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Mini-review

Long non-coding RNAs in prostate cancer: Functional roles and clinical implications

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ABSTRACT

Long noncoding RNAs (lncRNAs) are defined as RNA transcripts longer than 200 nucleotides that do not encode proteins. LncRNAs have been documented to exhibit aberrant expression in various types of cancer, including prostate cancer. Currently, screening for prostate cancer results in overdiagnosis. The consequent overtreatment of patients with indolent disease in the clinic is due to the lack of appropriately sensitive and specific biomarkers. Thus, the identification of lncRNAs as novel biomarkers and therapeutic targets for prostate cancer is promising. In the present review, we attempt to summarize the current knowledge of lncRNA expression patterns and mechanisms in prostate cancer. In particular, we focus on lncRNAs regulated by the androgen receptor and the specific molecular mechanism of lncRNAs in prostate cancer to provide a potential clinical therapeutic strategy for prostate cancer.

1. Introduction

Prostate cancer (PCa) is one of the most common malignancies in men, with morbidity and mortality rates ranking first and second, respectively, among male cancers in the United States. According to the Cancer Statistics Report, PCa accounted for 19% of all new cancer cases and a mortality rate of 9% among total cancer-related deaths [1]. Currently, screening for PCa is based on the measurement of serum prostate-specific antigen (PSA), also known as gamma-seminoprotein or kallikrein-3 (KLK3), and digital rectal examination (DRE), but whether screening improves outcomes is controversial [2]. Most cases of PCa can initially be affected by androgen deprivation therapy (ADT); however, over 12–36 months, the cancer will become resistant to current therapies and can progress to recurrent castration-resistant prostate cancer (CRPC). Although protein-coding genes have long been heavily researched in prostate cancer, with the development of high-throughput technology, the majority of the human genome was found to comprise noncoding transcripts, such as long noncoding RNAs (lncRNAs).

LncRNAs were previously considered junk genes because of their lack of an open reading frame (ORF) and protein-coding ability. However, recent studies have found that these “junk RNAs” play critical roles in human diseases and cancers. Recent studies have demonstrated that lncRNAs such as PCA3, GAS5, and HOTAIR are related to the occurrence and progression of prostate cancer. Aberrant expression of lncRNAs may promote prostate cancer cell proliferation, invasion, migration or epithelial–mesenchymal transition (EMT) but inhibit tumor cell apoptosis and antitumor drug sensitivity. However, the molecular mechanisms of action of lncRNAs are not very clear to date. In the present review, we focus on the specific molecular mechanisms of lncRNAs in prostate cancer to better understand lncRNAs and provide potential clinical therapeutic strategies for prostate cancer. (The molecular function, potential mechanism and its representative lncRNA are shown in Fig. 1).

2. The expression pattern and potential function of lncRNAs

2.1. The expression pattern of lncRNAs in prostate cancer

The majority of lncRNAs that are associated with PCa are overexpressed in tumor tissues and cancer cells relative to their expression

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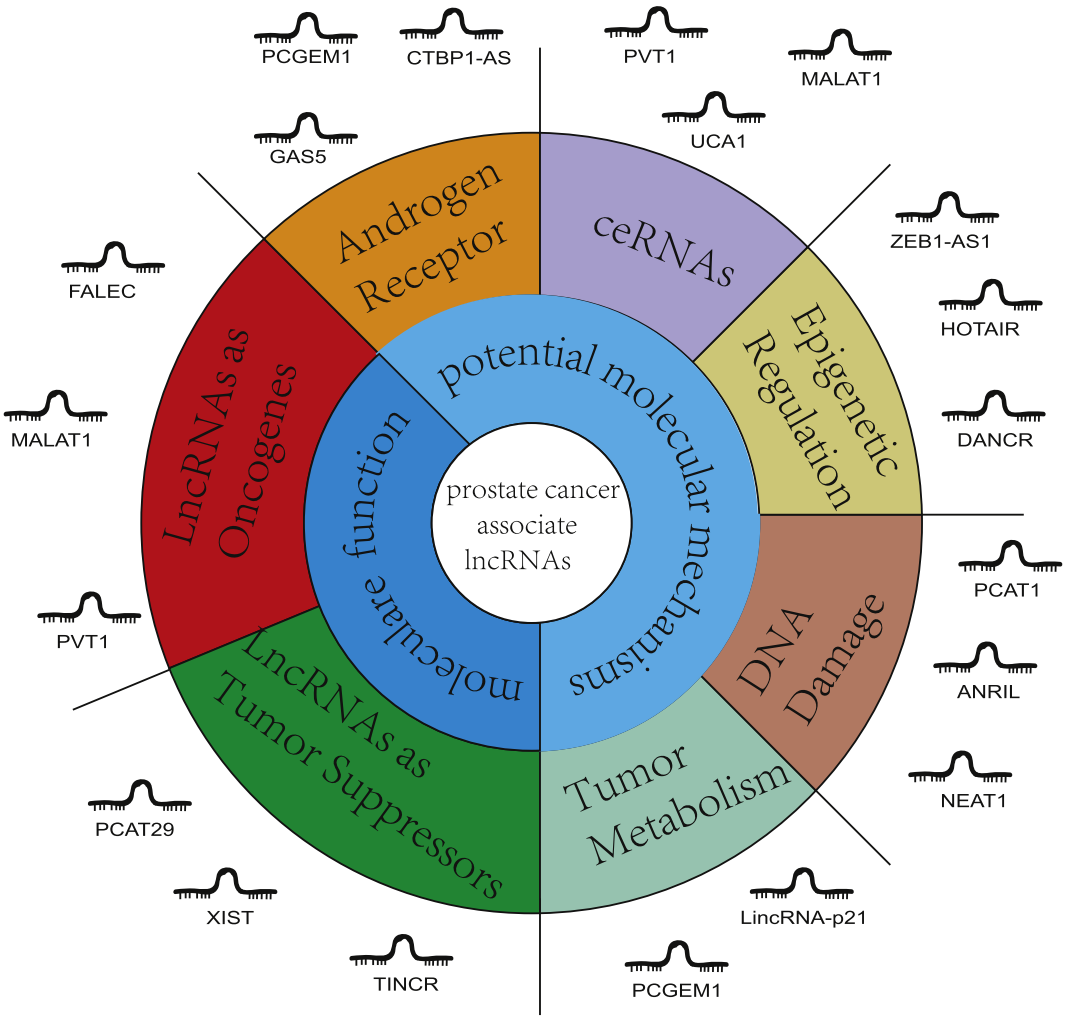

Fig. 1. The molecular function, potential mechanism of lncRNA and its representative lncRNA in prostate cancer. The molecular function of lncRNAs is showing as mazarine and is divided into oncogenes (red) and tumor suppressors (green). The potential mechanism of lncRNAs is exhibiting as baby blue, and the specific mechanism is showing as different color. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

in normal tissue and nontumorigenic cells. Moreover, most are hypothesized to exert oncogenic effects. Only a few lncRNAs are downregulated and may act as tumor suppressors. The expression patterns and potential molecular functions of lncRNAs related to PCa and the relevant references are summarized in Table 1.

2.2. The molecular function of lncRNAs in prostate cancer

Representing an emerging layer of cancer biology, lncRNAs contribute to tumor proliferation, invasion, and metastasis and may act as oncogenes or tumor suppressors. (Exhibited in Fig. 2 and Fig. 5A and B).

2.2.1. LncRNAs as oncogenes

LncRNA MALAT1 was reported to maintain the tumorigenicity and progression of prostate cancer. Ren S. *Et al* [3] found that MALAT1 was upregulated in prostate cancer and that higher MALAT1 expression was correlated with high prostate-specific antigen levels and Gleason scores as well as with tumor stage and castration-resistant prostate cancer. Downregulation of MALAT1 expression by siRNA targeting MALAT1 has a potential effect on prostate tumorigenicity and prostate cancer progression *in vitro* and *in vivo*. Downregulation of MALAT1 attenuated the growth, invasion and migration of prostate cancer cell lines and induced cell cycle arrest in G0/G1 phase in CRPC. Furthermore, downregulation of MALAT1 *in vivo* using therapeutic siRNA delayed tumor growth and decreased the metastasis of prostate cancer xenografts in castrated male nude mice as well as prolonged the survival of tumor-bearing mice. MALAT1 also plays a critical role in pre-mRNA processing and regulates the alternative splicing of pre-mRNA through the modulation of serine/arginine splicing factors [4,5]. Aberrant expression of MALAT1 has an impact on the normal splicing of a subset of mRNAs. However, it remains largely unknown whether MALAT1 affects normal mRNA splicing in prostate cancer. LncRNA SChLAP1 is frequently overexpressed in aggressive prostate cancers and plays a critical role in cancer cell invasiveness and metastasis. Mehra R. examined the expression of SChLAP1 by *in situ* hybridization (ISH) in 937 PCa patients with long-term follow-up and found that upregulation of SChLAP1 was strongly associated with the development of lethal PCa but not with age, Gleason score, pathologic stage, or PTEN status (HR, 2.2; 95% confidence interval, 1.1–4.1), indicating that SChLAP1 may be a biomarker for predicting PCa patients at higher risk of lethal progression [6]. Further mechanistic research elucidated that SChLAP1 contributed to the development of lethal prostate cancer by antagonizing the tumor-suppressive functions of the SWI/SNF chromatin-modifying complex [7]. SChLAP1 can directly disrupt SNF5 (sucrose Nonfermentable 5), which is a core subunit of the SWI/SNF complex, thus preventing the SWI/SNF complex from binding to its target promoters, which leads to decreased target gene expression and drives the

Table 1
Prostate cancer-associated long non-coding RNAs.

Category	LncRNA	Description	Function	Alteration in PC	Clinical Association	Ref
LncRNAs as Oncogenes	MALAT1	metastasis associated lung adenocarcinoma transcript 1	Promotes cell growth, invasion and migration	overexpression	diagnosis	[3–5]
	SChLAP1	SWI/SNF complex antagonist associated with prostate cancer 1	Relates with invasiveness and metastasis	overexpression	risk prediction	[6–8]
	PCAT1	prostate cancer associated transcript 1	Promotes cell proliferation	overexpression		[18,19]
	FALEC	focally amplified long non-coding RNA in epithelial cancer	Promotes proliferation and migration	overexpression	prognostic biomarker	[23]
	TUG1	taurine up-regulated 1	Promotes proliferation and migration	overexpression		[24]
	POU3F3	POU class 3 homeobox 3	Promotes proliferation	overexpression		[25]
	MYU	VPS9D1 antisense RNA 1	Promotes proliferation	overexpression		[26]
	NAP1L6	nucleosome assembly protein 1 like 6	Promotes cell proliferation, invasion and migration	overexpression		[27]
	LUCAT1	lung cancer associated transcript 1	Promotes cell invasion and migration	overexpression		[28]
	AFAP1-AS1	AFAP1 antisense RNA 1	Enhances cell metastasis and proliferation	overexpression		[29]
	ROR	regulator of reprogramming	Promotes cell proliferation, invasion and migration	overexpression		[30]
	GHET1	gastric carcinoma proliferation enhancing transcript 1	Promotes cell proliferation, inhibits apoptosis	overexpression		[31]
	HOTTIP	HOXA distal transcript antisense RNA	Promotes cell proliferation and chemosensitivity, inhibits apoptosis	overexpression		[32,33]
	PART1	prostate androgen-regulated transcript 1	Promotes cell proliferation, inhibit apoptosis	overexpression		[34]
	PVT1	plasmacytoma variant translocation 1	Promotes cell proliferation, migration, inhibits apoptosis	overexpression		[35,36]
LncRNAs as Tumor Suppressors	PCAT29	prostate cancer associated transcript 29	Suppresses cell migration and proliferation	down-expression	recurrence risk prediction	[40,41]
	DRAIC	downregulated RNA in cancer, inhibitor of cell invasion and migration	Suppresses cell migration, invasion, and EMT	down-expression		[40,41]
	H19	imprinted maternally expressed transcript	Suppresses cell migration	down-expression		[49]
	GAS5	growth arrest-specific 5	Suppresses proliferation, promotes apoptosis and chemotherapy/radiotherapy sensitivity	down-expression		[51,52,54]
	XIST	X inactive specific transcript	Suppresses cell proliferation and metastasis	down-expression		[56]
	BDNF-AS	BDNF antisense RNA	Suppresses cell proliferation and invasion	down-expression	prognostic biomarker	[57]
	TINCR	TINCR ubiquitin domain containing	Suppresses cell proliferation, migration and invasion	down-expression	prognostic biomarker	[58]
	IGF2AS	insulin growth factor 2 antisense	Suppresses cell proliferation and invasion	down-expression		[59]

