

Exploring non-coding RNAs in Prostate Cancer: from Biomarkers to Therapeutic Strategies

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ABSTRACT

Prostate cancer (PCa) is the second most prevalent malignancy and a leading cause of cancer-related mortality in males worldwide. Despite advancements in therapeutic strategies, such as radical prostatectomy, radiotherapy, androgen deprivation therapy (ADT), and chemotherapy, treatment outcomes for metastatic castration-resistant PCa (mCRPC) remain suboptimal. The androgen receptor (AR) and its downstream signaling pathways play a critical role in PCa progression. Genetic aberrations such as AR amplification, TP53 and PTEN loss, and MYC oncogene activation further drive disease advancement. Although prostate-specific antigen (PSA)-based screening is widely used, its limited impact on survival underscores the need for more reliable biomarkers. Emerging evidence indicates that non-coding RNAs (ncRNAs), including long non-coding RNAs (lncRNAs), circular RNAs (circRNAs), and microRNAs (miRNAs), act as key regulators of gene expression. These molecules influence PCa cell proliferation, apoptosis, invasion, and metastasis. Their differential and stage-specific expression patterns suggest strong potential as diagnostic and prognostic biomarkers, as well as therapeutic targets. This review summarizes recent advancements in ncRNA research in PCa, providing insights into their mechanistic roles, clinical applications, and future directions in precision oncology.

Keywords: Prostate cancer; Non-coding RNA; Long non-coding RNAs; Circular RNAs; microRNAs; Therapeutic targets



INTRODUCTION:

The World Health Organisation (WHO) has classified prostate cancer (PCa) as the second most ubiquitous type of cancer that causes cancer-related mortality in males worldwide. The International Agency for Research on Cancer (IARC) published the Global Cancer Statistics (GLOBOCAN) 2020, which states that PCa makes up 14.1% of all cancers in men and has a 6.8% mortality rate [1]. The global incidence of PCa has increased substantially in recent years, posing a major threat to men's health. Since over 75% of PCa patients are diagnosed after the age of 65, the disease incidence rises sharply with advancing age. Although Asian populations exhibit comparatively lower incidence rates, marked regional variations persist [2].

Localized PCa with low to intermediate risk is typically treated with radiation therapy, radical prostatectomy, hormone therapy, focal therapies, and active surveillance [3]. In contrast, androgen suppression and chemotherapy are primarily used in locally advanced and metastatic disease stages. Despite these approaches, therapeutic efficacy remains limited, particularly in advanced stages. Overall Survival (OS) dramatically declines as patients develop metastatic castration-resistant PCa (mCRPC). Therefore, identifying novel molecular targets for PCa diagnosis and treatment is crucial.

A higher relative risk of PCa has been linked to single-nucleotide polymorphisms (SNPs) and many susceptibility genes, such as BRCA2, CHEK2, HOXB13, and NBS1. Furthermore, the progression of PCa is made easier by the combination of TP53 and PTEN deletion or mutation, MYC oncogene amplification, and androgen receptor (AR) amplification or mutation in its advanced stages [4]. Identifying new AR activation mechanisms and downstream signaling pathways may improve therapeutic strategies for advanced disease.

Although advances in detection and treatment have reduced PCa mortality in some regions, prostate-specific antigen (PSA)-based screening has not consistently improved survival outcomes [5]. The limited accuracy of PSA testing has therefore prompted the search for alternative biomarker. In this context, non-coding RNAs (ncRNAs), including lncRNAs, circRNAs, and miRNAs, have emerged as promising candidates for PCa diagnosis and prognosis.

Non-coding RNAs (ncRNAs) are now recognized as key regulators of gene expression and signal transduction in both normal physiology and disease, including PCa [6]. The potential of ncRNAs as predictive and diagnostic biomarkers is shown by changes in their expression patterns at different phases of PCa progression [7]. Moreover, ncRNAs influence critical cellular processes

such as proliferation, migration, invasion, and apoptosis of PCa cells. This review summarizes recent advances in ncRNA research in PCa, highlighting their molecular mechanisms, clinical applications, future potential as biomarkers and therapeutic target.

2. Non-coding RNAs (ncRNAs) in cancer

Over the past three decades, numerous RNA species have been identified, among which ncRNAs have emerged as key regulatory molecules. Although ncRNAs do not encode proteins, they known to carry out diverse regulatory functions in cellular processes [8]. Large portions of the non-protein-coding genome are transcribed into thousands of ncRNA molecules that regulate fundamental biological processes, including growth, development, and organ function. Dysregulation of these molecules play crucial role in a broad range of human diseases, particularly cancer,

More than 90% of transcripts produced from the human genome are ncRNAs; however, the most have been identified only within the past decade and still their functions remain poorly characterized. NcRNAs are classified based on their length, structure, function, genomic origin and mechanism of action [9] (Fig. 1). The discovery of ncRNAs has substantially expanded our understanding of cancer biology and revealed potential therapeutic opportunities. It has been discovered that genetic alterations affecting ncRNA genes have been directly linked to cancer development [10].

RNAs are broadly classified into coding RNAs, which include messenger RNAs (mRNAs), and non-coding RNAs (ncRNAs), which lack protein-coding capacity. ncRNAs are further divided into housekeeping ncRNAs (rRNAs, tRNAs, snRNAs, and snoRNAs) that are essential for basal cellular functions, and regulatory ncRNAs that modulate gene expression. Regulatory ncRNAs are categorized into small ncRNAs (<200 nucleotides), such as microRNAs (miRNAs), small interfering RNAs (siRNAs), and PIWI-interacting RNAs (piRNAs), and long ncRNAs (>200 nucleotides), including linear lncRNAs, antisense and intergenic lncRNAs, and circular RNAs (circRNAs). This classification reflects current consensus on ncRNA biogenesis, size, and regulatory function.

Numerous clinical studies have demonstrated that cancer cells can release ncRNAs into exosomes and circulating bodily fluids, including blood. Increasing evidence directs that ncRNAs exert both tumor-suppressive and oncogenic functions during tumorigenesis [11]. These effects are mediated through modulation of key signaling pathways, such as mitogen-activated protein kinase (MAPK), Wnt, and Notch signaling.

Individual ncRNAs can interact with DNA, mRNAs,

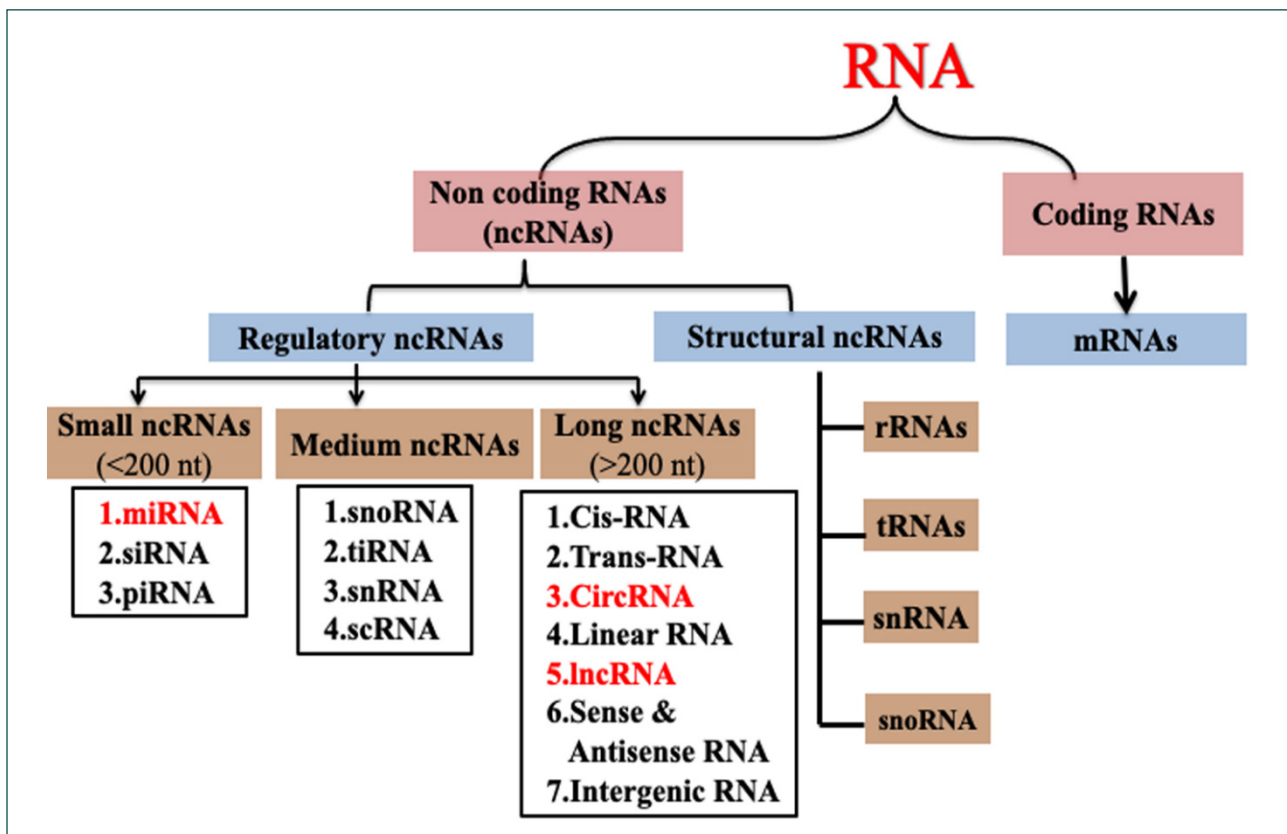


Figure 1: Classification of coding and non-coding RNAs.

proteins, and other ncRNAs, thereby regulating multiple biological pathways [12]. Given their central role in gene regulation, dysregulation of ncRNAs contributes to cancer initiation and progression, further studies are needed to develop ncRNA-based diagnostic and therapeutic strategies. The major classes of ncRNAs implicated in cancer include circular RNAs (circRNAs), long non-coding RNAs (lncRNAs), and microRNAs (miRNAs) [13], which are discussed in detail below.

