Interaction between Non-Coding RNAs and Androgen Receptor with an Especial Focus on Prostate Cancer

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Abstract: The androgen receptor (AR) is a member of the nuclear receptor superfamily and has three functional domains, namely the N-terminal, DNA binding, and C-terminal domain. The N-terminal domain harbors potent transactivation functions, whereas the C-terminal domain binds to androgens and antiandrogens used to treat prostate cancer. AR has genomic activity being DNA binding-dependent or through interaction with other DNA-bound transcription factors, as well as a number of non-genomic, non-canonical functions, such as the activation of the ERK, AKT, and MAPK pathways. A bulk of evidence indicates that non-coding RNAs have functional interactions with AR. This type of interaction is implicated in the pathogenesis of human malignancies, particularly prostate cancer. In the current review, we summarize the available data on the role of microRNAs, long non-coding RNAs, and circular RNAs on the expression of AR and modulation of AR signaling, as well as the effects of AR on their expression. Recognition of the complicated interaction between non-coding RNAs and AR has practical importance in the design of novel treatment options, as well as modulation of response to conventional therapeutics.

Keywords: androgen receptor; miRNA; lncRNA; circular RNAs; prostate cancer

1. Introduction

The androgen receptor (AR), alternatively named as NR3C4 (nuclear receptor subfamily 3, group C, member 4), is a nuclear receptor [1] that is activated by a number of androgens, such as testosterone and its more active form, dihydrotestosterone [2]. AR has three protein domains, namely the N-terminal transcriptional regulation, DNA binding, and C-terminal ligand binding domain [3]. After being activated by its ligands in the cytoplasm, AR is transferred into the nucleus, where it exerts its main DNA-binding-dependent functions [4]. In fact, AR is a cytoplasmic protein in the absence of its ligands associated with chaperone proteins, such as heat shock proteins and co-chaperones. Androgen binding to the AR results in conformational changes, dissociating it from chaperone proteins [4]. After translocation to the nucleus, the androgen/AR complex dimerizes and binds to androgen response elements (AREs), which are present in the AR target genes. This process is involved in the regulation of the expression of target genes [5]. In addition to this canonical route of action, the androgen/AR complex has other functions that are mediated through non-DNA-binding-dependent routes [6]. Modulation of activity of ERK, AKT, and MAPK pathways are examples of this kind of function [6–8].
Notably, specific coregulators have been found to modulate the transcriptional activity of androgen/AR complex. The binding of coregulators with androgen/AR complex can either enhance (via coactivators) or suppress (via corepressors) its transactivation capability. This process is accomplished via the epigenetic changing of chromatin configuration and histone modifications [5].

A bulk of evidence indicates that non-coding RNAs (ncRNAs) have functional interactions with AR. This type of interaction is implicated in the pathogenesis of human malignancies, particularly prostate cancer. In the current review, we summarize the available data on the role of microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs) on expression of AR, as well as the effects of AR on their expression.

2. Effects of miRNAs on AR

2.1. Acting on AR mRNA to Directly Negatively Regulate AR Expression

Several miRNAs have been found to suppress the expression of AR. In fact, most of these miRNAs have been shown to bind with 3′ UTR of AR transcript, thus inducing its degradation or translation suppression. The interactions between miRNAs and AR mRNA, mainly through binding with its 3′ UTR, have been mostly assessed in the context of prostate cancer. MiR-299-3p is one of the AR-interacting miRNAs. Expression of miR-299-3p has been reported to be decreased in prostate cancer samples, compared to noncancerous prostate samples. The restoration of miR-299-3p in prostate cancer cells has led to the induction of cell cycle arrest, reduction of cell proliferation and migration, and enhancement of levels of apoptotic markers. Moreover, the up-regulation of miR-299-3p leads to reduced expressions of AR, PSA, and VEGFA, suppressed epithelial mesenchymal transition (EMT), reduced levels of Slug, TGF-β3, p-AKT, and p-PRAS40, and enhanced E-cadherin levels. Taken together, miR-299-3p exerts anti-tumor effects via affecting activity of AR and VEGFA pathways [9].

Another study in prostate cancer cells has identified miR-185-binding sites in the 3′ UTR of the AR transcript. Notably, the suppression of AR expression by miR-185 has compromised the interaction between AR and ARE and decreased the levels of the AR target gene PSA [10]. Moreover, miR-185-mediated inhibition of AR has suppressed the proliferation of prostate cancer cells and enhanced their apoptosis. Thus, the miR-185 has been suggested as a negative regulator of AR signaling and tumor suppressor miRNA in LNCaP cells [10].

MiR-381 is another down-regulated miRNA in prostate cancer. Forced over-expression of miR-381 in LNCaP cells inhibited their proliferation, migratory aptitude, and invasion. Mechanistically, miR-381 suppresses AR mRNA expression by binding to its 3′ UTR [11].

MiR-let-7c is another miRNA that decreases expression and activity of AR in prostate cancer cells. It modulates AR transcription through c-Myc. MiR-let-7c-mediated inhibition of AR can reduce the proliferation of prostate cancer cells [12].

Figure 1 depicts a number of tumor suppressor miRNAs that regulate expression of AR in prostate cancer cells.

2.2. Indirectly Regulate AR Expression or AR Signal

On the other hand, a handful of miRNAs have been found to exert oncogenic roles in prostate cancer, through the regulation of transcription of AR expression or signaling. Following androgen deprivation therapy, hormone-sensitive prostate cancer can evolve to castration-resistant prostate cancer (CRPC). MiRNAs can contribute to this process. For instance, miR-221/-222 has been shown to be up-regulated in bone metastatic CRPC samples. In vitro studies have demonstrated that stable overexpression of miR-221 induces the androgen-independent growth of prostate cancer cells, by releasing these cells from androgen deprivation-related G1 arrest. The up-regulation of this miRNA in LNCaP has led to the reduction of expression of a subclass of androgen-responsive genes, without influencing the expression of AR or integrity of AR-androgen. MiR-221 has been found to regulate the expressions of HECTD2 and RAB1A, two genes being capable of the induction
of CRPC phenotype in various prostate cancer cells. Further, the up-regulation of miR-221 has led to alterations in the expression levels of several cell cycle-related genes and the activation of EMT-related pathways. Taken together, it has been hypothesized that miR-221 has a major role in AR signaling reprogramming and the subsequent evolution of the CRPC phenotype [13].

Experiments in mice models have indicated the effect of surgical castration in the induction of an early upsurge in the serum levels of miR-125b. Moreover, bicalutamide-mediated AR blocking has resulted in the prompt release of this miRNA into the media of cultured prostate cancer cells. NCOR2, as a corepressor of AR, has been shown to be targeted by miR-125b. Thus, miR-125b has been suggested as a key regulator of AR, which alters the efficacy of anti-androgen therapies [14].

MiR-96 is another oncogenic miRNA that can target a RARγ network to control AR signaling. Down-regulation of RARγ, a member of the nuclear receptor superfamily, has been shown to significantly affect the viability of prostate cancer cells and gene signature of these cells. A gene network, comprising of numerous RARγ target genes, such as SOX15, has been found to be correlated with poor disease-free survival of prostate cancer patients [15].

MiR-541 is another oncogenic miRNA that can affect prostate cancer course through modulation of AR signaling. In fact, infiltrating CD4(+) T cells, which are associated with poor clinical outcomes in this type of cancer, can increase FGF11 levels. Up-regulation of this growth factor leads to increases of miR-541. The subsequent down-regulation of AR signaling regulates MMP9 levels, in favor of tumor metastasis [16]. Figure 2 shows the effects of oncogenic miRNAs in the progression of prostate cancer, through the modulation of AR signaling.

In addition to above-mentioned miRNAs, several miRNAs can directly or indirectly affect AR signaling by binding with 3’UTR, the coding region of AR, or influencing the levels of AR co-activators/co-repressors (Table 1).
Table 1. The effects of different miRNAs on AR in prostate cancer (prostate cancer (PCa), FUS: fused in sarcoma, AR-V7: androgen receptor variant 7, BCa: breast cancer, BPH: benign prostatic hyperplasia, ANCTs: adjacent non-cancerous tissues, PEITC: phenethyl isothiocyanate, Enz: enzalutamide, CIN: cervical intraepithelial neoplasia, AI: androgen-independent, 5-hmC: 5-Hydroxymethylated cytosine, ↓: decrease in, ↑: increase in).

