Chapter 3

The Biological Role of Androgen Receptor in Prostate Cancer Progression

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Additional information is available at the end of the chapter

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Abstract

Prostate cancer is the most commonly diagnosed cancer in men all over the world. Localized cancers in the early stages can be well managed by surgical or radiation therapy. Metastatic prostate cancer is treated with androgen deprivation therapy because androgen signaling is essential to the prostate tumor growth and anti-apoptotic ability. However, resistance develops quickly in the clinical course and leads to castration-resistant prostate cancer (CRPC). Androgen receptor (AR) functions as a nuclear receptor to facilitate ligand-dependent transcriptional activation in the nucleus. AR interacts with several tissue-specific transcription factors such as forkhead box protein A1 (FOXA1) and regulates epigenetic status by recruiting epigenetic factors. In addition, AR transcriptional activity is modulated by interacting directly or indirectly with non-coding RNAs such as long non-coding RNAs (lncRNAs) and micro RNAs (miRNAs). Notably, enhanced AR signaling in CRPC has been documented in several studies; however, which of these factors are important for the biological function it remains poorly understood. Here, I review our current knowledge of the mechanistic roles of AR involved in prostate cancer progression and discuss the importance of the prostate cancer-associated signals.

Keywords: androgen receptor, prostate cancer, non-coding RNA, transcription, epigenetic

1. Introduction

Released hormone to an entire body is responsible for the development of various human diseases and physiology. Androgens, male sex hormones, mediate their effects predominantly by binding to the androgen receptor (AR), a member of the ligand-dependent nuclear receptor superfamily. Two major androgens, testosterone and dihydrotestosterone (DHT), bind and activate

AR to regulate target gene expression [1]. Testosterone produced in the testes is the most abundant androgen. After diffusing into cells, testosterone is converted to dihydrotestosterone (DHT) by the enzyme 5α-reductase [2]. DHT directly binds to and activates AR even more tightly than testosterone [3]. Androgens play a key role in the development of the male genital tract favoring differentiation and external genitalia during fetal life and sexual characteristic during puberty and are required for the establishment of adult sexual function. In addition to the classical activities in the male reproductive system, androgens also have anabolic functions in other tissues such as bone, muscle and central nervous systems [4]. Notably, AR has a central role in prostate cancer progression. In this review, we focus on AR functions through epigenetic factors and non-coding RNAs that have been shown to play a role in prostate cancer progression.

2. De-regulation of AR during the progression of prostate cancer

AR is a member of the nuclear receptor superfamily [5] and plays a key role in androgen signaling (**Figure 1A**). In the absence of ligand, AR is expressed mainly in the cytoplasm forming a complex with molecular chaperones and co-chaperones from the heat shock protein (Hsp) family. Upon androgen treatment, a conformational change in the complex leads to nuclear translocation of AR. In the nucleus, AR binds as a dimer to specific DNA sequences called androgen responsive elements (AREs), which are found in the vicinity of AR target genes [6]. AR activates gene expressions by modifying the epigenetic condition of AR binding regions [7]. Generally, nuclear receptors including AR have multiple domains called DNA binding domain, a ligand-binding domain (LBD), and an N-terminal domain (NTD), [2, 8, 9]. In the NTD, the transcriptional activation function 1 (AF1) domain promotes transcriptional activation with or without ligand binding [10], which is associated with enhanced AR function. AF2 domain in the LBD interacts with co-regulators with LXXLL motif [3]. Point mutations mapped to the LBD have been identified to have relevance with the treatment-resistance to drugs targeting AR in prostate cancer [11, 12].

Prostate cancer is one of the leading causes of cancer morbidity and mortality in developed countries. Androgens induce proliferation of prostate epithelial cells or prostate cancer tumor growth [13]. Early diagnosis of prostate cancer is currently based on the measurement of serum prostate-specific antigen (PSA), a representative AR target gene. Treatment of localized prostate cancer is determined based on clinico-pathological factors such as Gleason score, initial PSA level, patient's age and clinical tumor stage [14]. Because AR and its downstream signaling are essential for the development and progression of both localized and advanced metastatic prostate cancer, hormone therapy is a first-line and initially successful strategy for treating advanced prostate cancer. Androgen deprivation therapy decreases the circulating testosterone levels to a very low amount, a condition called chemical castration of men [15].