3. Major classes of ncRNAs in Prostate Cancer

3.1. LncRNAs

Long non-coding RNAs are transcripts longer than 200 nucleotides lack an open reading frame and do not code for proteins. The human genome is estimated to encode over 100,000 lncRNAs, many of which resemble mRNAs in structure and may contain poly(A) tails. LncRNAs are essential for several biological processes. Recent research indicates that lncRNAs are increasingly recognized as key regulators of cancer signaling networks [14].

It has been demonstrated that several lncRNAs have been shown to function as tumor suppressants, whereas others promote cancer progression [15]. These context-dependent roles suggest that lncRNAs could be useful therapeutic targets and biomarkers for PCa. Another risk factor for PCa is emerging association between SNPs within lncRNA and cancer [16]. Dysregulated gene expression mediated by lncRNAs is thought to contribute to PCa initiation, phenotypic development, and disease progression.

In a PCa, numerous lncRNAs are aberrantly upregulated or downregulated, making them as potential therapeutic target. These lncRNAs have been shown to modulate multiple signaling pathways to influence the PCa pathophysiology. Although several key downstream targets of lncRNAs have been found include STAT3, NF-kb, PTEN, PI3K/Akt, and miRNAs [17, 18]. Table 1&2 summarizes the functional roles of lncRNAs in PCa, including mechanistic insights into Prostate Cancer Antigen 3 (PCA3) and second chromosome locus associated with prostate-1 (SchLAP1). Collectively, these findings support the potential of lncRNAs as therapeutic targets in PCa.

3.1.1. PCA3

PCA3 is one of the most PCa-specific lncRNAs identified to date. By regulating gene expression, lncRNAs play important roles in a broad range of biological activities, and tumor growth has been associated with their dysregulation. In addition to causing apoptotic cell death, transient by suppressing PCA3 reduces PCa cell survival

Table 1. List the role of the various upregulating lncRNAs involved in prostate cancer (PCa) and highlight their specific mechanisms of action

lncRNA	Pathways	Role in PCa
Androgen receptor-regulated long non-coding RNA (ARLNC)-1	Androgen Receptor interaction	Promote AR stabilization and also increase progression
Antisense non-coding RNA in the INK4 locus (ANRIL)	TGF- β /SMAD signaling	Binds with PRC2 and positively regulates the expression of the adjacent gene
Apoptosis-associated transcript in Bladder cancer (AATBC)	miR-1245 b-5p/CASK axis	Promotes progression
Bladder cancer-associated transcript (BLACAT)-1	miR-29a-3p/DVL3 axis	Facilitates the proliferation, migration, and invasion
Breast cancer anti-estrogen resistance 4 (BCAR)-4	GLI2 signaling	Prognostic marker promotes cell growth and migration
Cancer susceptibility (CASC)-11	p53 pathway	Enhances proliferation and migration
CERS6-AS1	miR-16-5p/HMGA2 axis	Prevent the proliferation and migration
Colon cancer-associated transcript (CCAT)-1	miR-490-3p/FRAT1 axis	Enhances the proliferation, migration, and invasion
Colorectal neoplasia differentially expressed (CRNDE)	miR-101/Rap1A axis	Induces the proliferation, migration, and invasion
C-terminal binding protein 1 antisense RNA (CTBP1-AS)	Androgen Receptor interaction	Role in cell proliferation and invasion
Deleted in lymphocytic leukemia (DLEU)-2	miR-582-5p/SGK1 axis	Promotes the proliferation, invasion, and migration
Differentiation antagonizing non-protein coding RNA (DANCR)	Glucose metabolism	Affects the proliferation, migration, and taxol resistance
FAM66C	EGFR-ERK signaling	Induces cell growth
HOXD-Antisense growth-associated long non-coding RNA (HOXD-AS1)	miR-361-5p/FOXO1 axis	Prognostic markers promote proliferation and chemoresistance
HOX transcript antisense RNA (HOTAIR)	Androgen Receptor Signaling	Therapeutic target modulates the PRC2 complex, suppressing AR transcription
Human leucocyte antigen complex group (HCG)-18	miR-370-3p/DDX3X axis	Promotes cell proliferation, invasion, and migration
Isocitrate dehydrogenase 1 long non-coding RNA (IDH1-AS1)	IDH1-AS1-IDH1 axis	Potential target
LINC01194	LINC01194/miR-486-5p/GOLPH3 axis	Serves as a tumor promoter and enhances progression
LINC01296	PI3K/Akt pathway	Promotes cell proliferation and tumor progression.
lncRNA AC008972.1	LncAC008972.1/miR-143-3p/TAOK2 axis	Promotes PCa progression and represents a potential therapeutic target.
Lnc-RNA-p21	p53 signaling	Regulates the Warburg effect by accumulating HIF-1
LncHUPC1	LncHUPC1/miR-133b/SDCCAG3 axis	Acts as an oncogene and increases the metastasis and growth
Long non-coding RNA 992 (LNC992)	Androgen Receptor signaling	Enhances the growth and metastasis

Metastasis-associated lung adenocarcinoma transcript (MALAT)-1	SMAD3/TGFβR2	Enhances the proliferation, migration, and invasion Elevated levels result in tumor recurrence
Motor neuron and pancreas homeobox 1 – Antisense RNA1 (MNX1-AS)-1	miR-2113/MDM2 axis	Enhances the proliferation, migration, and invasion
Micro-chromosome maintenance protein-associated protein antisense RNA1 (MCM3AP-AS)-1	miR-543-3p/SLC39A10/PTEN axis	Induces cell proliferation and invasion
miR4435-2HG	FAK/Akt/β-catenin	Leads to proliferation and invasion
Noncoding RNA activated by DNA damage (NORAD)	miR-30a-5p/RAB11A/Wnt/β-catenin pathway	Facilitates proliferation, invasion, and suppresses apoptosis
Nuclear enriched abundant transcript (NEAT)-1	miR-766-5p/E2F3 axis	Therapeutic target, Prognosis, chemotherapeutic resistance, progression
Nuclear enriched abundant transcript (NEAT)-2	β-MYB (Mybl2)	controls cell cycle progression
Nuclear receptor subfamily 2 group F member 2 antisense RNA (NR2F2-AS1)	CDK4	Acts as a tumor-promoting factor and mediates cell cycle progression
Plasmacytoma Variant translocation (PTV)-1	PTV1-NOP2 axis	Potential diagnosis, prognosis marker, induces metastasis
PlncRNA-1	PTEN/Akt pathway	Facilitates cell proliferation, migration, and invasion
Prostate cancer antigen (PCA)-3	Androgen Receptor signaling	Helps in early detection and acts as a prognostic marker and a potential therapeutic target
Prostate cancer-associated intergenic noncoding transcript (PAINT)	Androgen Receptor signaling	Functions as an oncogene
Prostate cancer-associated long non-coding chromosome on (PCAL)-7	Androgen Receptor signaling	Acts as an oncogene
Prostate Cancer Associated Transcript (PCAT)-1	C-MYC protein	Prognosis & tumorigenesis
Prostate cancer-associated transcript (PCAT)-6	PCAT6/miR-326/Hnrnpa2b1 signaling	Act as a potential prognostic marker and therapeutic target
Prostate cancer-associated transcript (PCAT)-14	Immune pathways	Potential diagnostic marker
Prostate gene expression marker (PCGEM)-1	Androgen Receptor signaling	Promotes the progression
RNA associated with metastasis (RAMS)-11	mTOR signaling	Enhances the growth and metastasis
Second chromosome locus associated with prostate (ScHLAP)-1	Interfering with the SWI/SNF tumor-inhibiting complex	Prognosis, critical role in invasiveness, and metastasis
Small nucleolar RNA host gene (SNHG)-1	Wnt/β-catenin and PI3k/Akt/mTOR	Increases migration and metastasis
Small nucleolar RNA host gene (SNHG)-12	miR-195, Caspase -3/9, Beclin-1, p62, PI3K/Akt, mTOR	Suppresses cell proliferation, alters apoptosis
Small nucleolar RNA host gene (SNHG)-17	Wnt/β-catenin pathway	Promotes progression and viability, but Suppresses apoptosis
Taurine-upregulated gene (TUG)-1	Nrf2 signaling	Exerts an oncogenic role and serves as a potential target
Urothelial carcinoma associated (UCA)-1	PI3K/Akt pathway	Plays an oncogenic role
VPS9D1-AS1	miR-4739/MEF2D axis	Enhances the proliferation, migration, and invasion

