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Review

Molecular Perspectives on Prostate Cancer: The Role of microRNAs in Androgen Receptor Regulation

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Abstract: Prostate cancer (PCa) is the most prevalent cancer among men globally. In addition to environmental risk factors, genetic factors play a crucial role in its development and progression, highlighting the regulation of key genes as an essential aspect. The androgen receptor gene (*AR*) plays a pivotal role in this disease, so its post-transcriptional regulation must be meticulously coordinated. In this review, we explore the role of microRNAs (miRNAs) in the regulation of AR in PCa, a field not yet fully investigated. We note that the AR, due to its extensive 3′UTR region, is targeted by numerous miRNAs, and that this regulation can occur at different levels: directly, indirectly, and through mutual regulation, thus amplifying the influence of these molecules on *AR* regulation.

Keywords: prostatic neoplasms; androgen receptor; gene expression regulation; microRNAs

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1. Introduction

Prostate Cancer: Epidemiology and Risk Factors

Prostate cancer (PCa) is characterized by malignant growth in the prostate gland [1]. It represents one of the most frequent neoplasms among men worldwide [2], and the latest reports from the Global Cancer Observatory (GLOBOCAN) reported that in 2022, PCa ranked behind lung cancer as the most common cancer in men worldwide with about 1,467,854 new cases diagnosed and 397,430 deaths [3].

Risk factors for developing PCa are diverse. Advanced age is one of the main factors, as the incidence of this cancer increases significantly in men over 50 years of age. Additionally, African men have a higher risk of developing PCa than men of other ethnicities [4]. Hormonal factors play a crucial role; elevated levels of testosterone and other androgens can promote the malignization of prostate cells. Genetic factors also significantly contribute to the development of PCa, with mutations in genes like *BRCA1* and *BRCA2* (breast cancer 1/2), along with variants in other genes, associated with increased risk. Additional factors such as diet, body mass index, persistent prostatitis, and exposure to tobacco, alcohol, and pesticides have also been linked to the onset of this disease [4–6].

Epigenetic mechanisms play a crucial role in PCa. One well-documented mechanism is the hypermethylation of gene promoters such as *RARβ* (retinoic acid receptor β) and *GSTP1* (glutathione S-transferase pi 1) [7]. Besides methylation, other epigenetic mechanisms involved in PCa include histone modification [8] and gene regulation by non-coding RNAs, including microRNAs (miRNAs), circular RNAs (circRNAs), and long non-coding RNAs (IncRNAs) [9].

Certain environmental factors have been observed to influence these epigenetic mechanisms, potentially contributing to cancer development. Tobacco, endocrine disruptors, and alcohol can induce changes in DNA methylation patterns, thereby altering gene expression. For instance, alcohol consumption has been shown to affect the expression profiles of specific miRNAs and modify histone modification patterns, which in turn can influence gene expression and contribute to cancer progression [10].

Diet plays a crucial role in shaping methylation patterns, with essential nutrients such as folate, methionine, and choline necessary for these processes. Compounds such as polyphenols and omega-3 fatty acids can modulate the enzymes involved in methylation, potentially reversing or mitigating harmful epigenetic changes [11,12].

Conversely, physical activity has been associated with alterations in global methylation and miRNAs' expression in PCa [13]. Regular exercise can induce beneficial epigenetic changes, which might counteract the adverse effects of other environmental factors.

While much is known about the risk factors and epigenetic mechanisms in PCa, the specific role of miRNAs in regulating the AR gene remains inadequately explored. AR is a nuclear hormone receptor that plays a pivotal role in the development and progression of PCa. AR regulates gene expression in cell proliferation and survival, making it a key driver in PCa pathogenesis [14–18].

miRNAs are crucial in PCa for early diagnosis, treatment, and prognosis [19–21]. Understanding miRNA-mediated regulation of AR could uncover new therapeutic targets and improve PCa management.

In this review, we provide a detailed analysis of those miRNAs that may play a significant role in regulating the *AR* gene, a master gene in PCa. In addition to reviewing the existing literature, we conduct an exhaustive review using bioinformatics platforms such as PolymiRTS 3.0 and dbDEMC. Utilizing in silico predictions and experimental validations provided by these platforms, we identify the miRNAs that directly regulate *AR*.

2. Androgen Receptor in Prostate Cancer

2.1. Genetic Aspects and Structure of Androgen Receptor

The *AR* gene is located on the long arm of the X chromosome, specifically in the Xq12 region, and encodes for the AR protein, which binds to androgenic hormones such as testosterone, thereby regulating the transcription of genes essential for cell growth. This receptor is essential for the development and maintenance of male sexual characteristics [22,23].

The AR contains an *N*-terminal domain essential for transcriptional activation (NTD), a DNA-binding domain (DBD) that binds to specific DNA sequences called androgen response elements (AREs), a hormone-binding domain (LBD) responsible for androgen binding and receptor dimerization, and a hinge region that regulates the receptor's subcellular localization [24].

2.2. Androgen Receptor Signaling Pathway

The AR signaling pathway begins with the binding of androgens to its LBD. This binding induces conformational changes in the receptor, facilitating its dimerization and subsequent translocation to the nucleus of the cell. Therefore, AR binds to specific DNA sequences known as AREs, which are localized to the promoters of various target genes. This binding leads to the transcription of genes that promote cell growth, proliferation, and survival [22,25] (Figure 1).

