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,
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-riboseylation 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...
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). Methylation 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. IncRNA

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 IncRNA is strikingly receiving attention among all. Prostate cancer gene expression marker 1 (PCGEM1) was found as an androgen-regulated and prostate tissue-specific IncRNA [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].
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).

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 AR regulated genes such as mTOR.
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 (CTBPI-AS) would be another mechanism to promote cancer progression. Androgen-regulated lncRNAs (PCGEM1, HOTAIR, CTBPI-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 IncRNAs 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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References

[1] Takayama K, Inoue S. Transcriptional network of androgen receptor in prostate cancer progression. International Journal of Urology. 2013;20(8):756-768. DOI: 10.1111/iju.12146

[2] Heemers HV, Tindall DJ. Androgen receptor (AR) coregulators: A diversity of functions converging on and regulating the AR transcriptional complex. Endocrine Reviews. 2007;28:778-808. DOI: 10.1210/er.2007-0019

[3] Heery DM, Kalkhoven E, Hoare S, Parker MG. A signature motif in transcriptional co-activators mediates binding to nuclear receptors. Nature. 1997;387:733-736. DOI: 10.1038/42750

[4] Ophoff J, Callewaert F, Venken K, De Gendt K, Ohlsson C, Gayan-Ramirez G, et al. Physical activity in the androgen receptor knockout mouse: Evidence for reversal of androgen deficiency on cancellous bone. Biochemical and Biophysical Research Communications. 2009;378(1):139-144. DOI: 10.1016/j.bbrc.2008.11.016

[5] Dasgupta S. Nuclear receptor coactivators: Master regulators of human health and disease. Annual Review of Medicine. 2014;65:279-292

[6] Shang Y, Myers M, Brown M. Formation of the androgen receptor transcription complex. Molecular Cell. 2002;9:601-610

[7] Lupien M, Eeckhoute J, Meyer CA, Wang Q, Zhang Y, Li W, et al. FoxA1 translates epigenetic signatures into enhancer-driven lineage-specific transcription. Cell. 2008;132(6):958-970. DOI: 10.1016/j.cell.2008.01.018

[8] Jenster G, van der Korput HA, van Vroonhoven C, van der Kwast TH, Trapman J, Brinkmann AO. Domains of the human androgen receptor involved in steroid binding, transcriptional activation, and subcellular localization. Molecular Endocrinology. 1991;5:1396-1404. DOI: 10.1210/mend-5-10-1396

[9] Jenster G, van der Korput HA, Trapman J, Brinkmann AO. Identification of two transcription activation units in the N-terminal domain of the human androgen receptor. The Journal of Biological Chemistry. 1995;270:7341-7346
[10] Dehm SM, Regan KM, Schmidt LJ, Tindall DJ. Selective role of an NH$_2$-terminal WxxLF motif for aberrant androgen receptor activation in androgen depletion-independent prostate cancer cells. Cancer Research. 2007;67:10067-10077. DOI: 10.1158/0008-5472.CAN-07-1267

[11] Buchanan G, Greenberg NM, Scher HI, Harris JM, Marshall VR, Tilley WD. Collocation of androgen receptor gene mutations in prostate cancer. Clinical Cancer Research. 2001;7:1273-1281

[12] Taplin ME, Bubley GJ, Shuster TD, Frantz ME, Spooner AE, Ogata GK, Keer HN, Balk SP. Mutation of the androgen-receptor gene in metastatic androgen-independent prostate cancer. The New England Journal of Medicine. 1995;332:1393-1398. DOI: 10.1056/NEJM199505253322101

[13] La Vignera S, Condorelli RA, Russo GI, Morgia G, Calogero AE. Endocrine control of benign prostatic hyperplasia. Andrology. 2016;4(3):404-411. DOI: 10.1111/andr.12186

[14] Attard G, Parker C, Eeles RA, Schröder F, Tomlins SA, Tannock I, Drake CG, de Bono JS, et al. Prostate cancer. Lancet. 2016;387:70-82. DOI: 10.1016/S0140-6736(14)61947-4