Table 2. List the role of the various downregulating lncRNAs involved in PCa and highlight their specific mechanisms of action

lncRNA	Pathways	Role in PCa
Bladder cancer-associated transcript (BLACAT)-1	Wnt/ β -catenin	Reduces the growth of PCa and induces cell death
DiGeorge syndrome critical region gene (DGCR)-5	TGF β 1	Reduces cell stemness
Empty spiracles homeobox 2 Opposite strand (EMX2OS)	cGMP/PKG	Suppresses tumor growth
ErbB4-IR	miR-21	Mediates the apoptosis
FER-1-Like family member (FER1L)-4	FER1L4/miR-92a-3p/FBXW7	Inhibits cell proliferation and promotes apoptosis
GAS5-007	PI3K-Akt/mTOR pathway	Acts as a therapeutic target
Growth arrest-specific transcript (GAS)-5	PI3K-Akt/mTOR pathway	Tumor suppressor and promote cell apoptosis
H19	miR-194/E2F3	Acts as a tumor suppressor gene
LBCS (LncRNA Bladder and Prostate cancer Suppressor)	hnRNPK/Androgen Receptor	Poor prognosis, preventing castration resistance
LINC00908	LINC00908/miR-483-5p/TSPYL5 axis	Suppresses progression
Long intergenic non-protein coding (LINC) RNA 00844	LINC00844/EBF1/GSTP1 axis	Acts as a prognostic marker, and promotes migration, invasion
MAGI2-AS3 (Membrane Associated Glycoprotein-like 2 – Antisense RNA 3)	STAT 3 signaling	Inhibits proliferation, migration, and invasion
Maternally Expressed Gene (MEG)-3	p53 signalling	Acts as a therapeutic target
MicroRNA 22 Host Gene (MIR22HG)	miR22HG/miR-9-3p axis, p53, and JAK-STAT	Inhibits proliferation, promotes apoptosis, and serve as a diagnostic biomarker.
Prostate Cancer Associated Transcript (PCAT) 14	Immune pathways	Facilitates early detection and acts as a tumor-suppressive prognostic marker.

and viability while inducing apoptosis, suggesting a role in tumor survival. Similarly, PCA3 transient silencing causes transient PCa cell viability, permanent silencing causes total loss of PCa cell viability [19]. Furthermore, PCA3 and Protein PRUNE Homolog (PRUNE)-2 might share evolutionary patterns and response mechanisms. Salameh et al., [20] showed that PCA3 negatively regulates PRUNE2 expression through an Adenosine Deaminase Acting on RNAs (ADAR)-mediated RNA duplex mechanism, highlighting a complex regulatory interaction [20,21] and a functional link between the two proteins. This complex binds to ADAR proteins, which control the levels of PCA3 and PRUNE2 and these enzymes are necessary for a co-regulatory action on both RNAs.

Furthermore, PRUNE2's tumor suppressor function is demonstrated by overexpression of PRUNE2 showed reduced motility, adhesion, and propagation, whereas loss of PRUNE2 in PCa cells showed tumor xenografts [20]. Inhibition of ADAR1 increased PRUNE2 expression and simultaneously reduces PCA3 levels, leading to decreased tumor cell proliferation. A subsequent study showed that knockdown of PCA3 significantly upregulated multiple androgen receptor (AR) cofactors, including ARA70, ARA54, CBP, P300, β -catenin, TIF-2, SRC1, EBP1, and NCoR1[22]. These findings suggest that PCA3 silencing negatively modulates androgen responsive genes by overexpressing AR cofactor transcripts. Collectively these data support PCA3 knockdown as a potential therapeutic strategy to inhibit PCa progression (Fig. 2).

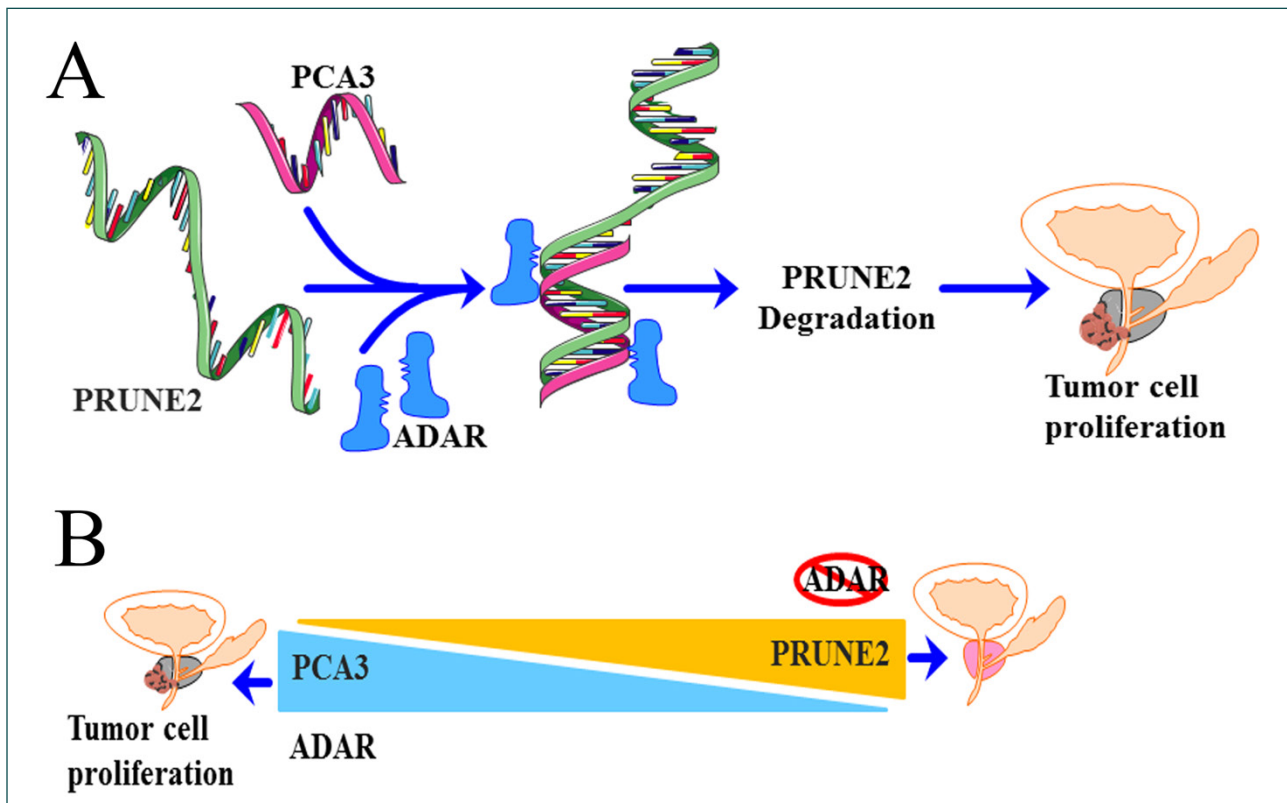


Figure 2: PCA3 promotes prostate cancer proliferation through ADAR-mediated degradation of PRUNE2.

(A) In prostate cancer cells, the lncRNA PCA3 interacts with the RNA-editing enzyme ADAR, facilitating ADAR-mediated editing of PRUNE2 transcripts. This interaction promotes PRUNE2 mRNA degradation, resulting in reduced tumor-suppressive activity and enhanced tumor cell proliferation.

(B) Inhibition of ADAR disrupts the PCA3-ADAR interaction, leading to stabilization and increased expression of PRUNE2. Restoration of PRUNE2 expression suppresses tumor cell proliferation. PCA3: Prostate Cancer Antigen 3, PRUNE2: Prune Homolog 2, ADAR: Adenosine Deaminase Acting on RNA.

3.1.2. SchLAP1

SchLAP1, another lncRNA, is minimally expressed in bladder, kidney, and testis tissues, but shows high specificity of prostate tissue. SchLAP1 physically interacts with the SWI/SNF chromatin-modifying complex and inhibits its tumor-suppressive function. Through inhibition of this multiprotein SWI/SNF chromatin-modifying complex, which regulates nucleosome organization at gene promoters, SchLAP1 promotes cancer cell invasiveness and metastasis. Surprisingly, SWI/SNF components were somatically inactivated in cancer, and this inactivation associated with enhanced disease progression [23]. SchLAP1 is the first lncRNA identified to disrupt a major epigenetic complex with a well-established tumor suppressor function. Li et al. [24] demonstrated that SchLAP1 overexpression markedly reduced miR-198 expression, whereas SchLAP1 knockdown significantly increased it. Consequently, SchLAP1 modulates MAPK1 signaling pathway in PCa by negatively regulating miR-

19. miR-198 is thought to suppress MAPK signaling thereby exerting its anticancer effects. Accordingly, SchLAP1 knockdown significantly reduces cell proliferation and increases the apoptosis-associated proteins. In addition, decreased expression of MMP-9, MMP-14, and VEGF following SchLAP1 silencing, highlights its role in cancer metastasis and invasiveness [25] (Fig. 3).

