MAGI2-AS3 is considered a novel negative modulator and one of the most low-expressed lncRNAs in PCa. It is indicated that the upregulated MAGI2-AS3 reduced cell viability and induced cell apoptosis in PC-3 and DU145 PCa cells. Also, the elevated MAGI2-AS3 diminished the activity of STAT3 in these cells. MiR-424–5p, a positive modulator of the STAT3 pathway, was found as a target of MAGI2-AS3. Therefore, MAGI2-AS3 deactivates the STAT3 signaling pathway to prevent PCa cellular proliferation by acting as a miRNA-424–5p sponge [113]. As another tumor-suppressor, lncRNA, MIR22HG is downregulated in PCa cells. The overexpressed MIR22HG repressed cellular proliferation stimulated cellular apoptosis, decreased Bcl-2 and Ki67 expressions, and increased cleaved caspase 3 and Bax expressions. Besides, MIR22HG was recognized as a sponge of miR-9–3p, and the effects of the upregulated MIR22HG on cellular proliferation and apoptosis were partly prevented via miR-9–3p upregulation. In short, MIR22HG functions as an anti-tumor gene in PCa by hindering cellular proliferation and stimulating apoptosis by sponging miR-9–3p [143]. Also, it evaluated the function and potential mechanism of RP1–59D14.5 in PCa. The down-regulation of RP1–59D14.5 was indicated in PCa cells. The elevated RP1–59D14.5 decreased cellular proliferation, migration, and invasion and induced autophagy in PCa cells. It is validated that RP1–59D14.5 acted as a ceRNA to modulate large tumor-suppressor kinase 1/2 (LATS1/2) by targeting miR-147a. Furthermore, RP1–59D14.5 employed HUR to stimulate casein kinase 1 (CK1) expression. Together, RP1–59D14.5 promoted the degradation of the yes-associated protein (YAP) to trigger the Hippo pathway in PCa progression by targeting the miR-147a/LATS1/2 axis and employing HUR to help the interaction of CK1 and β-transduction repeat-containing protein (βTrCP). Therefore, RP1–59D14.5 can be a tumor-suppressor and a key target in PCa [154].

Furthermore, the depletion of LINC01679 as a tumor-suppressor increased cellular proliferation and metastasis and prevented apoptosis in vivo and in vitro. LINC01679 sponges miR-3150a-3p, and the elevated miR-3150a-3p was correlated to the promoted proliferation and reduced apoptosis of PCa cells [77]. Also, ADAMTS9-AS1 can have a

Table 1
Interactions between oncogenic lncRNAs and miRNAs.

LncRNA	target miRNA	Expression pattern	Effects	Ref
DANCR	miR-33b-5p	Upregulated	Chemoresistance	[110]
MYCNOS	miR-466	Upregulated	Proliferation	[9]
PBC11	hsa-miR-137	Upregulated	EMT	[15]
LINC00184	miR-105–5p	Upregulated	Drug-resistance Immune escape	[144]
MNX1-AS1	miR-2113	Upregulated	Viability Migration Invasion	[63]
LINC01963	miR-216b-5p	Upregulated	Chemosensitivity Metastasis	[122]
PCAT1	miR-25–3p	Upregulated	Drug resistance	[52]
LINC01207	miR-1182	Upregulated	Proliferation Colony formation Apoptosis	[88]
PCGEM1	miR-129–5p	Upregulated	Viability Apoptosis Cell cycle	[32]
FOXD1-AS1	miR-3167	Upregulated	Viability, Proliferation Migration Invasion Apoptosis	[89]
AC245100.4	miR-145–5p	Upregulated	Proliferation Migration	[119]
CCAT1	miR-490–3p	Upregulated	Proliferation Apoptosis Migration Invasion	[4]
AATBC	miR-1245b-5p	Upregulated	Growth	[142]
SNHG11	miR-184	Upregulated	Proliferation Migration Invasion	[121]
FAM83H-AS1	miR-15a	Upregulated	Proliferation, Cell cycle, Migration	[65]
AFAP1-AS1	miR-15b	Upregulated	Proliferation Invasion	[64]
PCGEM1	miR-506–3p	Upregulated	Proliferation Migration Invasion	[67]
SNHG1	miR-383–5p	Upregulated	Proliferation Apoptosis Migration Invasion	[48]
DANCR	miR-214–5p	Upregulated	Proliferation Apoptosis Migration	[17]
LINC00115	miR-212–5p	Upregulated	Proliferation Invasion	[86]
Linc00963	miR-655	Upregulated	Proliferation Colony formation	[2]
LINC01116	miR-744–5p	Upregulated	Proliferation Migration Invasion EMT	[135]
DLX6-AS1	miR-497–5p	Upregulated	Proliferation Apoptosis	[159]
OGFRP1	miR-149–5p	Upregulated	Chemoresistance	[102]
CASC11	miR-145	Upregulated	Proliferation Colony Migration	[6]
SNHG8	miR-384	Upregulated	Proliferation Migration Invasion	[94]
OIP5-AS1	miR-128–3p	Upregulated	Cell growth Ferroptosis	[146]
LINC01213	miR-597–3p	Upregulated	Viability Proliferation	[151]