[15] Bill-Axelson A, Holmberg L, Ruutu M, Garmo H, Stark JR, Busch C, et al. Radical prostatectomy or watchful waiting in early prostate cancer. The New England Journal of Medicine. 2014;370:932-942. DOI: 10.1056/NEJMoa1011967

[16] de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, et al. Abiraterone and increased survival in metastatic prostate cancer. The New England Journal of Medicine. 2011;364:1995-2005. DOI: 10.1056/NEJMoa1014618

[17] Tran C, Ouk S, Clegg NJ, Chen Y, Watson PA, Arora V, et al. Development of a second-generation antiandrogen for treatment of advanced prostate cancer. Science. 2009;324:787-790. DOI: 10.1126/science.1168175

[18] Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. The New England Journal of Medicine. 2012;367:1187-1197. DOI: 10.1056/NEJMoa1207506

[19] Elahe A. Mostaghel. Cancer Management and Research. 2014;6:39-51. DOI: 10.2147/CMAR.S39318

[20] Chen CD, Welsbie DS, Tran C, Baek SH, Chen R, Vessella R, Rosenfeld MG, Sawyers CL. Molecular determinants of resistance to antiandrogen therapy. Nature Medicine. 2004;10:33-39. DOI: 10.1038/nm972

[21] Locke JA, Guns ES, Lubik AA, Adomat HH, Hendy SC, Wood CA, et al. Androgen levels increase by intratumoral de novo steroidogenesis during progression of castration-resistant prostate cancer. Cancer Research. 2008;68:6407-6415. DOI: 10.1158/0008-5472.CAN-07-5997

[22] Sun S, Sprenger CC, Vessella RL, Haugk K, Soriano K, Mostaghel EA, et al. Castration resistance in human prostate cancer is conferred by a frequently occurring androgen receptor
splice variant. The Journal of Clinical Investigation. 2010;120:2715-2730. DOI: 10.1172/JCI41824

[23] Waltering KK, Helenius MA, Sahu B, Manni V, Linja MJ, Jänne OA, Visakorpi T. Increased expression of androgen receptor sensitizes prostate cancer cells to low levels of androgens. Cancer Research. 2009;69:8141-8149. DOI: 10.1158/0008-5472.CAN-09-0919

[24] Antonarakis ES, Lu C, Wang H, Luber B, Nakazawa M, Roeser JC, et al. AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. The New England Journal of Medicine. 2014;371:1028-1038. DOI: 10.1056/NEJMoa1315815

[25] Antonarakis ES, Armstrong AJ, Dehm SM, Luo J. Androgen receptor variant-driven prostate cancer: Clinical implications and therapeutic targeting. Prostate Cancer and Prostatic Diseases. 2016;19:231-241. DOI: 10.1038/pcan.2016.17

[26] Massie CE, Lynch A, Ramos-Montoya A, Boren J, Stark R, Fazli L, et al. The androgen receptor fuels prostate cancer by regulating central metabolism and biosynthesis. The EMBO Journal. 2011;30(13):2719-2733. DOI: 10.1038/emboj.2011.158

[27] Wang Q, Li W, Zhang Y, Yuan X, Xu K, Yu J, et al. Androgen receptor regulates a distinct transcription program in androgen-independent prostate cancer. Cell. 2009;138(2):245-256. DOI: 10.1016/j.cell.2009.04.056

[28] Sahu B, Laakso M, Ovaska K, Mirtti T, Lundin J, Rannikko A, et al. Dual role of FoxA1 in androgen receptor binding to chromatin, androgen signalling and prostate cancer. The EMBO Journal. 2011;30(19):3962-3976. DOI: 10.1038/emboj.2011.328

[29] Obinata D, Takayama K, Urano T, Murata T, Ikeda K, Horie-Inoue K, et al. ARFGAP3, an androgen target gene, promotes prostate cancer cell proliferation and migration. International Journal of Cancer. 2012;130(10):2240-2248. DOI: 10.1002/ijc.26224