| miRNAs          | Expression of miRNAs in PCa mRNA/Effect of miRNAs on AR Targeted Region of AR | Targeted Pathway | Cell Line/Samples/Animal Models | Function of miRNAs in Cancer Cells | References |
|-----------------|---------------------------------------------------------------------------------|------------------|---------------------------------|-----------------------------------|------------|
| miR-299-3p      | ↓                                                                                | ↓                | VEGFA signaling                 | LNCaP-104S, MDA-PCa-2b, 22Rv-1, C4-2B, PC-3, WPE-1/TCGA PRAD publication: 330 matching tumor and 51 normal samples | ↓ proliferation, EMT process and migration, ↑ cell cycle arrest, apoptosis, and drug sensitivity | [9]        |
| miR-185         | ↓                                                                                | ↓ 3′UTR          | ARE, PSA                        | LNCaP                            | ↓ proliferation, ↑ apoptosis     | [10]       |
| miR-381         | ↓                                                                                | ↓ 3′UTR          | FUS, IGF1R, and EGFR            | WPE1-NA22, MDA-PCa-2b, PC-3, E006AA, E006AA-hT, LNCaP, C4-2B, RWPE-1 | ↓ proliferation, migration, and invasion | [11]       |
| miR-1207-3p     | ↑                                                                                | ↑                | FNDC1, FN1, AR                  | TGFB2R1, Smad2/3                  | ↑ tumor-suppressive activity of TGFβ pathway | [18]       |
| miR-124         | ↓                                                                                | ↓ suppression of AR at the level of transcription | Lin28, c-Myc                    | LNCaP, C4-2B/22 PCa samples/nude mice | ↓ proliferation, ↓ transactivation, potential of AR | [12]       |
| miR-133a-5p     | ↓                                                                                | ↓ 3′UTR          | FUS, PSA, IGF1R, and EGFR       | RWPE-1, VCaP, and LNCaP/TCGA database: 497 tumor tissue samples and 52 non-cancerous tissue samples | ↓ proliferation and viability | [19]       |
| miR-103a-2-5p/miR-30c-1-3p | ↓                                               | ↓ 3′UTR AR-V7    | VCaP                           | PC3, LAPC4/15 primary PCa samples, 15 adjacent normal prostate samples, and 15 metastatic CRPC samples | ↓ cell growth and proliferation | [20]       |
| miR-30b-3p and miR-30d-5p | ↓                                               | ↓ 3′UTR          | LNCaP, PC3, LAPC4/15 primary PCa samples, 15 adjacent normal prostate samples, and 15 metastatic CRPC samples | ↓ cell growth                     | [21]       |
| miR-31          | ↓                                                                                | ↓ coding region  | RWPE-1, VCaP, LNCaP, 22Rv1, PC3, DU145, and HEK293 | ↓ proliferation, cell growth and colony formation, ↑ cell cycle arrest | [22]       |
| miR-205         | ↓                                                                                | ↓ 3′UTR          | DU145, PC3, 22Rv1, LNCaP/49 PCa, and 25 samples without PCA | ↓ proliferation, colony formation and metastases, ↑ cell adhesion, overall survival | [23]       |
| miR-124         | ↓                                                                                | ↓ 3′UTR          | LNCaP, 22Rv1, DU145, PC-3, C4-2/male BALB/C nude mice | ↓ proliferation, migration, and cell growth | [24]       |
| miR-145         | ↓                                                                                | ↓                | Ago2, PSA, TMRSS2, KLK2          | PC3, DU145, LNCaP, 22Rv1, VCaP, PNT2/49 PCa, and 25 samples without PCA | ↓ proliferation, ↑ G1 arrest         | [25]       |
| miR-8080        | ↓                                                                                | ↓ AR-V7 3′-UTR   | IGF-1R and NKKX3.1              | 22Rv1 and VCaP/male TRAP rats and male nude mice | Lutetin treatment: ↑ MIR-8080: ↓ proliferation, growth and oxidative stress, ↑ apoptosis, and Enz effects under castration conditions | [26]       |
| miR-124         | ↓                                                                                | ↓ 3′UTR          | p53                             | RWPE-1, 5kBS-1-1, LNCaP, C4-2B, cdc2, 22Rv1, and LAPC4/8 matched pairs of CaP and BPH tissues/male athymic nu/nu mice | ↓ cell growth, ↑ apoptosis             | [27]       |
| miR-124         | ↓                                                                                | ↓ 3′UTR          | EZH2 and Scc                    | LNCaP, C4-2B, 22Rv1, and VCaP/male athymic nude mice | ↓ proliferation and cell growth, ↑ apoptosis, sensitivity to Enz | [28]       |
| miR-125b        | ↑                                                                                | ↑ indirectly by decreasing the co-repressor of AR | NCO2R | HEK293 and LNCaP/male nude mice | ↑ cell growth and survival, ↓ apoptosis                      | [14]       |
| miR-473p        | ↑                                                                                | -                | MEKK1                           | LNCaP/38 pairs of tumor tissues and ANCTs | ↑ cell survival, ↓ docetaxel-induced apoptosis in AR+ prostate cancer cells | [29]       |
Table 1. Cont.

| miRNAs | Expression of miRNAs in CaP | Target Region of AR mRNA/Effect of miRNAs on AR | Targeted Pathway | Cell Line/Samples/Animal Models | Function of miRNAs in Cancer Cells | References |
|--------|----------------------------|-----------------------------------------------|-----------------|--------------------------------|-----------------------------------|------------|
| miR-185 | ‡ | ↓ directly by binding 3′UTRs, ↓ indirectly by suppressing co-activator of AR | BRD8 IS02 | LNCaP, PC-3/10 pairs of tumor tissues and ANCTs | ↓ proliferation and invasion | [30] |
| miR-449 | ‡ | AR-v7 | EZH2 | CWR22Rv1 and VCaP/male nude mice | ↓ cells growth and invasion, Enz resistance | [31] |
| miR-34b | ‡ | ↓ 3′UTR | ETV1 | MDA-PCa-2b, DU-145/143 PCa samples (from 3 different groups), and GEO analysis: GSE21032 | ↓ proliferation, ↑ apoptosis | [32] |
| miR-302a | ‡ | ↓ 3′UTR | – | 22Rv1, VCaP, and LNCaP/10 PCa samples/SD rats | OBP-801 treatment: ↑ miR-302a: ↓ proliferation and cell growth | [33] |
| miR-17 | ↓ | ↓ indirectly by suppressing co-activator of AR | PCAF | RWPE1, LNCaP, PC-3, DU145, C4-28, and ALVA31 | PeITC treatment: ↑ miR-17; ↓ cell growth | [34] |
| miR-141 | ↑ | ↑ AR-regulated transcriptional activity | Shp | RWPE-1, LNCaP, DU145, and C4-2B | PeITC treatment: ↑ miR-141 and AR signaling activation | [35] |
| miR-449a | ‡ | ↓ 3′UTR | PSA | C4-2 and LNCaP | Capsaicin treatment: ↑ miR-449a; ↓ proliferation, ↑ G0/G1 cell cycle arrest | [36] |
| miR-331-3p | ‡ | ↓ indirectly by regulating ERBB-2 | ERBB-2, PI3K/AKT signaling pathway, PSA | LNCaP, 22Rv1, DU145/tumor tissues, and ANCTs | ↓ indirectly AR pathway target genes via cross-talk between ERBB-2 and AR signaling pathways | [37] |
| miR-371 | ‡ | ↓ 3′UTR | KLK3 | LNCaP and PC3/83 PCa samples and 6 BPH as controls/male nude mice | ↓ proliferation and tumor growth | [38] |
| miR-1207-3p | ‡ | ↓ indirectly by regulating FNDC1 | FNDC1, FN1 | RWPE-1, CM, WPE-NA22, RWPE-1, MDA PCa 2b, PC-3, E006AA, E006AA-1t, LNCaP, C4-2b | ↓ proliferation, migration, ↓ apoptosis | [39] |
| miR-301a | ↑ | ↑ 3′UTR | TGF-β1/Smad/ MMP9 signals | CWR22Rv1, 3T3-L1/21 pairs of tumor tissues, and ANCTs/male nude mice | Recruitment of pre- adipocytes: ↑ miR-301a: ↓ cell growth | [40] |
| miR137 | ↓ | ↓ indirectly by regulating AR cofactor complexes | NCoA2, KDM1A, KDM2A, KDM4A, KDM5B, KDM7A and MED1 | PREC, LNCaP, LNCaP:C4-2, and PC-3/TCGA database | miR137: suppressor of androgen signaling by modulating expression of transcriptional coregulators | [41] |
| miR-361-3p | ↓ | ↓ 3′UTR of ARv7 | – | CW22Rv1, C4-2, and LNCaP/TCGA analysis/male nude mice | ↑ Enz sensitivity | [42] |
| miR-2909 | ↑ | ↑ | TGF/BR2, TGF/β signaling, PSA | PC3 and LNCaP | ↑ cell growth | [43] |
| miR-200a | ↓ | ↓ AR-V7 indirectly by regulating BRD4 | BRD4 | LNCaP and C4-2B/10 ADPC tissue and 10 CRPC tissue samples | ↓ proliferation, ↑ apoptosis | [44] |
| miR-135b | ‡ | ↓ | MUC1-C | LNCaP | ↑ invasion and EMT process | [45] |
| miR-17-5p | ↓ | ↓ indirectly by regulating co-activator of AR | PCAF, PSA | RWPE1, LNCaP, C4-2B, PC3, and PrEC | ↓ cell growth | [46] |
| miR-3162-5p | ↑ | ↑ in PCa tissues with higher Gleason grade | ↓ 3′UTR | KLK3, PSA | LNCaP, PC3 | ↓ proliferation, migration, and colony formation | [47] |
Table 1. Cont.