(continued on next page)

Table 1 (*continued*)

LncRNA	target miRNA	Expression pattern	Effects	Ref
RHPN1-AS1	miR-7–5p	Upregulated	Proliferation Cell cycle Apoptosis Autophagy Invasion	[74]

critical role in cancer development. The expression of ADAMTS9-AS1 is down-regulated in PCa. Increasing ADAMTS9-AS1 expression hinders PCa cellular proliferation by inducing cellular apoptosis. Outstandingly, miR-142–5p mimic and small-interfering RNA targeting cyclin D1 (CCND1, si-CCND1) can decrease the blockage impacts of ADAMTS9-AS1 upregulation on PCa cell proliferation. In summary, ADAMTS9-AS1 reduces PCa progression by modulating the miR-142–5p/CCND1 axis, which provides a novel therapeutic strategy for PCa patients [158]. Further, PCa-related interactions between tumor-suppressor lncRNAs and miRNAs are shown in Table 2.

4. EMT-related lncRNAs in prostate cancer

EMT is considered a vital originating factor driving this procedure for metastatic cancer and shows a key role, which confers metastatic features on cancer cells by inducing mobility and invasion [81]. EMT is a reversible procedure accompanied by the depletion of cell polarity and intercellular adhesion of stable epithelial cells. Also, the morphology of cells transforms from epithelial into spindle-shaped mesenchymal cells and gains migration capacity [56]. During the development of EMT, the level of numerous epithelial cell biomarkers reduces, for example, E-cadherin, cytokeratin, and laminin, which results in the damage of cell-to-cell adhesion. On the contrary, mesenchymal biomarkers containing N-cadherin, β-catenin, Vimentin, and Snail protein, are overexpressed; as a result, the cells migrate or metastasize to several organs [82]. UCA1, a tumor-promoting lncRNA, is critical in many human malignancies through increasing cellular proliferation and migration. Also, a new and different biological function of UCA1 is reported. Uniquely, it is responsible for preserving the low-tumorigenic, non-metastatic activities in primary prostate epithelial cells. Functionally, UCA1 can help stabilize E-cadherin's protein expression by preventing its interaction with E3 ligase murine double minute 2 (MDM2), inhibiting ubiquitination-mediated E-cadherin degradation by the proteasome. UCA1 indicated a novel essential function in efficiently maintaining high expression of E-cadherin via a dual molecular mechanism, which resulted in the suppression of tumorigenesis and metastasis in primary prostate cancer cells [150].

Table 2
Interactions between tumor-suppressor lncRNAs and miRNAs.

LncRNA	Target miRNA	Expression pattern	Effects	Ref
FGF14-AS2	miR-96–5p	Downregulated	Tumor growth Metastasis	[60]
LINC00641	miR-365a-3p	Downregulated	Growth Invasion	[70]
MAGI2-AS3	miR-142–3p	Downregulated	Proliferation Migration Invasion	[47]
MBNL1-AS1	miR-181a-5p	Downregulated	Proliferation Migration Invasion	[20]
PGM5-AS1	miR-587	Downregulated	Proliferation Apoptosis	[22]
CASC2	miR-183	Downregulated	Proliferation Apoptosis Drug sensitivity	[33]
FER1L4	miR-92a-3p	Downregulated	Proliferation Apoptosis	[51]
MEG3	miR-9–5p	Downregulated	Apoptosis Proliferation Migration Invasion	[118]
HCG11	miR-543	Downregulated	Apoptosis Proliferation Migration Invasion	[112]