(*continued on next page*)

Table 1 (*continued*)

Category	LncRNA	Description	Function	Alteration in PC	Clinical Association	Ref
Interact with AR	PCGEM1	Prostate cancer gene expression marker 1	Promotes cell proliferation, inhibits apoptosis interact with hnRNP A1 then repress the AR3 expression	overexpression	Risk prediction	[66,68–71]
	PRNCR1	prostate cancer associated non-coding RNA 1	Decreases cell viability and the AR transactivation	overexpression		[66,73]
	PCA3	prostate cancer antigen 3	Promotes cell growth and viability and modulating AR signaling genes	overexpression	Screening, prognostic marker and potential therapeutic target	[75,147]
	PlncRNA-1	prostate cancer up-regulated long noncoding RNA 1	Promotes cell proliferation, inhibit apoptosis	overexpression		[76]
	CTBP1-AS	CTBP1 antisense RNA	Regulates AR signaling and cell cycle	overexpression		[77,78]
	GAS5	growth arrest-specific transcript 5	inhibited by AR	overexpression		[84]
	SOCS2-AS1	suppressor of cytokine signaling 2-antisense transcript 1	Promotes cell growth and moderates AR target genes	overexpression in LTAD cells		[85]
	TMPO-AS1	TMPO antisense RNA 1	Promotes proliferation and migration, inhibits apoptosis	overexpression	diagnostic and prognostic marker	[86]
	LINC00304	long intergenic non-protein coding RNA 304	AR target lncRNA and promotes proliferation and migration, inhibits apoptosis	overexpression		[87]
	LINC00844	long intergenic non-protein coding RNA 844	AR target lncRNA and promotes migration and invasion	down-expression	prognostic marker	[88]
	LOC283070	Homo sapiens hypothetical protein LOC283070	Inhibits AR signaling pathway	overexpression		
	ARLNC1	androgen receptor regulated long noncoding RNA 1	Interacts with AR affecting cell growth	overexpression		[90]
	Linc00963	long intergenic non-protein coding RNA 00963	Promotes proliferation and migration, inhibits apoptosis	overexpression in AI cells		[91]
	HOTAIR	HOX transcript antisense RNA	Drivers of androgen-independent AR activation, cell growth and invasion	overexpression in ADT and CRPC		[92,98]
	HOXD-AS1	HOXD antisense growth-associated long non-coding RNA	Promote cell proliferation and chemo-resistance	overexpression in CRPC	prognostic marker	[101]
	PCAT5	prostate cancer associated transcript 5	Promotes cell growth, invasion, migration and clone formation, inhibits apoptosis	expresses in ERG-positive PCa		[102]
	BCAR4	breast-cancer anti-estrogen resistance 4	Promotes cell growth and migration	overexpression in CRPC	prognostic marker	[103]
	HORAS5	Hormone-Resistance Associated non-coding Sequences 5	Maintains AR activity and AR target gene	overexpression in CRPC	prognostic marker	[104]
	PCAT1	prostate cancer associated transcript 1	Regulates progression of CRPC	overexpression in CRPC	progressive marker	[105]
	MIR222HG	miR222/221 cluster host gene	Promotes cell growth	overexpression in CRPC	progressive marker	[106]
ceRNA	PVT1	plasmacytoma variant translocation 1	Adsorbs miR-146a, miR-186, promote cell viability and EMT, inhibit apoptosis	overexpression		[116,117]
	MALAT1	metastasis associated lung adenocarcinoma transcript 1	Adsorbs miR-145, miR-320, miR-1, promotes cell proliferation, migration and invasion, inhibits apoptosis	overexpression		[118–120]
	NEAT1	nuclear paraspeckle assembly transcript 1	Adsorbs miR-34a, regulate sensitivity of anti-tumor drugs	overexpression		[121]
	UCA1	urothelial cancer associated 1	Adsorbs miR-184, miR-204, regulates cell growth, metastasis and sensitivity of chemotherapy	overexpression		[123–126]
	HOTTIP	HOX transcript antisense RNA	Adsorbs miR-216a, promotes cell proliferation, migration and invasion	overexpression		[127]
	PCGEM1	Prostate cancer gene expression marker 1	Adsorbs miR-148a, induces apoptosis	overexpression		[128]
	LEF1-AS1	LEF1 antisense RNA 1	Adsorbs miR-330, promotes cell proliferation, invasion, migration and EMT	overexpression		[129]
	PCA3	prostate cancer antigen 3	Adsorbs miR-218, promotes cell proliferation, invasion, migration and inhibit apoptosis	overexpression		[130]
	SNHG15	small nucleolar RNA host gene 15	Adsorbs miR-338, promotes cell proliferation, invasion, migration and EMT	overexpression		[131]
	SNHG7	small nucleolar RNA host gene 7	Adsorbs miR-503, modulates cell cycle	overexpression		[132]
	ANRIL	CDKN2B antisense RNA 1	Adsorbs let-7a, promotes cell proliferation and migration	overexpression		[133]

(*continued on next page*)

Table 1 (*continued*)

Category	LncRNA	Description	Function	Alteration in PC	Clinical Association	Ref
Epigenetic Regulation	NEAT1	nuclear enriched abundant transcript 1	Alters the chromatin landscape of target promoters	overexpression	progressive marker	[134]
	ANRIL	CDKN2B antisense RNA 1	Regulates gene silencing			[135,136]
	PCAT1	prostate cancer associated transcript 1	Transcriptional repressor	overexpression		[18]
	HOTAIR	HOX transcript antisense RNA	Modulates the PRC2 complex suppressing AR transcription			[99]
	DANCR	differentiation antagonizing non-protein coding RNA	Binds to EZH2 promoting invasion			[137]
	ZEB1-AS1	the lncRNA ZEB1 antisense 1	Binds to and recruit MLL1 inducing H3K4me3 and promoting ZEB1 expression			[138]
DNA Damage	PCAT1	prostate cancer associated transcript 1	Suppresses homologous recombination (HR) and DNA repair	overexpression		[18,22]
	ANRIL	CDKN2B antisense RNA 1	Binds with PRC2 and positively regulates homologous recombination and represses the expression of adjacent gene	overexpression		[136,139]
	NEAT1	nuclear paraspeckle assembly transcript 1	Binds with transcription factors-CDC5L inhibiting its target gene and affecting DNA damage, cell cycle, proliferation			[140]
	GAS5	growth arrest-specific 5	Interacts with miR-18a affecting cell viability and survival, apoptosis and DNA damage			[141]
Tumor Metabolism	LincRNA-p21	tumor protein p53 pathway corepressor 1	Regulates the Warburg effect by accumulating of HIF-1 and affecting VHL-mediated ubiquitination	overexpression		[142]
	PCGEM1	Prostate cancer gene expression marker 1	Promotes prostate cancer growth by upregulating multiple metabolic pathways			[144]

Abbreviations:Ref:References; LTAD: long term androgen deprived; AI: androgen-independent; ADT: androgen deprivation therapies; ERG: early growth response; PCa: prostate cancer; CRPC: castration-resistant prostate cancer; EMT: epithelial-mesenchymal transition.

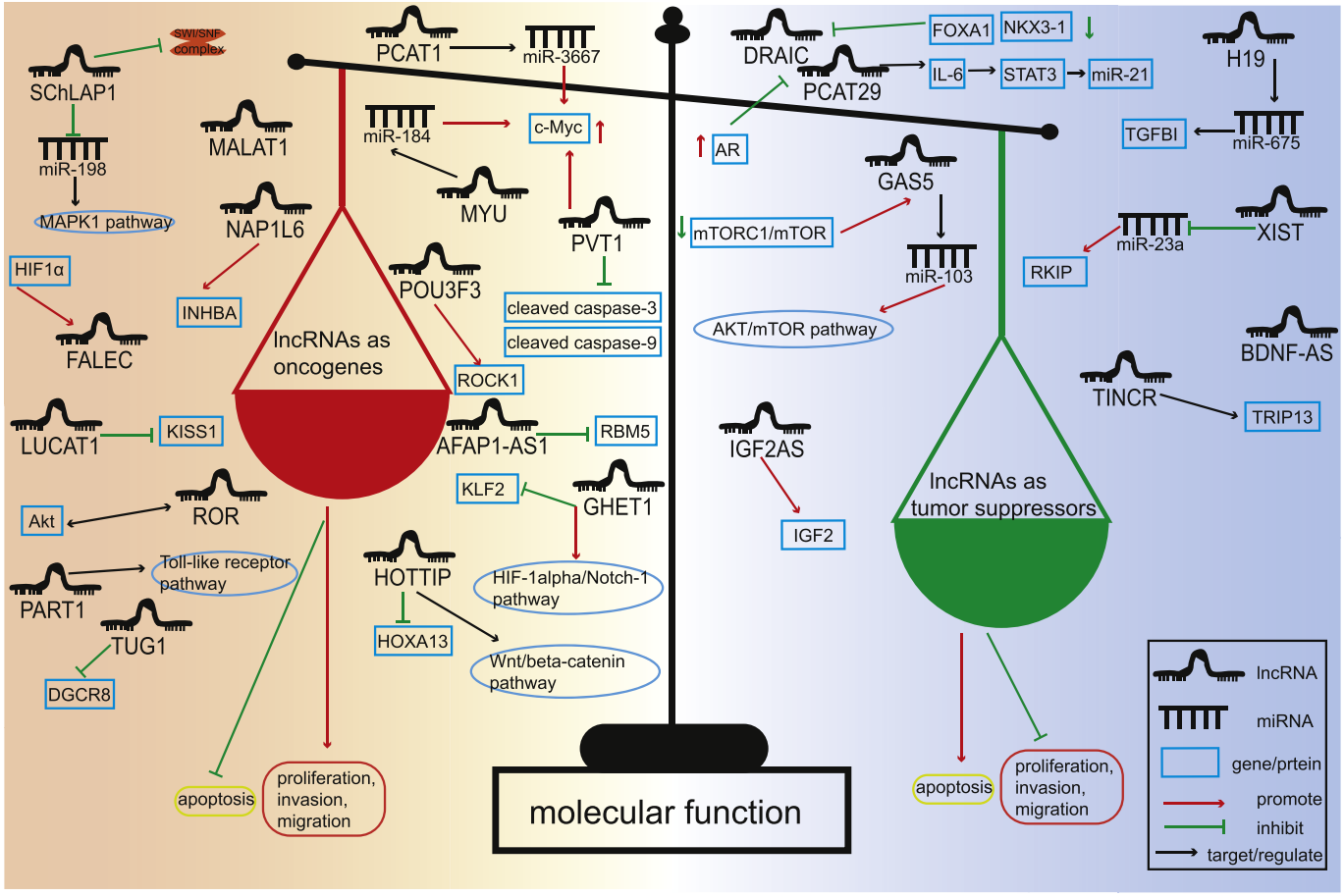

Fig. 2. The molecular function of lncRNAs regulates prostate cancer progression. LncRNA function as oncogenes or tumor suppressors just like an unbalanced balance. On the right of balance (red), lncRNAs act as oncogenes and are overexpressed in prostate cancer, on the contrary in left (green), lncRNA acts as tumor suppressors. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

development of lethal prostate cancer [7,8]. In contrast, SChLAP1 can exert its oncogenic effects at the miRNA level in PCa. Li Y. found that SChLAP1 negatively regulated miR-198 and subsequently affected the MAPK1 signaling pathway [9].