[30] Takayama K, Tsutsumi S, Suzuki T, Horie-Inoue K, Ikeda K, Kaneshiro K, et al. Amyloid precursor protein is a primary androgen target gene that promotes prostate cancer growth. Cancer Research. 2009;69(1):137-142. DOI: 10.1158/0008-5472.CAN-08-3633

[31] Obinata D, Takayama K, Fujiwara K, Suzuki T, Tsutsumi S, Fukuda N, et al. Targeting Oct1 genomic function inhibits androgen receptor signaling and castration-resistant prostate cancer growth. Oncogene. 2016;35(49):6350-6358. DOI: 10.1038/onc.2016.171

[32] Ashikari D, Takayama KI, Obinata D, Takahashi S, Inoue S. CLDN8, an androgen-regulated gene, promotes prostate cancer cell proliferation and migration. Cancer Science. 2017;108(7):1386-1393. DOI: 10.1111/cas.13269

[33] Takayama K, Horie-Inoue K, Suzuki T, Urano T, Ikeda K, Fujimura T, et al. TACC2 is an androgen-responsive cell cycle regulator promoting androgen-mediated and castration-resistant growth of prostate cancer. Molecular Endocrinology. 2012;26(5):748-761. DOI: 10.1210/me.2011-1242

[34] Ashikari D, Takayama K, Tanaka T, Suzuki Y, Obinata D, Fujimura T, et al. Androgen induces G3BP2 and SUMO-mediated p53 nuclear export in prostate cancer. Oncogene. 2017;36(45):6272-6281. DOI: 10.1038/onc.2017.225
[35] Asangani IA, Dommeti VL, Wang X, Malik R, Cieslik M, Yang R, et al. Therapeutic targeting of BET bromodomain proteins in castration-resistant prostate cancer. Nature. 2014;510(7504):278-282. DOI: 10.1038/nature13229

[36] Sanchez R, Meslamani J, Zhou MM. The bromodomain: From epigenome reader to druggable target. Biochimica et Biophysica Acta. 2014;1839(8):676-685. DOI: 10.1016/j.bbagrm.2014.03.011

[37] Groner AC, Cato L, de Tribolet-Hardy J, Bernasocchi T, Janouskova H, Melchers D, et al. TRIM24 is an oncogenic transcriptional activator in prostate cancer. Cancer Cell. 2016;29(6):846-858. DOI: 10.1016/j.ccell.2016

[38] Zhang P, Wang D, Zhao Y, Ren S, Gao K, Ye Z, et al. Intrinsic BET inhibitor resistance in SPOP-mutated prostate cancer is mediated by BET protein stabilization and AKT-mTORC1 activation. Nature Medicine. 2017;23(9):1055-1062. DOI: 10.1038/nm.4379

[39] Takayama K, Tsutsumi S, Katayama S, Okayama T, Horie-Inoue K, Ikeda K, et al. Integration of cap analysis of gene expression and chromatin immunoprecipitation analysis on array reveals genome-wide androgen receptor signaling in prostate cancer cells. Oncogene. 2011;30(5):619-630. DOI: 10.1038/onc.2010.436

[40] Eissenberg JC, Shilatifard A. Histone H3 lysine 4 (H3K4) methylation in development and differentiation. Developmental Biology. 2010;339:240-249. DOI: 10.1016/j.ydbio.2009.08.017

[41] Malik R, Khan AP, Asangani IA, Cieślik M, Prensner JR, Wang X, et al. Targeting the MLL complex in castration-resistant prostate cancer. Nature Medicine. 2015;21(4):344-352. DOI: 10.1038/nm.3830

[42] Metzger E, Yin N, Wissmann M, Kunowska N, Fischer K, Friedrichs N, et al. Phosphorylation of histone H3 at threonine 11 establishes a novel chromatin mark for transcriptional regulation. Nature Cell Biology. 2008;10:53-60. DOI: 10.1038/ncb1668