As another lncRNA involved in EMT, lncRNA CHRF stimulated EMT, indicating E-cadherin down-regulation and the overexpression of N-cadherin, Vimentin, and Zinc finger E-box binding homeobox 1 (ZEB1) [68]. Besides, SNHG1 is an oncogenic lncRNA and indicates a biological function in the development and progression of PCa. Functionally, the elevated SNHG1 induced PCa cells EMT, accompanied by low-expression of the epithelial biomarker, E-cadherin, and the overexpression of mesenchymal biomarker, Vimentin. In a mechanistic view, SNHG1 competitively interrelates with hnRNPL to damage the E-cadherin translation, resulting in EMT processes and stimulating PCa cell metastasis [99]. It has been evidenced that PlncRNA-1 and TGF-β1 expression levels were considerably upregulated in PCa tissues. N-cadherin, TGF-β1, and Cyclin-D1 were low-expressed, and E-Cadherin was overexpressed in LNCAP cells after blocking PlncRNA-1. PlncRNA-1 can modulate PCa cell growth and EMT functionally via TGF-β1 signaling [54]. The CCAT2 expression was upregulated in PCa cells and tissues and indicated poorer overall survival. The reduced expression of CCAT2 could cause PCa cell growth, invasion, and migration in vitro. Furthermore, the suppression of CCAT2-induced EMT by abolishing the expression of N-cadherin and Vimentin and increasing E-cadherin expression [152]. LncRNA PVT1 stimulates PCa metastasis and invasion by regulating EMT. It sponges miRNA-186–5p to induce EMT by enhancing the expression of Twist1 as a transcription factor related to EMT [8].

The upregulated expression of prostate cancer-associated intergenic non-coding transcript (PAINT) was illustrated in the metastatic form of PCa and the advanced stage of the malignancy. Silencing PAINT reduced migration ability and Slug and Vimentin expression. In contrast, Ectopic expression of PAINT repressed E-cadherin and increased higher expression of mesenchymal markers [43]. LncRNA HULC expression was elevated in PCa and positively correlated to the advanced stage of PCa patients. HULC blockage inhibited PCa cell growth and metastasis by reducing Vimentin and N-cadherin expression and increasing E-cadherin levels [153]. LncRNA-ATB expression was remarkably increased in patients with PCa. LncRNA-ATB triggered EMT related to ZNF217 and ZEB1 levels by activating phosphatidylinositol-3-kinase (PI3K)/ protein kinase B (AKT) and extracellular signal-regulated kinases 1 (ERK) pathways [124]. For example, it is reported that patients with high expression levels of SSTR5-AS1 presented poorer survival. Functionally, SSTR5-AS1 induction stimulated the PCa cells' proliferation, migration, and invasion. At the molecular level, silencing SSTR5-AS1 prevented the protein levels of N-cadherin, PCNA, and Vimentin and upregulated E-cadherin expression in PC-3 cells [137]. LncRNA VIM-AS1, as an oncogene, increased migration and invasion, and cell growth in PCa cells. Also, VIM-AS1 provoked vimentin expression, which induced EMT in these cells [147]. UBE2R2-AS1 exerts an oncogene modulator in PCa tissues. UBE2R2-AS1 suppressing prevented proliferation, migration, and invasion, triggered cell cycle G0/G1 arrest and apoptosis in PCa cells, accompanied by reduced expression of N-cadherin, Vimentin, Proliferating cell nuclear antigen (PCNA), CDK4, Bcl-2, Cyclin D1, and increased E-cadherin expression [104]. It is found the differentially expressed lncRNA AC245100.4 that promoted the migration of PCa cells by modulating PAR2. The AC245100.4 or PAR2 suppression led to a reduction in Vimentin but an increase in E-cadherin protein levels [66]. The reported LINC01296-expression level was higher in PCa tissues and cells and correlated with lymph node metastasis. *In vitro* biological evaluation has further verified that LINC01296 reduction inhibited PCa proliferation, migration, and invasion, involving the modulation of the PI3K-Akt-mTOR signaling pathway and EMT [117]. Another study presented that the lncRNA DUXAP10 was

upregulated in PC3 and DU145 cell lines. It could stimulate PCa progression by modulating the process of EMT [109].

Fig. 1 represents lncRNAs involved in various aspects of prostate tumorigenesis, including the EMT process.

4.1. LncRNAs regulate cell death in prostate cancers

Apoptosis is a central mode of "programmed" cell death that contains two pathways: intrinsic and extrinsic. The process of programmed cell death is strongly modulated via molecular pathways, and based on the function of lncRNAs as tumor-promoting or tumor-suppressor factors, they can prompt or prevent apoptosis activity in malignant tumors. Bcl-2, Bax, and Caspase cascades are the most vital factors associated with apoptosis ability in tumor cells [26]. As the first research of a death-stimulating lncRNA in PCa cells, Growth Arrest-Specific 5 (GAS5) encodes many snoRNAs inside its introns. Still, exonic sequences have lncRNA production, functioning as the glucocorticoid riborepressor and correlated receptors. GAS5 is abnormally expressed in numerous malignancies, especially PCa. It is reported that cell death was tightly related to cellular GAS5 levels. So, after transfection of 22Rv1 cells with plasmids encoding GAS5 transcripts, basal apoptosis improved, and cell survival was reduced. Therefore, GAS5 stimulates the apoptosis of PCa cells, and exonic sequence, i.e., GAS5 lncRNA, is adequate to intermediate this process [87].