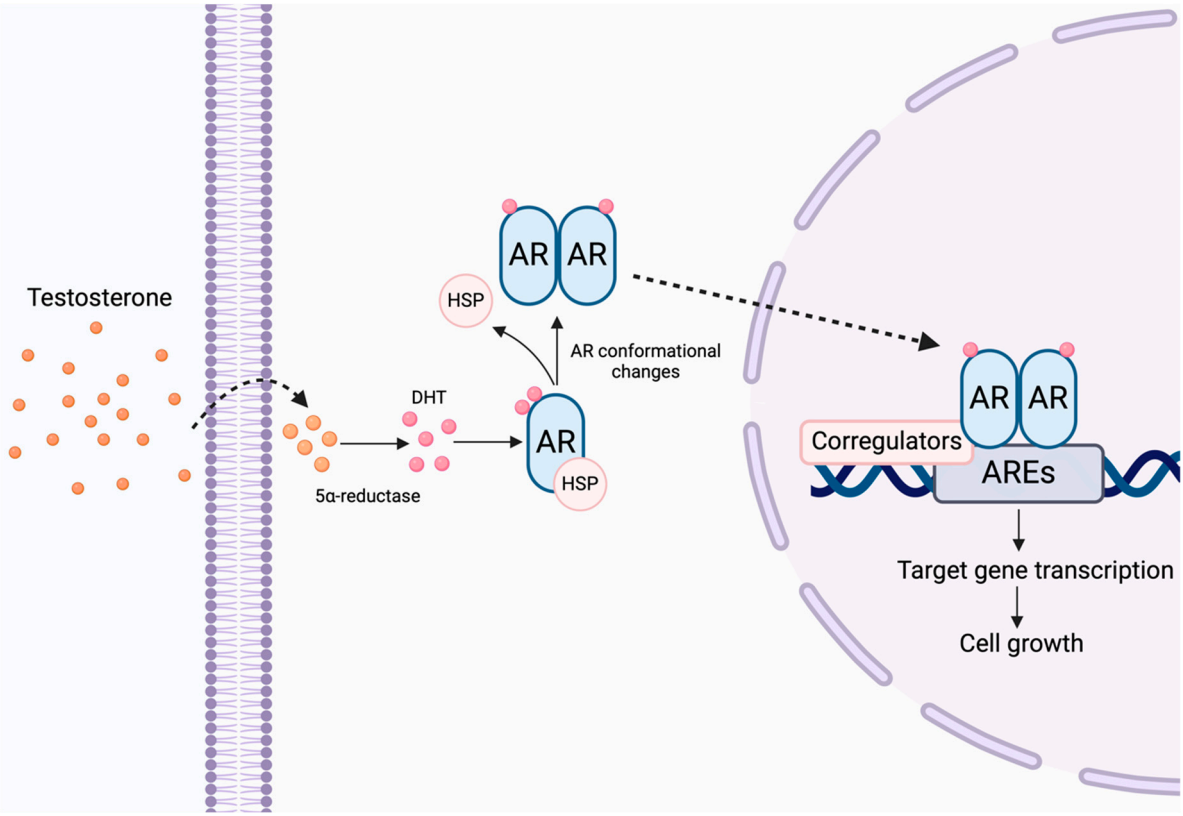

Figure 1. AR pathway. Free androgens in the bloodstream can diffuse freely across the plasma membrane of cells. Within the cell cytoplasm, testosterone is converted to dihydrotestosterone (DHT) by the action of the enzyme 5α-reductase. This conversion is essential because DHT has an increased affinity for AR. Within the cell cytoplasm, the AR remains inactive and bound to chaperone proteins, such as HSPs. However, when the androgen binds to the AR, it undergoes conformational changes that allow dissociation from chaperone proteins and subsequent activation. Once active, the androgen-bound AR forms a homodimer with another complex. This complex then translocates to the cell nucleus, where it binds to the AREs, located in the promoters of various target genes. The binding of the AR to the AREs allows the recruitment of coactivator proteins that modulate the transcription of genes involved in cell proliferation, differentiation, and apoptosis [14–16,26]; created with Biorender.com.

2.3. Clinical Significance of Androgen Receptor in Prostate Cancer

The role of *AR* in the development and progression of PCa is fundamental. Dysregulation of the *AR* signaling pathway is a hallmark of PCa development and progression. Furthermore, *AR* signaling within the prostate stroma plays a significant role in the initiation and progression of PCa. Clinical observations suggest that the loss of *AR* in the PCa stroma correlates with the disease progression [17,22,24].

The *AR* gene is highly expressed in prostate cells and regulates the expression of genes critical for cell proliferation and differentiation in response to androgens [27]. PCa is classified as either androgen-sensitive or insensitive, indicating its ability to respond to stimulation by testosterone. Androgens normally promote prostate epithelial growth and survival by binding and activating the *AR* [28]. Following intranuclear compartmentalization from the cytoplasm and DNA binding, the *AR*–androgen complex acts as a nuclear transcription factor for the activation of genes promoting the synthesis of prostate-specific antigen (PSA) and proteins involved in cell proliferation [29]. Early-stage PCa is highly dependent on *AR* activation for survival, but recurrence is in most cases, characterized by androgen-independent tumors due to adaptations to low androgen levels [30].

Despite low androgen levels, *AR* signaling remains active in PCa, continuing to promote tumor growth. This persistent activity is due to mechanisms such as gene amplifications and variants that promote constant activation of the gene. Some variants result in AR proteins lacking the LBD, which leads to continuous activation of AR independent of androgens [15,18,24,26].