Another lncRNA, PCAT1 (prostate cancer-associated intergenic noncoding RNA transcript 1), an ectopically expressed lncRNA in extrahepatic cholangiocarcinoma (ECC) and hepatocellular carcinoma [10,11], was also extensively investigated and found to be critical for prostate cancer pathogenesis. This lncRNA resides on chromosome 8q24, a locus that harbors prostate cancer-associated SNPs and exhibits frequent chromosomal amplification [12–17]. On the basis of whole-transcriptome analysis, Prensner JR et al. previously identified PCAT1 as the top-ranked and most upregulated lncRNA in prostate cancer tissues [18]. In addition, independent studies corroborated the overexpression of PCAT1 in prostate cancer [19] and the promise of its development into a prognostic biomarker for colorectal cancer metastasis and poor survival in patients [20]. The prostate-specific PCAT1 is markedly overexpressed in a subset of high-grade localized and metastatic prostate cancers, particularly metastatic prostate cancers, and is implicated in prostate cancer progression [18]. It was observed that overexpression of PCAT1 even at physiological levels increased cell proliferation, whereas its knockdown with three independent siRNA oligos resulted in a decrease in the cell proliferation rate of approximately 25%–50%. As mentioned above, PCAT1 is transcribed from a gene desert on chromosome 8q24 approximately 725 kB upstream of the c-MYC oncogene. Further study revealed that PCAT1 promoted prostate cell proliferation in a manner dependent on upregulation and stabilization of the oncogenic c-Myc protein. Antagonism of c-Myc reversed PCAT1-mediated cell proliferation. Mechanistically, PCAT1 regulates c-Myc post-transcriptionally via the c-Myc 3′UTR. PCAT1 has a protective effect on c-Myc by disrupting the regulation of c-Myc via miR-3667-3p targeting. Conversely, targeting PCAT1 with miR-3667-3p reverses its protective effect on c-Myc [21]. Furthermore, PCAT1 implicated in the regulation of DSB (double-stranded DNA breaks) repair, inhibited homologous recombination by repressing the BRCA2 tumor suppressor gene [22]. Collectively, these data suggest that PCAT1 functions as an oncogene and is gradually emerging as a molecular biomarker in molecular research and therapy.

LncRNA FALEC can predict the prognosis of PCa patients, and the different expression levels of FALEC are statistically associated with the Gleason score and tumor invasion depth in patients. Upregulation of FALEC promotes proliferation and migration in prostate cancer cell lines. These researchers found that FALEC is a potential hypoxia-induced lncRNA; it can be induced by HIF1α (a master regulator of hypoxia) because HIF1α can interact with the hypoxia response element (HRE) in the promoter region of FALEC [23]. Similarly, lncRNA TUG1 is overexpressed in PCa samples, and upregulation of TUG1 expression may enhance the migration and invasion abilities of PCa cells; in contrast, TUG1 downregulation promotes DGCR8 expression at the mRNA and protein levels [24].

Serval lncRNAs were found to possibly promote cancer progression by promoting the malignant proliferation or migration and invasion of cancer cells. For example, ectopic expression of lncRNA POU3F3 may activate ROCK1 to promote PCa cell proliferation [25], and the c-Myc-upregulated lncRNA MYU (VPS9D1 antisense RNA1, annotated as VPS9D1-AS1) is upregulated in prostate cancer tissues and may

competitively bind miR-184, resulting in c-Myc upregulation and subsequent promotion of cell proliferation [26]. In contrast, lncRNA NAP1L6 is overexpressed in PCa and promotes the expression of INHBA, affecting cell migration, invasion, and proliferation [27]. Conversely, upregulation of lncRNA LUCAT1 enhances the migration and invasion of prostate cancer cells by downregulating the mRNA and protein expression of KISS1 [28]. In addition, ectopic expression of lncRNA AFAP1-AS1 enhances cell metastasis and proliferation by suppressing RBM5 in prostate cancer [29]. Zhai. et al. found that the strikingly increased expression of lncRNA ROR in PCa tissues was strongly associated with tumor stage and with lymph node and distant metastasis. Mechanistically, ROR may promote PCa cell proliferation, invasion and migration via mutual regulation between ROR and Akt [30]. LncRNA GHET1 is highly expressed in PCa, and downregulation of GHET1 suppressed cell proliferation and promoted cell apoptosis by promoting KLF2 expression but inhibiting the HIF-1alpha/Notch-1 signaling pathway [31].

Apoptosis is a type of programmed cell death that occurs in multicellular organisms and is important for maintaining internal stability. However, several studies have found that some dysregulated lncRNAs participate in apoptosis bioprocesses. HOTTIP is a lncRNA that can regulate HOXA13 expression and contribute to the progression, including the proliferation and apoptosis of prostate cancer, as reported by Zhang SR et al. [32]. In contrast, Jiang H. et al. found that HOTTIP expression was increased in PCa samples at the mRNA level and that HOTTIP downregulation suppressed the proliferation of PCa cells but promoted cell cycle arrest and cisplatin chemosensitivity, which may be attributed to the regulation of the Wnt/beta-catenin signal pathway [33]. Similarly, Sun M discovered that lncRNA PART1 influenced cell proliferation and apoptosis by modulating Toll-like receptor pathways and that downregulation of lncRNA PART1 inhibited prostate cancer cell proliferation and accelerated cell apoptosis [34]. PVT1 (plasmacytoma variant translocation 1) is a well-known lncRNA reported in numerous cancers due to its aberrant expression. Yang J. et al. found that PVT1 was overexpressed in prostate cancer tissues and cells and that higher levels of PVT1 predicted poor prognosis. PVT1 knockdown via siRNA significantly suppressed prostate cancer growth *in vivo* and *in vitro* and promoted cell apoptosis, and the decrease in the level of PVT1 resulted in upregulation of cleaved caspase-3 and cleaved caspase-9 expression but downregulation of c-Myc expression [35]. In addition, downregulated PVT1 in prostate cancer cells and found that proliferation and migration were significantly inhibited, which may be associated with the suppression of the p38 phosphorylation [36]. Moreover, several lncRNAs have recently been reported to be associated with EMT (epithelial-mesenchymal transition) to moderate proliferation and apoptosis, such as lncRNA CCAT2, lncRNA ATB, and PlncRNA-1 [37–39]. The expression of these lncRNAs was found to be significantly upregulated in tumor tissues compared with that in normal tissues, and knockdown of these lncRNAs stimulated EMT through regulating EMT-associated genes, such as E-cadherin, N-Cadherin and CyclinD1.

Altogether, these data propose an important role of lncRNAs as oncogenes in prostate cancer and indicate that the cancer-specific functions of these lncRNAs may be harnessed to regulate tumorigenesis.

2.2.2. LncRNAs as tumor suppressors

Malik R et al. first reported a novel long nuclear noncoding RNA, prostate cancer-associated transcript 29 (PCAT29), which is located on chromosome 15q23 and composed of 6 exons that are alternatively spliced to produce multiple isoforms [40]. PCAT29 can regulate oncogenic phenotypes *in vitro* as well as *in vivo*. PCAT29 knockdown with two independent shRNAs significantly increased the proliferation and migration of prostate cancer cells. However, PCAT29 overexpression reversed these effects, as demonstrated in chick chorioallantoic membrane assays. Furthermore, patients with lower PCAT29 expression have a significantly higher risk of biochemical recurrence than patients with higher PCAT29 expression, consistent with the experimental findings *in vitro* and *in vivo*. Mechanistically, the androgen receptor can directly bind to the PCAT29 promoter and lead to the suppression of gene expression. Another study also identified the regulatory effects of AR and FOXA1 on PCAT29 [41]. Additionally, Sakurai K et al. discovered a novel tumor suppressor locus that encodes two hormone-regulated lncRNAs, PCAT29 and DRAIC (LOC145837); structurally, DRAIC is located 20 kB upstream of PCAT29 [41]. LncRNA DRAIC is downregulated as prostate cancer cells progress from androgen-dependent (AD) to CRPC, a phenomenon attributed to the decreased activity of FOXA1 and NKX3-1, and the aberrant AR activation and increased DRAIC levels in prostate cancer are associated with extended disease-free survival (DFS) times. DRAIC prevents cuboidal epithelial cells from transforming into a fibroblast-like morphology and reduces the rate of cellular migration and invasion. Similar to the regulation of PCAT29 by AR [40], androgen induces the binding of the androgen binding to the DRAIC locus and can lead to repressed DRAIC expression. However, scientists found that PCAT29 functions as a tumor suppressor in prostate cancer via the IL-6/STAT3/miR-21 pathway. PCAT29 was downregulated in prostate cancer tissue and cell lines, while IL-6 (a cytokine), which can activate signal transducer and activator of transcription 3 (STAT3), was upregulated; the high level of STAT3 negatively modulated the expression of PCAT29, and miR-21 is a downstream target of STAT3, the inhibition of which enhanced basal PCAT29 expression [42]. Taken together, these findings identify PCAT29 as the first androgen-regulated tumor suppressor in prostate cancer and suggest that its loss of function may differentiate a subset of patients at increased risk and with poor prognostic outcomes for disease recurrence. The tumor-suppressive nexus of the lncRNA DRAIC/PCAT29 locus is a prognostic factor for a wide variety of cancer types.

Another well-known lncRNA that functions as a tumor suppressor in PCa is H19. The gene containing lncRNA H19 produces a spliced, capped, and polyadenylated lncRNA with a length of 2.3 kB [43]; this gene, an imprinted oncofetal gene, is transcribed from the H19/Igf2 gene cluster on chromosome 11p11.5 and does not code for a protein. This gene is abundantly expressed during embryogenesis, is downregulated after birth and shuts off in most tissues except for adult skeletal muscle and heart, but it is usually aberrantly expressed in both pediatric and adult tumors. This observation identified H19 as a candidate oncogene [44]. For instance, accumulating evidence has demonstrated that H19 promotes breast [45] and choriocarcinoma carcinogenesis [46] and additionally affects chemoresistance in breast cancer [47]. Sun S. C. et al. found that H19 expression was higher in both HGPC (highdouble ended arrowGleason score prostate cancer) and LGPC (lowdouble ended arrowGleason score prostate cancer) than in BPH (benign prostatic hyperplasia). Downregulating H19 inhibited cell growth, glucose consumption and lactic acid production in AR-negative cells, indicating that H19 may play an oncogenic role in prostate cancer [48]. However, Zhu M. et al. found that lncRNA H19 can also act as a suppressor of prostate cancer metastasis [49]. Compared to the nonmetastatic prostate epithelial cell line, the metastatic PCa cell line exhibited significant downregulation of both H19 and H19-derived miRNA. When H19 was upregulated in the nonmetastatic prostate epithelial cell line, the level of miR-675 was significantly increased, and cell migration was repressed. The expression levels of H19 and miR-675 were opposite those of TGFBI (transforming growth factor β-induced protein), which was reported to be involved in cancer metastasis. Furthermore, miR-675 targeted TGFBI by directly binding to the 3′UTR of TGFBI mRNA, thereby repressing its translation. Taken together, these results implicate the H19-miR-675 axis as a suppressor of prostate cancer metastasis.