However, most of these tumors relapse and progress to hormone therapy resistant prostate cancer (HRPC) or castration-resistant prostate cancer (CRPC). To overcome CRPC/HRPC, new AR inhibitors have been developed. Abiraterone acetate, a potent inhibitor of CYP17 reduces testosterone synthesis from cholesterol [16]. Despite suppression of circulating testosterone, castration does not decrease androgens enough from the prostate tumor microenvironment and residual androgen levels are well within the range capable of activating AR. Accordingly,

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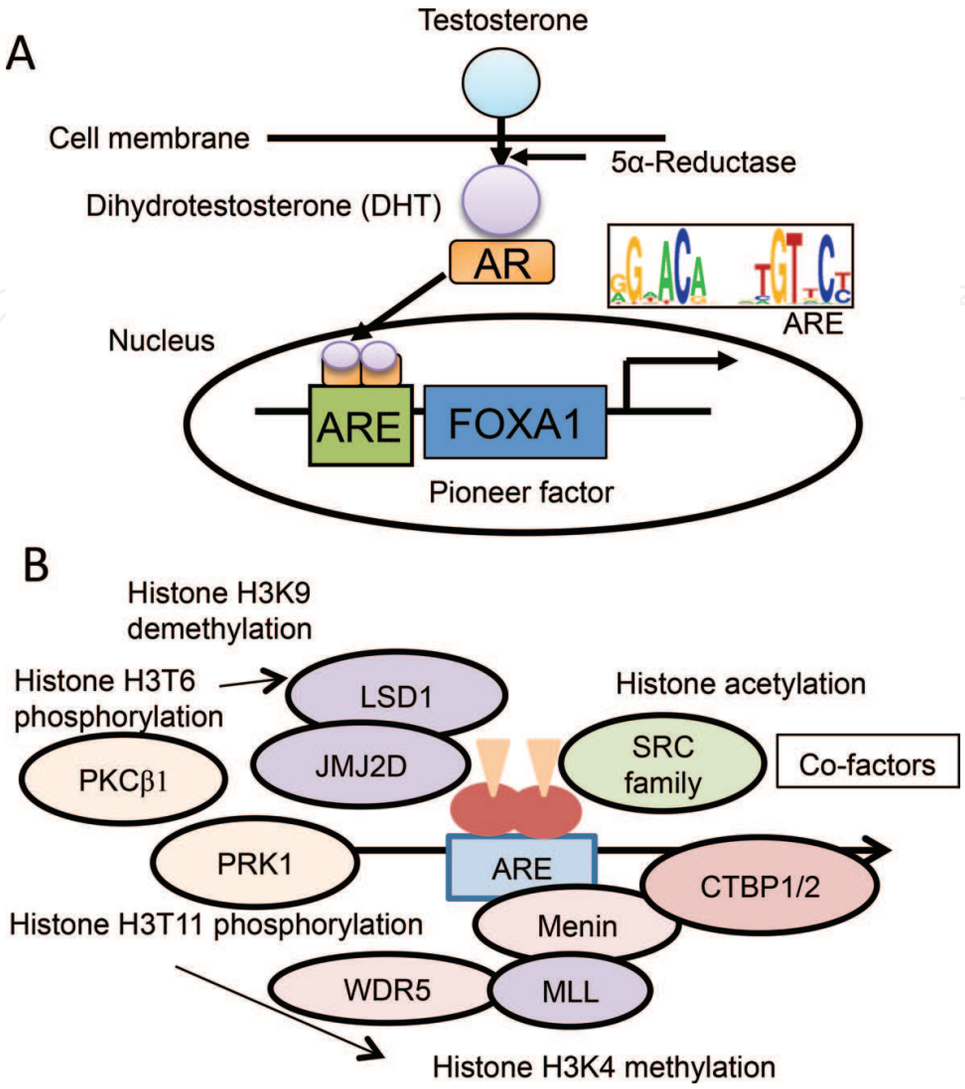

Figure 1. Epigenetic regulation of AR binding regions. (A) Androgen receptor (AR) translocates into the nucleus. By collaborating with FOXA1, AR is recruited to specific loci called androgen responsive elements (AREs) to activate its target genes. (B) Upon androgen treatment, several histone modifying enzymes were recruited to AR binding sites. PKCβ1-mediated histone H3T6 phosphorylation directs LSD1 for not H3K4 but H3K9 demethylation by cooperating with JMJ2D. H3T11 phosphorylation also accelerates WDR5-mediated MLL recruitments and LSD1 activity. MLL complex interacts with AR through menin and promotes histone H3K4 methylation to enhance AR dependent gene expression. SRC family and CTBP1/2 are AR interacting cofactors for histone acetylation or deacetylation.

therapeutic strategies effectively targeting production of intratumoral androgens are necessary. Clinical studies showed that abiraterone improved overall survival, progression free survival, delayed initiation of chemotherapy and doubled the time to first skeletal event. Enzalutamide (MDV3100) is another novel endocrine treatment with reported significant anti-tumor activity [17]. It is an AR-receptor-signaling inhibitor, blocking nuclear translocation, DNA binding, and co-activator recruitment. Enzalutamide significantly prolonged the survival of men with metastatic CRPC after chemotherapy [18]. Although these new types of drugs bring impressive results, the duration of response is variable, and a majority eventually progress with a rising PSA. While the mechanisms determining resistance have not been fully elucidated, persistent AR activation provides a compelling rationale for developing more strategies to inhibit AR [19].