It is recognized lncRNAs prompted via androgen in AR-positive PCa cells. The suppressor of cytokine signaling 2-antisense transcript 1 (SOCS2-AS1), an androgen-regulated lncRNA, was upregulated in castration-resistant PCa model cells. SOCS2-AS1 increased androgen-dependent cell growth and was castration-resistant. Functionally, the silenced SOCS2-AS1 induced gene expression in the apoptosis pathway, such as tumor necrosis factor superfamily member 10 (TNFSF10), and increased docetaxel chemosensitivity of PCa cells. SOCS2-AS1 is vital in castration-resistant PCa progression by inhibiting apoptosis [79]. MEG3, another example of lncRNA involved in apoptosis, indicates significantly low expression in PCa tissues. MEG3 repressed intrinsic cellular survival by decreasing the protein expression of Bcl-2, increasing Bax, and stimulating Caspase 3 in vitro and in vivo [72]. The expression of POTEF-AS1, an androgen-dependent lncRNA, was controlled via an androgen receptor. It is reported that POTEF-AS1 stimulated cellular growth, suppressed genes associated with the Toll-like receptor signal and apoptosis pathways, and blocked apoptosis in docetaxel-treated LNCaP cells [80]. Also, it is revealed that lncRNA PVT1's oncogenic role in PCa can notably stimulate PCa growth and inhibit cellular apoptosis. PVT1 reduction also significantly increased apoptosis and cleaved Caspase-3 and Cleaved caspase-9 expression levels but decreased the expression of c-Myc [127]. An overexpressed and prognosis-associated lncRNA, PART1, induced PCa cell proliferation and inhibited cellular apoptosis. Furthermore, PART1 regulated downstream gene expression in TLR pathways containing TNFSF10, Toll-like receptor 3 (TLR3), and CXCL13 to affect PCa cells further, signifying its carcinogenesis on PCa. PART1 stimulated proliferation ability and decreased apoptosis via the presentation of TLR pathways in PCa [97]. It is indicated the role of oncogenic lncRNA PRRT3-AS1 on the PCa progression with the involvement of peroxisome proliferator-activated receptor γ (PPARγ) as a target gene of this lncRNA. The silenced PRRT3-AS1 can induce apoptosis activity and autophagy, hindering proliferation, migration, and invasion of PCa cells by activating PPARγ and blocking the mammalian target of rapamycin (mTOR) signaling pathway [29]. Research about other lncRNAs illustrated that lncRNA GASL1 was considerably low-expressed in patients' PCa tissue and serum. The upregulated GASL1 withdrew PCa cell growth and intensified the expression of Bcl-2 and downregulated GLUT-1 expression that involved cell proliferation [62]. Recent research has revealed that HOXA Transcript Antisense RNA, Myeloid-Specific 1 (HOTAIRM1), was upregulated in PC3 cells. Silencing HOTAIRM1 alleviated PC3 cell proliferation and amplified apoptosis so that the pro-apoptotic agents'