| miRNAs   | Expression of miRNAs in PCa | Target Region of AR mRNA | Targeted Pathway | Cell Line/Samples/Animal Models | Function of miRNAs in Cancer Cells                                      | References |
|----------|------------------------------|--------------------------|------------------|--------------------------------|------------------------------------------------------------------------|------------|
| miR-644a | ↓                            | ↓ 3′UTR (directly) and indirectly by regulating co-activators of AR | SRC-1, SRC-2, SRC-3, CCND1, CBP, and ARA24 | LNCaP, LAPC4, and 22Rv1/1 male athymic nude male mice | ↓ invasion, EMT process, metastasis and Warburg effect, ↑ apoptosis | [48]       |
| miR-221  | ↑                            | ↓ indirectly by regulating co-activators of AR | HECTD2 and RAB1A | LNCaP and LNCaP-Ab1, LAPC-4, PC-3, Du145, and 22Rv1 | ↑ AI cell growth, emt process, and metastasis | [13]       |
| miR-29b  | ↑                            | ↑ indirectly by regulating co-activators of AR | TET2, FOXA1, mTOR | LNCaP, BicR, VCaP, and 293T/male BALB/C nude mice | ↑ 5-hmC-mediated tumour progression | [49]       |
| miR-141-3p | _                          | _ 3′UTR                   | _                | LNCaP                                 | ↓ both mRNA and protein expression levels of AR | [50]       |
| miR-96   | ↑                            | ↓ indirectly by regulating co-activators of AR | RARγ, TACC1      | LNCaP, C4-2B, RWPE-1/1 male athymic nude mice | ↓ proliferation, clonogenicity, tumorigenicity, cell growth, migration and invasion, ↑ apoptosis | [15]       |
| miR-185  | ↓                            | ↓ indirectly by regulating co-activators of AR | SREBP signaling | LNCaP, C4-2B, RWPE-1/1 male athymic nude mice | ↓ proliferation, clonogenicity, tumorigenicity, cell growth, migration and invasion, ↑ apoptosis | [51]       |
| miR-342  | ↓                            | ↓ indirectly by regulating co-activators of AR | SREBP signaling | LNCaP, C4-2B, RWPE-1/1 male athymic nude mice | ↑ proliferation, clonogenicity, tumorigenicity, cell growth, migration and invasion, ↑ apoptosis | [52]       |
| miR-204  | ↓                            | ↓ indirectly by regulating XRN1 | XRN1, PSA, miR-34a | LNCaP, 22Rv1 and PC-3 and CL1/171 BPH, plus PCa samples/nude mice and rats | ↓ growth and colony formation of LNCaP and 22Rv1 cells but ↑ growth and colony formation of CL1 and PC-3 cells | [16]       |
| miR-541  | ↑                            | _                        | _                | LNCaP, CWR22RV1 and C4-2/20 PCa samples/male nude mice | ↑ invasion and metastasis (while infiltrated T cells co-cultured with PCa cells) | [53]       |
| miR-205  | ↓                            | ↓ indirectly by regulating SQLE | SQLE             | LNCaP, C4-2, PC-3, DU145, RWPE-1, HEK293T, VCaP, and LNCaP-Ab1 | ↓ cell growth and de novo cholesterol biosynthesis | [54]       |
| miR-130a | ↓                            | ↓ indirectly by regulating coregulators of AR | CDK1, PSAP, PSMC3P, GTF2H1 | LNCaP, PC-3, Du145 and RWPE-1/5 low Gleason grade PCa samples, 6 high Gleason grade PCa samples, 3 recurrent PCa samples, and 6 nonmalignant samples | ↑ apoptosis | [55]       |
| miR-203  | ↓                            | ↓ indirectly by regulating coregulators of AR | PARK7, MNAT1, TFIH, NCOA4, CDK1 | LNCaP, PC-3, Du145 and RWPE-1/5 low Gleason grade PCa samples, 6 high Gleason grade PCa samples, 3 recurrent PCa samples, and 6 nonmalignant samples | ↑ apoptosis and cell cycle arrest | [56]       |
| miR-205  | ↓                            | ↓ indirectly by regulating coregulators of AR | PARK7, RAN, KHDBR5 | LNCaP, PC-3, Du145 and RWPE-1/5 low Gleason grade PCa samples, 6 high Gleason grade PCa samples, 3 recurrent PCa samples, and 6 nonmalignant samples | ↑ cell cycle arrest | [57]       |
| miR-212  | ↓                            | ↓ (AR and AR-V7) indirectly by regulating hnRNPH1 | hnRNPH1, SRC-3 | LNCaP, MDA-PCa-2b and C4-28/13 African American samples, and 17 Caucasian American samples/SCID mice | ↓ cell growth and ↑ sensitivity to bicalutamide | [58]       |
| miR-34a  | ↓                            | ↓ 3′UTR                   | Notch-1           | C4-2B, CWR22rv1, LNCaP, and VCaP | ↓ proliferation and self-renewal capacity | [59]       |
| miR-190a | ↓                            | ↓ indirectly by regulating the activator of AR | YB-1              | LNCaP, C4-2, PC-3, DU145, 22Rv1/male nude mice | ↓ proliferation and cell growth | [60]       |
Figure 1. Several miRNAs have been shown to affect levels of androgen receptor (AR), thus influencing the progression of prostate cancer. Detailed information about these miRNAs is presented in Table 1.

Figure 2. Effects of oncogenic miRNAs in progression of prostate cancer, through the modulation of AR signaling (↑ increased levels of, ↓ decreased levels of).

2.3. Effects of miRNAs on AR in Other Different Cancer Types

In addition to prostate cancer, the effects of miRNAs on AR have been investigated in other cancer types (Table 2). For instance, experiments in two AR-positive bladder cancer cell lines have shown that phenyl glucosamine can inactivate and degrade AR through the restoration of miR-449a expression. Lentivirus-mediated up-regulation of miR-449a has been shown to further suppress the proliferation of these cells via the induction of cell cycle arrest [58].

Table 2. Effects of miRNAs on AR in different cancer types (↓: decrease in, ↑: increase in).

| Cancer Types               | miRNAs  | Expression of miRNAs in Different Cancer Types | Target Region of AR mRNA/How microRNAs Affect AR | Molecular Mechanisms | Cell Line/Samples/Animal Models | Function of miRNAs in Cancer Cells | References |
|----------------------------|---------|-----------------------------------------------|-------------------------------------------------|----------------------|---------------------------------|-----------------------------------|------------|
| Bladder cancer             | miR-449a| ↓                                             | 3′-UTR                                          | ↓                    | UMUC3 and TCCSUP                | ARD/IA treatment: + miR-449a, ↓ proliferation, viability, ↑ cell cycle arrest [58] |
| Breast cancer              | miR-9-5p| ↓                                             | 3′-UTR                                          | +                    | MDA-MB-435, MCF-7, T-47D/11 pairs of tumor tissues and ANCs | ↓ proliferation and cell growth [59] |
| Cervical cancer            | miR-13a-3p| +                                           | 3′-UTR                                          | –                    | 20 CIN I, 20 CIN II, 30 CIN III tissue and 20 healthy tissue samples | ↑ proliferation and invasion [60] |
| Hepatocellular carcinoma   | miR-13b-5p| ↓                                           | 3′-UTR                                          | –                    | SK-hep1, HepG2, SNK, HuH7 and HA22T | ↓ proliferation, colony formation [61] |
| Glioma                     | miR-367-3p| +                                           | 3′-UTR                                          | ↑ indirectly by regulating MDM2, MMP2, FKB5, PHLF3, p41, pAKT and pERK signals | SK-hep1 and HA22T / 166 HCC samples | ↑ invasion [62] |
|                           | miR-599 | ↓                                            | 3′-UTR                                          | –                    | U251, L929, LN229               | ↓ proliferation, migration and invasion [64] |

Note: + indicates up-regulation, − indicates down-regulation.
In addition, miR-9-5p has been identified as a suppressor of AR expression in breast cancer. A feedback loop has been recognized between these genes in breast cancer cells, in which androgen agonists of AR can increase expression of miR-9-5p. In fact, miR-9-5p can inhibit the proliferation of breast cancer cells in a manner independent from the estrogen receptor (ER) status of these cells. Moreover, miR-9-5p can decrease the activity of AR-downstream signals, even in the conditions that breast cancer cells are induced by AR-agonists [59].

In cervical cancer, the oncogenic miR-130a-3p has been found to target both ERα and AR. MiR-130a-3p silencing, ERα up-regulation, and AR up-regulation have suppressed proliferation and invasion of cervical cancer cells. Besides, antagoniR-130a could decrease tumor bulk in animal models. Taken together, miR-130a-3p has a possible role in the progression of cervical cancer, through the suppression of ERα and AR [60].