LncRNA GAS5, namely, growth arrest-specific 5, is encoded on a prostate cancer-associated locus on chromosome 1q25 that is a risk locus for sporadic prostate cancer [50]. Downregulation of GAS5 expression was associated with the progression of LNCaP cells to CRPC [51]. Pickard MR et al. [52] found that cell death was strongly correlated with the level of cellular GAS5, which promoted the apoptosis of

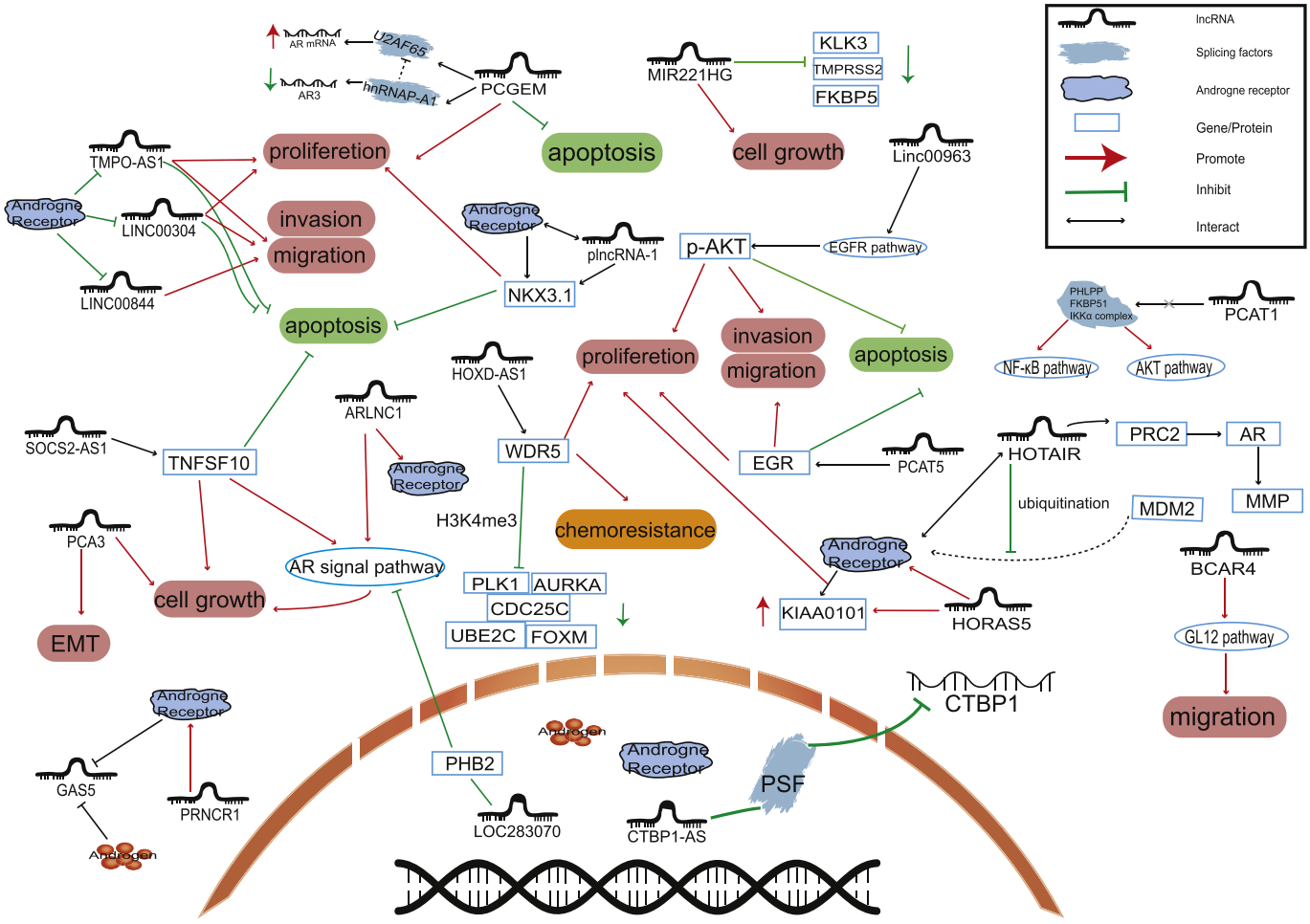

Fig. 3. LncRNAs regulate prostate cancer by interacting with androgen receptor (AR). Red arrow indicates promotion and the green solid line represents suppression. Solid lines signify an active pathway, and dashed lines an inactive pathway. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

prostate cells. When transfected with GAS5-encoding plasmids, 22Rv1 and PC-3 prostate cancer cells exhibited increased apoptosis and reduced survival. Furthermore, the UV-C irradiation- and chemotherapeutic drug-induced death of 22Rv1 cells was augmented or attenuated following upregulation or downregulation of GAS5 expression, respectively, suggesting that the level of GAS5 was related to radio- and chemosensitivity and that abnormally low levels of GAS5 expression may decrease the effectiveness of chemotherapeutic agents. Moreover, another study demonstrated that mTORC1/mTOR inhibitors can both enhance cellular GAS5 expression and inhibit growth in androgen-dependent and androgen-sensitive prostate cancer cells but not in androgen-independent cells and that the level of GAS5 was positively correlated with the sensitivity to mTOR inhibitors [53]. Similarly, Xue D. studied GAS5 in prostate cancer and found via ISH (*in situ* hybridization) and RT-PCR that its expression levels were appreciably lower in PCa tissues and cell lines than in normal tissue or normal cell lines. Moreover, lncRNA GAS5 can inhibit PCa proliferation and progression by inactivating the AKT/mTOR signaling pathway by targeting miR-103 *in vitro* and *in vivo* [54]. In addition, the levels of lncRNAs HCG11 and XIST were found to be significantly lower in PCa specimens than in nontumor tissues, and low levels of both of these lncRNAs were associated with poor prognosis [55,56]. Yang Du et al. demonstrated that XIST can suppress cell proliferation and metastasis *in vivo* and vitro in prostate cancer; mechanistically, XIST promotes RKIP expression at the posttranscriptional level through negatively regulating the expression of miR-23a [56].

LncRNA BDNF-AS is downregulated in PCa samples and cells, and low BDNF-AS expression is associated with poor prognosis and shorter overall survival in patients. Upregulation of BDNF-AS inhibited cell proliferation and invasion *in vitro*, indicating that BDNF-AS may be a good prognostic biomarker and a candidate molecular target [57]. Similarly, lncRNA TINCR was downregulated in PCa tissues, and low expression of TINCR was associated with advanced clinical T stage, lymph node involvement, distant metastasis, high Gleason score and poor prognosis in PCa patients. Functional assays revealed that TINCR regulates prostate cancer cell proliferation, migration and invasion by modulating TRIP13 expression [58]. In addition, lncRNA IGF2AS (insulin growth factor 2 antisense) is downregulated in PCa tumors and cell lines, and IGF2AS upregulation suppresses IGF2 expression and its effects on PCa proliferation and invasion [59].

Considering the evidence mentioned above, lncRNAs serve as transcriptional regulators, oncogenes or tumor suppressor genes in prostate cancer. We may infer the possibility that the reactivation of tumor suppressor lncRNAs or the inhibition of oncogenic lncRNAs could be a powerful approach for therapeutic intervention in prostate cancer. However, current knowledge of the lncRNA mechanisms of action is considerably limited. Hence, to better understand the regulatory networks in order to discover new approaches for prostate cancer intervention, further efforts to characterize additional lncRNAs and, more importantly, their mechanisms of action, are necessary.

2.3. *The potential molecular mechanism of lncRNAs*

The mechanisms of lncRNAs are complex and involve the androgen

receptor (AR), competing endogenous RNAs (ceRNAs) and DNA damage. (summarized in Fig. 1). Below, we elaborate on the specific mechanisms, putative functions and molecular targets of lncRNAs in PCa.

2.3.1. LncRNAs mediate prostate carcinogenesis through the androgen receptor

The androgen receptor (AR) is essential for the growth and differentiation of the healthy prostate; however, it is also an important risk factor for PCa. Aberrant AR hyperactivity is a decisive factor in prostate carcinogenesis. The proliferation of prostate cancer cells relies uniquely on androgen activity [60], and blocking the AR signaling pathway with androgen deprivation therapy has a significant effect on tumor regression in the early stages of prostate cancer [61,62]. Strikingly, almost all patients with advanced prostate cancer will eventually progress to castration-resistant states, in which the prostate cancer becomes androgen-independent and acquires the ability to metastasize after 1–2 years of androgen deprivation therapy [63]. Although the concrete mechanisms involved in the regulation of aberrant AR activity remain largely unclear, and further research is needed, it is critical and essential to define the early molecular events to better comprehend the development and progression of prostate cancer. Takayama et al. elucidated via AR transcriptional network analysis that the intergenic or antisense region of genes transcribe the AR-regulated transcripts of unknown function in prostate cancer, indicating that the transcripts of unknown function regulated by AR may partly comprise a series of noncoding RNAs [64,65]. As mentioned above, lncRNAs account for a large proportion of noncoding RNAs, and their mutation and aberrant expression affects prostate cancer susceptibility and viability. Therefore, it is important to elucidate the regulatory mechanisms of lncRNAs involved in the AR signaling pathway in PCa. The lncRNAs that participate in AR regulation are summarized in Fig. 3 and Fig. 5 C.

Several lncRNAs are involved in prostate carcinogenesis. Among these, PCGEM1 and PRNCR1 (prostate cancer noncoding RNA1, also known as PCAT8) have been identified as critical actors in disease progression through coordination with AR signaling [66]. LncRNA PCGEM1, located at a high-risk locus for prostate cancer on chromosome 2q32, is a highly prostate tissue-specific, androgen-regulated gene [67–69]. PCGEM1 is expressed particularly in an AR-positive prostate cancer cell line [69], and its uniform subcellular localization remained unaltered upon AR transcriptional activation [70]. Overexpression of PCGEM1 affects PCa cell growth by dramatically promoting cell proliferation and colony formation [68]; in addition, it suppressed doxorubicin-induced apoptosis of PCa cells in an androgen-dependent manner [71]. However, whether AR mediated the resistance to chemotherapy-induced cell death associated with this gene was not determined. Recently, Zhang Z et al. revealed that PCGEM1 participates in AR alternative splicing [72]. This study suggested that androgen deprivation (AD) upregulated PCGEM1 expression and altered its subcellular redistribution. In addition, the functional interaction of PCGEM1 with splicing factors, including heterogeneous nuclear ribonucleoprotein (hnRNP) A1 and U2AF65, determined the expression of AR3 (AR-V7), which is a predominant and clinically important AR splice variant that plays an important role in castration resistance. Mechanistically and of considerable interest, the PCGEM1-hnRNP A1 interaction inhibits the binding of hnRNP A1 to AR pre-mRNA, thus suppressing AR3 transcription by exon skipping, whereas the interaction of PCGEM1 with U2AF65 promotes PCGEM1 binding to AR pre-mRNA. This binding leads to increased AR3 transcription by exonization, which implies that hnRNP A1 functions as a repressor and that U2AF65 functions as an enhancer of AR3 expression. LncRNA PRNCR1 is transcribed from chromosome 8q24, which is a prostate cancer susceptibility locus [73]. Yang et al. demonstrated that PRNCR1 and PCGEM1 were overexpressed in therapy-resistant prostate cancer [66]. Inhibition of PRNCR1 attenuated cell viability and decreased AR transactivation in prostate cancer, suggesting that PRNCR1 contributes to prostate carcinogenesis through affecting the AR pathway [73].