[43] Kim JY, Banerjee T, Vinckevicius A, Luo Q, Parker JB, Baker MR, et al. A role for WDR5 in integrating threonine 11 phosphorylation to lysine 4 methylation on histone H3 during androgen signaling and in prostate cancer. Molecular Cell. 2014;54(4):613-625. DOI: 10.1016/j.molcel.2014.03.043

[44] Metzger E, Wissmann M, Yin N, Müller JM, Schneider R, Peters AH, et al. LSD1 demethylates repressive histone marks to promote androgen-receptor-dependent transcription. Nature. 2005;437(7057):436-439. DOI: 10.1038/nature04020

[45] Metzger E, Imhof A, Patel D, Kahl P, Hoffmeyer K, Friedrichs N, et al. Phosphorylation of histone H3T6 by PKCbeta(I) controls demethylation at histone H3K4. Nature. 2010;464(7289):792-796. DOI: 10.1038/nature08839

[46] Takayama K, Suzuki T, Fujimura T, Urano T, Takahashi S, Homma Y, et al. CtBP2 modulates the androgen receptor to promote prostate cancer progression. Cancer Research. 2014;74(22):6542-6553. DOI: 10.1158/0008-5472.CAN-14-1030
[47] Cai C, He HH, Chen S, Coleman I, Wang H, Fang Z, et al. Androgen receptor gene expression in prostate cancer is directly suppressed by the androgen receptor through recruitment of lysine-specific demethylase 1. Cancer Cell. 2011;20:457-471. DOI: 10.1016/j.ccr.2011.09.001

[48] Yu J, Yu J, Mani RS, Cao Q, Brenner CJ, Cao X, et al. An integrated network of androgen receptor, polycomb, and TMPRSS2-ERG gene fusions in prostate cancer progression. Cancer Cell. 2010;17:443-454. DOI: 10.1016/j.ccr.2010.03.018

[49] Urbanucci A, Sahu B, Seppälä J, Larjo A, Latonen LM, Waltering KK, et al. Overexpression of androgen receptor enhances the binding of the receptor to the chromatin in prostate cancer. Oncogene. 2012;31:2153-2163. DOI: 10.1038/onc.2011.401

[50] Tan PY, Chang CW, Chng KR, Wansa KD, Sung WK, Cheung E. Integration of regulatory networks by NKKX3-1 promotes androgen-dependent prostate cancer survival. Molecular and Cellular Biology. 2012;32:399-414. DOI: 10.1128/MCB.05958-11

[51] He B, Lanz RB, Fiskus W, Geng C, Yi P, Hartig SM, et al. GATA2 facilitates steroid receptor coactivator recruitment to the androgen receptor complex. Proceedings of the National Academy of Sciences of the United States of America. 2014;111(51):18261-18266. DOI: 10.1073/pnas.1421415111

[52] Takayama K, Suzuki T, Tsutsumi S, Fujimura T, Urano T, Takahashi S, et al. RUNXI, an androgen- and EZH2-regulated gene, has differential roles in AR-dependent and -independent prostate cancer. Oncotarget. 2015;6:2263-2276. DOI: 10.18632/oncotarget.2949

[53] Sharma NL, Massie CE, Ramos-Montoya A, Zecchini V, Scott HE, Lamb AD, et al. The androgen receptor induces a distinct transcriptional program in castration-resistant prostate cancer in man. Cancer Cell. 2013;23(1):35-47. DOI: 10.1016/j.ccr.2012.11.010

[54] Pomerantz MM, Li F, Takeda DY, Lenci R, Chonkar A, Chabot M, et al. The androgen receptor cistrome is extensively reprogrammed in human prostate tumorigenesis. Nature Genetics. 2015;47(11):1346-1351. DOI: 10.1038/ng.3419