3.2. miRNAs

MicroRNAs (miRNAs) are a class of endogenous single-stranded non-coding RNAs of approximately 20 nucleotides in length. They negatively regulate gene expression by binding to complementary messenger RNAs (mRNAs), leading to translational repression or mRNA degradation [26]. Every year, thousands of miRNAs have been identified different species with numbers continuing to expand. Following the discovery of lin-4 in 1993, extensive research has focused on miRNA biogenesis, structure, and function [27].

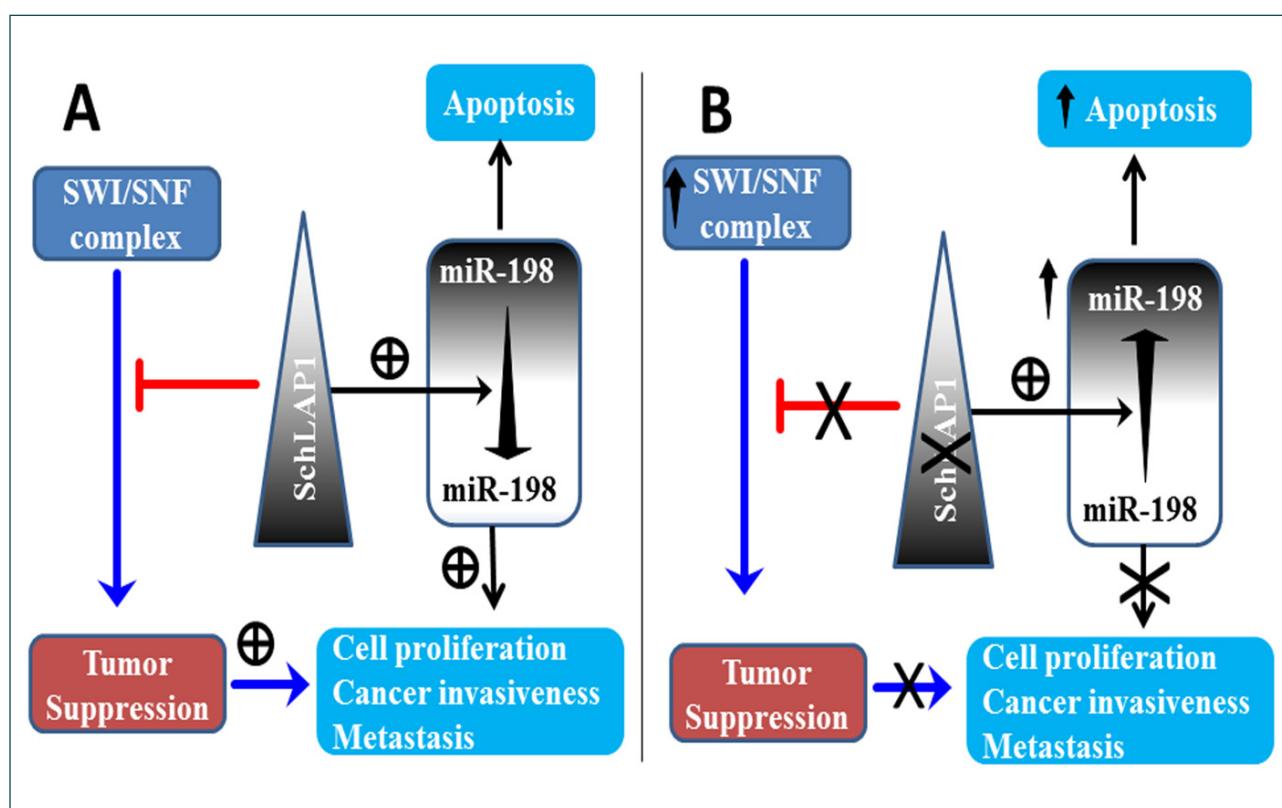


Figure 3: SChLAP1 regulates prostate cancer progression through miR-198 and SWI/SNF signaling.

(A) In prostate cancer cells with high SChLAP1 expression, SChLAP1 antagonizes the tumor-suppressive SWI/SNF chromatin-remodeling complex and suppresses miR-198 expression. Reduced miR-198 levels lead to enhanced cell proliferation, invasiveness, and metastatic potential, while apoptosis is decreased.

(B) Upon SChLAP1 silencing, SWI/SNF complex activity is restored, leading to enhanced tumor-suppressive signaling. Increased miR-198 expression promotes apoptosis and suppresses cell proliferation, invasion, and metastasis.

SWI/SNF: SWItch/Sucrose Non-Fermentable, SChLAP1: Second chromosome Locus Associated with Prostate-1. [T-bar] blunt arrow indicate inhibition; circled plus: Stimulation, up and down curly arrow inside box indicate increased and decreased levels, respectively, and "X" denotes suppression of tumor-related cellular processes.

miRNAs are playing essential role in cellular homeostasis and cancer pathogenesis including PCa of global interest. Different miRNAs regulate key processes such as apoptosis, tumor growth, metastasis, and chemoresistance. According to Ghamlouche et al. [28], miRNAs have emerged as promising diagnostic and therapeutic targets in PCa [28,29]. The first miRNAs associated with PCa were identified in 2006. Accumulating evidence indicates that these miRNAs influence tumor development and progression and serve as biomarkers for diagnosis, prognosis, and therapeutic response. Functional studies have demonstrated that miRNA dysregulation is closely linked to molecular mechanisms underlying carcinogenesis. Genomic amplification of oncogenic miRNAs can suppress tumor-suppressor genes or upregulate oncogenes respectively whereas loss of tumor-suppressive miRNAs can lead to oncogene activation, thereby promoting tumorigenesis and

metastasis [30]. Such alterations of miRNA expression disrupt gene regulatory networks and cellular function, contributing to cancer development and progression. Recent studies have shown that set of distinct miRNAs expression profiles in PCa discriminate malignant from benign tissues, assess tumor invasiveness, and predict disease progression. Metcalf et al. 2024, [31] reported that aberrantly expressed miRNAs reflect tumor biology, indicate malignancy and aggressiveness, and may predict patient responsiveness to specific therapies. Collectively, these findings support the clinical utility of miRNAs as biomarkers for PCa diagnosis and prognosis. Table 3&4 summarizes the roles of key miRNAs in PCa with detailed discussion of miR-221, miR-222, and miR-122. Overall, miRNAs represent promising targets for PCa therapy.

Table 3. List the role of the various upregulated miRNAs involved in prostate cancer (PCa) and highlight their specific mechanisms of action

miRNAs	Mechanism	Role in PCa
miR-7-5p	By targeting EGFR/MAPK and PI3K/Akt signaling	Tumor suppressor, inhibiting proliferation, invasion, and migration
miR-18a	By targeting the iron transporter solute carrier family 40-member 1	Promotes cancer progression
miR-21	By targeting transforming growth factor beta receptor 2	It promotes tumor invasiveness and induces a castration-resistant phenotype
miR-25	By targeting Caspase 7, an apoptosis-related cysteine peptidase	Facilitates tumor progression
miR-32	By targeting on both B-cell translocation gene (BTG-2) and Phosphoinositide-3-kinase interacting protein 1 (PIK3IP1)	Inhibits apoptosis and enhances proliferation
miR-106	By targeting Caspase 7, an apoptosis-related cysteine peptidase	Facilitates tumor progression
miR-122	Targeting through the enzyme pyruvate kinase M2	Increased proliferation, inhibited apoptosis, and chemotherapeutic resistance
miR-221	Attenuating the expression of p27kip1	Enhance cell proliferation, invasion, cell survival, and tumorigenicity
miR-375	By promoting the activity of the ERK signaling pathway	Early diagnosis and a biomarker for early diagnosis
miR-615-3p	By the TGF- β signaling pathway	Increases cell viability, apoptosis, and proliferation
miR-650	By suppressing the cellular stress response 1	Increased cell proliferation, invasion

3.2.1. miR-221 & miR-222

The two miRNAs, miR-221 and miR-222, play crucial role in prostate carcinogenesis and the progression from androgen-dependent to androgen-independent PCa, and are commonly dysregulated in PCa. Silent information regulator 1 (SIRT1) regulates several cellular processes, including proliferation, inflammation, the cell cycle control and migration. SIRT1 exhibits context-dependent functions, acting as a tumor suppressor by inhibiting many oncoproteins, such as β -catenin, or as an oncogene by repressing tumor suppressor genes, including p53 [32]. Yang et al. (2014) [33] demonstrated that downregulation of miR-221 or miR-222 in PCa cells, increased apoptosis and reduced cell migration and proliferation. Consistently, the suppression of miR-221 and miR-222, PCa cells resulted in increased SIRT1 expression, suggesting that SIRT1 counteracts the tumor-promoting effects of miR-221 and miR-222.