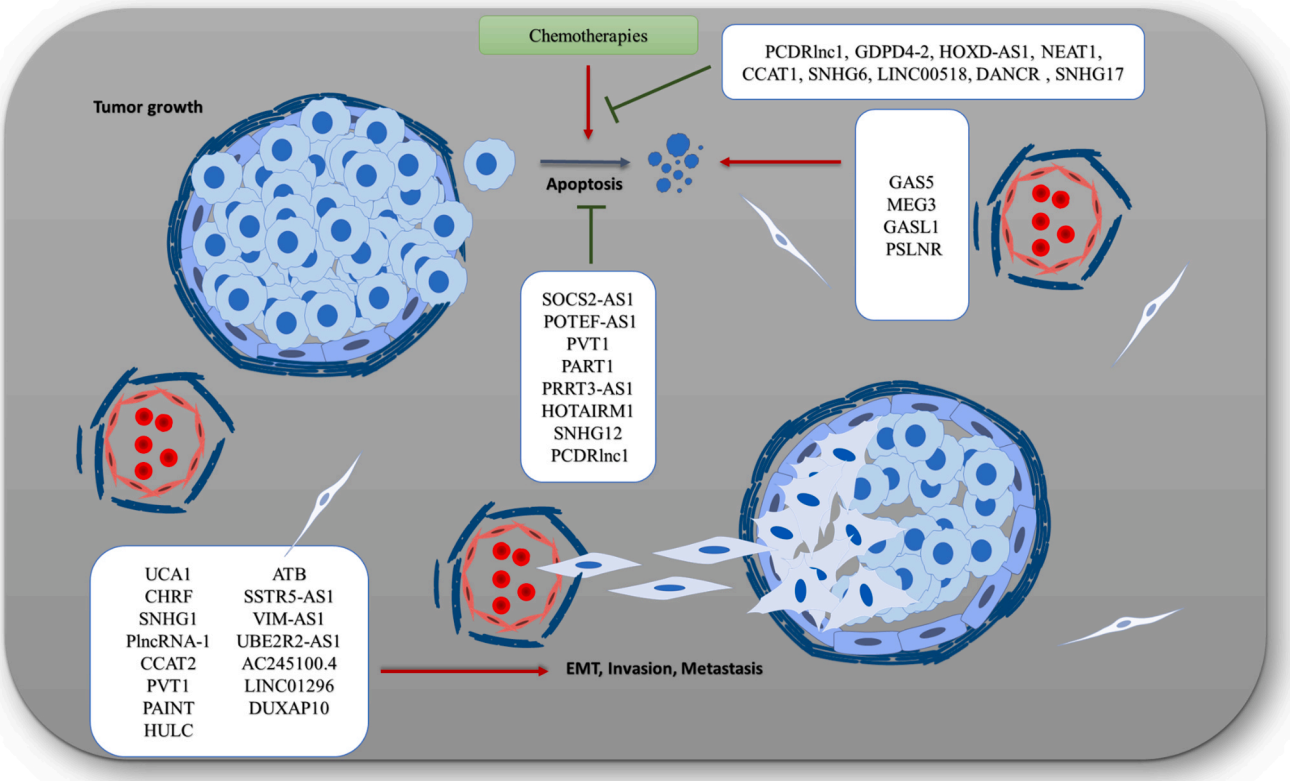

Fig. 1. LncRNAs are involved in PC pathogenesis by affecting EMT, Invasion, Metastasis, Tumor growth, apoptosis, and chemoresistance.

expression, for example, Bax and Bad was notably induced. Still, the expression of Bid and Bcl-2 as anti-apoptotic factors were reduced [106]. Also, PSLNR, a tumor-suppressor, remarkably decreased PCa proliferation by prompting cellular apoptosis in a p53-dependent way [103].

Along with apoptosis, viability, and survival of tumor cells mainly depend on autophagy as another form of programmed cell death. Autophagy is well-known; the development of autophagosomes accompanies a highly conserved self-degradative process as a double-membrane vesicle. The enclosed portions of cytosol and organelles into autophagosomes are transported into the vacuole/lysosome, a degradative organelle, for breakdown and subsequent recycling of the resulting macromolecules. This way rescues the cell from many stress conditions. Therefore, autophagy is critical during cell developmental processes and acts in tumor blockage [130]. It is reported that autophagy is controlled via numerous molecular pathways such as AMP-activated protein kinase (AMPK), Beclin-1, mTOR, and ATGs. It functions like a double-edged sword in cancer and indicates pro-survival and pro-death roles, so both have roles in a single malignancy [26]. The mammalian target of rapamycin complex 1 (mTORC1) and AMPK are two main proteins that distinguish external stimuli for the initiation of autophagy [128]. Among many identified new molecular modulators in autophagy regulation, lncRNA affects the autophagy mechanism in tumors via various signaling pathways. SNHG12 was highly expressed in the serum of PCa cells and patients as a lncRNA involved in autophagy.

Moreover, silencing of SNHG12 prevented viability and stimulated apoptosis and autophagy in LNCaP cells. Stimulating the PI3K/AKT/mTOR pathway is a crucial downstream mechanism modulating SNHG12-mediated PCa progression [107]. The upregulated PCDRlnc1 stimulated autophagy. Functionally, PCDRlnc1 interacted with UHRF1 (ubiquitin-like with plant homeodomain and ring finger domains 1) and increased its transcription level in PCa cells, enabling the autophagic Beclin-1 signal [120]. For another example, lncRNA GDPD4–2 is engaged in PCa treatment via Astragaloside IV-PESV. The silenced GDPD4–2 inverted the therapeutic impacts of Astragaloside IV-PESV by modulating the PI3K/AKT/mTOR pathway. Functionally, GDPD4–2 suppression decreased Beclin1 and LC3 expression and increased P62 protein levels in LNCaP cells. These findings demonstrated that this drug prevents PCa development by modulating GDPD4–2 and autophagy [132].