In hepatocellular carcinoma, miR-135b-5p has been shown to suppress AR-mediated cell proliferation, through the regulation of HIF-2α/c-Myc/P27 axis [61]. Moreover, macrophage-derived miR-92a-2-5p-containing exosomes could increase the invasiveness of liver cancer cells, through the modulation of AR/PHLPP/p-AKT/β-catenin axis [62]. Finally, miR-367-3p could increase the effectiveness of sorafenib in the suppression of liver cancer metastasis via the modulation of AR signals [63].

In glioma, the circ-ASPH/miR-599/AR/SOCS2-AS1 axis has been identified as a molecular mechanism for cancer progression. In fact, circ-ASPH could mediate this function by sponging miR-599 [64].

3. Regulatory Impact of lncRNAs on AR

3.1. Regulation of AR Expression

PCGEM1 is a lncRNA with important roles in splicing events. This lncRNA has been found to interact with the splicing factors heterogeneous nuclear ribonucleoprotein (hnRNP) A1 and U2AF65. Experiments have shown correlation between PCGEM1 and AR3, a principal and clinically important alternatively spliced form of AR in prostate cancer. Besides, androgen deprivation leads to enhanced expression of PCGEM1 and its accretion in nuclear speckles. Androgen deprivation-induced PCGEM1 has a role in regulation of the competition between two splicing factors for AR pre-mRNA [65]. Another study has identified HORAS5 as a CRPC-promoting lncRNA through assessment of patient-derived xenografts, clinical information with subsequent in vitro and in vivo confirmation studies. This lncRNA is a cytoplasmic lncRNA, which increases proliferation and viability of prostate cancer cells via sustaining AR activity even in androgen-depleted settings. Notably, HORAS5 silencing has reduced AR expression, as well as expression of oncogenic targets of AR, including KIAA0101. In clinical samples, up-regulation of HORAS5 has been associated with poor survival. Taken together, HORAS5 has been identified as targetable contributor in the induction of CRPC phenotype through maintaining oncogenic activity of AR [66]. Recent investigations identified a novel lncRNA SAT1 as AR-interacting partner. The expression of this lncRNA is down-regulated in PCa tumor tissue compared to non-tumor tissue indicating a tumor suppressive function. LncRNA SAT1 is up-regulated by the treatment with supraphysiological androgen level (SAL) in PCa cells and human PCa tissue ex vivo and mediates the SAL-induced cellular senescence [67]. Further, it has been shown that lncRNA SAT1 interacts with AR on chromatin level regulating AR transactivation and AR target gene expression [68]. Another study has identified a feed-forward regulatory circuit between AR and PlncRNA-1, which enhances progression of prostate cancer [69]. In addition, PCAL7 lncRNA is another lncRNA that enhances progression of this type of cancer through promoting AR signaling [70]. Figure 3 depicts the role of a number of lncRNAs in progression of prostate cancer through modulation of AR signaling.
3.2. Regulation of AR Activity as AR-Interacting Partner

Several other oncogenic lncRNAs have been found to regulate AR signaling. For instance, HOTAIR increases AR-mediated transcriptional program and induces CRPC phenotypes [71]. Moreover, MALAT1 has been shown to suppress cell cycle progression in this type of cancer through regulation of AR signaling [72]. LINC00844 is another lncRNA that affects migration and invasion of prostate cancer cells through modulation of this route [73].

In brief, lncRNAs can affect AR levels through interacting with AR on chromatin level, regulation of AR transactivation and modulation of AR target gene expression. Some lncRNAs can also regulate stability of AR transcripts and preventing its ubiquitination. Table 3 shows the effects of different lncRNAs on AR in prostate cancer.

Table 3. Effects of different lncRNAs on AR in prostate cancer (ANCT: PCa: prostate cancer, DHT: dihydrotestosterone, CRPC: castration-resistant prostate cancer, ADPC: androgen-dependent prostate cancer, AD: androgen deprivation, DIM: 3,3’-Dindolylmethane, SAM: Synergistic activation mediator, LBD: ligand-binding domain, ↓: decrease in, ↑: increase in).

| LncRNAs     | Expression of lncRNAs in PCa | Target Region of AR mRNA/How lncRNAs Affect AR | Molecular Mechanisms | Cell Lines/Samples/Animal Models | Function of lncRNAs in Cancer Cells | References |
|-------------|-------------------------------|-----------------------------------------------|---------------------|--------------------------------|-----------------------------------|------------|
| ARLNC1      | ↑                             | stabilizing AR transcript                     | –                   | VCaP and LNCaP/11 benign prostate samples, 85 localized prostate cancer samples, and 37 from metastatic PCa samples/thymic nude mice | ↑ Proliferation and cell growth, ↓ apoptosis | [74]       |
| PRNCR1 and PCGEM1 | ↑                             | interact with, and increase its ligand-independent activation | DOT1L               | LNCaP, RWPE, WPE, CWR22x1/BPH and PCa tissues male athymic Nu/Nu mice | ↑ Proliferation and cell growth | [75]       |
| HOTAIR      | ↑                             | By preventing AR ubiquitination and blocking its interaction with MDM2 | –                   | LNCaP, C4-2B/GEO analysis: GSE35988 and GSE21034 | ↑ cell growth and invasion | [71]       |
| MALAT1      | ↑                             | ↑ indirectly by inhibiting miR-320             | miR-320             | DU145, 22Rv1, PC3, LNCaP/BALB/c-Au mice | DHT treatment: ↑ proliferation and cell cycle progression | [72]       |
| LINC00844   | ↓                             | modulated AR binding to chromatin             | NDRG1               | LNCaP, VCaP, and 22Rv1/GEO database: GSE109336 | ↓ migration and invasion | [73]       |
| LINC00675   | ↑                             | directly modulate AR interaction with MDM2, inhibited AR’s ubiquitination, ↑ indirectly by regulating the co-activator of AR | MDM2, GATA2         | LNCaP-SE, LNCaP-JP, LNCaP, LNCaP-C4-2B, 293T/male BALB/c nude mice | ↑ tumor formation, tumor growth and Epx resistance | [76]       |
Table 3. Cont.

| lncRNAs | Expression of lncRNAs in PCs | Target Region of AR mRNA/How lncRNAs Affect AR | Molecular Mechanisms | Cell Lines/Samples/Animal Models | Function of lncRNAs in Cancer Cells | References |
|---------|-----------------------------|-----------------------------------------------|---------------------|----------------------------------|-------------------------------------|------------|
| CCAT1   | ↑                           | ↑ by binding to P68                           | DDX5(P68), mir-28-5p | PC3, Du145, and LNCaP/8 ADPC tissues and 4 CRPC samples/BALB/C nude mice | ↑ proliferation, colony formation, and cell cycle progression, ↓ apoptosis | [77]       |
| PCGEM1  | ↑ in AD                     | ↑ AR3 by interacting with U2A65, ↓ AR3 by interacting with hnrRNPA1 | U2A65, hnrRNA A1 | LNCaP, CWR22Rv1, LNCaP95, HECK293T/male SCID mice | ↑ castration resistance | [65]       |
| SOCS2-AS1 | ↑ Castration-resistant Prostate Cancer Cells | ↑ by regulating cofactor recruitment for epigenetic controls | TNSFSF10 | LNCaP, VCaP, LTAD | ↑ castration-resistant and cell growth, ↓ apoptosis | [78]       |
| HORS5   | ↑                           | ↑ post-transcriptional maintenance of AR mRNA stability | -                  | LNCaP and C4-2 male, immunocompromised NOD/SCID mice | ↑ proliferation and survival | [66]       |
| PCLN16  | ↑                           | ↑ indirectly by regulating HIP1               | HIP1               | NCaP and VCaP/tumor tissues and ANCTs | ↑ proliferation, migration and cell growth | [79]       |
| HOTAIR  | ↑ in PCs cells after co-culture with HMC-1 cells | ↓ at the transcriptional level | PR2C, MMP9 | recruitment of mast cells: ↑ invasion and stem/progenitor cell population | [80]       |
| PlncRNA-1 | ↑                           | ↑ by spaying AR-targeting microRNAs | miR-34c and miR-297 | LNCaP, CWR22Rv1, C4-2, C4-2B and HMC-1/male nude mice | ↑ proliferation, migration and viability, ↓ apoptosis | [69]       |
| PCAL7   | ↑                           | ↑ indirectly by regulating HIP1               | HIP1               | 104 tumor tissues and ANCTs | ↑ proliferation, migration | [70]       |
| Malat1  | ↑                           | ↑ AR-v7 indirectly by interacting with NF2 to splice the AR transcript | SF2                | VCaP and EnzR-PcA C4-2/10 CRPC samples before (Pre-Enz) and after (Post-Enz) Enz treatment/nude mice | ↑ Enz resistance | [81]       |
| PlncRNA-1 | ↑                           | ↑ indirectly by regulating HIP1               | NIKO3-1            | LNCaP, LNCaP-AL, PC-3, C4-2, RWE-1 and FWRI-16 pairs of PCa tissues and ANCTs, 14 pairs of PCa tissues and BPH tissues | ↑ proliferation and viability, ↓ apoptosis | [82]       |
| LBCS    | ↓                           | ↓ 3′ UTR                                     | hnrNPK             | LNCaP, LNCaP-18c, and LNCaP-130 PCa tissues and 32 BPH tissues plus 70 PCa tissues and 10 BPH | ↓ castration resistance | [83]       |
| PCGEM1  | ↑                           | upregulation of PCGEM1 by SAM: ↑ AR3         | p54/rub            | LNCaP and CWR22Rv1/1 male SCID mice | ↑ tumor growth and castration resistance, ↓ apoptosis | [84]       |
|         |                             | facilitating AR binding to some promoters     | c-Myc              | LNCaP | ↑ glucose uptake and glycolysis, cell-cycle progression, proliferation, and survival | [85]       |
| LO280070 | ↑                           | ↑ indirectly by inhibiting PHB2               | PHB2               | LNCaP and LNCaP-AL | ↑ proliferation and migration | [86]       |
| Inc-OIPH1-1-5 | –                     | ↓ 3′UTR                                      | hnrNPA1            | C4-2R, C4-2B, C4-2B/75 PCa samples/male NOD CRISPR/BrdC  Il2r Gamma triple-immunodeficient mice | ↑ Enz sensitivity | [87]       |
| GASS    | ↓                           | ↓ directly by interacting with LBD of AR      | –                  | C4-2, Du145, 293T/GS66919 | ↓ proliferation, ↑ apoptosis | [88]       |
| GHSROS  | ↑                           | ↓                                           | PFP2R2C            | PC3, LNCaP, Du145, Ducap | ↑ proliferation, growth, migration, survival, and resistance to the cytotoxic drug docetaxel | [89]       |
| PCA3    | ↑                           | PCA3 knockdown → ↑ regulation of AR cofactors | –                  | LNCaP | modulating the expression of EMT markers and AR cofactors | [90]       |
| PRNCR1  | ↑                           | ↑                                           | –                  | LNCaP and C4-2 | ↑ proliferation and invasion, ↓ apoptosis | [91]       |