However, in contrast to prior reports, a study including more than 230 high-risk prostate cancer patients conclusively demonstrated that neither PCGEM1 nor PRNCR1 had prognostic relevance or interacted with AR to render androgen independence and that neither was a component of AR signaling [74]; these findings refute the suggestions that either PCGEM1 or PRNCR1 interacts with the AR signaling pathway. Notably, all research about the regulation of PCGEM1/PRNCR1 by AR had been conducted *in vitro*. Thus, recently, Parolia A et al. specifically investigated the relationship between AR and PCGEM1/PRNCR1 *in vivo* using patient-derived xenograft PCa models and concluded that PCGEM1 was regulated by androgen receptor activity *in vivo* [70]. In this study, the PCGEM1-and PCGEM1-associated gene expression signature (GES) was sharply downregulated following androgen castration therapy and upregulated upon AR activation *in vivo*, though parallel evidence following AR stimulation *in vitro* was not found.

Another study by Ferreira LB [75] suggested that lncRNA PCA3 could be an additional therapeutic strategy for prostate cancer, based on the findings that LNCaP cells transfected with siPCA3 exhibited significantly inhibited cell growth and viability along with an increased proportion of G0/G1 phase cells and an increased percentage of pyknotic nuclei. Correspondingly, the expression of AR target genes was downregulated, which suggests that the mechanism of PCA3 in PCa operates at least in part through modulating AR signaling. In addition, knockdown PCA3 increased the expression of several transcripts coding for AR cofactors and EMT markers [166]. Cui Z reported that PlncRNA-1 (prostate cancer upregulated long noncoding RNA 1) is significantly upregulated in prostate cancer cells and tissues and, further, found reciprocal regulation between PlncRNA-1 and the androgen receptor that contributes to prostate cancer pathogenesis [76]. Silencing of PlncRNA-1 significantly inhibited proliferation and induced apoptosis in prostate cancer cell lines, accompanied by a decrease in the expression of AR and NKX3.1. Notably, in contrast, blockade of AR signaling also inhibited PlncRNA-1 expression. These results suggest a mutual feedback loop between PlncRNA-1 and AR and identify PlncRNA-1 as a potential target for prostate cancer therapy. Another study provided new insight into the functions of lncRNA CTBP1-AS, which is derived from the antisense region of the CTBP1 (C-terminal binding protein 1) gene, a corepressor of the androgen receptor. This lncRNA is predominantly located in the cell nucleus, and its upregulation promotes tumor growth in both hormone-dependent and castration-resistant prostate cancer [77,78]. CTBP1-AS directly inhibits CTBP1 expression by recruiting histone deacetylases and the RNA-binding transcriptional repressor PSF. Furthermore, CTBP1-AS exhibits global androgen-dependent activity by repressing the expression of tumor suppressor genes via a PSF-dependent mechanism, thus contributing to cell cycle progression [78].

LncRNA GAS5 (growth arrest-specific transcript 5), has been reported to be a suppressor in many tumors [79–82]. In prostate cancer, two transcripts of GAS5 (GAS5-O1 and GAS5-AE) that can promote PCa cell apoptosis were researched by Pickard MR et al. [83]. However, Zhang Y et al. found that GAS5 may function as an oncogene and be correlated with AR. The GAS5-007 (ENST00000456293.5) transcript was downregulated by androgen treatment and inhibited by AR, and was overexpressed in PCa tissue relative to its expression in normal tissue in both human tissue samples and public database cohorts [84]. LncRNA SOCS2-AS1 (suppressor of cytokine signaling 2-antisense transcript 1) is another lncRNA regulated by AR that can inhibit the apoptosis and promote the growth of prostate cancer cells [85]. The expression of SOCS2-AS1 was higher in long-term androgen-deprived (LTAD) cells—castration-resistant prostate cancer model cells—than in the parental androgen-dependent LNCaP cells. High expression of SOCS2-AS1 promoted androgen-dependent cell growth and castration resistance. Mechanistically, SOCS2-AS1 moderates the expression of the AR target gene TNFSF10 (tumor necrosis factor superfamily 10)

through epigenetic control to promote androgen signaling. Recently, a novel lncRNA, TMPO-AS1, was identified as a diagnostic and prognostic marker in PCa. Researchers found that TMPO-AS1 is highly expressed in PCa tissues and cell lines and that high levels of TMPO-AS1 are associated with diminished prognosis. A functional gain/loss assay showed that overexpression of TMPO-AS1 in PCa cells promotes proliferation through accelerating cell cycle progression and promoting migration but inhibits apoptosis. Furthermore, TMPO-AS1 is located in the cytoplasm, and its levels can be directly reduced by AR in PCa cells [86]. Similar to TMPO-AS1, LINC00304 is another novel lncRNA that is also a direct target of AR and performs a similar function [87]. LINC00844 is another lncRNA target of AR, but its expression is downregulated in malignant and metastatic prostate cancer samples compared with that in normal samples, and low LINC00844 expression is linked to poorer prognosis and higher rates of biochemical recurrence. A functional loss assay found that LINC00844 prevents the migration and invasion of PCa cells [88]. Expression of the nuclear lncRNA LOC283070 was upregulated in AI-LNCaP cells compared with that in LNCaP cells, and LOC283070 can bind to PHB2, inhibiting its effect and subsequently influencing the AR signaling pathway [89]. In contrast, lncRNAs may affect PCa progression by interacting with AR. Zhang, Y. et al. found, on the one hand, that lncRNA ARLNC1 stabilized the AR transcript by RNA-RNA interaction; on the other hand, ARLNC1 can be induced by the AR protein. Knockdown of ARLNC1 expression suppressed AR expression, globally repressing AR signaling and PCa growth *in vitro* and *in vivo* [90].

As mentioned above, almost all patients with advanced prostate cancer will eventually experience progression to a virulent and androgen-independent (AI) state that is hormone-insensitive and has acquired metastatic ability. However, the functions and molecular mechanisms associated with the progression of this transition remain elusive. Strikingly, a study conducted by Wang et al. revealed that Linc00963 was differentially expressed and upregulated most noticeably in the androgen-independent (AI) C4-2 cell line compared with the androgen-dependent (AD) LNCaP cell line, which suggested that Linc00963 may be involved in this transition via the EGFR (epidermal growth factor receptor) signaling pathway [91]. Silencing linc00963 attenuated the ability for proliferation, motility and invasion but induced apoptosis in C4-2 cells, accompanied by downregulation of the expression of EGFR and its downstream gene p-AKT (phosphorylated protein kinase B). In a recent study. It was elucidated that lncRNA HOTAIR (HOX transcript antisense RNA) functions as a driver of androgen-independent AR activation and promotes CRPC progression even in low-androgen milieus [92]. HOTAIR, a 2.2 kB transcript located in the HOXC gene cluster, is associated with metastasis in a variety of cancer types, such as breast cancer [93,94], lung cancer [95], colorectal cancer [96] and pancreatic cancer [97]. HOTAIR is markedly upregulated upon exposure to androgen deprivation therapies and in CRPC. Functionally, HOTAIR overexpression enhances—and correspondingly, HOTAIR knockdown weakens—prostate cancer cell growth and invasion [92]. As Yoon JH et al. reported, lncRNA HOTAIR interacts with the RNA-binding domains of E3 ubiquitin ligases to facilitate substrate ubiquitination and protein degradation [98]. HOTAIR stabilizes the AR protein and mediates AR regulation by directly interacting with the AR protein to block its binding with the E3 ubiquitin ligase MDM2, thus inhibiting AR ubiquitination and protein degradation [92]. Consequently, HOTAIR drives androgen-independent AR activation and induces the AR-mediated transcriptional program in the absence of androgen. Moreover, Li L et al. described lncRNA HOTAIR/PRC2-androgen receptor (AR)-MMP9 signaling as another new mechanism underlying ADT (androgen deprivation therapy)-enhanced PCa metastasis [99]. In addition to AR signaling, HOTAIR is a REST (element-1 silencing transcription factor)-regulated lncRNA that promotes neuroendocrine differentiation by participating in the neuroendocrine differentiation (NED) pathway in PCa progression. HOTAIR is highly expressed in NED PCa cells and CRPC, and overexpression of HOTAIR promoted—conversely, knockdown of HOTAIR suppressed—the NED pathway in PCa cells [100]. Similarly, lncRNA HOXD-AS1 was highly expressed in CRPC cells and correlated strongly with some clinical indexes, such as the Gleason score, the T stage, lymph node metastasis, and progression-free survival. Knockdown of HOXD-AS1 inhibited the proliferation and chemoresistance of CRPC cells *in vitro* and *in vivo*. HOXD-AS1 can moderate the expression of several cell cycle, chemoresistance, and castration resistance-related target genes, such as PLK1, AURKA, CDC25C, FOXM1, and UBE2C, by mediating histone H3 lysine 4 tri-methylation (H3K4me3) through the recruitment of WDR5 [101].

Castration-resistant prostate cancers (CRPCs) are the main cause of most of deaths from prostate cancer, intensifying the need to identify key molecular markers, especially for CRPC, and fully understand CRPC pathophysiology. A recent report revealed a key molecule, PCAT5, that determines the differences between untreated prostate cancer and locally recurrent CRPC at the transcriptome level [102]. The group found that PCAT5 is a novel lncRNA that is specifically expressed in ERG-positive prostate cancers and CRPC. In addition, PCAT5 acts as a regulatory target of the transcription factor ERG, whose activation is increased in prostate cancer by approximately 50%. Furthermore, *in vitro* functional validation revealed that PCAT5 plays a critical role in regulating tumor growth and malignancy. Inhibiting the expression of PCAT5 dramatically decreased cell growth, invasion and migration as well as the colony-forming potential; additionally, it also increased the rate of apoptosis. Altogether, these findings established PCAT5 as a novel oncogenic lncRNA with implications for defining CRPC biomarkers and new methods for therapeutic interventions. Similarly, lncRNA BCAR4 (breast cancer anti-estrogen resistance 4), a critical mediator of tamoxifen resistance in breast cancer, was highly overexpressed in CRPC but not in castration-sensitive prostate cancer (CSPC) relative to its expression in normal prostate tissue. High expression levels of BCAR4 were correlated with poor prognosis. Upregulation of BCAR4 in AR-positive PC346 cells can promote cell growth and migration and may be associated with BCAR4-mediated activation of GLI2 signaling [103]. Recently, Parolia A. et al. reported a CRPC-associated lncRNA, HORAS5, which is a stable, cytoplasmic lncRNA that can maintain AR activity under androgen-depleted conditions to mediate CRPC proliferation and survival. Overexpression of HORAS5 is correlated with poor clinical outcomes. Knockdown of HORAS5 expression inhibits the expression of not only AR itself but also oncogenic AR target genes such as KIAA0101 [104]. LncRNA PCAT1 participates in regulating the PHLPP/FKBP51/IKKalpha complex and CRPC progression in PTEN-deficient prostate cancers. The expression level of PCAT1 is positively correlated with CRPC progression. PCAT1 activates AKT and NF-kappaB signaling because it disrupts the PHLPP/FKBP51/IKKalpha complex. Mechanistically, PCAT1 instead of PHLPP binds directly to FKBP51 in the PHLPP/FKBP51/IKKalpha complex, leading to activation of AKT and NF-kappaB signaling, while targeting PCAT1 restores PHLPP binding to FKBP51 and inhibits AKT signaling [105]. It has been previously reported that miR-212/222 is upregulated in prostate cancer. LncRNA MIR222HG was transcribed in the promoter region of miR-221/222. Up-regulation of MIR221HG expression promotes androgen-independent (AI) cell growth and inhibits the expression of CRPC markers, such as KLK3, TMPRSS2, and FKBP5, which are usually induced by dihydrotestosterone (DHT). Clinically, high expression of MIR222HG is connected with PCa progression to CRPC [106].