Enhanced AR downstream signals are caused by AR gene amplification, point mutation, AR variants (particularly AR-Vs), hypersensitivity to androgens, or intratumoral steroidogenesis [20–23]. AR mRNA is alternatively spliced to AR-Vs and results in prematurely termination of the full AR protein. Most AR-Vs are missing LBD, however, retain the NTD to drive transcription androgen-independently. Among these variants, AR-V7 is expressed in HRPC/CRPCs most frequently and could be the therapeutic target of tumors resistant to existing therapies directed to androgen/AR [24, 25]. In addition, elevated AR expression increased the reactivity of prostate cancer cells to castrate levels of androgens and promotes resistance to AR-targeting drugs. Increased AR expression in CRPC is often mediated by AR gene amplification. Thus, it is critical to investigate AR downstream-signaling or regulatory mechanisms by AR to understand how CRPC develop among the patients.

3. Investigation of AR-regulators and target genes

Chromatin immunoprecipitation (ChIP) and sequencing studies have revealed locations of AR bindings have been found in prostate cancer cells [26–28]. AR target genes such as ADP-ribosylation factor GTPase-activating protein 3 (ARFGAP3) [29], Amyloid Beta Precursor Protein (APP) [30], Acyl-CoA Synthetase Long Chain Family Member 3 (ACSL3) [31], claudin-8 [32] and Transforming acidic coiled-coil-containing protein 2 (TACC2) [33], which promotes tumor growth by regulating cell cycle, intratumoral steroidogenesis, cell structure, have been identified in my research. Calcium/calmodulin-dependent protein kinase kinase 2 (CAMKK2) is overexpressed in prostate cancer and regulates cancer cell growth via its unexpected role as a hormone-dependent modulator of anabolic metabolism, contributing to prostate cancer progression [26]. Ubiquitin-conjugating enzyme E2 C (UBE2C) was identified to be a CRPC-specific AR target gene and promoted G2/M mitotic cell division in prostate cancer cells [27]. Interestingly, androgen regulates p53 localization by inducing GTPase-activating protein-binding protein 2 (G3BP2), which is an AR target gene [34]. G3BP2 associates with p53 and SUMO E3 ligase RAN binding protein 2 (RanBP2), promoting p53 nuclear export via increased p53 sumoylation. Elevated G3BP2 expression repressed docetaxel-mediated apoptosis and promoted CRPC tumor growth.

3.1. Epigenetic factors

In prostate cancer, deregulation of AR interaction with its coregulators within nucleus is common and activation of coregulators is frequently observed. AR has a role in the ligand-dependent epigenetic changes by interacting with various coregulators such as histone-modifying enzymes. DNA, histones and other proteins formed chromatin as a highly ordered structure. Chromatin forms a unit called the nucleosome consisting of a histone octamer (H2A, H2B, H3 and H4, two pairs of each) and DNA. Both DNA methylation and histone modification patterns have also been investigated in prostate cancer. Histone modifications affect the interaction of DNA with histones, transcription factors or other proteins binding to DNA, thus playing a role in the epigenetic control of biological events. Lysine, arginine, serine and threonine residues enriched in N-terminal histone tails serve as substrates for post-translational modifications such as acetylation, phosphorylation, methylation, ubiquitination, sumoylation

and deamination. Histone H3, one of the major histones, is most representative for epigenetic regulation. The methylation of lysine on position 9 (H3K9) and H3K27 is an epigenetic mark of condensed chromatin and silent loci. The methylation of H3K4 and H3K36 is associated with open chromatin structures. Acetylation of lysine residues of H3 is also correlated with enhanced enhancer/promoter activation. [5].

In a recent report, the potential for BET bromodomain protein inhibitors as a novel epigenetic approach to treatment of CRPC has been shown [35]. In prostate cancer cell lines, BET bromodomain inhibitor, JQ1, was demonstrated to induce apoptosis and down-regulate AR target gene expression. Bromodomain and the extra-terminal (BET) subfamily of human bromodomain proteins (BRDs), with a focus on BRD4, were found to play a major role in AR signaling and interact with AR via bromodomain 1/2. JQ1 inhibits this BRD4-AR bond, resulting in removal of RNA polymerase II from AR target genes [35]. This study suggests for the first time that modulating epigenetic function of AR could be a useful strategy to overcome clinical problems associated with AR signals.