AR variants (AR-Vs), resulting from alternative mRNA splicing, are characterized by the absence of the ligand-binding domain (LBD) and exhibit constitutive transcriptional activity. This ligand-independent activity is particularly problematic, as it enables AR-Vs to drive tumor growth and promote resistance to androgen deprivation therapies (ADTs), proposing a significant challenge in the treatment of PCa [31–34]. For example, the splice variant AR-V7 has been linked to resistance against ADT [16,25,35], by activating AR target genes in the absence of androgens, facilitating cell proliferation and survival despite treatment. Notably, AR-V7 is associated with poor prognosis and resistance to second-generation AR-targeted therapies, such as enzalutamide [35,36].

Other AR-Vs, including AR-V1, AR-V3, AR-V4, AR-V9, and AR-V567es, share similar properties that contribute to therapeutic resistance in PCa [31,32,37–41]. Reports suggest potential therapeutic strategies targeting these variants, such as the use of novel AR degraders known as proteolysis-targeting chimeras (PROTACs), which aim to promote the degradation of AR-Vs and restore sensitivity to ADT [42].

Additionally, the downregulation of *AR* in stromal fibroblasts disrupts the expression levels of extracellular matrix (ECM) proteins, creating a microenvironment that facilitates PCa cell metastasis [17]. The interaction between AR and other signaling pathways, such as the PI3K/AKT/mTOR pathway, has also been implicated in promoting PCa progression and therapeutic resistance [43,44]. A recent study suggests that inhibiting both AR and PI3K pathways through the combination of inhibitors like darolutamide and copanlisib enhances therapeutic efficacy and induces apoptosis in androgen-sensitive PCa cells [45].

3. microRNAs: Definition and Functional Mechanism

3.1. Characteristics and Biogenesis of microRNAs

miRNAs are short non-coding RNAs (approximately 22 nucleotides) essential for post-transcriptional gene regulation of genes. The biogenesis of miRNAs is a multi-step process starting in the nucleus, where primary miRNAs (pri-miRNAs) are transcribed by RNA polymerase II. These are processed by Drosha and DGCR8 into precursor miRNAs (pre-miRNAs), which are then exported to the cytoplasm and further cleaved by Dicer into mature miRNAs. The guide strand of the miRNA is incorporated into the RNA-induced silencing complex (RISC), which mediates gene silencing by binding to complementary sequences on the 3′UTR region of their target mRNAs [46–51].

Interestingly, due to the nature of AR activity, it has been observed that this gene can dysregulate the global expression of miRNAs. AR regulates genes that serve as transcription factors for miRNAs, thereby influencing their overall expression profile [52–55]. This regulatory mechanism underscores AR's role not only in direct gene regulation but also in modulating broader cellular processes through miRNA networks. Such interactions highlight the complexity of AR-mediated transcriptional control and its implications in various physiological and pathological contexts.

3.2. Gene Regulation Mediated by microRNAs

Once the RISC complex is formed, the miRNA seed region conformed by nucleotides 2–8 recognizes complementary sites located in the 3′UTR region of its target mRNAs [35,48]. A single miRNA associated with the complex can recognize and regulate multiple genes, and a gene can be recognized and regulated by multiple miRNAs [48,56]. It is estimated that approximately 60% of protein-coding genes are regulated by miRNAs [57]. When the RISC complex binds to the target mRNA, Ago2 interacts with the TNRC6/GW182 complex, which is responsible for recruiting the PAN2–PAN3 and CCR4–NOT deadenylase complexes [58], the mRNA can be degraded by the activity of the PAN2–PAN3 and CCR4–NOT

complexes, which deadenylate the mRNA strand, making it susceptible to expression silencing by two different mechanisms. First, the mRNA can be directly degraded by the activity of the PAN2–PAN3 and CCR4–NOT complexes that deadenylate the mRNA strand, leading to its degradation. [57]. Second, the RISC complex can also directly repress the translation process by inhibiting the initiation or elongation of protein synthesis. By blocking this critical step, protein formation from mRNA is prevented, contributing to the effective silencing of gene expression [59,60].

Post-transcriptional regulation by miRNAs is a well-regulated and highly complex process, involving multiple mechanisms that ensure precision and specificity in gene expression [61,62]. Although miRNAs can bind to specific sites on mRNAs, not all protein-coding genes are regulated by miRNAs—only about 60% of them are subject to such regulation [57], In addition, cells have mechanisms to regulate this interaction to maintain proper gene expression. For example, the global expression of miRNAs is tightly controlled, and their availability within the cell can be reduced by various transcriptional regulations [63–65]. These regulations can include the modulation of transcription factors [65], the overall cellular state (such as cellular stress), and pathological conditions [49].

4. The Role of microRNAs in Cancer

Recently, there has been considerable interest in studying the role of miRNAs in cancer development and progression. Recent research has highlighted the pivotal role of miRNAs in PCa diagnostics, development, and progression [19–21]. While miRNAs commonly act as tumor suppressors by targeting genes that promote tumorigenesis, they can paradoxically function as oncogenes by suppressing genes involved in cell growth regulation [49,66–70]. This dual functionality underscores the complex regulatory mechanisms orchestrated by miRNAs in PCa and other cancers biology. For example, dysregulation of miRNAs has been reported in several types of malignancies, including breast cancer [71,72], colon cancer [73], and PCa [74], which regulate master genes in carcinogenesis and tumor progression [75].