Hence, specifically, these findings augment investigators' comprehension of prostate carcinogenesis via the consideration of lncRNAs and AR-mediated signaling pathways.

2.3.2. LncRNA and miRNA interplay——"competing endogenous RNA" (ceRNA)

Although numerous lncRNAs have been discovered over the past two decades, only a very small portion have been identified and

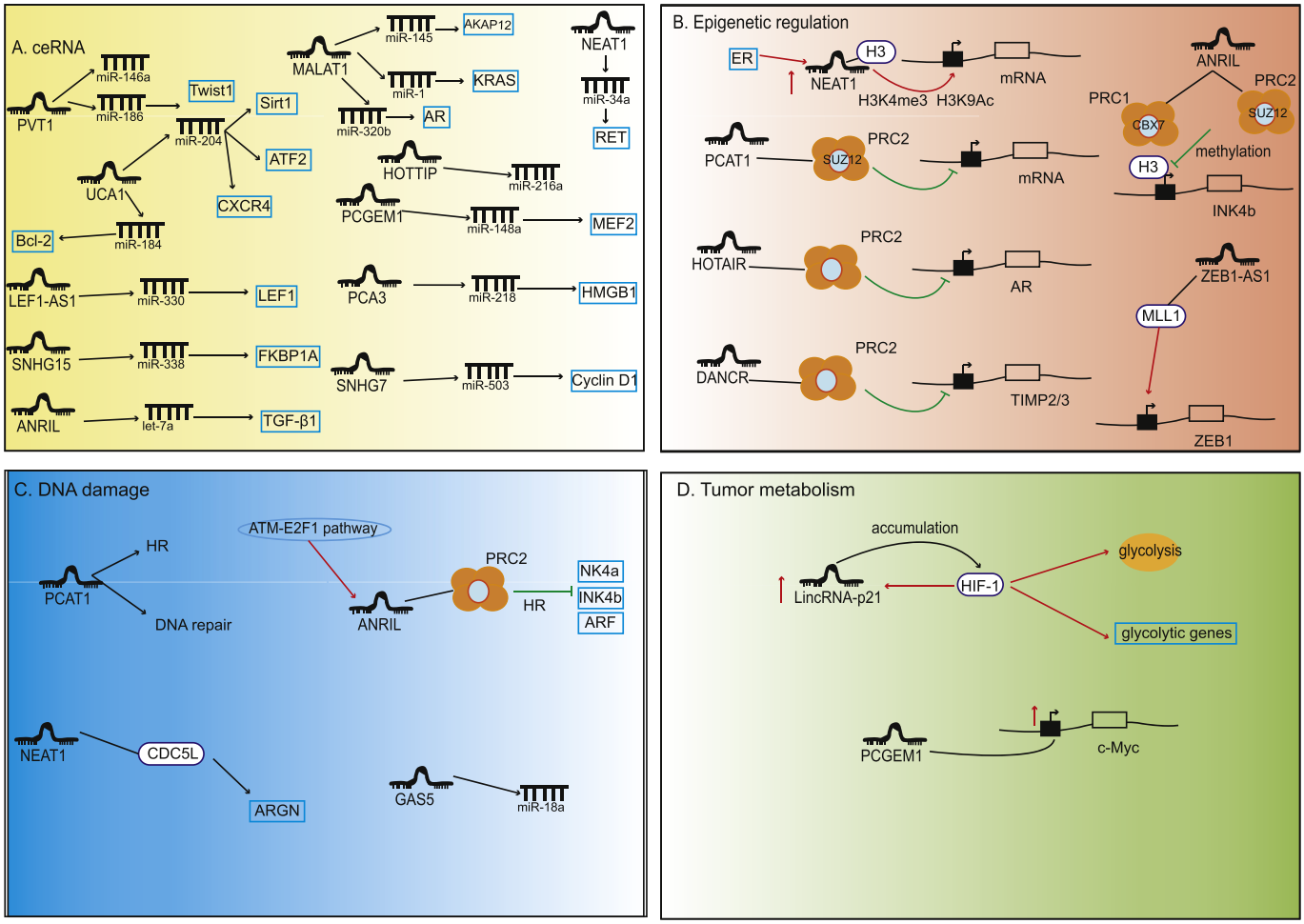

Fig. 4. LncRNAs modulate prostate cancer by ceRNA network, epigenetic regulation, DNA damage and tumor metabolism. (A) LncRNA and miRNA interplay as a ceRNA. Black arrow signifies targeting. (B) LncRNAs in epigenetic regulation. Black line signifies binding, red arrow stand for promotion and green line represents inhibition. (C) LncRNAs in DNA damage. Black line signifies binding, black arrow stands for influence, red arrow signifies promotion and green line signifies inhibition. (D) LncRNAs in tumor metabolism. Black line signifies binding and red arrow represents promotion. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

validated to function as competing endogenous RNAs (ceRNAs) in cancers [107–109]. The concept of ceRNAs traces back to 2007 [110], and Salmena et al. perfected the ceRNA hypothesis in 2011 [111]. According to their ceRNA hypothesis, ceRNAs refer to all RNA transcripts, including mRNA, lncRNA, circular RNA (circRNA) and pseudogene transcripts, that harbor the same miRNA response elements (MREs) in their 3′ UTRs and function as miRNA sponges. CeRNAs can regulate and communicate with each other through competing for the same pool of miRNAs, thereby repressing the miRNA target genes [111–113]; the previous regulatory pattern of “miRNA→RNA” is thus evolved into a pattern of “RNA→miRNA→RNA” interplay [111]. This pattern implies that the transcriptome from a large gene regulatory network involves crosstalk among all RNA transcripts to achieve the regulation of gene expression. Some lncRNAs that act as ceRNAs in PCa are shown in Fig. 4A and Fig. 5 D.

Studies of ceRNA interplay in prostate cancer symbolized the dawn of ceRNA research era in cancer. In recent years, the roles of ceRNA interplay have gradually emerged and mediated the course of cancer initiation and progression [114]. One of the important studies regarding ceRNAs in prostate cancer focused on phosphatase and tension homolog (PTEN), which is a well-known tumor suppressor and plays a growth-suppressive role by inhibiting the phosphatidylinositol 3-kinase/serine-threonine protein kinase (PI3K/Akt) signaling pathway [115]. The possibility that lncRNA PVT1 may predict prognosis and regulate tumor growth was mentioned in the “LncRNAs as Oncogenes” section, but PVT1 can also act as a ceRNA. Liu H. T. and colleagues reported that PVT1 was more highly expressed in prostate cancer tissue than in normal tissue and was negatively correlated with miR-146a. PVT1 regulated miR-146a expression by inducing the methylation of CpG island in its promoter and subsequently mediated prostate cancer cell viability and apoptosis through miR-146a [116]. Another study reported by Chang Z. et al. found that PVT1 can upregulate Twist1, a transcription factor associated with EMT, to promote EMT. Mechanistically, PVT1 acts as a microRNA sponge for miR-186-5p and positively regulates Twist1 via this sponge effect [117]. In addition, several lncRNAs that correlate with chemotherapy resistance and act as ceRNAs in prostate cancer were reported. For instance, MALAT1 expression levels were high in clinically DTX (docetaxel)-resistant PCa samples and DTX-resistant cells. High expression of MALAT1 promoted the proliferation, migration and invasion but decreased the apoptosis rate of PCa cells despite DTX treatment, but this effect was abolished by miR-145-5p; moreover, further research found that AKAP12 was a target gene of miR-145-5p [118]. Dai X. et al. found that MALAT1 and AR expression was increased after androgen stimulation in prostate cancer cells and that downregulation of MALAT1 inhibited the dihydrotestosterone (DHT) administration-induced promotion of proliferation and cell cycle progression and increased the expression of AR in PCa cells, which was abolished by miR- 320b [119]. From another aspect, MALAT1 expression was increased in PCa tissues and cells and was negatively correlated with miR-1 expression. A functional assay

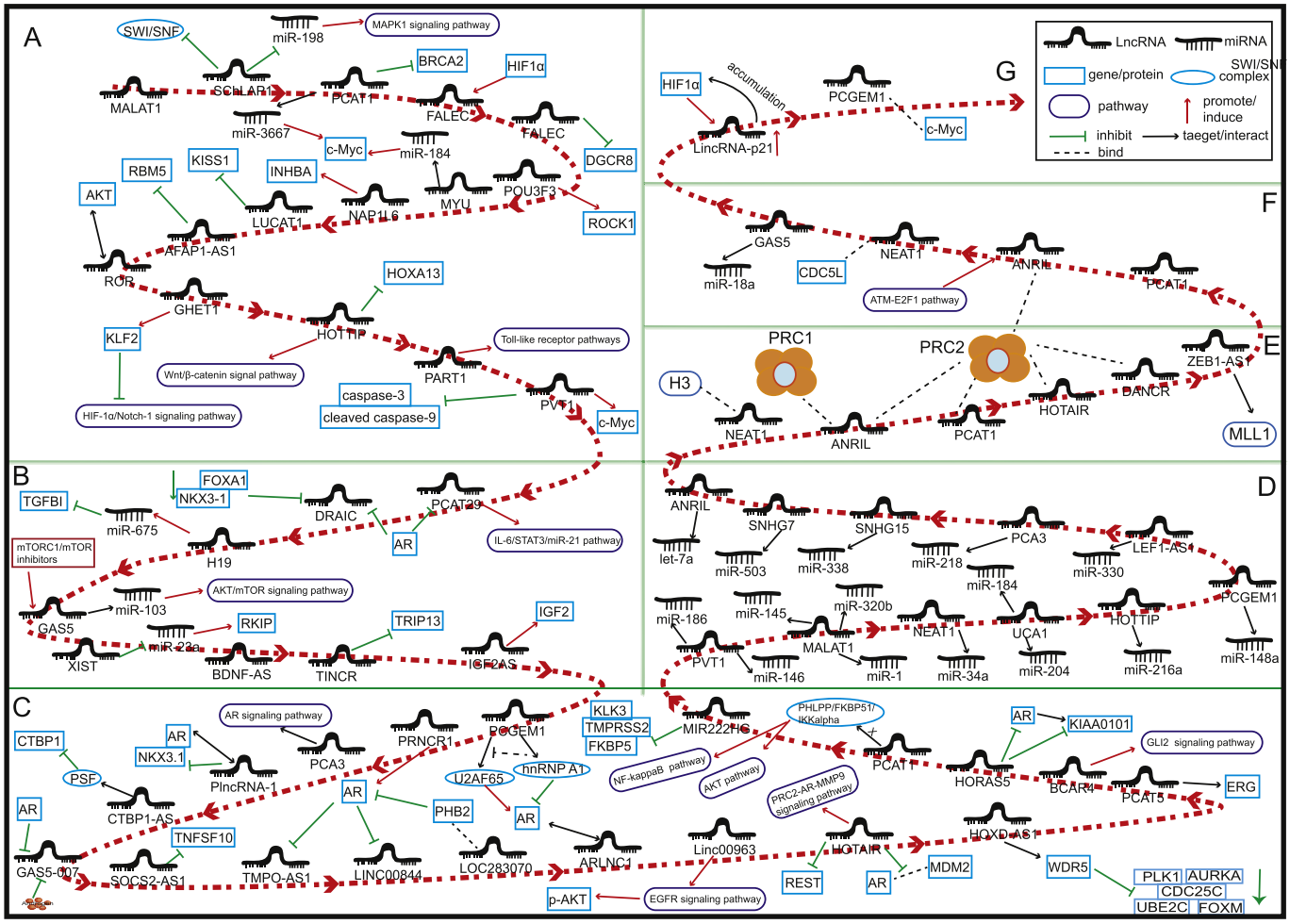

Fig. 5. The mechanisms of lncRNAs modulate prostate cancer. In this figure, we summarized the simple mechanism of lncRNAs in prostate cancer along with the direction of the dotted line according to the order of lncRNA appeared. (A) LncRNAs act as oncogenes in prostate cancer. These lncRNAs are usually over-expressed in PCa and promoting proliferation, invasion, migration, but inhibiting the apoptosis of cancer cells by targeting different gene or pathway. (B) LncRNAs act as suppressors in prostate cancer. These lncRNAs are commonly down-regulated in PCa and play the opposite role with (A). (C) lncRNAs regulate the progression of PCa via AR pathway. (D) LncRNAs function as ceRNA by interacting with miRNAs. (E) LncRNAs participate in epigenetic regulation by binding with histone or PRC complex. (F) LncRNAs regulate DNA damage response in PCa. (G) LncRNAs in tumor metabolism.