Histone acetylation loosens the nucleosome packing within chromatin to increase DNA accessibility, resulting in the recruitment of chromatin remodeling factors that lead to enhanced transcriptional activity. The BRD has the ability to recognize acetylated lysine residues [36]. This activity allows BRDs to play a vital role in histone acetylation-mediated gene transcriptional regulation in chromatin. Such BRDs included Tripartite motif containing 24 (TRIM24), which interacts with AR and are highly expressed in CRPC [37]. Other studies revealed that E3 ubiquitin ligase substrate binding adaptor speckle-type POZ protein (SPOP) binds to and induces ubiquitination of BRD4 for degradation. In many prostate cancer tissues, SPOP is the most frequently mutated to enhance the expression level of BRD4 [38].

AR regulates the histone modifications in AR binding sites (ARBSs) and promotes enhancer activity by directly interacting with many co-regulators including steroid receptor coactivators (SRCs) or other histone-modifying enzymes [6, 39] (**Figure 1B**). Methylations of H3K4 (mono-, di- or tri-methylation) indicate the active promoter/enhancer regions [40] and promoted by the SET1/MLL histone methyltransferase (HMTase) complex. Menin protein binding to the N-terminus of MLL is important for MLL target gene expressions. Menin directly binds to AR and recruited MLL complex. Menin is highly expressed in CRPC tissues and associated with castration-resistant tumor growth [41]. Importantly, small molecule inhibitors against menin-MLL interaction could be the new useful drugs for CRPC. MLL complex plays an important role for androgen-mediated gene induction and its activity is regulated finely. After androgen stimulation, protein kinase C-related kinase 1 (PRK1) promotes histone H3 threonine 11 phosphorylation (H3T11P) [42]. WD repeat containing protein 5 (WDR5), a subunit of the SET1/MLL complex, associates with H3T11P and then promotes the recruitment of the MLL complex for H3K4 tri-methylation (H3K4me3) in ARBSs [43]. WDR5 is a critical epigenetic integrator and is overexpressed in prostate cancers. PRK1 kinase activity facilitates demethylation of H3K9 by cooperating with lysine-specific demethylase 1 (LSD1) [42, 44]. In addition, Protein kinase C beta 1 (PKCβ1) phosphorylates histone H3T6 to prevent lysine specific demethylase including LSD1 from histone H3K4 demethylation [45]. Moreover, C-terminal binding protein 2 (CTBP2) is an androgen-responsive cofactor of AR. CTBP2 repressed tumor-suppressor genes and AR corepressors in prostate cancer cells, such as Nuclear receptor co-repressor (NCOR)

and receptor-interacting protein 140 (RIP140), by binding with AR to the promoter enhancers of these genes. Moreover, global gene-expression analyses revealed a positive effect on androgen-mediated gene expression, and CTBP2 silencing was found to increase AR interactions with corepressors that limit histone modification [46]. Thus, these findings have a clinical relevance to develop new drugs for treatment by regulating epigenetic status [41].

Histone modification is also important for increased AR expression in CRPC [47]. Recent studies showed that both transcriptional and epigenetic changes are important for AR upregulation in prostate cancer. To introns of the AR gene, recruitments of AR and its associated cofactors such as LSD1, which represses transcription by inhibiting histone H3K4 methylation are induced by androgen. This feedback loop mechanism regulates AR expression negatively by androgen. Interestingly, after long-term incubation in castration level of androgens, AR expression increases in prostate cancer cells and then low levels of androgens can activate AR regulated genes in CRPC without repressing genes such as the AR itself.

3.2. Collaborative transcription factors

Functional ARBSs were not only determined by sequence motifs but also chromatin accessibility. ChIP-sequence (ChIP-seq) analyses using next-generation sequencers have been developed as a high-throughput strategy to identify transcription factor binding regions [48]. For instance, AR ChIP-seq was performed in two LNCaP-derived prostate cancer cell lines with higher AR expression [49]. Interestingly, more ARBSs were obtained in these cell lines when they were treated with low concentrations of androgen. These data indicate that the higher expression of AR sensitizes the receptor binding to genome, thus illustrating the mechanism that the AR signaling pathway is enhanced in CRPC.

Furthermore, by analyzing enriched motifs around ARBSs, AR-associated transcription partners such as forkhead box protein A1 (FOXA1) [50], ERG, GATA2 [51], Oct1 [31], RUNX1 [52] and NKX3–1 [50] have been mapped to the prostate cancer genome and these studies suggested the global role of these factor to activate AR-driven transcriptional program. Among them, a chromatin-opening transcription factor, FOXA1, is able to directly bind to the chromatin to open up the local nucleosomal domain (**Figure 1A**). In prostate cells, FOXA1 protein has been shown physically interact with the AR protein and plays critical roles in regulating the transcription of prostate genes [7]. Moreover, ARBSs in CRPC tissues were found by ChIP-seq and most of them could not been identified in cell lines. Many adjacent genes were *in vivo* restricted set of AR-regulated genes. Transcription factor motifs such as E2F, Myc and STAT were significantly enriched in these CRPC-specific ARBSs [53]. Another study revealed the colocalization of FOXA1 and homeobox B13 (HOXB13) at a set of ARBSs in human tumor tissues. These ARBSs were consistently reprogrammed for prostate tumor development [54].