[55] Garzon R, Calin GA, Croce CM. MicroRNAs in cancer. Annual Review of Medicine. 2009;60:167-179. DOI: 10.1146/annurev.med.59.053006.104707

[56] GENCODE27. Data Statistic Browser [Internet]. 2018. Available from: https://www.genencodegenes.org

[57] Prensner JR, Chinnaiyan AM. The emergence of lncRNAs in cancer biology. Cancer Discovery. 2011;1:391-407. DOI: 10.1158/2159-8290.CD-11-0209

[58] Wang D, Garcia-Bassets I, Benner C, Li W, Su X, Zhou Y, et al. Reprogramming transcription by distinct classes of enhancers functionally defined by eRNA. Nature. 2011;474:390-394. DOI: 10.1038/nature10006

[59] Hsieh CL, Fei T, Chen Y, Li T, Gao Y, Wang X, et al. Enhancer RNAs participate in androgen receptor-driven looping that selectively enhances gene activation. Proceedings of the National Academy of Sciences of the United States of America. 2014;111(20):7319-7324. DOI: 10.1073/pnas.1324151111
[60] Puc J, Kozbial P, Li W, Tan Y, Liu Z, Suter T, et al. Ligand-dependent enhancer activation regulated by topoisomerase-I activity. Cell. 2015;160(3):367-380. DOI: 10.1016/j.cell.2014.12.023

[61] Srikantan V, Zou Z, Petrovics G, Xu L, Augustus M, Davis L, et al. PCGEM1, a prostate-specific gene, is overexpressed in prostate cancer. Proceedings of the National Academy of Sciences of the United States of America. 2000;97:12216-12221. DOI: 10.1073/pnas.97.22.12216

[62] Petrovics G, Zhang W, Makarem M, Street JP, Connelly R, Sun L, et al. Elevated expression of PCGEM1, a prostate-specific gene with cell growth-promoting function, is associated with high-risk prostate cancer patients. Oncogene. 2004;23:605-611. DOI: 10.1038/sj.onc.1207069

[63] Yang L, Lin C, Jin C, Yang JC, Tanasa B, Li W, et al. lncRNA-dependent mechanisms of androgen-receptor regulated gene activation programs. Nature. 2013;500:598-602. DOI: 10.1038/nature12451

[64] Lanz RB, McKenna NJ, Onate SA, Albrecht U, Wong J, Tsai SY, et al. A steroid receptor coactivator, SRA, functions as an RNA and is present in an SRC-1 complex. Cell. 1999;97(1):17-27

[65] Lanz RB, Razani B, Goldberg AD, O'Malley BW. Distinct RNA motifs are important for coactivation of steroid hormone receptors by steroid receptor RNA activator (SRA). Proceedings of the National Academy of Sciences of the United States of America. 2002;99(25):16081-16086. DOI: 10.1073/pnas.192571399

[66] Tsai MC, Manor O, Wan Y, Mosammaparast N, Wang JK, Lan F, et al. Long noncoding RNA as modular scaffold of histone modification complexes. Science. 2010;329(5992):689-693. DOI: 10.1126/science.1192002

[67] Gupta RA, Shah N, Wang KC, Kim J, Horlings HM, Wong DJ, et al. Long non-coding RNA HOTAIR reprograms chromatin state to promote cancer metastasis. Nature. 2010;464:1071-1076. DOI: 10.1038/nature08975

[68] Zhang A, Zhao JC, Kim J, Fong KW, Yang YA, Chakravarti D, et al. LncRNA HOTAIR enhances the androgen-receptor-mediated transcriptional program and drives castration-resistant prostate cancer. Cell Reports. 2015;13(1):209-221. DOI: 10.1016/j.celrep.2015.08.069

[69] Misawa A, Takayama K, Urano T, Inoue S, et al. Androgen-induced IncRNA SOCS2-AS1 promotes cell growth and inhibits apoptosis in prostate cancer cells. The Journal of Biological Chemistry. 2016;291(34):17861-17880. DOI: 10.1074/jbc.M116.718536