SIRT1 knockdown, in PCa, did not significantly change cell proliferation but increased cell migration and decreased apoptosis in PCa cells. In contrast, transfection

with miR-221/miR-222 inhibitor, elevated SIRT1 level, increased apoptosis and suppressed migration. These findings indicate that miR-221 and miR-222 indirectly repress SIRT1 expression (Fig. 4).

3.2.2. miR-122 and Rho-associated protein kinase (ROCK)-2

miR-122 functions have been reported to function as a tumor suppressor, and to inhibit the progression of several cancer types. Rho-associated protein kinase (ROCK2) 2 signalling plays a critical role in PCa and its suppression inhibits tumor development [34]. Although, miR-122 is downregulated in prostate cancer tissues, overexpression of miR-122 in PCa cells decreases ROCK2 expression and suppresses cell proliferation [35]. These findings support a tumor-suppressive role for miR-122 in prostate cancer.

Elevated ROCK2 expression has been observed in several malignancies, including prostate cancer, with higher levels in tumor tissues than in adjacent normal tissues. miR-122 may therefore inhibits prostate cancer growth by

Table 4. List the role of the various downregulated miRNAs involved in prostate cancer (PCa) and highlight their specific mechanisms of action

miRNAs	Mechanism	Role in PCa
has-miR-135-a-1	By targeting EGFR	Inhibits cell growth, cell cycle progression, migration, and invasion
Let-7 miRNAs	Targeting multiple oncogenes including RAS, HMGA2, Ezh2, Lin28 and c-Myc	Regulate cell cycle, cell migration, and cell proliferation
miR-17-92a	By the JAK-STAT pathway	Decreases cell cycle regulatory proteins
miR-30a	By reduced expression of a cyclin E2	Reduces the expression of the cell cycle protein
miR-34a	Wnt/ β -catenin signaling	Induces cell cycle arrest and apoptosis
miR-34b	By TGF- β /SMAD3 signaling	Controls proliferation, migration, and invasion
miR-34c	By TGF- β /SMAD3 signaling	Controls proliferation, migration, and invasion
miR-92-a-3p	Through the PTEN/Akt signaling pathway	Regulates cell viability, migration, and invasion
miR-125b	Activates p53 network	Enhances cell proliferation and inhibits apoptosis
miR-133	By targeting EGFR	Suppress tumor progression
miR-135a	Modulating the expression of RB-associated KRAB zinc finger (RBAK) and MMP-11	Acts as a tumor suppressor
miR-141-3p	Activating NF- κ B signaling	Participate in PCa metastasis and invasiveness
miR-145	By targeting the post-transcriptional expression of cadherin-2	Inhibits invasion, migration, and arrests the cell cycle
miR-146a	By targeting EGFR	Suppress tumor progression
miR-148-3p/ miR-152-3p	By inhibiting KLF4 expression	Inhibition of proliferation and induction of apoptosis
miR-181a	By directly targeting transforming growth factor beta-induced factor 2 protein	Inhibits proliferation and cell cycle
miR-200b	By directly targeting the key transcriptional factors	Inhibits cell growth and invasion
miR-204-5p	By controlling the expression of the Homeobox a10 and Meis Homeobox 1	Promotes apoptosis
miR-222	By activation of SIRT1	Role in inhibiting the malignant progression
miR-224	By targeting Apelin genes	Inhibits invasion and migration
miR-372	By regulating the transcriptional activity of the target p65 and affecting MMP-9 and PSA	Inhibits cell proliferation, migration, and invasion
miR-382	By attacking snail and MMP-2	Inhibits cell proliferation, migration, and invasion
miR-452	By regulating the Wnt/ β -catenin signaling pathway	Regulates the cell cycle and cellular adhesion

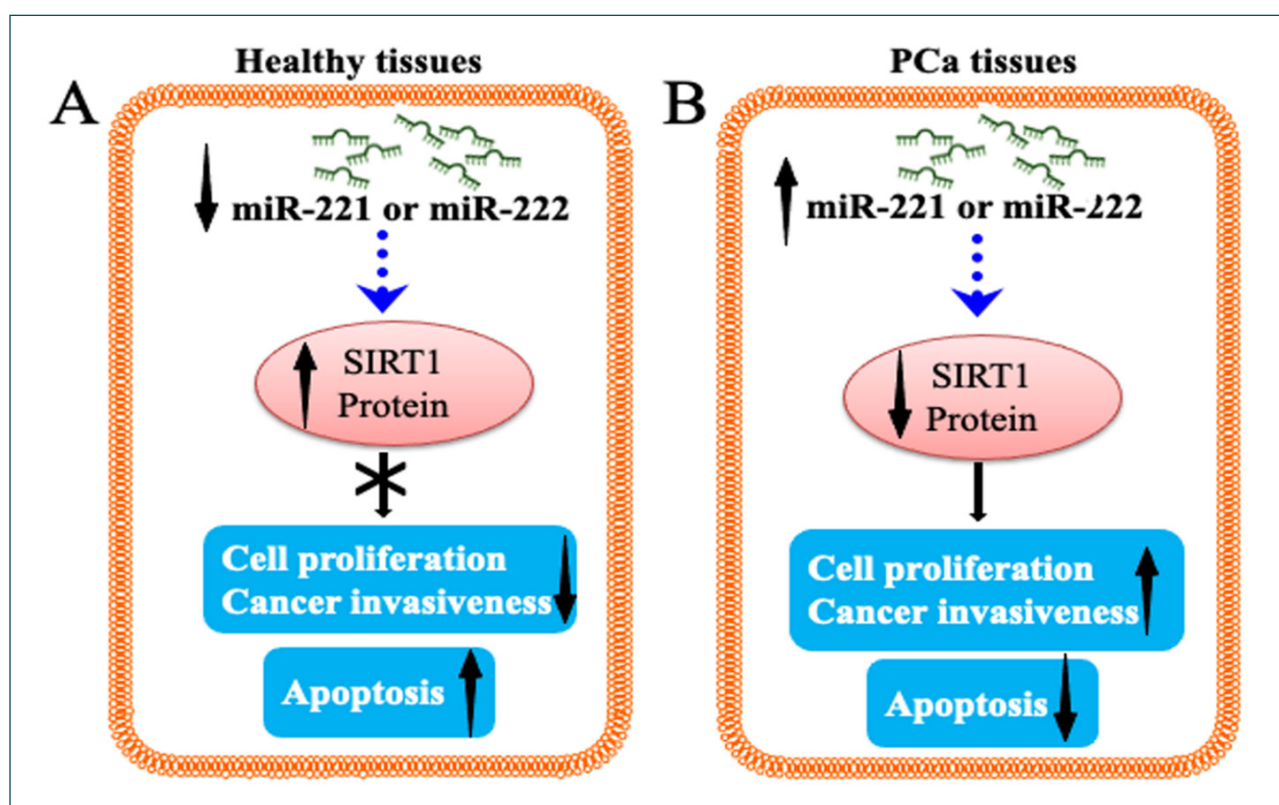


Figure 4: Dysregulation of the miR-221/miR-222-SIRT1 axis in prostate cancer.

(A) In healthy prostate tissue, low expression of miR-221/miR-222 permits higher SIRT1 protein levels, resulting in reduced cell proliferation and invasiveness and increased apoptosis.

(B) In prostate cancer tissues, miR-221/miR-222 are upregulated and inhibit SIRT1 expression, leading to enhanced cell proliferation and invasiveness and reduced apoptosis. Blunt arrows indicate inhibitory interactions, solid arrows denote downstream functional effects, and upward/downward curly arrows inside box represent relative changes in expression or activity and "X" denotes suppression of tumor-related cellular processes.

downregulating ROCK2 expression. However, because the ROCK2's gene lacks a canonical miR-122 binding site, it might not be a direct target of miR-122 suggesting the involvement of intermediary regulating factors between ROCK2 and miR-122. Notably, reduced serum level of miR-122 could serve as a potential biomarker for prostate cancer and a sign of poor prognosis (Fig. 5).

3.2.3. miR-122 and Pyruvate kinase muscle isoform (PKM)-2

Zhu et al. (2020) [36] reported that miR-122 can restore treatment sensitivity in multiple tumors types. In PCa cells, miR-122 mimic transfection significantly reduced cell proliferation and increased apoptosis whereas miR-122 inhibitor transfection produced opposite effects. These findings suggest that miR-122 is involved in regulating docetaxel resistance in PCa by modulating cell proliferation and apoptotic pathways.

miR-122 expression was inversely correlated with pyruvate kinase M2 (PKM2) levels in PCa cells and miR-122 was shown to bind the 3'-untranslated region

(UTR) of PKM2 thereby suppressing its expression. Notably, PKM2 overexpression in PCa reversed the anti-proliferation, and pro-apoptotic effects induced by miR-122 mimic transfection. Collectively, these results indicate that upregulating miR-122 may overcome docetaxel resistance in PCa by targeting PKM2. Targeting miRNA-122 therefore represents a potential therapeutic strategy for PCa chemoresistance, and these findings established a connection between them (Fig. 5).