3.3. Effects of lncRNAs on AR in Other Different Cancer Types

The effects of lncRNAs on AR signaling have also been assessed in other types of cancers. In bladder cancer, XIST has been found to be up-regulated parallel with up-regulation of AR. Over-expression of XIST and AR has been correlated with advanced TNM stage in this cancer. XIST silencing has decreased proliferation, invasion, and migratory potential of bladder cancer through modulation of AR signaling. Mechanistically, XIST suppresses expression of miR-124 through direct interaction. Besides, miR-124 has been
shown to target 3′UTR of AR [92]. Another experiment in bladder cancer has shown over-expression of LINC00460. LINC00460 levels have been correlated with poor prognosis of these patients. LINC00460 silencing decreased proliferation of 5637 and T24 bladder cancer cells. Based on the observed down-regulation of AR in bladder urothelial cancer tissues, it has been suggested that LINC00460 might exert its oncogenic roles through modulation of AR expression [93]. LINC00278, SLNCR1, SARCC and HOTAIR are other lncRNAs whose effects on AR have been investigated in different cancer types (Table 4).

Table 4. Effects of lncRNAs on AR in different cancer types (ND: nutrient deprivation, ccRCC: clear cell renal cell carcinoma, ↓: decrease in, ↑: increase in).

| Cancer Types                        | LncRNAs      | Expression of LncRNAs in Different Cancer Types | Target Region of AR mRNA/How LncRNAs Affect AR | Molecular Mechanisms | Cell Lines/Samples/Animal Models | Function of LncRNAs in Cancer Cells | References |
|-------------------------------------|--------------|-------------------------------------------------|-----------------------------------------------|----------------------|---------------------------------|-------------------------------------|------------|
| Bladder cancer                      | XIST         | ↑                                               | ↑ by sponging AR-targeting microRNA            | miR-124              | TCC-SUP, J82, TCCSUP, UM-UC-3 and SV-HUC-1/TCGA database | ↑ proliferation, migration and invasion [92] |           |
|                                    | LINC00460    | ↑                                               | ↓                                             |                      | 5637, T24, J82, TCCSUP, UM-UC-3 and SV-HUC-1/TCGA database | ↑ proliferation and migration [93] |           |
| Esophageal squamous cell carcinoma  | LINC00278    | ↓                                               | indirectly inhibited interaction between YY1 and AR |                      | YY1, cEF2K, YY1BMM | DMMB, RPMI1640, FBS, Eca-109, TE-1, and KYS-30/281 pairs of ESCC tissues and ANCTs, ND treatment: ↑ LINC00278: ↓ survival, ↓ apoptosis [94] |           |
| Melanoma                            | SLNCR1       | ↑                                               | SLNCR1 binds to AR-binding motifs 1 and 2     |                      | A375, HEK290T, WM1976 | ↓ binding SLNCR1 to AR: ↓ SLNCR1-mediated invasion [95] |           |
|                                    | SLNCR1       | ↑                                               | ↑ AR binding to the MMP9 promoter             |                      | Bm3a, MMP9                  | ↑ invasion [96]                                           |           |
| Renal cell carcinoma                | SARCC        | ↓                                               | destabilizing AR protein                      | miR-143-3p, AKT, MMP-13, K-RAS and P-ERK | SW839, OSIRC-2, A498, 769-P, 786-O, Caki-1, Caki-2, HK2/66 ccRCC tissues and 8 metastatic ccRCC tissues/male athymic nude mice | ↓ proliferation, invasion, migration and resistance to Sunitinib [97] |           |
|                                    | SARCC        | Differentially expressed by hypoxia in a VHL-dependent manner | ↓ binding and destabilizing AR protein        |                      | SW839, OSIRC-2, A498, 769-P, 786-O, Caki-1, Caki-2, HK-2 and 293T/16 cccRCC samples/male athymic nude mice | Differentially modulates proliferation under hypoxia [98] |           |
|                                    | HOTAIR       | ↑                                               | ↑ GLI2                                        |                      | HK-2, 786-O, ACHN, 769-P, SW839, OSIRC-2, HUVEC/male nude mouse | ↑ angiogenic phenotype and stemness [99] |           |

4. Effects of circRNAs on AR

circZMIZ1 has been shown to be over-expressed in plasma samples of patients with prostate cancer compared with those having benign prostatic hyperplasia (BPH). In vitro studies have shown that circZMIZ1 silencing inhibits cell proliferation and arrests cells at G1. Functionally, circZMIZ1 enhances expression of AR and its splice variant 7 (AR-V7) [100].

On the other hand, expression of cir-ITCH has been shown to be decreased in the tissues and cell lines of prostate cancer compared to corresponding controls. Up-regulation of cir-ITCH could suppress proliferation, migratory potential, and invasiveness of human prostate cancer cells. A reciprocal inhibitory effect has been found between this circRNA and miR-17. Several molecules within Wnt/β-catenin and PI3K/AKT/mTOR cascades have been found to be influenced by cir-ITCH. This circRNA could indirectly reduce expression of AR through regulating the coactivator of this nuclear factor [101]. hsa_circ_0004870 [102] and circRNA17 [103] are two other circRNAs that reduce AR-V7 levels through U2AF65 and miR-181c-5p mediated routes, respectively, thus enhancing efficacy of enzalutamide. Table 5 shows the effects of different circRNAs on AR in prostate cancer.
Table 5. The effects of different circRNAs on AR in prostate cancer (HCs: healthy controls, Enz: enzalutamide, ↓: decrease in, ↑: increase in).

| circRNAs      | Expression of circRNAs in PCs | Target Region of AR mRNA/How circRNAs Affect AR | Regulated Pathway | Cell Lines/Samples/Animal Models | Function of circRNAs in Cancer Cells | References |
|---------------|-------------------------------|-----------------------------------------------|-------------------|---------------------------------|-------------------------------------|------------|
| circZMIZ1     | ↑                             | ↑ AR and AR-V7                               | miR-17, Wnt/β-Catenin, and mTOR Signaling Pathways | DU145, C4-2, LNCaP, RWPE-1, 22Rv1, 14 PCa samples, and 14 HCs | ↑ proliferation, ↓ G1 arrest | [100]      |
| circ-ITCH     | ↓                             | ↓ indirectly by regulating the coactivator of AR | miR-17, Wnt/β-Catenin, and mTOR Signaling Pathways | RWPE-1, LNCaP, PC-3/10 pairs of tumor tissues and ANCTs | ↓ migration and invasion | [101]      |
| hsa_circ_0004870 | ↓                            | ↓ AR-V7 indirectly through U2AF65             | miR-181c-5p        | C4–2, CWR22Rv1, and 293T/13 BPH samples, and 14 PCa samples/male nude mice | ↓ Enz resistance and invasion | [102]      |
| circRNA17     | ↓                             | ↓ indirectly by regulating miR-181c-5p         | miR-181c-5p        | C4–2, CWR22Rv1, and 293T/13 BPH samples, and 14 PCa samples/male nude mice | ↓ Enz resistance and invasion | [103]      |

5. Effects of AR on ncRNAs

5.1. AR Responsive miRNA

AR has been found to regulate the expression of several ncRNAs. For instance, activated AR has been shown to increase the expression of miR-203 and decrease the expression of SRC kinase in prostate cancer model systems. MiR-203 has a direct interaction with the 3′UTR of SRC and affects its stability following AR activation. A reduction in AR-induced miR-203 levels has been associated with an increased growth and migration potential of prostate cancer cells. The dysregulation of the AR signaling in prostate cancer cells results in the over-expression of SRC and enhancement of metastatic ability of these cells [104].