The mechanisms by which miRNAs may fail to perform their function properly are diverse. One of the most recognized factors is the presence of variants in the 3′UTR region of the target genes [76]. When variants occur in this region, particularly single nucleotide variants (SNVs), the RISC complex cannot effectively carry out its function, thus failing to bind to the target site and potentially disrupting post-transcriptional regulation [77–79]. Another mechanism involves the presence of such variants in the seed site of the miRNAs, which prevents proper recognition of the target genes by the RISC complex [80,81]. Furthermore, it has been documented that numerous miRNAs are dysregulated in various neoplasms, along with the genes regulated by these molecules. In this context, patterns of correlation between miRNA and gene expression have been observed across different cancer types; for example, when the expression of a particular miRNA decreases, the expression of its target gene increases, and vice versa [49,82–86].

5. microRNAs in Prostate Cancer

miRNAs undoubtedly hold promising clinical implications in oncology, particularly in the diagnosis, prognosis, and development of therapeutic options for PCa [21,74,87,88]. Dysregulation of these molecules can lead to the development and progression of PCa [89].

It has been described that miRNAs can serve as biomarkers for the early diagnosis of the disease, and in a recent study, it was observed that it is possible to detect at least six miRNAs that can serve as early markers of the disease, including hsa-miR-429, hsa-miR-10a-5p, hsa-miR-183-5p, hsa-miR-181a-5p, hsa-miR-1231, and hsa-miR-129-5 [88], as well as hsa-miR-148a-3p and hsamiR-106a-5p [90].

A previous study [87] showed that in TCGA samples from PCa patients, there are at least 292 miRNAs dysregulated in PCa, 208 upregulated and 53 downregulated. In addition, they showed that in a cohort of a population of men with PCa, there were 40 miRNAs downregulated, 16 upregulated and 44 downregulated.

In addition to their function as early disease biomarkers, some miRNAs have also been reported as markers of tumor progression. A recent study demonstrated that hsa-miR-93-5p was associated with repression of tumor invasion, whereas hsa-miR-210-3p, hsa-miR-23c, hsa-miR-592, and hsa-miR-93-5p were associated with a higher risk of producing tumor dissemination [91]. Furthermore, it has been shown that miRNAs hsa-miR-182 and hsa-miR-187 are dysregulated in PCa, with the latter potentially playing an important role as a marker for metastatic PCa [92].

Recently, it was observed that hsa-miR-636 might play a role in PCa metastasis to bone [93].

Interestingly, miRNAs may play an important role as markers in the development of PCa. A recently published study demonstrated differences in miRNA expression between young patients with PCa and older patients with the same disease. These miRNAs include hsa-miR-146a, hsa-miR-140-5p, hsa-miR-184, hsa-miR-9, hsa-let-7f-5p, hsa-miR-124-3p, hsa-miR-29b, hsa-miR-373, and hsa-miR-146b-5p [94].

Additionally, miRNAs have been described as therapeutic options in cancer, involving the design of therapies targeted at or based on miRNAs. For instance, this includes the development of miRNA inhibitors (antagomirs or miRNA sponges) specifically designed to regulate miRNAs with oncogenic roles. Conversely, another therapeutic approach involves the development of miRNA mimics or synthetic miRNAs that mimic the function of tumor-suppressive miRNAs [95,96].

Regarding miRNA inhibitors, a recent study suggests that CircRNA-UCK2 regulates the expression of hsa-miR-767-5p, thereby inhibiting proliferation and invasion in PCa [97]. Additionally, it has been reported that LncRNA DANCR inhibits hsa-miR-135a, suppressing both cell proliferation and paclitaxel resistance [98]. These findings underscore the critical role of circRNAs and lncRNAs as key regulators of tumor biology in PCa, potentially offering new therapeutic avenues through miRNA modulation.

Conversely, studies have revealed that mimics of hsa-miR-217 and hsa-miR-181b-5p promote metastasis in PCa tumor cells [99]. In contrast, mimics of hsa-miR-133 [100] and hsa-miR-29b have been shown to inhibit crucial cellular processes in PCa [101], highlighting the complexity of specific miRNA functions in tumor progression. These results emphasize the need to understand the specific interactions of miRNAs in different cellular and tumor contexts to develop effective, targeted therapies for PCa.

5.1. Regulation of Androgen Receptor by microRNAs in Prostate Cancer

While numerous studies have identified miRNAs dysregulated in PCa [88,102–107], the regulation of *AR* by these miRNAs has not been as extensively explored. Instead, many miRNAs have been associated with the regulation of other master genes in PCa, such as *TP53* (tumor protein p53), *EFGR* (epidermal growth factor receptor) [102], and *KPNA2* (karyopherin subunit alpha 2) [105].

The regulatory mechanisms of *AR* by miRNAs remain complex and not fully understood, but it has been suggested that *AR* may be regulated at multiple levels. Including through binding sites in its 3′UTR region, as well as via the regulation of its downstream effector genes and potential reciprocal *AR*–miRNA regulation [108,109]. However, the interaction and regulation of *AR* with miRNAs are particularly relevant in pathologies such as PCa, where *AR* signaling plays an important role in tumor promotion and progression [108].

5.1.1. Direct Regulation of Androgen Receptor at Its microRNAs Complementary Sites in the 3′ Untranslated Region

It has been described that the 3′UTR region of the *AR* gene is up to 2.6 times longer than its coding region (6 kb), suggesting extensive regulation of this gene by miRNAs [110,111]. Thus, by binding to complementary sites in its 3′UTR region, miRNAs may regulate the expression of this gene by the direct mechanism.