5. LncRNAs involved in PCa cells' resistance to treatments

Multi-Drug Resistance (MDR) is cancer therapy's critical main problem. It is defined as the innate and/or acquired ability of cancer cells to avoid the impacts of chemotherapeutics [1]. In innate drug resistance, tumor cells overexpress the expression level of tumor-promoting genes after administration of chemotherapeutic agents, decreasing tumor-suppressor genes to increase proliferation and cell cycle progression and inhibit apoptosis. They also acquired drug resistance from genetic instabilities and evolutionary mechanisms. Overall, the epigenetic modifications, drug efflux pumps, interactions, and bypass signaling pathways in the tumor microenvironment may lead to chemoresistance development [155]. The investigations indicate the function of lncRNA in the chemoresistance development in various cancers, especially PCa, so the impact of lncRNA in drug resistance can be different based on the function of lncRNAs and their targets [19]. As one of the lncRNAs involved in drug resistance, lncRNA HOXD-AS1 is upregulated in CRPC cells and closely correlates with lymph node metastasis and progression-free survival. *In vitro* and in vivo, the downregulated HOXD-AS1 prevented the proliferation and drug resistance of CRPC cells. Also, some cell cycle, drug resistance, and castration-resistance-associated genes, such as polo-like kinase 1 (PLK1), cell division cycle 25 C (CDC25C), Aurora kinase A (AURKA), Forkhead Box M1 (FOXM1), and Ubiquitin-conjugating enzyme E2C (UBE2C), were identified and stimulated transcriptionally via HOXD-AS1. It is recognized that HOXD-AS1 employed WDR5 to modulate the target genes' expression directly. Overall, HOXD-AS1 stimulates proliferation, chemoresistance, and castration resistance in PCa through recruiting WDR5 [37]. Another study revealed that lncRNA LOXL1-AS1 and EGFR were at a low expression, while miR-let-7a-5p was overexpressed in doxorubicin-resistant PCa DU-145 cells. This miRNA could target epidermal growth factor receptor (EGFR) and lncRNA LOXL1-AS1, affecting PCa progression. Generally, the lncRNALOXL1-AS1/miR-let-7a-5p/EGFR axis notably affected proliferation, apoptosis, and migration of doxorubicin-resistant DU-145 Cells, which can suggest a potential management method for drug-resistant PCa patients [3].

As mentioned earlier, NEAT1 was overexpressed in docetaxel-resistant PCa samples. The silenced NEAT1 resulted in a decrease in cell proliferation and invasion in docetaxel-resistant PCa cells. Functionally, NEAT1 participates in the docetaxel resistance by intensifying the expression of ACSL4 via sponging miR-204–5p and miR-34a-5p in PCa cells [53]. The expressions of another lncRNA, CCAT1, were overexpressed in PCa and Paclitaxel or PTX-resistant PCa cells. The suppressed CCAT1 prevented survival rate and stimulated apoptosis in cells after treatment with PTX [61]. Besides, the expression of lncRNA SNHG6 was upregulated in drug-resistant PCa tissues and cells. The suppressed SNHG6 increased the sensitivity of PTX-resistant PCa cells to PTX in vitro and in vivo and inhibited proliferation, migration, and invasion of PTX-resistant PCa cells in vitro. SNHG6 knockdown elevated the sensitivity of PTX-resistant PCa cells to PTX by sponging miR-186 as a tumor-suppressor, suggesting that SNHG6 can be a therapeutic factor for PCa [5]. Also, Linc00518 was upregulated in PCa, which was related to paclitaxel resistance. The deficiency of Linc00518 compromised the PTX-resistance in PCa cell lines [46]. DANCR was significantly upregulated in Docetaxel or DTX-resistant PCa. Suppressing DANCR increased the DTX efficacy in DTX-resistant PCa cells [75].

As a basic form of resistance, castration-resistant PC (CRPC) is considered an advanced form of malignancy that correlates with the poor survival of patients; this is a consequence of the insensitivity of PC cells to ADT due to the activation of alternative pathways for AR signaling. Some of these pathways controlled by lncRNA are mentioned in Fig. 2. In an interesting study, it has been shown that lncRNA-p21 is overexpressed in xenograft tissues derived from patients who have Neuroendocrine prostate cancer (NEPC) as a result of resistance to hormonal therapies. Antiandrogen enzalutamide (Enz), an effective drug increases the survival rate of CRPC patients, has also been shown to upregulate lncRNA-p21 expression contributing to neuroendocrine differentiation (NED). Functional in vitro analysis further revealed that exposure of cells to Enz led to upregulation of lncRNA-p21 by modulating AR activity, which in turn causes Enhancer of zeste homolog 2 (EZH2)-mediated activation of STAT3 signaling. This signaling pathway has been reported to be involved in promoting neuroendocrine differentiation. Besides, in vivo studies demonstrated that the inhibition of EZH2 could dampen the neuroendocrine differentiation induced by Enz treatment in mice models, suggesting that targeting lncRNA-p21 may be an effective strategy in better management of CRPC patients in confronting the progression of NEPC [73]. LncRNA-PCAT1 is another oncogenic lncRNA that participates in the development of CRPC. AKT signaling pathway is activated by inhibiting AR signaling in PTEN-deficient, leading to castration resistance in patients. LncRNA-PCAT1 was reported to disturb an essential regulatory complex containing PH domain, and Leucine-rich repeats Protein Phosphatases (PHLPP), FK506-binding protein 51 (FKBP51), an inhibitor of nuclear factor kappa B (IKKα) by interacting with FKBP51 and displacing PHLPP from the complex, activating AKT and Nuclear factor kappa B (NF-κB) signaling.