Another experiment has shown that AR represses the expression of both miR-221/-222. The derepression of their expression after androgen deprivation has enhanced proliferation of prostate cancer cells via facilitating G1/S phase transition. Although this effect might be transient, it has a possible role in the evolution of CRPC. The restoration of AR activity via AR up-regulation could subsequently down-regulate miR-221/-222 [105]. MiR-182-5p is another AR-regulated miRNA that facilitates the progression of prostate cancer by targeting the ARRDC3/ITGB4 axis [106]. Another study has shown the effects of AR on the down-regulation of miR-1 expression and subsequent suppression of TCF7. This process has been shown to participate in the evolution of resistance to androgen deprivation in this type of cancer [107].

AR has been shown to differentially affect the metastasis of prostate and breast cancers, through distinctively changing vasculogenic mimicry (VM) formation. In fact, AR can enhance miR-525-5p transcription in prostate cancer, while decreasing its transcription in breast cancer by binding to different AREs in the precursor promoter of this miRNA. NFIX and HDAC2 have been identified as co-factors of AR in prostate and breast cancer cells, respectively [108]. Figure 4 shows the impact of AR on miRNAs expressions, in the context of prostate cancer.

5.2. AR Responsive lncRNA and circRNA

AR has also been shown to affect expression of several lncRNAs. For instance, LINC00304 is an androgen-responsive lncRNA that induces cell cycle transition and increases the proliferation of prostate cancer cells, through the regulation of CCNA1 [109]. Moreover, the androgen-associated up-regulation of POTEF-AS1 has been shown to affect apoptosis-associated pathways, in favor of prostate cancer cells survival [110]. On the other hand, the expression of PSLNR has been shown to be decreased by androgens. This lncRNA suppresses prostate cancer progression partly through regulation of the p53-dependent axis [111]. PART1, as another androgen-regulated lncRNA, can influence the toll-like receptor pathways in this type of cancer. The expression of PART1 has been induced in prostate cancer cells treated with 5α-dihydrotestosterone, indicating that this lncRNA is directly induced by androgen [112]. Figure 5 shows the effects of AR on lncRNAs in prostate cancer.
Figure 4. Effects of AR on miRNAs expressions, in the context of prostate cancer. Detailed information about these miRNAs is shown in Table 6 (↓ reduction or inhibition of, ↑ increased levels of, ↔ decreased levels of).

Figure 5. Effects of AR on lncRNAs in prostate cancer (↓ reduction or inhibition of, ↑ increased levels of, ↔ decreased levels of).

Other studies, in the context of prostate cancer, have identified AR-regulated miRNAs and lncRNAs. Moreover, a number of circRNAs, such as circRNA-51217, circRNA-ARC1, and circZMIZ1, have been found to be influenced by AR signaling (Table 6). A recent study has identified more than 3000 androgen-responsive circRNAs, using a microarray technique. Notably, the expression of more than 1000 of these circRNAs has been consistent with the expression of their parent genes, suggesting that AR may modulate their expression at the transcriptional level [113].
Table 6. Effects of AR on different ncRNAs in prostate cancer. (PCa: prostate cancer, CRPC: castration-resistant prostate cancer, HCs: healthy controls, BPH: benign prostatic hyperplasia, CRPC: castration-resistant prostate cancer, DOX: doxorubicin, NED: neuroendocrine differentiation, NE: neuroendocrine, Enz: enzalutamide, PRAD: prostate adenocarcinoma, R-2HG: R-2-hydroxyglutarate, ↓: decrease in, ↑: increase in).

| ncRNAs | Regulation by AR | Molecular Mechanisms | Cell Line/Samples/Animal Models | Function of ncRNAs in Cancer Cells | References |
|--------|------------------|----------------------|-------------------------------|-----------------------------------|------------|
| miR-203 | ↑                | SRC                  | LNCaP and C4-2B/LuCaP 35 and LuCaP 35CR xenografts | ↓ migration, growth, and metastasis | [104]      |
| miR-221/-222 | ↓            | FOXA1                | LNCaP and C4-2B/LuCaP 35 and LuCaP 35CR xenografts | ↑ proliferation and development of CRPC | [105]      |
| miR-182-5p | ↑            | ARLD3, ITGB4         | RWPE-1, 22Rv1, LNCaP, DU145/65, pairs of tumor tissues and ANCTs, and 18 pairs of tumor tissues and ANCTs/male nude mice | ↑ proliferation, invasion, migration and growth, ↓ apoptosis | [106]      |
| miR-1 | ↑                | TCF7                 | PC3, LNCaP/111 Pc samples/nude mice | ↓ proliferation | [107]      |
| miR-525-5p | ↑            | SLP, NFIX             | -                             | ↓ PCa metastasis | [108]      |
| miR-21 | ↑                | TGFBR2, Smad2/3      | RWPE-1, MDA-PCa-2b, 22Rv1, PC-3, and LNCaP/male athymic nude mice | ↓ tumor-suppressive activity of TGFβ pathway | [109]      |
| miR-21 | ↑                | LNCaP, LAPC-4, C4-2, CWR22Rv1/10 Pc samples/male athymic Nu/Nu mice | ↑ proliferation and development of CRPC | [110]      |
| miR-133a-3p | ↑           | AJUBA                | LNCaP, C4-2B | ↑ migration and metastasis | [111]      |
| miR-4496 | ↑            | β-catenin signals    | C4-2 and PC3 | ↓ invasion | [112]      |
| miR-135a | ↑            | ROCK1 and ROCK2      | LNCaP, PC-3/56 pairs of tumor tissues, and ANCTs/chick embryos and adult male mice | ↓ invasion | [113]      |
| miR-32 | ↓                | NSE                  | RWPE1, LNCaP, and CWR22Rv1/1/male nude mice | ↑ androgen-dependent and -independent proliferation, tumor growth, and castration resistance | [114]      |
| miR-21 promoter | ↑           | PDCD4                | LNCaP and HEK 293, LAPC4/male athymic nu/nu mice | ↑ androgen-dependent and -independent proliferation, and castration resistance | [115]      |
| miR-22 | ↓                | LAMC1                | LNCaP, PC3, DU145, VCaP, CWR22Rv1, DUCaP, BPH-1, PC3-AR, LAPC-4, RWPE-1, and EpS1/14 pairs of tumor tissues and ANCTs, TCGA analysis: 52 pairs of tumor tissues and ANCTs, | ↓ migration | [116]      |
| miR-29a | ↓                | MCL1                 | LNCaP, PC3, DU145, VCaP, CWR22Rv1, DUCaP, BPH-1, PC3-AR, LAPC-4, RWPE-1, and EpS1/14 pairs of tumor tissues and ANCTs, TCGA analysis: 52 pairs of tumor tissues and ANCTs, | ↓ migration and viability, ↓ apoptosis | [117]      |
| miR-99a/let7c/125b-2 cluster | ↓            | IGF1R                | LNCaP, C4-2, and PC3 | ↓ proliferation | [118]      |
| miR-2909 | ↑            | TGFB2, TGFβ signaling, PSA | PC3 and LNCaP | ↑ cell growth | [119]      |
| miR-32 | ↑                | BTG2                 | LNCaP / 5 BPH and 28 PCs, plus 7 BPH and 14 CRPCs | ↑ cell growth | [120]      |
| miR-148a | ↑            | PIK3IP1              | LNCaP / 5 BPH and 28 PCs, plus 7 BPH and 14 CRPCs | ↑ cell growth and the number of cells in the S phase | [121]      |
| miR-194 | ↓                | FOX1, ERK Signaling  | LNCaP, PC3, and CWR22Rv1 | ↑ EMT process, migration, invasion and epithelial-neuroendocrine transdifferentiation | [122]      |
| miR-27a (miR-23a27a24-2cluster) | ↑            | PHB                  | HeLa, Cos-1, LNCaP, DuCaP, VCaP, C42, DU145, PC3, and PC3wtAR | ↑ cell growth | [123]      |
| miR-200b | ↑            | -                    | PC3/male athymic mice | ↓ proliferation, invasion, cell growth, EMT process and metastasis | [124]      |
| ncRNAs | Regulation by AR | Molecular Mechanisms | Cell Line/Samples/Animal Models | Function of ncRNAs in Cancer Cells | References |
|--------|-----------------|----------------------|-------------------------------|-----------------------------------|------------|
| miR-19a | ↑ | SUZ12, RAB13, SC4MOL, PSAP, and ABCA1 | LNCaP | ↑ cell viability | [128] |
| miR-27a | ↑ | ABCA1 and PDSSB | LNCaP | ↑ cell viability | |
| miR-133b | ↑ | CDC2L5, PTTRK, RB1CC1, and CPNE3 | LNCaP | ↑ cell viability | |
| miR-22 | ↑ and ↓ during two different mechanisms | IL-6, AR c-MYC, miR-22, P63, KDM3A (↑) and AR c-MYC, miR-22, P63, KDM3A (↓) | LNCaP-Abl, LNCaP-IL-6, LNCaP-male mice | ↑ sensitivity LNCaP-Abl cells to the enzalutamide treatment, ↓ proliferation | [129] |
| miR-17-92a | ↑ | ATG7 NCaP, 22Rv1, DU145, and PC-3 | ↓ autophagy induced by celastrol treatment | [130] |
| miR-204 | ↓ | XRN1, PSA, miR-34a | LNCaP, 22Rv1, PC-3, and CL1/171, BPH, plus PCa samples/nude mice and rats | ↓ growth and colony formation of LNCaP and 22Rv1 cells but ↑ growth and colony formation of CL1 and PC-3 cells | [52] |
| miR-34 | ↑ after DOX, but did not change with si-AR, miR-34c↑ after DOX, but to a small extent changed with si-AR | HOXC6 and NKX2-2 | RWPE-1 and LNCAP | ↓ metastasis and EMT process | [133] |
| miR-101 | ↑ | HOXC6 and NKX2-2 | LNCaP, 22Rv1, DU145, and PC-3 | ↓ celastrol-induced autophagy | [134] |
| miR-27a | ↓ | MAP2K4, PI3K signaling pathways | TCGA database: GSE45604 and GSE21036 | ↓ proliferation and migration, ↑ apoptosis | [135] |
| miR-190a | ↓ | YB-1 | LNCaP, C4-2, PC-3, DU145, 22Rv1/mal nude mice | ↓ proliferation and cell growth | [57] |
| ARLNCI | ↑ | VCaP and LNCaP/11 benign prostate samples, #5 localized prostate cancer samples, and 37 from metastatic PCa samples/athymic nude mice | P53, SIAK, MDC1, and CaMKII | ↑ Proliferation and cell growth, ↓ apoptosis | [74] |
| PRCAT38 | ↑ | TMPRSS2, FOXA1 | LNCaP, DU145, and VCaP/20 samples (HCs and PCa) | ↑ cell growth and migration | [136] |
| H19 | ↓ | LNCaP | Enzalutamide treatment: ↑ H19 | | [137] |
| GASS | ↓ | PC3 and 22Rv1 | dexamethasone treatment in AR-PCa cell line PC3. ↑ GASS ↓ proliferation, ↑ GO/G1 cell arrest | | [138] |
| p21 | ↓ AR binding to the ARE5, ↑ AR binding to the AGRE | EZH2, STAT3 | C4-2, CWR22RV1, NE1.8, NCI-H660, and DU145 | Enz treatment: ↓ AR binding to the ARE5 region of p21: ↑ p21. ↑ NED, NE-like structure | [139] |
| LINC00304 | ↓ | CCNA1 | LNCaP, 22Rv1, DU145, PC-3, and WPMY-1/GEO database: GSE38241: 18 PCa samples and 21 HCs | ↑ proliferation and cell cycle progression | [109] |
| PTEF-AS1 | ↑ | TLR signaling pathway | LNCaP, VCaP, LTAD, and VCaP-LTAD | ↑ cell growth, ↓ apoptosis | [110] |
| PLSNR | ↓ | p53 signaling pathway | LNCaP, 22Rv1, DU145, PC-3, and WPMY-1/GEO database: GSE35909, 3 pairs of tumor tissues and ANCTs, 13 tumor tissues and ANCTs, plus 20 pairs of PCa sample | ↑ proliferation and cell-cycle progression, ↓ apoptosis | [111] |
| PART1 | ↑ | TLR pathways | LNCaP and PC3/30 pairs of tumor tissues and ANCTs | ↑ proliferation, ↓ apoptosis | [112] |
| GA55 | ↓ | LNCaP, 22Rv1, DU145, PC3, WPMY-1/14 tumor tissues, and 11 normal tissues | ↓ proliferation, ↓ apoptosis | [114] |
| PCLN16 | ↑ | HIP1 | NCaP and VCaP/tumor tissues and ANCTs | ↑ proliferation, migration, and cell growth | [79] |
Table 6. Cont.