Several miRNAs have been identified as direct regulators of *AR* in PCa, acting predominantly as a tumor suppressor. For instance, hsa-miR-124 [112] and hsa-miR-381 have

been shown to inhibit androgen-dependent cell proliferation by directly targeting *AR* [113]. In addition, hsa-miR-145 has been reported to reduce *AR* expression in PCa cells, and an inverse correlation between the expression of these molecules and serum PSA levels was demonstrated [114].

Other miRNAs, such as hsa-miR-125, also play an important role in several carcinogenic processes in PCa by directly regulating *AR* [115]. Similarly, miRNAs like hsa-miR-488* [116], hsa-miR-34a [117], hsa-miR-346, hsa-miR-361-3p, and hsa-miR-197 [118] have been shown to inhibit cell proliferation and promote apoptosis in PCa cells by modulating *AR* expression. hsa-miR-299-3p of interest known to reduce tumor growth and improve therapeutic response in PCa by targeting *AR* [119].

An experimental study performed on PCa cells [111] identified a broader set of miRNAs, including hsa-miR-135b, hsa-miR-185, hsa-miR-297, hsa-miR-299-3p, hsa-miR-34a, hsa-miR-34c, hsa-miR-371-3p, hsa-miR-421, hsa-miR-449a, hsa-miR-449b, hsa-miR-634, hsa-miR-654-5p, and hsa-miR-9, all of which directly regulate *AR*. Notably, the expression of hsa-miR-34a and hsa-miR-34c was negatively correlated with *AR* levels. Thus, this suggests that miRNAs regulating *AR* are crucial in modulating *AR*-driven signaling pathways, thereby influencing the progression and aggressiveness of PCa.

Moreover, certain miRNAs have been implicated in mediating resistance to PCa treatments by modulating *AR* activity [120]. For example, underexpression of hsa-miR-185 [115] has been associated with castration-resistant PCa, while hsa-miR-31[121] has been linked to chemotherapy resistance. Conversely, hsa-miR-320 [122], which also regulates *AR*, has been associated with chemoresistance and castration resistance, and hsa-miR-205 [123] has been implicated in castration resistance as well as resistance to chemotherapy and radiotherapy.

5.1.2. Indirect Regulation of Androgen Receptor Through the Regulation of Its Effector Genes

Indirect regulation of the *AR* by miRNAs involves the modulation of genes that function as cofactors, corepressors, and other *AR* modulators [108] (Figure 2). It has been described that *AR* possesses at least 200 coregulators, and many miRNAs target these coregulators to indirectly regulate *AR* expression [124]. For instance, miRNAs such as hsa-miR-let-7c, hsa-miR-1207-3p, hsa-miR-204, and hsa-miR-212 regulate key genes like *MYC* (MYC proto-oncogene, bHLH transcription factor), *FNDC1* (fibronectin type III domain containing 1), *DNMT1* (DNA methyltransferase 1), and *hnRNPH1* (heterogeneous nuclear ribonucleoprotein H1), respectively [125–128]. These genes, when modulated by miRNAs, can subsequently alter *AR* expression.

A notable example is hsa-miR-141, which has been shown to modulate *AR* expression by directly regulating the *HSP* (small heterodimer partner protein) gene [129].

The overexpression of *MYC* has been linked to reduced *AR* activity, promoting castration resistance and metastasis in PCa [130]. This suggests that when miRNAs regulating *MYC*, such as hsa-miR-let-7c, fail to adequately control this gene, they may initiate signaling cascades that indirectly affect *AR* regulation and various aspects of PCa.

A recent study suggests that the underexpression of hsa-miR-1207-3p is common in PCa and that this miRNA directly regulates *FNDC1*. Overexpression of *FNDC1*, which interacts with *FN1* (fibronectin 1), AR, and cMYC, suggests a coordinated regulatory mechanism contributing to PCa pathology [131]. The dysregulation of hsa-miR-1207-3p and its downstream targets exemplifies the complexity of miRNA-mediated gene regulation in PCa, underscoring the potential for these interactions to serve as therapeutic targets.

In another study, reduced expression of *DNMT1* was associated with tumor promotion and metastasis in PCa [132]. This gene, in conjunction with *E2F* (early 2 factor), is known to inhibit *AR* expression [133]. Dysregulation of hsa-miR-204, which directly targets *DNMT1*, could therefore lead to altered *AR* expression, contributing to PCa progression. Underexpression of hsa-miR-204 might result in upregulation of *DNMT1*, impacting the *AR* pathway and facilitating tumorigenesis and metastasis.