found that MALAT1 acted as a molecular sponge of miR-1, increasing the expression of KRAS, a target of miR-1 in androgen receptor-negative PCa cells, thus affecting cell proliferation, migration and apoptosis [120]. In addition, Tian X. et al. found that lncRNA NEAT1 was over-expressed in PC samples and cells, in contrast with miR-34a expression. NEAT1 knockdown increased the sensitivity of PC-resistant cells to docetaxel. NEAT1 played a ceRNA role positively regulating RET [121]. Ghiam A. F. et al. demonstrated that lncRNA UCA1 correlates with the radiation response [122]; in addition, UCA1 can function as a ceRNA. Zhou Y. et al. found that UCA1 was highly expressed in PC tissue and that a high expression level predicts poor prognosis. These researchers suggested that the miR-184/Bcl-2 axis might be the downstream signaling pathway of UCA1 resulting in the sensitivity of PC cells to ART (artesunate) treatment [123] and the UCA1/miR-204/Sirt1 axis contributes to docetaxel sensitivity [124]. Similarly, Zhang S. found that UCA1 competes with ATF2 for miR-204, promoting prostate cancer cell progression [125]. Furthermore, He C. reported that UCA1 functions as a sponge of miR-204 to increase CXCR4 expression, which regulates the growth and metastasis of PCa [126].

LncRNA HOTTIP not only functions as an oncogene, as described in the abovementioned section [32,33] but also functions as a miRNA sponge to promote PCa progression. Yang B. et al. reported that HOTTIP was upregulated in PCa tissues with lymph node metastasis. Upregulation of HOTTIP increased the proliferation, migration, and invasion abilities of PCa cells, while downregulation of HOTTIP decreased these abilities. Bioinformatics analysis and luciferase reporter assays revealed that HOTTIP negatively regulated the expression of miR-216a-5p in PCa cells [127]. Similarly, lncRNA PCGEM1 positively interacts with MEF2 (myocyte enhancer factor 2) and negatively regulates the effect of miR-148a on PCa cell apoptosis [128]. LEF1 (lymphoid enhancer-binding factor-1) and its antisense lncRNA LEF1-AS1 are concurrently overexpressed in PCa, while miR-330-5p is down-regulated. Studies of RNA crosstalk identified LEF1 as a target gene of miR-330-5p and that LEF1-AS1 combined with miR-330-5p. A series of functional assays revealed the effect of LEF1-AS1 on epithelial-mesenchymal transition (EMT) and the proliferation, invasion, and migration of PCa cells *in vitro* [129]. LncRNA PCA3 acts as a sponge of miR-218-5p and regulates HMGB1 to facilitate PCa progression [130], and Zhang Y. reported that lncRNA SNHG15 acts as an oncogene by sponging miR-338-3p and regulating its target gene FKBP1A in PCa [131]. Recently, the regulation of cell cycle progression by lncRNA SNHG7 via the miR-503/Cyclin D1 pathway and the promotion of proliferation and migration by lncRNA ANRIL via regulation of the let-7a/TGF-beta 1/Smad signaling pathway in prostate cancer were discussed [132,133]. Overall, lncRNAs function as competing endogenous RNAs to sponge different miRNAs and subsequently affect prostate

cancer progression.

2.3.3. LncRNAs in epigenetic regulation

The transition of PCa to CRPC involves a series of considerably complicated regulatory mechanisms and processes, in which alteration of the epigenetic landscape is generally one of the key players. On the basis of epigenetic reprogramming, cancer cells exhibit antiapoptotic and stemness properties that contribute to their survival during the processes of therapeutic intervention and resistance. As an indispensable participant in cancer biology, lncRNAs play their roles by functioning as epigenetic modulators of gene regulation (Figs. 4B and 5E).

NEAT1 (nuclear enriched abundant transcript 1) is a typical example of a lncRNA that regulates gene expression through epigenetic modulation [134]. NEAT1 is associated with aggressiveness in prostate cancer and is upregulated by the estrogen receptor (ER). Prostate cancer cells with high levels of NEAT1 are resistant to androgen or AR antagonists. Overexpression of NEAT1 alters the chromatin landscape of the target promoters via increases in H3K4me3 and H3K9Ac by directly binding to histone H3 and consequently promoting active transcription [134]. These data suggest a high possibility that ER-NEAT1-mediated chromatin alteration drives oncogenic growth and prostate cancer progression. Similar to NEAT1, lncRNAs such as ANRIL and PCAT1 are also related to epigenetic regulation. ANRIL (antisense noncoding RNA in the INK4 locus) physically interacts with polycomb repressive complex 1 (PRC1) and polycomb repressive complex 2 (PRC2) through their subunits CBX7 (chromobox Homolog 7) and SUZ12 (suppressor of zeste 12 homolog), respectively, and increases PRC recruitment and methylation of histone 3 at lysine 27 in the INK4b locus to regulate gene silencing [135,136]. PCAT1 predominantly functions as a transcriptional repressor and binds to SUZ12, a subunit of PRC2 [18]. Recently, HOTAIR was also reported to mediate target gene repression via the polycomb repressive complex (PRC). HOTAIR suppresses AR transcription through the formation of a complex with PRC2 on the AR promoter [99]. Jia J. reported that lncRNA DANCR binds to EZH2 (enhancer of zeste homolog 2), a catalytic subunit of PRC2, in the promoters of TIMP2/3 and represses the expression of these genes, subsequently promoting prostate cancer invasion [137]. In addition, Su W., with his team, reported that lncRNA ZEB1-AS1 (lncRNA ZEB1 antisense 1), which derives from the promoter region of the ZEB1 gene, activates ZEB1 and downstream genes through epigenetic regulation. Mechanistically, ZEB1-AS1 induces H3K4me3 and promotes ZEB1 expression by binding and recruiting MLL1 to the ZEB1 promoter region [138].

2.3.4. LncRNAs in DNA damage

As a consequence of rapid and explosive cell growth, cancer cell DNA is incessantly exposed to various types of damage factors, resulting in genomic instability. A number of studies have identified the role of lncRNAs in DNA repair. Double-strand break (DSB) repair is one of the important mechanisms of DNA repair, and mutations of genes involved in this process are common in cancers. Prensner et al. first investigated the mechanisms underlying the involvement of lncRNA in DSB repair [22]. LncRNA PCAT1 is specifically expressed in prostate cancer tissues and is markedly upregulated in a subset of metastatic and high-grade localized tumors, suggesting the possibility that PCAT1 could act as a predictive biomarker for prostate cancer [18]. Dysregulated PCAT1 could regulate the cellular response to genotoxicity by inhibiting the expression of the BRCA2 tumor suppressor in order to impair homologous recombination (HR) and DNA repair [22], providing a new mechanism for HR impairment in prostate cancer. LncRNA ANRIL is another example of a lncRNA that functions in the DNA damage response. Under conditions of DNA damage, ANRIL expression is enhanced via the ATM-E2F1 pathway. ANRIL positively regulates homologous recombination and suppresses the expression of the adjacent NK4a, INK4b and ARF genes by binding with PRC2 to promote cell reentry into the cell cycle [136,139]. We elaborated on the function of lncRNA NEAT1 above, while Li X. discussed the other role of NEAT1 in prostate cancer—DNA damage. Suppression of NEAT1 induces DNA damage, perturbs the cell cycle, and inhibits the proliferation of PCa cells. Mechanistically, NEAT1 binds directly to the TF (transcription factor) CDC5L and regulates the activity of ARGN, a target gene of CDC5L [140]. In addition, Yang J. reported that lncRNA GAS5 interacts with miR-18a, affecting cell viability and survival, apoptosis and DNA damage in prostate cancer [141] (Figs. 4C and 5F).

2.3.5. LncRNAs in tumor metabolism

It is crucial for cancer cells to alter their metabolism to sustain rapid proliferation and survive in the dynamic tumor microenvironment. LincRNA-p21 was reported to be a mediator of metabolic regulation that is a critical regulator of the Warburg effect in tumors, especially in hypoxia-induced glycolysis and tumor growth [142]. In terms of the molecular mechanism, upon exposure to hypoxia, hypoxia-inducible factor (HIF)-1 enhances lincRNA-p21 expression, which increases the accumulation of HIF-1 by affecting VHL-mediated ubiquitination. As a result, the accumulated HIF-1 further facilitates the expression of glycolytic genes and hypoxia-induced glycolysis. Furthermore, a significantly elevated level of exosomal lincRNA-p21 was observed in PCa [143], implying an optional mechanism for hypoxic metabolism in prostate cancer.

PCGEM1 is another metabolic regulator. As we mentioned above, the tumorigenic activity of PCGEM1 is not dependent on AR *in vitro* [68,69] but it is *in vivo* [70]. It was reported that [144] lncRNA PCGEM1 functions as a metabolic regulator in PCa cells to promote prostate cancer growth, predominantly by upregulating multiple metabolic pathways, primarily aerobic glycolysis, the pentose phosphate pathway (PPP) and lipid and glutamine metabolism. PCGEM1 regulates tumor metabolism at the transcriptional level, regardless of the presence of androgen or AR, and is mediated by c-Myc activation. Mechanistically, PCGEM1 can directly physically bind to c-Myc, potentiate the recruitment of c-Myc to its target promoters, and enhance the transactivation of c-Myc. As a regulator of tumor metabolism, PCGEM1 transcriptionally regulates tumor metabolism in an androgen- and AR-independent manner, suggesting the possibility that PCGEM1-mediated metabolic regulation is likely to lead to early cellular adaptation and survival upon androgen removal; making PCGEM1 a promising target for therapeutic intervention in CRPC (Figs. 4D and 5G).