4. The roles of non-coding RNAs in AR action and prostate cancer biology

Recent advances in DNA sequence technology have demonstrated that more than 90% of the human genome is actively transcribed. The encyclopedia of DNA elements (ENCODE) project

has shown that only 2% of these transcripts are translated into proteins [55]. The non-coding RNAs (ncRNAs), that occupy the majority of transcripts in the nucleus, were initially thought as the "dark matter." Non-coding RNAs are broadly categorized into short and long transcripts. Short non-coding RNAs with a length within 200 nucleotides include such as transfer RNA, microRNA (miRNA), and snoRNA. miRNAs play important roles in cancer by post-transcriptional modification of target mRNA or protein expression. Long non-coding RNAs (lncRNAs) represent most of the transcribed ncRNA in the human genome longer than 200 bp. GENCODE v27 includes 15,778 human lncRNA-related genes, which produce 27,908 lncRNAs [56].

4.1. lncRNA

LncRNAs exhibit similar structure and biogenesis as mRNAs. They are polyadenylated and may function in either nuclear or cytoplasmic compartments. Growing number of evidences have shown that lncRNAs are involved in numerous human diseases including cancer [57]. Global nuclear run-on sequencing (GRO-seq) was developed as a new technology to detect androgen-induced transcripts including lncRNAs [58]. This study has demonstrated that the production of enhancer-templated non-coding RNAs (eRNAs) is important for nucleosome remodeling to induce enhancer/promoter interaction by looping and gene activation. It was also shown that androgen promotes both transcriptional initiation and elongation. These active enhancers are tuned dynamically to modulate gene expression network in prostate cancer. AR is widely recruited to these eRNA-bound enhancer- promoter regions for activating the genes in the vicinity. Interestingly, knockdown of eRNA represses androgen-dependent enhancer promoter interaction and gene activation [59]. DNA nicking activity of topoisomerase I (TOP1) was found to produce robust eRNA for enhancer activation. Furthermore, DNA damage repair machinery is recruited kinetically to the AR-regulated enhancers [60].

LncRNAs are able to fold into secondary and tertiary structures by which they perform their function (**Figure 2A**). Direct regulation of AR epigenetic function by lncRNA is strikingly receiving attention among all. *Prostate cancer gene expression marker 1* (*PCGEM1*) was found as an androgen-regulated and prostate tissue-specific lncRNA [61]. Overexpression of *PCGEM1* in prostate tumors were observed and associated with the anti-apoptotic activity by inhibiting p53 and p21 induction [62]. *Prostate cancer noncoding RNA 1* (*PRNCR1*) was identified by investigating the surrounding region of SNPs (single nucleotide polymorphisms) correlated with prostate cancer susceptibility. Importantly, both *PCGEM1* and *PRNCR1* cooperatively functions for AR-mediated gene expression [63]. The association of *PCGEM1* and *PRNCR1* with AR was shown to be essential in the process of AR activation. Moreover, *PCGEM1* was found to interact with pygopus homolog2 (Pygo2) and *PRNCR1* with DOT1-like histone H3 methyltransferase (DOT1L). By modulating AR proteins with such interacted enzymes, these two lncRNAs were shown to be responsible for AR-associated loop formation between enhancer and promoter.

Another lncRNA, *steroid receptor RNA activator* (*SRA*) modulates the functions of various nuclear receptors, such as AR, estrogen receptor (ER), progesterone receptor (PR), glucocorticoid receptor (GR) and thyroid hormone receptor (TR). *SRA* associates with a coactivator SRC-1 (steroid receptor coactivator) and six stem-loop motifs in *SRA* are required for co-activation. Interestingly, overexpression of *SRA* was found in various tumors including prostate cancer compared with normal tissues [64, 65].