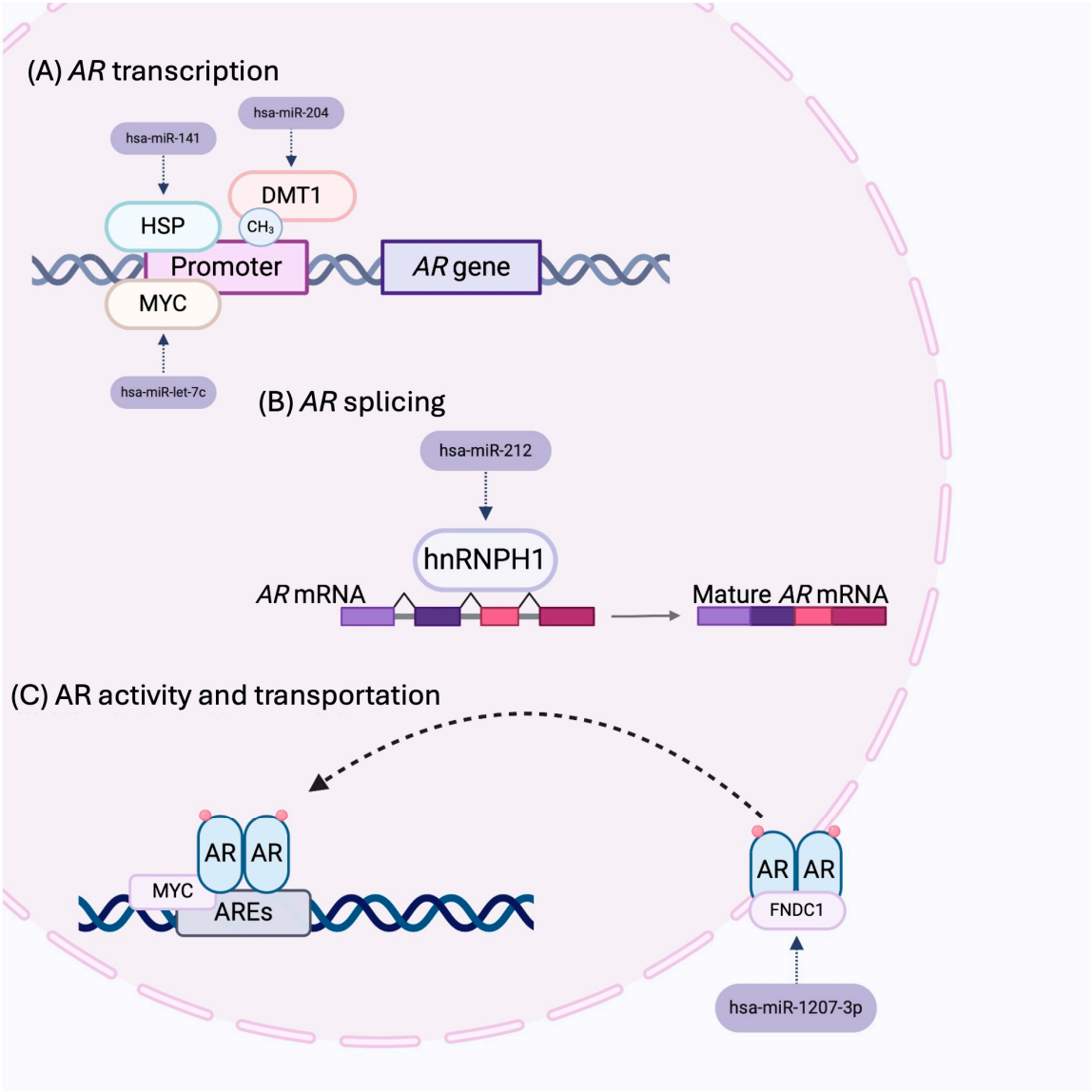

Figure 2. Indirect regulatory mechanisms of miRNAs on the *AR* gene. (**A**) Some miRNAs regulate *AR* regulators, such as *HSP* and *MYC*, which act as transcription factors for *AR* expression, or *DMT1*, which is responsible for methylating the *AR* promoter, thereby regulating its expression. (**B**) Furthermore, it has been observed that *AR* can be regulated by miRNAs that control master genes in *AR* splicing, such as hnRNPH1, or genes that act as cofactors (*MYC*) or transporters (*FNDC1*) (**C**), thus affecting the overall activity of *AR*; created with Biorender.com.

Additionally, *hnRNPH1* directly regulated by hsa-miR-212 shows co-expression with *AR*. Both *hnRNPH1* and *AR* negatively correlate with the expression of this miRNA, promoting a regulatory pathway, where hsa-miR-212 modulates *hnRNPH1* expression and, indirectly, the expression and activity of *AR* [128]. This regulatory mechanism underscores the complexity of miRNA-mediated gene expression control in PCa. The negative correlation between hsa-miR-212 and *hnRNPH1/AR* suggests that hsa-miR-212 acts as a tumor suppressor by downregulating *hnRNPH1*, which in turn may reduce *AR* expression. Understanding these interactions is vital, as they provide insights into the molecular pathways driving PCa progression. Targeting hsa-miR-212 or its downstream effectors could offer new therapeutic strategies to manage *AR*-driven tumorigenesis in PCa.

Furthermore, overexpression of hsa-miR-141 in PCa has been linked to decreased *SHP* expression, a key regulator of *AR*. Furthermore, the expression of *SHP* and the

underexpression of hsa-miR-141 have been observed to decrease *AR* activity [129]. This suggests a critical mechanism in *AR* regulation, where the overexpression of hsa-miR-141 and its negative impact on *SHP* expression could significantly contribute to aberrant *AR* activation and, consequently, tumor progression. Therefore, interventions aimed at reducing hsa-miR-141 levels or increasing *SHP* expression may offer new therapeutic strategies to inhibit *AR* signaling in PCa, presenting a promising approach for chemoprevention and treatment of this disease.

5.1.3. Androgen Receptor–microRNAs Mutual Regulation

It has been reported [124] that the regulatory role of *AR* in modulating the expression of several miRNAs, which reciprocally influence *AR* expression. Particularly, hsa-miR-21 is notably affected by *AR*, as *AR* facilitates its transcription, while this miRNA promotes *AR* expression by directly regulating *PTEN* (phosphatase and tensin homolog deleted on Chromosome 10) through a positive feedback loop [109,134]. Conversely, *AR* increases the expression of hsa-miR-31 and hsa-miR-421, leading to the inhibition of *AR* expression via a negative feedback mechanism [111,121,135]. Furthermore, reciprocal repressions have been described [124]; the expression of hsa-miR-190a is repressed by *AR*; and in turn, the expression of *AR* is repressed by this miRNA by regulating the activity of *YB1* (Y box-binding protein 1), a coactivator of *AR* [136,137] (Figure 3).