Furthermore, lncRNA-PCAT1 suppression hampered the CRPC progression in mouse models. LINC00675 has also been involved in activating AR singling in CRPC patients and androgen-insensitive cells. On the one hand, LINC00675 upregulation interacts with MDM2 protein, which diminishes AR ubiquitination and its subsequent degradation. On

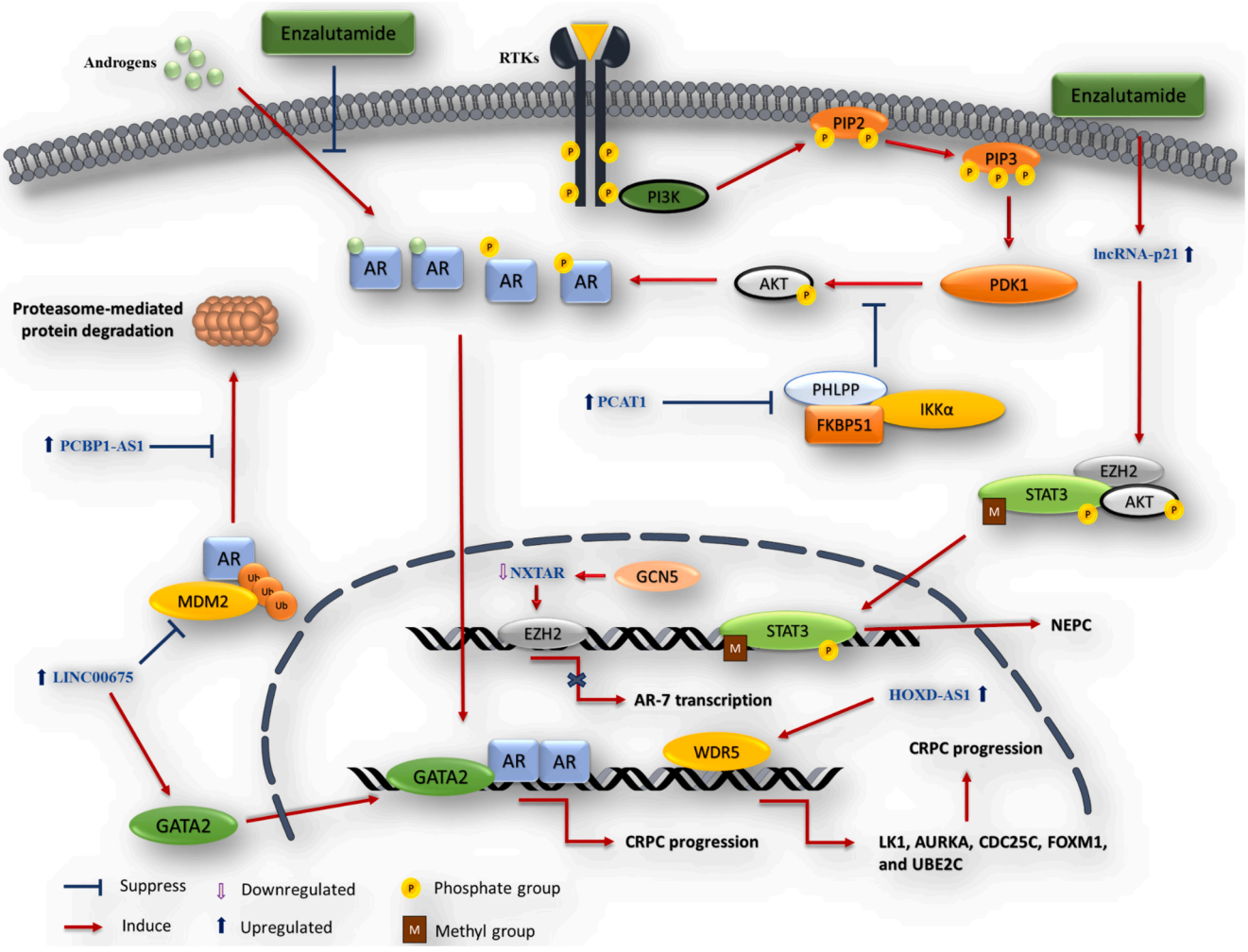

Fig. 2. Castration-resistant PC (CRPC), an advanced form of cancer associated with a low patient survival rate, arises from PC cells' resistance to androgen deprivation therapy (ADT) due to the activation of alternative AR signaling pathways in these cells. Fig. 2 demonstrates these lncRNA-controlled pathways.