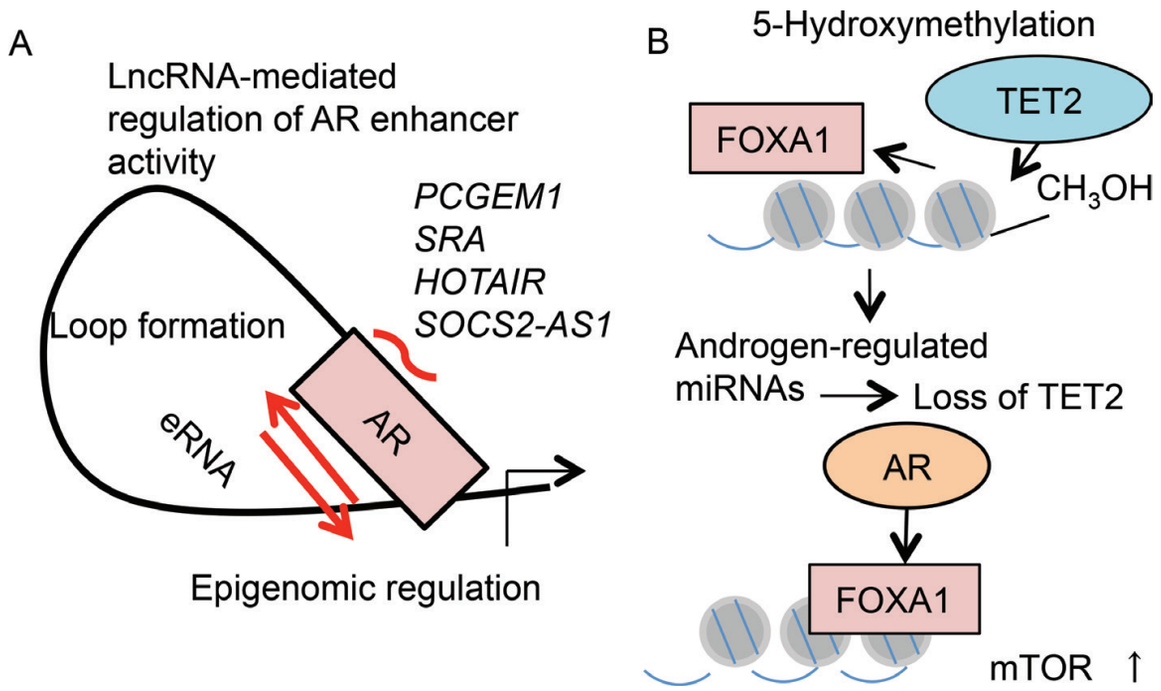

Figure 2. The role of non-coding RNA in AR-mediated transcription. (A) The role of enhancer RNA (eRNA) or other AR interacting lncRNAs. These lncRNAs (eRNA, *PCGEM1, PRNCR1 or SRA*) promotes loop formation for promoter/enhancer interaction. *HOTAIR* enhances AR protein stability by inhibiting ubiquitylation of AR. *SOCS2-AS1* regulates cofactor recruitments to AR. (B) Androgen-induced miRNA mediated TET2 repression inhibits 5-hmC modifications in FOXA1 occupied enhancer regions. By removal of 5-hmC, FOXA1 is activated and induce FOXA1 or ARregulated genes such as mTOR.

HOX Antisense Intergenic RNA (*HOTAIR*) is an lncRNA transcribed in the antisense direction from the *HOXC* gene cluster. *HOTAIR* associates with the polycomb repressive complex 2 (PRC2) for acting as a transcriptional regulators in trans. PRC2 is recruited to the HOXD locus *HOTAIR*-dependently, leading to silenced transcription across a 40-kb region. Moreover, *HOTAIR* associates with LSD1/CoREST/REST complex. This interaction coupled PRC2 and LSD1 to induce histone H3K27 methylation and K4 demethylation for gene silencing [66]. Thus, lncRNAs interacts with chromatin remodeling complexes to promote heterochromatin formation in specific loci, resulting in target gene expression changes. In addition, *HOTAIR* expression is correlated with the disease progressions of breast and prostate cancer [67, 68]. *HOTAIR* high expressions in these cancers are correlated with poor prognosis. This finding reflects the regulation of steroid hormone function by *HOTAIR*. *HOTAIR* is negatively regulated by androgen treatment and induced by depleting androgen. Mechanistically, *HOTAIR* blocks the association of E3-ubiquitine ligase MDM2 with AR by binding to AR. This binding inhibits ubiquitin-mediated degradation and stabilizes AR protein level to activate the AR mediated transcription for driving CRPC development [68].

Suppressor of cytokine signaling 2-antisense transcript 1 (*SOCS2-AS1*) was found in our directional RNA-seq and ChIP-seq analysis [69]. *SOCS2-AS1* is highly expressed in castration-resistant model cells and promotes cell proliferation and inhibits apoptosis induced by docetaxel. *SOCS2-AS1* repressed apoptosis-related genes such as TNFSF10/TRAIL, which are AR target genes. For molecular mechanism in this gene regulation, *SOCS2-AS1* is involved with AR activation by promoting the recruitments of coregulators to AR-occupied regions by interacting with AR (**Figure 2A**).