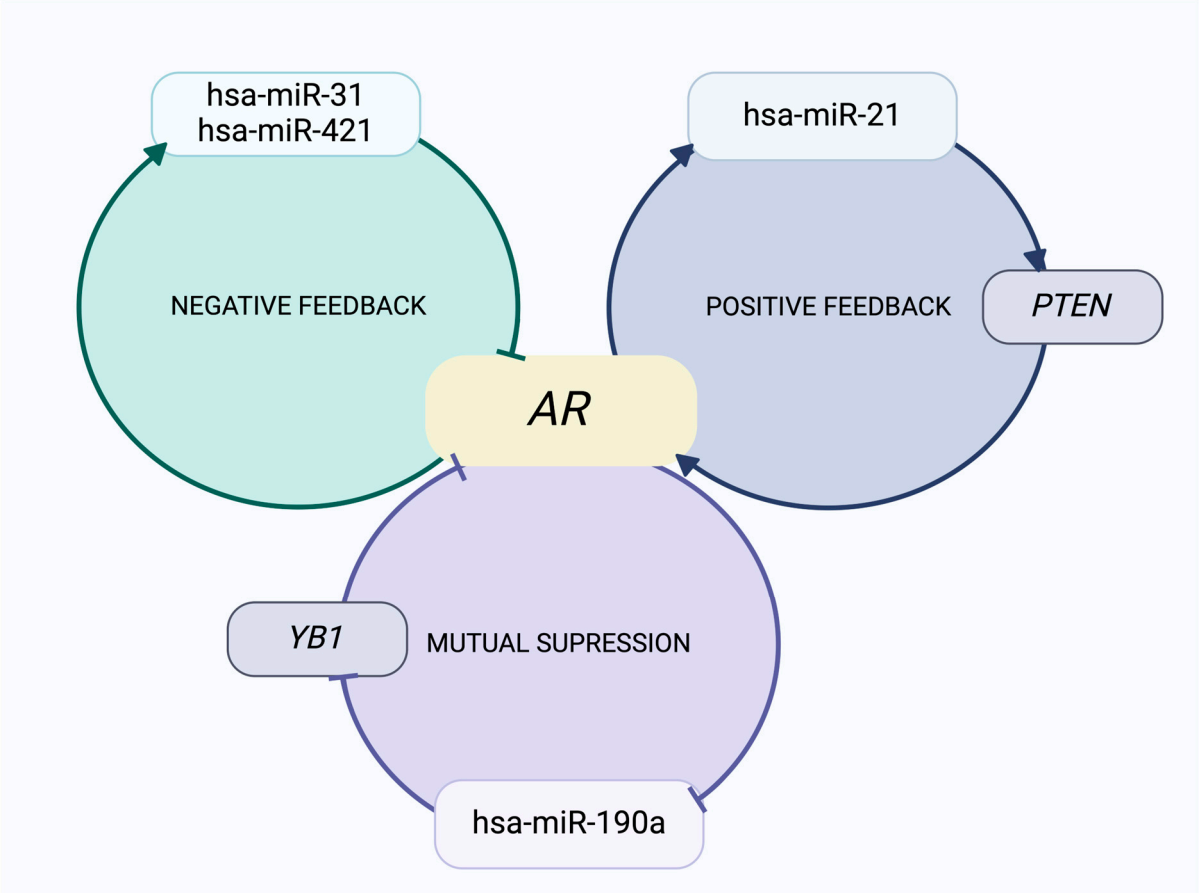

Figure 3. AR–miRNAs mutual regulation. In positive feedback, *AR* facilitates the transcription of hsa-miR-21, which in turn promotes *AR* expression by regulating *PTEN*, creating a reinforcing cycle. In negative feedback, AR increases the expression of hsa-miR-31 and hsa-miR-421, which inhibit *AR* expression, establishing a control mechanism that prevents *AR* overexpression. Finally, mutual feedback shows how *AR* represses hsa-miR-190a, and this miRNA, in turn, represses *AR* expression by regulating the activity of *YB1*, a coactivator of *AR*, forming a reciprocal suppression cycle; created with Biorender.com.

5.2. Identification of microRNAs Targeting Androgen Receptor Using Databases

The Polymirts 3.0 database (https://compbio.uthsc.edu/miRSNP/home.php, accessed on 18 May 2024) [138] was used to identify *AR*-targeting miRNAs and the specific gene locus where their target site is located.

PolymiRTS 3.0 [138] is a database that compiles information on the binding sites of miRNAs in human genes and provides details on genetic variants in both the 3′UTR region of the target genes and the seed site of the miRNAs.

As shown in Table 1, the *AR* gene has 12 variants, including SNVs and insertions and deletions (INDELS). In addition, 45 miRNAs were identified that potentially regulate this gene and target these genomic regions.