the other hand, this lncRNA binds to GATA2 mRNA and stabilizes its expression, which functions as a co-activator of AR signaling, promoting in vitro and in vivo CRPC progression [131]. NEAT1, which was previously mentioned to function as an oncogene in PCa progression, plays a crucial role in the docetaxel resistance of this malignancy. NEAT1 suppression in Docetaxel resistant- PCa cells decreased ceRNA activity on the miR-34a tumor-suppressor and rescued RET expression as a miR-34a target. Subsequently, targeting the NEAT1/miR-34a/RET axis increased the docetaxel chemosensitivity of PCa cells in vitro and in vivo [100]. As another oncogenic lncRNA overexpressed through CRPC progression, lncRNA PCBP1-AS1 has been evidenced to increase AR/AR-complex deubiquitylation and inhibit its degradation, leading to castration resistance in PCa cells. However, PCBP1-AS1 suppression increased the sensitivity of resistant tumors and cells to enzalutamide treatment in vitro and in vivo [138]. AR signaling in CRPC is reported to be modulated by another tumor-suppressor, lncRNA, namely NXTAR (LOC105373241). This lncRNA is downregulated through prostate tumorigenesis and in PCa cells, playing a pivotal role in enzalutamide resistance. NXTAR upregulation through the activity of GCN5 histone acetyltransferase or pharmacologic restoration using (R)− 9b, ACK1/TNK2 small molecule inhibitor diminishes cell proliferation. It increases enzalutamide sensitivity in vivo and in vitro by down-regulating AR expression and signaling. Mechanistically, NXTAR binds to the upstream of the AR promoter and decreases AR-7 expression by recruiting EZH2. In turn, AR suppression by (R)− 9b also leads to the overexpression of NXTAR in positive feedback [36]. Additionally, SNHG17, which shows higher expression levels in PCa tumor samples and correlates with poor prognosis of patients, also participates in the resistance of PCa cells to Docetaxel. Consequently, SNHG17 suppression inhibited cell invasion and proliferation, diminished in vivo tumor growth, and increased Docetaxel chemosensitivity in C4–2 tumor cells [148].

6. Conclusion and perspectives

Since lncRNA is involved in various aspects of prostate tumorigenesis through modulating major signaling pathways, they hold great promise as novel molecular targets for the treatment and prognosis of PCa. Targeting dysregulated lncRNAs could diminish in vitro and in vivo PCa progression, providing new therapeutic approaches for targeting tumor metastasis and recurrence. In particular, some of this dysregulated lncRNA regulates AR signaling and could be more effective in managing patient resistance to androgen deprivation therapy. However, some limitations and challenges must be addressed in applying lncRNAs in treating PCa. To be mentioned, humans and rodents share low conservation in the sequence and function of lncRNAs, which makes mechanistic and pre-clinical investigations more challenging. Hence, most functional studies are done in vitro, and the significance of target lncRNA should find its way to clinical levels. In this case, patient-derived tumor cells and xenografts (PDXs) are promising for more precise pre-clinical evaluation [93]. The other limitation concerns targeting lncRNAs, particularly oncogenic lncRNAs, because of their low

abundance and nuclear localization.

Nevertheless, antisense oligonucleotides (ASOs) technology may be a helpful tool to overcome these obstacles considering the nuclear enrichment of its effector, RNase H [58]. Besides, the innovations in CRISPR technology, such as RNA-guided endogenous CRISPR activation (CRISPRa), and viral delivery systems, such as lentiviruses, adenoviruses, and adeno-associated viruses (AAVs), have opened new avenues for targeted gene therapy [14,69]. A recent study reported that lncRNA XIST overexpression, mediated by adenovirus vectors, as a tumor suppressor suppressed in vitro and in vivo PCa cell proliferation and metastasis by targeting miR-23a expression [23]. Last but not least, considering the tissue-specific and tumor-specific expression of lncRNAs, their direct delivery for efficient activity and avoiding side effects is also a challenge in the clinical application of lncRNAs for PCa [116].

Consent for publication

All authors and institutions have confirmed this manuscript for publication.

CRediT authorship contribution statement

Ramin Haghighi, **Mojgan Mirzaei:** Conceptualization, Visualization, Writing – original draft**. Roxana Yolanda Castillo-Acobo**, **Ali H Amin**, **Hadi Mohammed Ehymayed**, **Farah Alhili:** Writing – review & editing**. Saman Mohammadzadeh Saliani**, **Hadis Kheradjoo:** Conceptualization, Supervision**.**

Declaration of Competing Interest

None.

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