| ncRNAs         | Regulation by AR | Molecular Mechanisms                        | Cell Line/Samples/Animal Models                                                                 | Function of ncRNAs in Cancer Cells                                                                 | References |
|----------------|------------------|---------------------------------------------|--------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|------------|
| PlncRNA-1      | ↑                | miR-34c and miR-297                         | RWPE-1, 22RV1, LNCaP, PC3 and DU145/16 PCA tissue samples, 35 biopsy-negative and 37 biopsy-positive blood samples/male nude mice | ↑ proliferation, migration and viability, ↓ apoptosis                                            | [69]       |
| PCAL7          | ↑                | HIP1                                        | 104 tumor tissues and ANCTs                                                                      | ↑ proliferation, migration                                                                       | [70]       |
| PCGEM1         | ↑                | –                                           | 131 primary PCa, 19 metastatized PCa, and 29 normal prostatic tissue samples/intact mice          | ↑ PCGEM1 in primary PCa Androgen receptor regulated PCGEM1 in vivo                               | [141]      |
| DRAIC          | ↓                | –                                           | VCap, PC3M-luc                                                                                 | ↓ transformation of cuboidal epithelial cells to fibroblast-like morphology, migration, and invasion | [142]      |
| PCAT29         | ↓                | –                                           | VCap, PC3M-luc                                                                                 | ↓ migration and metastasis                                                                     |            |
| a subset of TPCATs, most notably EPCART | ↑ | ERG                                        | LNCaP, VCaP, and DuCaP/87 prostatectomy-treated samples                                          | ↑ proliferation, migration                                                                      | [143]      |
| PCAT29         | ↓                | –                                           | VCap, LNCaP, and DU145/GEO database: GSE50397/male nude athymic BALB/c nu/nu mice                | ↓ proliferation, migration                                                                      | [144]      |
| Malat1         | ↓                | –                                           | VCaP and Enz-R-PCA C4-2, 10 CRPC samples, before (Pre-Enz) and after (Post-Enz) Enz treatment/male nude mice | Enz treatment: ↑ Malat1                                                                       | [81]       |
| PlncRNA-1      | ↑                | NKX3-1                                      | LNCaP, LNCaP-AI, PC-3, C4-2, RWPE-1 and PWR-1/E16 pairs of PCa tissues and ANCTs, 14 pairs of PCa tissues and BPH tissues | ↑ proliferation and viability, ↓ apoptosis                                                      | [82]       |
| CTBP1-AS       | ↑                | PSE, CTBP1                                  | VCaP, LNCaP, DU145, RWPE and PC/105 PCa samples                                                | ↑ castration-resistant tumour growth                                                              | [145]      |
| RP11-709K16.13, RP11-228B15.4, and CTD-222K2.7 | ↑ | –                                           | Higher expression of the lncRNAs were significantly correlated with shorter DFS time in PRAD. |                                                                                                  |            |
| PLAT1          | ↑                | rs463708 increases binding ONECUT2 and AR to the PCAT1 promoter | ONECUT2, L5D1, GNMT, and DHC24                                                               | ↑ proliferation and tumor growth                                                                | [147]      |
| FAM8H-AS1      | ↑                | miR-15a, CCNE2                              | LNCaP, LNCaP-AI and DU145/GEO datasets: GSE512217 and GSE55562, plus 200 PCa and 8 normal samples | ↑ proliferation, migration, and cell cycle progression                                            | [148]      |
| DANCr          | ↓                | TIMP2/3                                     | CWR22Rv1, PC3, and C4-2/R+/nude mice                                                          | ↑ proliferation and invasion                                                                     | [149]      |
| GASS           | ↓                | –                                           | LNCaP/GSE22606                                                                                 | ↓ proliferation, ↑ apoptosis                                                                     | [88]       |
| PCAT18         | ↑                | PES                                         | LNCaP, C4-2, BPH/131 PCa, and 29 normal samples/NOD/SCID mice                                   | ↑ proliferation, migration, ↓ G1 arrest                                                          | [150]      |
| RPI-4514.2, LINC01138, and SUZ12P1 | ↓ | –                                           | 22RV1, DU145, PC-3 and LNCaP, WMPY-1/3 tumor tissues and 11 ANCTs, plus 14 tumor tissues, and 11 ANCTs and TCGA database | ↑ proliferation and migration, ↑ invasion                                                        | [151]      |
| KLKP1          | ↑                | –                                           | 22 RV1, DU145, PC-3 and LNCaP, WMPY-1/3 tumor tissues, 11 ANCTs plus 14 tumor tissues, and 11 ANCTs and TCGA database |                                                                                                  |            |
| TMPO-AS1       | ↓                | –                                           | LNCaP, DU145, 22RV1, PC-3, and WMPY-1/54 pairs of PCa samples and TCGA data                     | ↑ proliferation and migration, ↓ apoptosis                                                        | [152]      |
| circRNA-51217  | ↓                | R-2HG, miRNA-646, TGFβ1/p-Smad2/3 signaling, ADAR2 | C4-2, PC3, DU145, LNCaP, and HEK293T/TCGA database                                           | IDH1 mutation And R-2HG: ↑ circRNA-51217: ↑ invasion                                              | [153]      |
| circRNA-ARC1   | ↓                | miR-123b-2-3p/miR-4736/PPARγ/MMP-9 signals   | CWR22Rv1 and C4-2                                                                            | Enz treatment: ↑ invasion                                                                       | [154]      |
| circZMIZ1      | ↑                | –                                           | DU145, C4-2, LNCaP, 22RV1, RWPE-1, 14 PCa samples, and 14 HCs                                   | ↑ proliferation, ↓ G1 arrest                                                                      | [100]      |

In brief, the effect of AR on the expression of ncRNAs is mainly associated with its role as a transcription factor.