3. The clinical application of lncRNAs in prostate cancer

The current commonly used screening methods for PCa include digital rectal examination (DRE), prostate-specific antigen (PSA) testing, transrectal ultrasonography (TRUS), prostate MRI, and TRUS-guided transrectal prostate biopsy, among which digital rectal examination and PSA testing are the most common and basic screening methods, while the prostate biopsy is still considered the gold standard for PCa diagnosis [145]. DRE is an economical and straightforward method for prostate cancer screening. Abnormalities can be found in approximately 15%–40% of prostate cancer patients by DRE, but the diagnostic accuracy is low and depends on the clinical experience of the doctor. In addition, most prostate cancers found by DRE are advanced prostate cancers, and the combination of DRE with PSA testing can significantly improve the diagnosis rate. In 1986, the U.S. FDA (Food and Drug Administration) approved PSA as a prostate cancer screening biomolecule, which appears to have greatly transformed the PCa screening and diagnosis landscape. The level of PSA can be used not only as a diagnostic and screening marker for PCa but also to monitor PCa progression. Although the diagnosis rate of PCa has markedly increased from the use of PSA screening, this method leads to overdiagnosis and overtreatment due to its limited specificity [146,147].

Table 2
Potential lncRNA biomarkers under research in prostate cancer. Adapted and update from Ref. [155].

lncRNA	Alteration in prostate cancer	Location	Clinical Association	Description	References
SChLAP1	Upregulation	Tissues	Risk prediction	Strongly associates with development of lethal PCa	[6–8]
PCAT29	Downregulation	Tissues	Recurrence risk	Lower expression have a significantly higher risk of biochemical recurrence	[40,41]
PCGEM1	Upregulation	Tissues	Risk prediction	Polymorphisms were associated with an increased risk of prostate cancer	[163–165]
MALAT1	Upregulation	Tissues, urinary	Diagnosis	Preventing unnecessary biopsies	[3–5]
TMPO-AS1	Upregulation	Tissues	Diagnosis, progression	Associates with prognosis	[86]
PCA3	Upregulation	Tissues	Screening, prognosis, potential therapeutic target	FDA appoved screening marker	[75,148]
FALEC	Upregulation	Tissues	Prognosis	Correlates with Gleason sco re and tumor invasion depth in patients	[23]
BDNF-AS	Downregulation	Tissues	Prognosis	Associates with prognosis and os	[57]
TINCR	Downregulation	Tissues	Prognosis	Low expression associates with clinical T stage, lymph node involvement, distant metastasis, high Gleason score and poor prognosis	[58]
LINC00844	Downregulation	Tissues	Prognosis	Associates with prognosis	[88]
HOXD-AS1	Upregulation	Tissues	Prognosis	Associates with Gleason score, T stage, lymph node metastasis, and PFS	[101]
BCAR4	Upregulation	Tissues	Prognosis	Associates with prognosis	[103]
HORAS5	Upregulation	Tissues	Prognosis	Associates with prognosis	[104]
PCAT1	Upregulation	Tissues	Prognosis	Correlates with CRPC progression	[105]
MIR222HGs	Upregulation	Tissues	progression	Correlates with progression to CRPC	[106]
NEAT1	Upregulation	Tissues	progression	Associates with aggressive	[134]

Abbreviations:os: overall survival; PFS: progression-free survival.

3.1. LncRNAs as a diagnostic marker

Currently, PCA3 is one of the most well-studied lncRNAs used as a PCa biomarker and approved by the FDA [148]. The PCA3 level is a more specific and sensitive biomarker than other biomarkers such as the PSA level, and its combination with the PSA level or other biomarkers will significantly improve the sensitivity, specificity, and accuracy of PCa screening and diagnosis [149]. For example, PCA3 plus TMPRSS2-ERG assays can reduce the excessive number of prostate biopsy and increase diagnostic accuracy [149]. However, it's not an unassailable diagnostic biomarker of PCA3 urine assay, some scientists reported that PCA3 assay islimited by the low detection rate at PCA3 < 100, remarkable intra-individual variability, and can't distinguish higher-grade and lower-grade diseases [150,151]. Therefore, it needs further study to determine the optimal application of PCA3 in PCa diagnosis.

MALAT1 is another putative diagnostic potential marker of PCa. Ren S. et al. [3] reported that MALAT1 was overexpressed in prostate cancer and that higher MALAT1 expression is correlated with high prostate-specific antigen levels and Gleason scores as well as with tumor stage and castration-resistant prostate cancer. In another study, Wang. et al. found that urinary levels of MALAT1 are better than PSA and %fPSA (ratio of the free-to-total (f/t) PSA) as an independent predictor of PCa prior to biopsy in 434 patients [152]. What's more, MALAT1-derived mini-RNA (MD-mini-RNA) was found to be a promising plasma-based biomarker to enhance diagnostic accuracy for predicting prostate biopsy outcomes in patients with high PSA levels (> 4 ng/ml) [153].

3.2. LncRNAs as a prognostic marker

Recent research has found that some other lncRNAs may also be promising biomarkers for PCa diagnosis and progression, such as lncRNA TMPO-AS1 and FALEC [86, 23]. The aberrant expression of SChLAP1 was correlated with the development of lethal PCa, with the high expression level of SChLAP1 in PCa tissue significantly associated with bio-chemical recurrence (BCR), clinical progression, and PCa-specific mortality [6,7]. What's more, SChLAP1 can be easily detected in urine [154], which adds potential applicability for guide therapy with the development of SChLAP1-assay. Additionally, other lncRNAs with prognostic potential such as BDNF-AS [57], TINCR [58], LINC00844 [88], PCAT1 [105] etc. were also reported by different studies (Table 1).

3.3. LncRNAs as a predictive marker

Although, a progress has benn made in the therapeutic landscape for metastatic CRPC with the approval of several new drugs in recent years, there are still exists an urgent challenge due to lack of ideal biomarkers to predict response, resistance and recurrence. Thus, exploiting lncRNAs as biomarkers will be a great potential because of their unique features. As we mentioned above, PCAT1 binding with the 3′UTR of BRCA2, that implicated in the regulation of DSB (double-stranded DNA breaks) repair, and inhibited homologous recombination. It suggests that the high expression of PCAT1 will sensitive PCa xenografts to Olaparib, a PARP1 inhibitor [22]. Therefore, PCAT1 can be a potential biomarker of sensitivity to PARP1 inhibition agents. Similarly, GAS5 was positively correlated with the sensitivity to mTOR inhibitors [53]. In contrast, the high levels of NEAT1 will resist to androgen or AR antagonists [134]. In addition, lncRNAs have a potential to predict biochemical recurrence, for example, the lower PCAT29 expression of PCa patients has a significantly higher risk of biochemical recurrence [41]. In short, lncRNAs will become a new target to be developed as a predictive biomarker of PCa (Table 1).

As we previously reported [155], lncRNAs may play a critical role in the diagnose, screening, prognosis and progression for prostate cancer,

all of these lncRNAs are currently in an early research stage and need further research for better understand and use (Table 2).

3.4. LncRNAs as a therapeutic target

An ideal anti-tumor drug can specifically and effectively kill tumor cells without impairing healthy cells. Unfortunately, the current anti-tumor drugs have more or less adverse reactions. The lncRNAs that are specifically or abundantly expressed in tumor tissue and function as drivers of tumor formation or progression will become attractive candidates for therapeutic targets by using RNAi (RNA interference) technology with small interfering RNAs (siRNAs), small hairpin RNAs (shRNAs), miRNAs, and antisense oligonucleotides (ASOs). Prensner et al. reported that using the specific shRNA of SChLAP1 decreased metastasis *in invivo* assay [7]. Furthermore, Ren et al. reported that delivered the siRNA of MALAT1 can delay xenograft growth in castrated mice [156] and silencing MALAT1 with ASO can prevent lung cancer metastasis *in vivo* [157]. However, this strategy is not unassailable, further research is needed to develop optimal delivery systems for protecting the stability of RNAi-based agents and to study the indications of various diseases with these agents in both early and late clinical trials.

4. Conclusions and outlook

The rapidly increasing number of novel discovered lncRNAs and various research has unraveled the crucial roles of lncRNAs in the initiation and development of malignant tumors. Summarizing the biological roles of lncRNAs in prostate cancer allows us to determine the efficiency of these lncRNAs as predictive, diagnostic and even prognostic biomarkers. Importantly, the study of lncRNAs has gradually become one of the most noticeable themes in RNA biology. It is apparent that lncRNAs are critical to biological functions in prostate cancer. The lncRNAs outlined in this review display high specificity and sensitivity for detecting prostate cancer. It is extremely likely that lncRNA analysis will be incorporated to improve the specificity and sensitivity of existing biomarkers. Collectively, these lncRNAs provide new insight into the complicated cancer signaling networks, along with novel strategies and methods for prostate cancer diagnosis and treatment.

With the progression of high-throughput sequencing technologies, such as RNA-seq and microarray, noncoding RNAs especially lncRNAs are found to play an important role in cancer instead of being regarded as genomic “noise” or “garbage”. As indispensable components of the human transcriptome, lncRNAs not only play a promising role in clinical prostate cancer screening but also indispensably participate in the initiation, development and progression of prostate cancer. In this review, we discussed the molecular function of dysregulated lncRNAs and summarized the molecular mechanism that can mediate prostate carcinogenesis through androgen receptor (AR) signaling, function as oncogenes or a tumor-suppressor, and be involved in the processes of ceRNA interplay, epigenetic regulation, DNA damage and tumor metabolism. Therefore, given the roles of lncRNAs in prostate cancer, it will be important to develop specific drugs that interfere with malignant signaling networks—specifically, in prostate cancer cells—through understanding and investigating the important roles and mechanisms of lncRNAs in prostate carcinogenesis. The content herein suggests that prostate cancer may be treated effectively through inhibiting the malignant signaling networks in which lncRNAs participate. Thus, it will be important to explore and improve the new clinical therapeutic interventions on the basis of the mechanisms of lncRNA actions in prostate cancer.

RNA-seq can detect all transcriptional activity of any species at the single nucleotide level. RNA-seq can not only analyze the structure and expression level of transcripts, but also find new isoforms and rare transcripts, accurately identifying variable splicing site and cSNP (coding sequence single nucleotide polymorphism), and providing more comprehensive transcriptome information. Zhang et al. reported that they found 9 novel lncRNAs which were differently expressed between PCa tumor and normal tissues by analyzing the RNA-seq data in public database [158]. According to the latest report, Giraldez et al. developed a modified RNA-seq method (Phospho-RNA-seq) to measure the fragments of mRNA/lncRNA in plasma which were usually missed by standard small RNA-seq due to lack of 5′ phosphate or presence of 3′ phosphate [159]. It means that the measurement of well-studied extracellular RNAs (exRNAs), primarily mRNA and lncRNA, by using Phospho-RNA-seq in biofluids as a new noninvasive method will be soon available. High-throughput RNA sequencing (RNA-Seq) has facilitated the research on lncRNAs. With the development of sequencing technique towardsthird and fourth generation which can analyze the full length of an individual transcript [160], the limitations of next-generation sequencing (e.g., short sequence length, mapping) will be overcomed. Recently, the advance in the design of fluorescence probe, imaging technology and image processing helps to detect subcellular localization and measure the absolute expression of endogenous transcripts in single cells with single-molecule resolution [161,162]. On the other hand, the RNA-protein interactions can be explored by using RIP-Seq (RNA immunoprecipitation sequencing) and UV crosslinking and CLIP-seq (immunoprecipitation sequencing) approaches. These new technologies are powerful tools to study the the function and characteristic of lncRNAs and underlying mechanisms of them in cancer cells. All in all, the more clear about lncRNAs, the more effective application in clinic will be.

Author contributions

Yun-Hua Xu and Jun-Li Deng collectively contributed to the literature search, as well as to the writing of the manuscript; Guo Wang, and Yuan-Shan Zhu revised the manuscript.

Conflicts of interest statement

The authors report no conflicts of interest in this work.

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