3.3. Circular RNAs (CircRNAs)

Chen et al. (2015) [37], demonstrated circular RNAs (circRNAs) are a class of non-coding RNAs characterized by a covalently closed loop structure lacking 5'-cap or 3'-polyadenylated tail. Based on their biogenesis, circRNAs are classified into, three primary categories, circular intronic RNAs (ciRNAs), exon-intron circRNAs (EiRNAs), and exonic circRNAs (ecRNAs) [38]. Advances in bioinformatics and RNA deep sequencing have led to the identification of numerous circRNAs in both healthy and malignant human tissues [39].

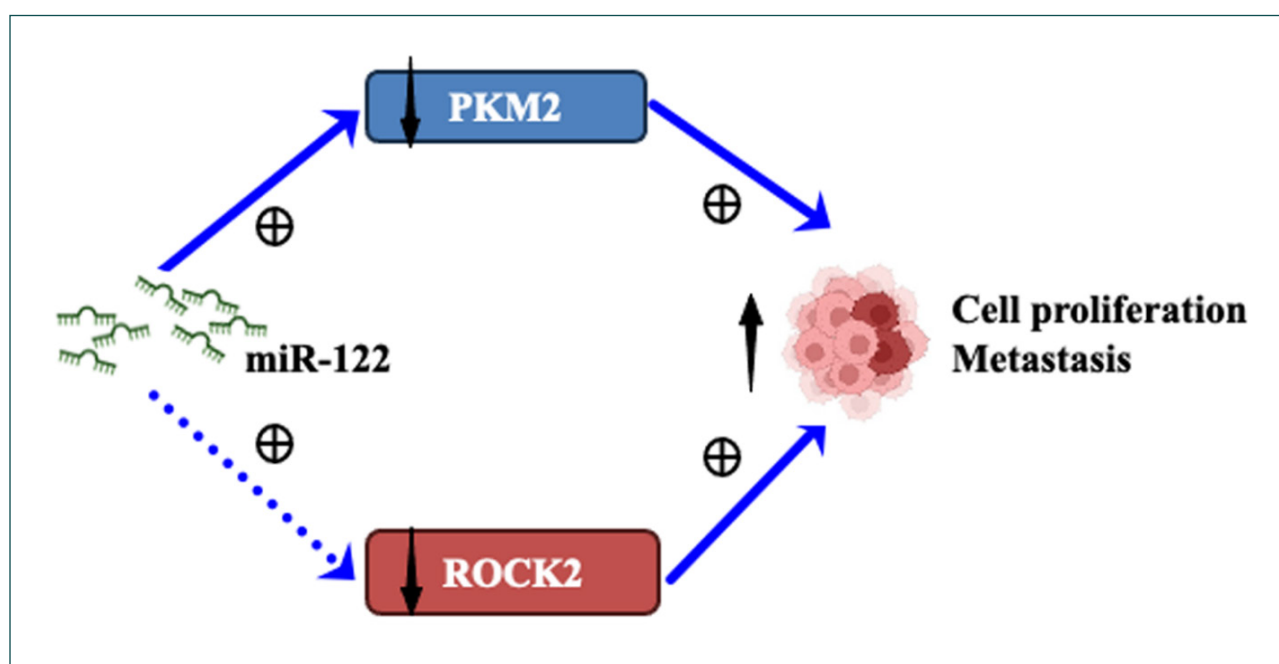


Figure 5: Tumor-suppressive role of miR-122 in prostate cancer via PKM2 and ROCK2 regulation.

miR-122 negatively regulates the expression of PKM2 and ROCK2, two key drivers of prostate cancer cell proliferation and metastasis. Increased miR-122 expression suppresses PKM2 and ROCK2 levels, resulting in reduced proliferative and metastatic capacity of prostate cancer cells. Solid arrows indicate downstream functional effects, blunt arrows represent inhibitory interactions, and dashed arrows denote indirect regulation. Downward arrows within protein boxes indicate decreased expression. Up and down curly arrows indicate increased and decreased levels, respectively. Dashed arrow indicates indirect regulation, and the circled plus indicates Stimulation.  arrow indicates activation/promotion.  inside box indicates reduced expression

Increasing evidence indicates that circRNAs play a role in pathological processes, including tumorigenesis, by regulating gene expression at multiple levels.[40]

Although the biological function of most circRNAs remain unclear, recent studies have shown that specific circRNAs can be translated to functional peptides, interact with RNA-binding proteins and modify their activity, regulate transcription or alternative splicing, and act as miRNAs sponge [41] Aberrant circRNA expression has been reported in several malignancies, including PCa [42] and breast cancer [43], and associated with drug resistance, tumor growth, and metastasis.

Targeting carcinogenic circRNA using small-interference RNA (siRNA) has emerged as a potential therapeutic strategy in gastric cancer. In addition, circRNAs show promise as diagnostic or prognostic biomarkers in cancer [45]. Table 5&6 summarizes circRNA'Ss impact in PCa, with focus on the molecular mechanisms underlying circFOXO3, circCRKL, and circPDHX.

3.3.1. circFOXO3

FoxO1, FoxO3, FoxO4, and FoxO6 are the principal transcription factors of the forkhead box O (FoxO) family. Although FoxO genes were initially associated with insulin signaling, accumulating evidence indicates that they regulate a broad range of biological processes, including cell cycle control, metabolism, apoptosis, and stress responses [46]. CircFoxo3 is abundantly expressed in normal tissues but is frequently downregulated during tumorigenesis.

Silencing circFoxo3 using siRNA markedly reduced FoxO3 protein levels without affecting its mRNA expression, indicating post-transcriptional regulation [47]. Mechanistically, circFoxo3 acts as a sponge for miR-29a-3p, thereby modulating SLC25A15 expression and promoting prostate cancer cell invasion, proliferation, apoptosis, and tumor progression. Collectively, circFoxo3 and the SIRT3/Wnt/ β -catenin/FoxO3A signaling axis represent promising prognostic markers and therapeutic targets in PCa (Fig. 6A).

3.3.2. circCRKL

Prostate cancer (PCa) tissues and cell lines exhibit low expression of circCRKL, a circular RNA derived from the CRKL gene. Functional studies demonstrated

Table 5. List the role of the various upregulated circRNAs involved in prostate cancer (PCa) and highlight their specific mechanisms of action

CircRNAs	Mechanism	Role in PCa
CDR1as	miR-641/XIAP	Promoted proliferation, invasion, and migration
circABCC4	miR-1182/FOXP4	Promote cell proliferation, migration, and invasion
circAGO2	-	Promote cell proliferation, migration, and invasion
circANKS1B	miR-152-3p/TGF	Promote migration and invasion
circCCNB2	miR-30b-5p/KIF 18A	Promote cell proliferation, migration, and autophagy, and inhibit apoptosis
circCRKL	miR-1285-5p/SMAD4	Promote cell cycle, migration, tumor growth, and inhibit apoptosis
circCSNK1G3	miR-181d	Promote cell proliferation
circFMN2	miR-1238/LHX2	Promote cell growth
circFOXO3	miR-1299/CFL2	Promote cell proliferation and inhibit apoptosis
circGOLPH3	miR-1299/LIF	Promote proliferation; inhibit apoptosis
circHIPK3	miRNA-338-3p/ADAM17	Promote viability, proliferation, migration, tumor growth, and inhibit apoptosis
circMBOAT2	miR-1271-5p/mTOR	Promote cell proliferation, migration, and invasion
cir-MYLK	miR-29a	Promote cell proliferation, migration, and invasion
circNOLC1	miR-647/PAQR4	Promote proliferation, migration
circPDHX	miR-378a-3p/IGF1R	Promote tumor growth, invasion, and colony formation
circSLC19A1	miR-497/ERK1&ERK2	Promote cell proliferation, migration, and invasion
circSMARCA5	miR-432/PDCD10	Accelerate the proliferation, metastasis, and glycolysis
circTRPS1	miR-124-3p/EZH2	Promote proliferation. Metastasis and stemness
circUBAP2	miR-1244/MAP3K2	Promoted proliferation
circXIAP	miR-1182/TPD52	Promote proliferation, migration, invasion, and docetaxel resistance
circZMIZ1	AR, AR-Vs	Promote proliferation and cell cycle
circZNF609	miR-186-5p/AMPK	Promote cell proliferation and metastasis
circ0005276	miR-1182/TPD52	Promote cell proliferation and migration
circ_0016068	miR-330-3p/BMI-1	Promote cell proliferation, migration, and invasion
circ0044516	miR-29a-3p	Promote cell proliferation and metastasis
circ_0057553	miR-515-5p/YES1	Promote proliferation, metastasis, and glycolysis, and inhibit cell apoptosis
circ0057558	miR-206/c-Myc	Promoted proliferation, colony formation, and inhibited cell cycle arrest
circ0062020	miR-615-5p/TRIP13	Promote cell proliferation, migration, and inhibit cell apoptosis
circ_0088233	miR-185-3p	Promote cell proliferation, migration, and inhibit cell apoptosis
circ102004	By the Hedgehog pathway	Promote cell proliferation, migration, and invasion; decrease cell apoptosis
has circ 0000735	miR-7	Promote cell viability, inhibit cell apoptosis, and increase cell resistance to docetaxel
has_circ_0062019	miR-195-5p/HMGA2	Promoted proliferation, invasion, and migration