Global transcriptome analysis showed that most of the genome can be transcribed from both sense and antisense strands. More than 1000 pairs of sense/antisense transcripts were obtained and antisense transcription is involved in such bidirectional gene regulation [70, 71]. Sense-transcript is regulated by antisense through several mechanisms. For example, post-transcriptional degradation is caused by antisense transcript. Another mechanism is recruitments of antisense RNA associated transcription factors for epigenetic regulation. In prostate cancer, an lncRNA, *Prostate cancer antigen 3* (*PCA3*), was found to be an overexpressed in prostate cancer tissues. In 95% of the prostate tumors, the expression of *PCA3* is upregulated compared with adjacent normal prostate tissues. *PCA3* RNA levels can also be measured by urinary test more specifically than prostate specific antigen (PSA) measurement [72]. Therefore, it can be a helpful biomarker to diagnose prostate cancer [73]. AS an antisense transcript, *PCA3* functions as an oncogenic lncRNA by inhibiting its overlapped gene Prune Homolog 2 (PRUNE2), which is a tumor suppressor gene. *PCA3* represses *PRUNE2* expression by formation of a double-stranded RNA with *PRUNE2* mRNA for reducing post transcriptionally [74].

Genome-wide androgen-regulated transcriptome analysis identified a new androgen-responsive lncRNA, *CTBP1-AS* [75]. C-terminal binding protein 1 (CTBP1) functions as a transcriptional repressor for AR and negatively regulates AR downstream signals. It was demonstrated that *CTBP1-AS* is regulated by AR-bindings to its promoter region. In addition, *CTBP1-AS* associates with a RNA binding protein, PSF (PTB-associated splicing factor) to transcriptionally repress its target genes such as CTBP1 via histone deacetylation [75]. Then androgen-regulated lncRNAs mediates AR function by modulating epigenetic status and gene expression. Moreover, *CTBP1-AS* promotes prostate cancer cell cycle progression by repressing cell cycle regulators such as p53 and SMAD3 globally [75]. Thus, *CTBP1-AS* and PSF modulate global gene expression transcriptionally and post-transcriptionally to promote AR and prostate cancer-associated signals. These findings suggest that targeting *CTBP1-AS* and PSF may represent a useful therapeutic strategy to overcome castration-resistance in prostate cancer.

Interestingly, another report has shown that PSF binds to another CRPC-associated lncRNA, *Second Chromosome Locus Associated with Prostate 1* (*SChLAP1*) [76], and mRNAs of various AR target genes to enhance their stability. In CRPC model cells, pathway analysis showed that PSF primarily targets spliceosome genes for enhancing their expressions. Interestingly, in addition to PSF, these wide-range of spliceosome genes are overexpressed in metastatic prostate cancer tissues, suggesting the importance of splicing factors in the disease progression. PSF also binds to *AR* mRNA promoting AR splicing such as AR-V7 and expression [76] in CRPC. In addition to PSF, heterogeneous nuclear ribonucleoprotein L (HNRNPL) was identified by CRISPR/Cas9 knockout screen to be required for prostate cancer growth. HNRNPL also regulates the alternative splicing of a set of RNAs, including *AR* transcript [77]. Collectively, these recent studies revealed the novel roles of RNA processing factors in modulation of AR splicing and expression. Aberrant expressions of splicing factors would induce the diversity of oncogenic gene expressions for promoting prostate cancer.

Growth arrest-specific 5 (*GAS5*) was originally identified as a gene that is preferentially expressed in growth arrested cells [78]. In prostate cancer cell lines, overexpression of *GAS5* induced apoptosis [79] and cell cycle arrest via enhanced expression of p27, a tumor suppressor [80]. *GAS5* associates with steroid receptors including AR and forms a structure that blocks the DNA-binding site of the steroid receptor, resulting in repression of steroid-mediated transcription [81].

These analyses of lncRNA functions revealed a novel transcriptional regulatory mechanism. Several lncRNAs such as *SRA* and *SOCS2-AS1* associate with AR protein and promote recruitment of cofactors (**Figure 2A**). Other mechanisms contain loop forming between promoter and enhancer (eRNA, *PCGEM1* and *PRNCR1*) or enhancing AR protein stability (*HOTAIR*) to activate AR action. Regulation of genes related with cancer development or cell cycle controls by interacting with RNA-binding transcriptional repressor (*CTBP1-AS*) would be another mechanism to promote cancer progression. Androgen-regulated lncRNAs (*PCGEM1*, *HOTAIR*, *CTBP1-AS* and *SOCS2-AS1*) have important roles in these gene expressions. Moreover, recent analyses have shown the importance of RNA-binding proteins (PSF/NONO, HNRNPL) in prostate cancer progression. Because only a limited number of lncRNA functions have been demonstrated, we should investigate molecular functions of more lncRNAs in tissue and spatial specific manner in the future.