[70] Katayama S, Tomaru Y, Kasukawa T, Waki K, Nakanishi M, Nakamura M, et al. Antisense transcription in the mammalian transcriptome. Science. 2005;309:1564-1566. DOI: 10.1126/science.1112009

[71] Hessels D, Schalken JA. The use of PCA3 in the diagnosis of prostate cancer. Nature Reviews. Urology. 2009;6:255-261. DOI: 10.1038/nrurol.2009.40

[72] Bussemakers MJ, van Bokhoven A, Verhaegh GW, Smit FP, Karthaus HF, Schalken JA, et al. DD3: A new prostate-specific gene, highly overexpressed in prostate cancer. Cancer Research. 1999;59:5975-5979
[73] Salameh A, Lee AK, Cardó-Vila M, Nunes DN, Efstathiou E, Staquicini FI, et al. PRUNE2 is a human prostate cancer suppressor regulated by the intronic long noncoding RNA PCA3. Proceedings of the National Academy of Sciences of the United States of America. 2015;112(27):8403-8408. DOI: 10.1073/pnas.1507882112

[74] Takayama K, Horie-Inoue K, Katayama S, Suzuki T, Tsutsumi S, Ikeda K, et al. Androgen-responsive long noncoding RNA CTBP1-AS promotes prostate cancer. The EMBO Journal. 2013;32:1665-1680. DOI: 10.1038/emboj.2013.99

[75] Takayama K, Suzuki T, Fujimura T, Yamada Y, Takahashi S, Homma Y, et al. Dysregulation of spliceosome gene expression in advanced prostate cancer by RNA-binding protein PSF. Proceedings of the National Academy of Sciences of the United States of America. 2017;114:10461-10466. DOI: 10.1073/pnas.1706076114

[76] Prensner JR, Iyer MK, Sahu A, Asangani IA, Cao Q, Patel L, et al. The long noncoding RNA SChLAP1 promotes aggressive prostate cancer and antagonizes the SWI/SNF complex. Nature Genetics. 2013;45(11):1392-1398. DOI: 10.1038/ng.2771

[77] Fei T, Chen Y, Xiao T, Li W, Cato L, Zhang P, et al. Genome-wide CRISPR screen identifies HNRNPL as a prostate cancer dependency regulating RNA splicing. Proceedings of the National Academy of Sciences of the United States of America. 2017;114(26):E5207-E5215. DOI: 10.1073/pnas.1617467114

[78] Mourtada-Maarabouni M, Pickard MR, Hedge VL, Farzaneh F, Williams GT. GAS5, a non-protein-coding RNA, controls apoptosis and is downregulated in breast cancer. Oncogene. 2009;28:195-208. DOI: 10.1038/onc.2008.373

[79] Pickard MR, Mourtada-Maarabouni M, Williams GT. Long non-coding RNA GAS5 regulates apoptosis in prostate cancer cell lines. Biochimica et Biophysica Acta. 2013;1832:1613-1623. DOI: 10.1016/j.bbadis.2013.05.005

[80] Luo G, Liu D, Huang C, Wang M, Xiao X, Zeng F, et al. LncRNA GAS5 inhibits cellular proliferation by targeting P27Kip1. Molecular Cancer Research. 2017;15:789-799. DOI: 10.1158/1541-7786.MCR-16-0331

[81] Hudson WH, Pickard MR, de Vera IM, Kuiper EG, Mourtada-Maarabouni M, Conn GL, et al. Conserved sequence-specific lincRNA-steroid receptor interactions drive transcriptional repression and direct cell fate. Nature Communications. 2014;5:5395. DOI: 10.1038/ncomms6395

[82] Takayama K, Misawa A, Inoue S, Significance of microRNAs in androgen signaling and prostate cancer progression, Cancers (Basel), 2017;9:pii: E102. DOI: 10.3390/cancers9080102