Table 6. List the role of the various downregulated circRNAs involved in prostate cancer (PCa) and highlight their specific mechanisms of action

circAMOTL1L	miR-193a-5p/Pcdha8	Inhibited cell migration and invasion
circCRKL	-	Repress cell cycle, migration, and promote apoptosis
circDDX17	miR-346/LHPP	Inhibited cell proliferation and invasion
circFoxo3	By FOXO3/EMT	Inhibit cell survival, migration, and invasion
circITCH	miR-17-5p/HOXB13	Inhibited cell proliferation, promoted cell apoptosis, and suppressed cell growth
circKATNAL1	miR-145-3p/WISP1	Inhibited proliferation, migration, and invasion
circLARP4	by FOXO3A	Inhibit cell migration and invasion
circMTO1	miR-17-5p	Inhibit cell proliferation and invasion
circPSMC3	By DGCR8	Inhibit migration and invasion
circRNA17	miR-181c-5p/ARv7	Inhibited cell growth and invasion
circSLC8A1	miR-21 and chemokine signaling	Inhibited proliferation, migration, and invasion
circSMAD2	miR-9/STAT3	Inhibited cell proliferation, migration, and invasion
circSOBP	miR-141-3p/p-MLC2	Inhibit migration, invasion, and metastasis
circUCK2	miR-767-5p/TET1	Inhibited cell proliferation and invasion
circ0004417	miR-1228, p-Akt, and E-cadherin	Inhibited proliferation and invasion
circ100395	miR-1228	Inhibited proliferation, migration, and invasion, altered cell cycle
has_circ_0007494	miR-616/PTEN	Inhibited proliferation, tumor growth, and invasion

that circCRKL overexpression inhibited cell cycle progression, migration, and invasion, while promoting apoptosis in vitro, and significantly suppressed tumor growth in vivo. In vivo studies showed overexpressing circCRKL inhibits the tumorigenesis of PCa. Mechanistically, circCRKL interacts with miR-141, a microRNA implicated in PCa progression. miR-141 promotes carcinogenesis by targeting Kruppel-like factor 5 (KLF5), a transcription factor that is expressed at low levels in PCa tissues and cells and is regulated by multiple miRNAs.

In overexpressing PCa cells, miR-141 increased KLF5 expression by inhibiting its circCRKL/miR-141/KLF5 axis. Overexpression of circCRKL antagonized miR-141 activity, leading to increased KLF5 expression, whereas miR-141 upregulation abrogated the tumor-suppressive effects of circCRKL. Collectively, these findings

indicate that circCRKL suppresses PCa proliferation and metastasis through the circCRKL/miR-141/KLF5 regulatory axis [48,49] (Fig. 6B).

3.3.3. circPDHX

circPDHX and miR-378a-3p axis

Silencing circPDHX significantly reduced PCa cell invasion and viability in both in vitro and in vivo models, whereas circPDHX overexpression exerted tumor-promoting effects. Mechanistically, circPDHX negatively regulates miR-378a-3p by binding to the Ago2-miR-378a-3p complex, thereby functioning as a competing endogenous RNA. Insulin-like growth factor 1 receptor (IGF1R) was identified as a direct target of miR-378a-3p in PCa cells, and its elevated expression

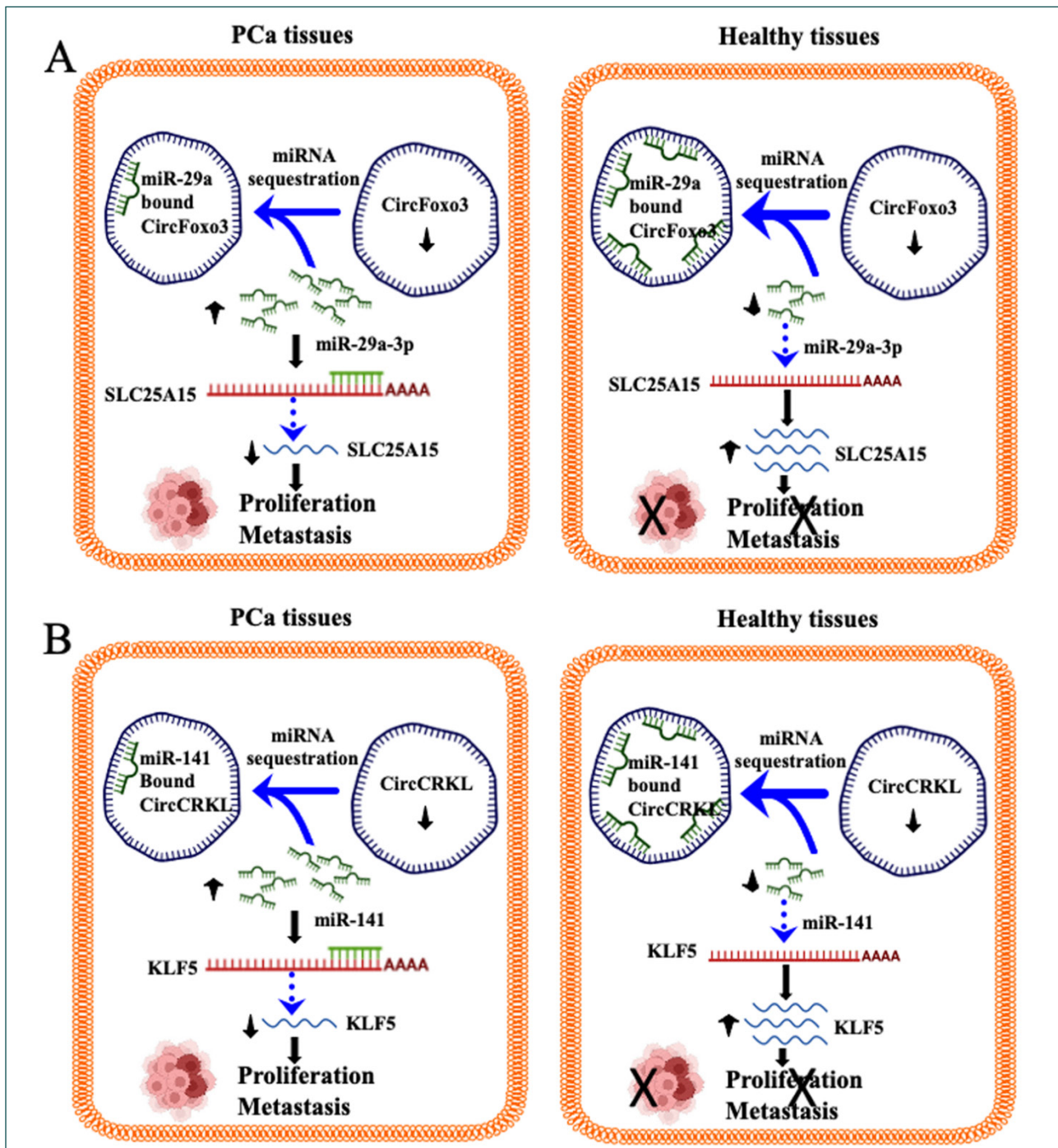


Figure 6: circRNA-miRNA-mRNA regulatory axes in prostate cancer progression.

(A) In PCa tissues, reduced circFOXO3 expression decreases sequestration of miR-29a-3p, leading to enhanced suppression of its target gene SLC25A15, thereby promoting cell proliferation and metastasis. In healthy tissues, higher circFOXO3 levels sponge miR-29a-3p, preserving SLC25A15 expression and limiting tumorigenic processes. (B) In PCa tissues, downregulation of circCRKL results in increased miR-141 activity, which suppresses KLF5 expression and contributes to enhanced proliferation and metastatic potential. In contrast, normal tissues exhibit higher circCRKL expression, which sequesters miR-141, maintains KLF5 levels, and restrains tumor progression. SLC25A15: Solute Carrier Family 25 Member 15, FOXO3: Forkhead Box O3, and KLF5: Kruppel-Like Factor 5. The up curly arrow and down curly arrow indicate increased and decreased levels, respectively and "X" denotes suppression of tumor-related cellular processes.