4.2. miRNA

MicroRNAs (miRNAs) are evolutionally conserved single-stranded small non-protein Generally miRNAs binds to the 3′ untranslated region (UTR) of mRNAs to inhibit their translation. For examples, dysregulation of miRNA expression profiles during the progression of prostate cancer have been discussed [82]. In these studies, miR-21, miR-29a/b, miR-32, miR-99a, miR-148a, miR-125b and miR-141 were found to be androgen-regulated miRNAs and dysregulated in prostate cancer. Upregulated miR-21 enhanced AR-dependent cell proliferation and associated with development of CRPC [83, 84]. Another androgen regulated miRNA, miR-125b targets apoptosis inducing factors regulated by p53 (PUMA and BAK1) [85]. Thus, by repressing these genes, overexpression of miR-125b in tumors collapses the balance between pro- and anti-apoptotic processes. It was shown that miR-148a is also regulated by androgen and highly induced in AR positive prostate cancer cells. miR-148a targets cullin-associated and neddylation dissociated 1 (CAND1), a cell cycle regulator, to promote cell proliferation [86]. Moreover, miR-32 inhibits apoptosis by targeting BIM, a pro-apoptotic member of the BCL2 family [87]. Both miR-32 and miR-148a were overexpressed in CRPC tissues, indicating that these miRNAs have important roles in the promotion of castration-resistance [87].

DNA methylation is also the representative epigenetic mark adding a methyl group to the 5′ position of cytosine (5-mC). DNA methylation is added or removed in a spatially and temporally defined context throughout the genome including enhancer/promoter regions. DNA methyltransferases (DNMTs) contributes to the process as enzymes. DNMTs include DNMT3A/DNMT3B for de novo and DNMT1 for maintenance of methylation. The ten-eleven translocation (TET) family proteins catalyzed the production of 5-hydroxymethylcytosine (5-hmC), an oxidation product of 5-mC. Several studies have demonstrated that 5-hmC is not only an intermediate product of a demethylation process, but can also function as a stable epigenetic mark [88].

Interestingly, recent study has demonstrated that miR-29 family and miR-22 are highly induced by androgen in hormone-therapy resistant prostate cancer [89]. In prostate cancer clinical samples revealed that the expression level of miR-29a/b is negatively associated with that of TET2. Interestingly, *in situ* hybridization (ISH) study of clinical samples indicated that miR-29a/b is highly expressed in a subset of prostate cancers with poor prognoses. Mechanistically, TET2 repression decreased 5-hmC levels, which is correlated with FOXA1

transcriptional activity. FOXA1 activation induced expressions of prostate cancer related genes. One of such 5-hmC regulated genes was mammalian target of rapamycin (mTOR) (**Figure 2B**). These experimental and clinical data suggested a novel oncogenic role of miR-29 family in prostate cancer progression [89]. The roles of miR-29 family in cancer are still controversial because their expressions are reduced in several cancer tissues in comparison with normal [90]. However, their overexpression inhibits apoptosis in lung cancer as oncogenic miRNAs [91]. Exome sequencing analysis revealed that somatic mutations of TET2 exon are involved in metastatic CRPC development [92]. Rare variation in TET2 is also associated with the development of prostate cancer [93]. TET2 could directly regulate AR-signaling by binding to AR [94]. Thus, the role of TET2 and 5-hmC-modification in prostate cancer deserves additional analysis and may define a subset of metastatic disease.

Studies of non-coding RNAs in AR signals are mainly reported in the research field of prostate cancer. However, knockout of the miRNA processing enzyme, Dicer 1, Ribonuclease III (DICER), in mice inhibited AR function tissue specifically in muscle. In addition, castration in rats inhibited the expression of a large set of miRNAs in prostate and muscle, suggesting the importance of miRNAs in the physiological functions of androgens in other tissues [95].

5. Conclusion and perspective

The majority of prostate cancer and CRPC tumors are driven by AR signaling. AR-mediated resistance to hormone therapy can be acquired by multiple mechanisms. AR mutation, amplification and truncated variants have been identified to explain aberrant AR activation in prostate cancer progression. AR coregulators and collaborating transcription factors are essentials for AR to exert its transcriptional activity. Recently the role of non-coding RNAs such as lncRNAs and miRNAs has been realized to play a critical role in AR activation and prostate cancer progression. Such alterations of AR function lead to positive or negative regulation of the growth and invasion ability of cancer cells. Although AR-targeting drugs have been developed, we could not eliminate CRPC due to the adaptive evolution of the disease during the treatment. Combinational therapies are required to overcome CRPC problems. Therefore, it is urgent to find better predictive biomarkers or therapeutic targets which have an efficacy for diagnosing and treating prostate cancer and CRPC.

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Conflict of interest

The author declares no conflict of interest.

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