[83] Ribas J, Ni X, Haffner M, Wentzel EA, Salmasi AH, Chowdhury WH, et al. miR-21: An androgen receptor-regulated microRNA that promotes hormone-dependent and hormone-independent prostate cancer growth. Cancer Research. 2009;69:7165-7169. DOI: 10.1158/0008-5472.CAN-09-1448

[84] Coppola V, Musumeci M, Patrizii M, Cannistraci A, Addario A, Mauger-Saccà M, et al. BTG2 loss and miR-21 upregulation contribute to prostate cell transformation by inducing
luminal markers expression and epithelial-mesenchymal transition. Oncogene. 2013; 32:1843-1853. DOI: 10.1038/onc.2012.194

[85] Shi XB, Xue L, Yang J, Ma AH, Zhao J, Xu M, et al. An androgen-regulated miRNA suppresses Bak1 expression and induces androgen-independent growth of prostate cancer cells. Proceedings of the National Academy of Sciences of the United States of America. 2007;104:19983-19988. DOI: 10.1073/pnas.0706641104

[86] Murata T, Takayama K, Katayama S, Urano T, Horie-Inoue K, Ikeda K, et al. miR-148a is an androgen-responsive microRNA that promotes LNCaP prostate cell growth by repressing its target CAND1 expression. Prostate Cancer and Prostatic Diseases. 2010;13: 356-361. DOI: 10.1038/pcan.2010.32

[87] Jalava SE, Urbanucci A, Latonen L, Waltering KK, Sahu B, Jänne OA, et al. Androgen-regulated miR-32 targets BTG2 and is overexpressed in castration-resistant prostate cancer. Oncogene. 2012;31:4460-4471. DOI: 10.1038/onc.2011.624

[88] Shen L, Zhang Y. 5-Hydroxymethylcytosine: Generation, fate, and genomic distribution. Current Opinion in Cell Biology. 2013;25(3):289-296. DOI: 10.1016/j.ceb.2013.02.017

[89] Takayama K, Misawa A, Suzuki T, Takagi K, Hayashizaki Y, Fujimura T, et al. TET2 repression by androgen hormone regulates global hydroxymethylation status and prostate cancer progression. Nature Communications. 2015;6:8219. DOI: 10.1038/ncomms9219

[90] Wang Y, Zhang X, Li H, Yu J, Ren X. The role of miRNA-29 family in cancer. European Journal of Cell Biology. 2013;92(3):123-128. DOI: 10.1016/j.ejcb.2012.11.004

[91] Langsch S, Baumgartner U, Haemmig S, Schlup C, Schäfer SC, Berezowska S, et al. miR-29b mediates NF-κB signaling in KRAS-induced non-small cell lung cancers. Cancer Research. 2016;76(14):4160-4169. DOI: 10.1158/0008-5472.CAN-15-2580

[92] Nickerson ML, Im KM, Misner KJ, Tan W, Lou H, Gold B, et al. Somatic alterations contributing to metastasis of a castration-resistant prostate cancer. Human Mutation. 2013;34(9):1231-1241. DOI: 10.1002/humu.22346

[93] Koboldt DC, Kanchi KL, Gui B, Larson DE, Fulton RS, Isaacs WB, et al. Rare variation in TET2 is associated with clinically relevant prostate carcinoma in African-Americans. Cancer Epidemiology, Biomarkers & Prevention. 2016;25(11):1456-1463. DOI: 10.1158/1055-9965.EPI-16-0373

[94] Nickerson ML, Das S, Im KM, Turan S, Berndt SI, Li H, et al. TET2 binds the androgen receptor and loss is associated with prostate cancer. Oncogene. 2017;36(15):2172-2183. DOI: 10.1038/onc.2016.376

[95] Narayanan R, Jiang J, Gusev Y, Jones A, Kearbey JD, Miller DD, et al. MicroRNAs are mediators of androgen action in prostate and muscle. PLoS One. 2010;5(10):e13637. DOI: 10.1371/journal.pone.0013637