Effects of AR on expression of ncRNAs are also implicated in the pathoetiology of bladder, breast, liver, renal, and gastric cancers (Table 7). Yet, these effects are largely...
context-dependent. For instance, AR could reduce the expression of miR-21 in breast cancer \[155\], while inducing its expression in hepatocellular carcinoma \[156\].

### Table 7. Effects of AR on ncRNAs in different cancer types (Enz: enzalutamide, VM: vasculogenic mimicry, DHEA: dehydroepiandrosterone, RBM: ccRCC bone metastases, ↓: decrease in, ↑: increase in).

| Cancer Types            | ncRNAs       | Regulation by AR | Molecular Mechanisms                                      | Cell Line/Samples/Animal Models                                      | Function of ncRNAs in Cancer Cells                      | References |
|-------------------------|--------------|------------------|-----------------------------------------------------------|---------------------------------------------------------------------|---------------------------------------------------------|------------|
| Bladder cancer          | miR-525-5p   | ↓                | SLPI, HDAC2                                               | SVHUC, T24, 182, 5037, and UMUC3/male athymic BALB/c nude mice       | ↑ metastasis                                            | [108]      |
|                         | circFNTA     | ↑                | ADAR2, miR-370-3p, FNTA pathway, KRAS signaling           | T24 and UMUC3                                                       | ↑ invasion, metastases, and cisplatin chemo-resistance  | [157]      |
|                         | circRNA-ARC1 | ↑                | miR-125b-2-3p/miR-4736/PPARγ/ MMP-9 signals               | T24 and UMUC3                                                       | Enz treatment: ↓ invasion                              | [154]      |
| Breast cancer           | let-7a       | ↑                | CMYC and KRAS                                            | MCF-7, MDA-MB-453, and MDA-MB-231/24 breast cancer samples         | ↓ proliferation, cell growth                            | [158]      |
|                         | miR-21       | ↓                | –                                                        | MCT-7, ZR-75-1, MDA-MB-231, SKBR3, and LNCap                      | ↑ proliferation (miboleron: ↓ miR-21: ↓ proliferation) | [155]      |
| Triple-negative breast cancer | ARNILA     | ↓                | miR-204, Sex4                                            | MDA-MB-231 and Hs578T, MDA-MB-436/88 TNBC samples/female BALB/c nude mice | ↑ migration, invasion, and EMT process                  | [159]      |
| Early Hepatocarcinogenesis | miR-216a | ↑                | TSLC1                                                    | HepG2/48tumor tissues and 13 non-tumor tissues/male athymic nude mice | ↑ proliferation and migration                          | [160]      |
|                         | miR-21       | ↑                | PDCD4, ERβ                                               | HepG2, HBEC2-K7/male C57BL/6 mice                                   | DHEA: ↑ miR-21: ↑ proliferation                         | [156]      |
|                         | miR-146a-5p  | ↓                | BRCA1 and BCL2, SK-HEP-1 and TCGA database analysis/male nude mice | Enz plus Olaparib treatment: ↑ miR-146a-5p: ↓ proliferation, cell growth, and viability |                                                | [161]      |
| Hepatocellular carcinoma | circRNA7    | ↓                | miR-7-5p, VE-Cadherin, Notch4                            | SHeep1, HAA2T                                                        | ↑ formation of VM                                       | [162]      |
|                         | circ-LNPEP   | ↓                | miR-532-3p, RAB9A                                        | HA22T, SK-HEP-1, and 293/male nude mice                              | ↑ invasion and metastasis                               | [163]      |
|                         | circARSP91   | ↓                | ADAR1                                                    | MHCC-97L, LM3 and LO2, HEK-293T/83 pairs of tumor tissues, and ANCTs/nude mice | ↓ tumor growth                                          | [164]      |
| Melanoma                | miR-539-3p   | ↑                | MITF-AXL signals, USP13                                   | A375 and WM115 and C32/102 melanoma tissue samples/male nude mice   | ↑ invasion and metastasis                               | [165]      |
|                         | SLNCR        | ↑                | p21, EGR1, MMP9                                         | WM1976 or A375, SK-MEL-28, WM85                                   | ↑ proliferation and invasion                           | [166]      |
|                         | SLNCR1       | ↑                | Brm3a, MMP9                                              | A375, HEK293T, CY and WM                                           | ↑ invasion                                              | [96]       |
| Cholangiocarcinoma       | ZEB1-AS1     | ↑                | miR-133b, HOXB8                                          | HIBEC, QRC939, CCLP-1, RBE, TFK-1/54 pairs of tumor tissues, and ANCTs/male BALB/c nude mice | ↑ migration, invasion, EMT process, viability, and stemness | [167]      |
| Gastric cancer           | PART1        | AR interacts with PART1 to stimulate PLZF expression     | PLZF, EZH2, PDGFRα/P3K/Akt signaling pathway              | GES-1, GCC-803, BCC-823, and SGC-7931/GEOdatabase: GSE27342, GSE33335, andGSE3072, plus 136 CC samples | ↓ migration, invasion, and metastasis                  | [168]      |
|                         | TANAR        | ↑                | TWIST1                                                   | 786O, SW809, HEK293T/51 ccRCC tissues, and 23 ANCTs/male athymic BALB/c nude mice | ↑ VM formation                                          | [169]      |
| Clear cell renal cell carcinoma | circHIAT1 | ↓                | HIAT1, miR-195-5p/29A-3p/29C-3p, and CDC42              | SRC-2, VHL(j) Caki-1, SW-839, and ACHN                              | ↓ migration and invasion                               | [170]      |
|                         | circEXOC7    | ↓                | DHX9, miR-149-3p, CSF1                                    | SW839, 786-O, Caki-1, ACHN, HEK293T/4 RCC samples with RBM, and 10 RCC samples without RBM/BALB/c nude mice | ↑ RBM and osteolytic formation                          | [171]      |
6. Discussion

AR has an essential role in the pathogenesis of human cancers, particularly prostate cancer. Since it is required for the development of prostate cancer, androgen deprivation therapy is regarded as a treatment for this type of cancer. Thus, the identification of the regulatory mechanisms of AR signaling is important in the design of treatment options. The importance of this process is further highlighted by the fact that castration resistance might occur during the course of treatment, as a result of expression of constitutively active AR splice variants [172], whose expressions can be modulated by ncRNAs.

Integrative transcriptomic analyses of diverse cancer cell lines and tissues have resulted in the identification of several AR-interacting ncRNAs. In the current study, we have listed ncRNAs that affect expression of AR, as well as those being affected by AR. Notably, mutual interactions have been identified between AR and some of these non-coding transcripts. For instance, the expression of the IncRNA ARLNC1 has been shown to be enhanced by the AR protein. Conversely, ARLNC1 can increase the stability of the AR mRNA through RNA-RNA interaction [74].

AR-targeting miRNAs have been suggested as potent tumor suppressors in prostate cancer. However, a number of other miRNAs have also been found to induce CRPC, by changing the activity of AR signaling. Moreover, AR signaling can affect the expression of miRNAs through different mechanisms, including feedback loops.

LncRNAs and circRNAs that regulate AR signaling have been found to interact with miRNAs. MALAT1/miR-320, CCAT1/miR-28-5p, PlncRNA-1/miR-34c, PlncRNA-1/miR-297, XIST/miR-24, SARCC/miR-143-3p, circ-ITCH/miR-17, and circRNA17/miR-181c-5p are examples of the cooperation between IncRNAs/circRNAs and miRNAs in the regulation of AR signaling. Similarly, AR-regulated IncRNAs and circRNAs have been shown to influence the expression or bioavailability of miRNAs, adding novel layers of complexity in this interaction network.

Taken together, the data presented above indicates the complexity of the transcriptional regulation of miRNAs by AR and the effects of AR on them. Moreover, the interactions between ncRNAs and AR signaling can be context-dependent.

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