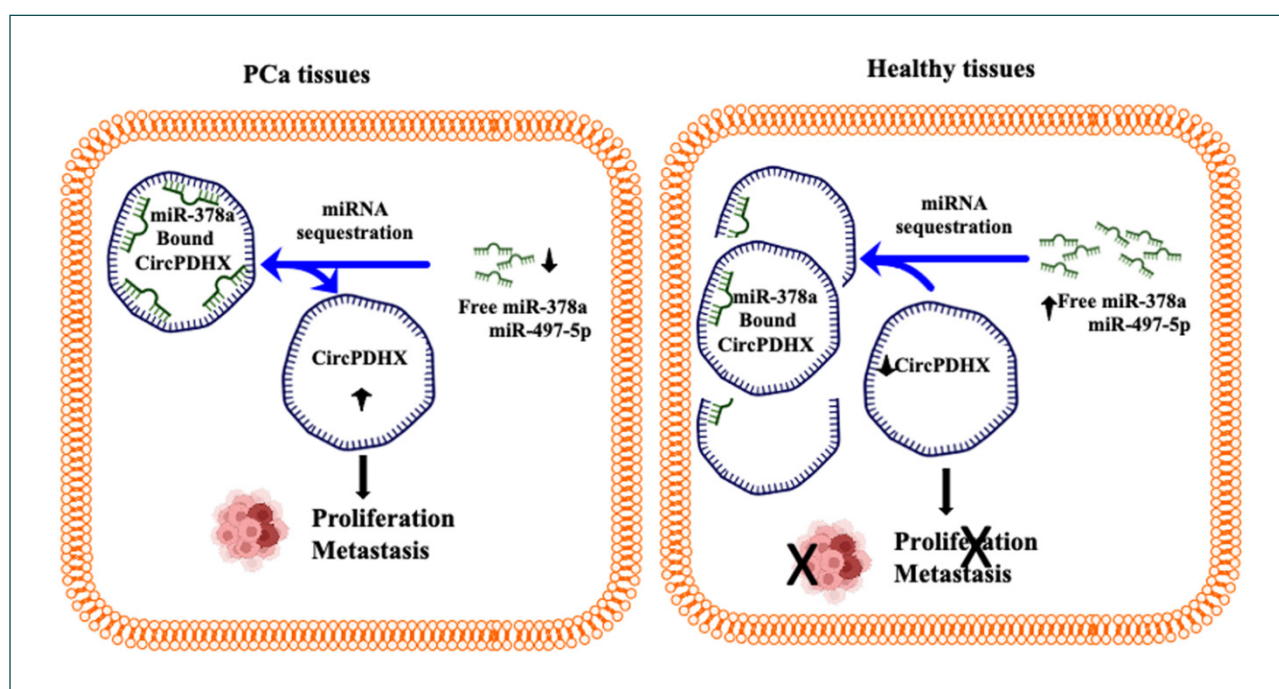


Figure 7: Differential regulatory role of circPDHX in prostate cancer (PCa) and healthy tissues.

In PCa tissues (left panel), circPDHX is upregulated and acts as a competing endogenous RNA (ceRNA) by sponging miR-378a and miR-497-5p, thereby reducing their availability. Sequestration of miR-378a leads to derepression of its downstream targets. Activation of these oncogenic pathways promotes PCa cell proliferation, invasion, and metastasis. In contrast, in healthy prostate tissues (right panel), circPDHX expression is relatively low, allowing miR-378a and miR-497-5p to remain functionally active. These miRNAs suppress downstream targets expression, thereby inhibiting abnormal cell proliferation and metastatic progression. PDHX: Pyruvate Dehydrogenase Complex Component X. Up curly arrow and down curly arrow indicate increased level, and decreased level, respectively, and "X" denotes suppression of tumor-related cellular processes

was associated with poor patient survival.

Consistently, miR-378a-3p overexpression attenuated circPDHX-induced cell proliferation and IGF1R expression and showed an inverse correlation with circPDHX levels. These findings indicate that circPDHX promotes PCa progression by sponging miR-378a-3p and upregulating IGF1R expression [50] (Fig. 7).

circPDHX-miR-497-5p axis

CircPDHX depletion markedly reduced PCa cell migration and proliferation. CircPDHX acts as a molecular sponge for miR-497-5p, thereby facilitating PCa progression, whereas miR-497-5p overexpression counteracted the oncogenic effects of circPDHX [51]. miR-497-5p directly targets acyl-CoA synthetase long-chain family member 1 (ACSL1), which is upregulated in PCa tissues. Restoration of ACSL1 expression reversed the suppressive effects of miR-497-5p on PCa cells. Collectively, these data suggest that PCa progression is associated with circPDHX and ACSL1 upregulation and concomitant miR-497-5p downregulation [52] (Fig. 7).

In PCa tissues (left panel), circPDHX is upregulated

and acts as a competing endogenous RNA (ceRNA) by sponging miR-378a and miR-497-5p, thereby reducing their availability. Sequestration of miR-378a leads to derepression of its downstream targets. Activation of these oncogenic pathways promotes PCa cell proliferation, invasion, and metastasis. In contrast, in healthy prostate tissues (right panel), circPDHX expression is relatively low, allowing miR-378a and miR-497-5p to remain functionally active. These miRNAs suppress downstream targets expression, thereby inhibiting abnormal cell proliferation and metastatic progression. PDHX: Pyruvate Dehydrogenase Complex Component X. Up curly arrow and down curly arrow indicate increased level, and decreased level, respectively, and "X" denotes suppression of tumor-related cellular processes

4. Future perspectives

NcRNAs play a promising role in regulating PCa invasion, metastasis, and disease progression. Therapeutic targeting of ncRNAs has been explored in several clinical trials, with encouraging outcomes. Our understanding of ncRNA function continues to expand through detailed investigations of their underlying

molecular mechanisms. In addition, inhibitors of lncMyoD have been evaluated as therapeutic agents in sarcoma, and the lncRNA HOTAIR is currently under clinical investigation as a diagnostic biomarker for colorectal cancer [53]. Collectively, these findings highlight the substantial clinical potential of ncRNAs in cancer diagnosis and treatment.

Several clinical trials have examined circulating and exosomal ncRNAs as diagnostic and prognostic biomarkers in PCa. One clinical trial (NCT06726070) evaluated blood expression levels of miR-107, miR-134-5p, miR-149-5p, miR-370-3p, and miR-221 to distinguish PCa from benign prostatic hyperplasia. Phase II studies have also been initiated to identify miRNA expression profiles in localized and high-risk PCa (NCT03338712 and NCT01220427) and to predict disease aggressiveness using exosomal miRNAs (NCT03911999). Together, these studies underscore the diagnostic and prognostic relevance of ncRNAs in PCa. Despite these advances, several challenges must be addressed before ncRNA-based therapeutics can be routinely implemented in clinical practice. RNA instability, limited delivery efficiency, lack of tissue specificity, and unintended off-target effects remain significant barriers. Moreover, differences between preclinical models and human disease biology contribute to a translational gap that hampers clinical success. Future research should prioritize the development of advanced delivery platforms, including nanoparticles, exosome-based systems, and chemical modifications, to enhance ncRNA stability and target specificity. Integrating ncRNA profiling with multi-omics data and precision medicine approaches may further improve patient stratification and therapeutic efficacy. Addressing these challenges will be essential to fully realize the clinical potential of ncRNA-based diagnostics and therapeutics in prostate cancer.

5. Conclusion

The precise pathophysiology of PCa is yet unknown, making it a complex condition. An extensive summary of the function of ncRNAs in PCa was given in this review. The ncRNAs control drug resistance, metastasis, cell proliferation, and survival by simultaneously targeting several signalling molecules. In addition to being prospective targets for PCa treatment, these ncRNAs have a significant regulatory role in carcinogenesis and can function as prognostic and diagnostic biomarkers. The importance of ncRNAs in

PCa has been well demonstrated, and the current issue is to identify ncRNAs that are functionally relevant to oncogenic alterations. The next issue is that the majority of the ncRNA marker candidates currently in use are derived from an insignificant sample, and their lack of validity restricts future advancements. There are still difficulties in managing metastatic CRPC, which highlights the need for innovative treatment. Therapeutics based on ncRNA have been contemplated as possible approaches to target PCa. However, this area of therapeutic application will advance with greater clarity on ncRNA activities. As seen with several FDA- and EMA-approved nano formulations in breast and lung cancers [54], the transition of innovative therapies from bench to bedside is both achievable and impactful. The promising outcomes from ongoing clinical trials involving miRNA and lncRNA biomarkers in prostate cancer may similarly pave the way for regulatory approval and clinical translation of ncRNA-based interventions

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Conflicts of interest

The authors have no conflict of interest.

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Literature search

We searched, using the keyword(s) "Prostate cancer, non-coding RNAs, and Signalling pathways from PubMed, Web of Science, Embase, Wan Fang, and China Science and Technology Journal Data databases from 2010 to 2024.

List of abbreviations

circRNAs - circular RNAs	OS - Overall Survival
ncRNAs - non-coding RNAs	mCRPC - metastatic castration resistant PCa
lncRNAs - long non-coding RNAs	PDHX - Pyruvate Dehydrogenase Complex Component X
PKM2 - Pyruvate Kinase Muscle isoform 2	KLF5 - Kruppel-Like Factor 5
ROCK2 - Rho-Associated Protein Kinase 2	FOXO3 - Forkhead Box O3
SIRT1 - Silent Information Regulator 1	SChLAP1 - Second Chromosomal Locus Associated with Prostate 1
PCa - Prostate cancer	AR - Androgen Receptor
PCA3 - Prostate Cancer Antigen 3	SLC25A15 - Solute Carrier Family 25-member 15
PRUNE2 - Prune Homolog 2	SWI/SNF - SWItch/Sucrose Non-Fermentable
HOTAIR - HOX Transcript Antisense RNA	MAPK - Mitogen-Activated Protein Kinase
SNP - Single Nucleotide Polymorphism	miRNAs - microRNAs
PSA - Prostate Specific Antigen	

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