Table 1. Variants in the miRNA binding sites in the *AR* gene.

dbSNP ID	Variant Type	miR ID	miRSite
rs11351755	INDEL	hsa-miR-129-5p	gcaaaCAAAAAAa
rs77029761	INDEL	hsa-miR-129-5p	gcaaaCAAAAAAa
rs185168988	SNV	hsa-miR-196a-5p hsa-miR-196b-5p hsa-miR-4668-5p hsa-miR-548m hsa-miR-6124 hsa-miR-553	ACTACCTtttccc ACTACCTtttccc actaccTTTTCCC acTACCTTTtccc actacCTTTTCCc actACCGTTTccc
rs190014544	SNV	hsa-miR-1248 hsa-miR-4297 hsa-miR-532-5p hsa-miR-5581-5p hsa-miR-219b-5p hsa-miR-4778-3p hsa-miR-6740-3p	AAGAAGGcatcaa aaGAAGGCAtcaa aagAAGGCATcaa aaGAAGGCAtcaa aagaaGACATCAa AAGAAGAcatcaa aAGAAGACAtcaa
rs188374642	SNV	hsa-miR-3912-5p	ATGGACAccatct
rs191798952	SNV	hsa-miR-3620-3p hsa-miR-10a-5p hsa-miR-10b-5p hsa-miR-3945 hsa-miR-4761-3p	CAGGGTGtgccct CAGGGTAtgccct CAGGGTAtgccct cagggTATGCCCt cagggtATGCCCT
rs73227886	SNV	hsa-miR-125a-3p hsa-miR-513a-5p hsa-miR-552-3p hsa-miR-4257 hsa-miR-6847-5p hsa-miR-7854-3p	TCACCTGtgaggg tcaCCTGTGAggg tCACCTGTgaggg tcACCTCTGAggg tcaCCTCTGAggg TCACCTCtgaggg
rs1931537	SNV	hsa-miR-3614-3p hsa-miR-483-5p	GAAGGCTccgtct gaaggcCCCGTCT
rs189763567	SNV	hsa-miR-5692a	ATTATTTttttaa
rs145911502	SNV	hsa-miR-4327 hsa-miR-520f-3p hsa-miR-5586-3p hsa-miR-636	GCAAGCActctat gcAAGCACTctat gcaagCACTCTAt gCAAGCACtctat
rs140808887	SNV	hsa-miR-219a-2-3p hsa-miR-511-5p hsa-miR-6830-3p hsa-miR-130b-5p hsa-miR-4753-3p hsa-miR-5571-5p hsa-miR-6809-3p	gaaagACAATTCt gAAAGACAAttct GAAAGACAattct GAAAGAGAattct gAAAGAGAAttct gaaaGAGAATTct gaAAGAGAAttct
rs2362520	SNV	hsa-miR-1225-3p hsa-miR-1233-3p hsa-miR-1252-3p hsa-miR-5680	GGGGCTCAtttct gGGGCTCAtttct ggggCTCATTTct ggggctCATTTCT

Furthermore, in Table 2, we can observe that there are variants in the seed region of 11 miRNAs that potentially regulate *AR* and that could block the binding to this gene.

Table 2. Variants in the seed region of miRNAs targeting AR.

miR ID	dbSNP ID	miR Seed	miRSite
hsa-miR-4311	rs142080198	AA[AG/-]GAGA	UCUCUUU
hsa-miR-3910	rs149611497	AAGGCA[GGCAT/-]	AUGCCUU
hsa-miR-6814-5p	rs185472832	CCCAA[G/A]G	CCUUGGG
hsa-miR-6818-5p	rs186621048	U[G/T]UGUGA	CACACAA
hsa-miR-488-5p	rs199722070	CCA[G/A]AUA	UAUCUGG
hsa-miR-488-5p	rs186200318	CC[A/G]GAUA	UAUCUGG
hsa-miR-124-3p	rs34059726	AA[G/T]GCAC	GUGCCUU
hsa-miR-3125	rs200914693	AG[A/G]GGAA	UUCCUCUA
hsa-miR-6805-5p	rs201627498	AGGGGG[C/T]	GCCCCCU
hsa-miR-499a-3p	rs3746444	AC[A/G]UCAC	UGAUGUA
hsa-miR-499a-3p	rs150018420	ACAUCA[C/T]	UGAUGUA

Despite presenting a total of 12 variants located in the 3′UTR region of *AR* in Table 1, which could potentially impact the binding to distinct miRNAs regulating *AR*, our literature search did not uncover any reports analyzing the role or association of these variants in PCa or any other type of cancer. This highlights a significant knowledge gap in the current scientific understanding.

The absence of studies on these *AR* 3′UTR variants and their relationship with specific miRNA regulation affecting *AR* presents a substantial opportunity for future research. Given the pivotal role of the *AR* gene in the development and progression of PCa, it is crucial to explore how these variants may influence the miRNA–*AR* interaction and consequently *AR* activity. Understanding these molecular and genetic mechanisms could not only advance our knowledge of PCa biology but also pave the way for the development of targeted therapies. Identifying these variants and their functional impact could help unravel complex post-transcriptional regulatory processes in cancer, potentially revealing new therapeutic targets and personalized treatment strategies.

On the other hand, upon reviewing the literature on variants located in the miRNA seed region that regulates AR (Table 2), we observed that one study reported the variant rs34059726 was not associated with susceptibility to developing PCa in Iranian patients [139]. However, it is possible that there could be an association with other populations. This discrepancy underscores the complexity of genetic susceptibility across different populations and highlights the need for further investigation.

Contrarily, recent studies have described that the variant rs3746444 is associated with an elevated risk of developing PCa [140,141]. This finding underscores the importance of investigating variants in miRNA seed regions, as they can significantly impact the regulation of genes like AR. Such research could potentially lead to the identification of novel biomarkers and therapeutic targets tailored to individuals based on their genetic profiles, enhancing both prevention and treatment strategies for PCa.

5.3. Experimental Evidence for the Expression of microRNAs Targeting Androgen Receptor in Prostate Cancer

With the dbDEMC tool (https://www.biosino.org/dbDEMC/index, accessed on 17 May 2024) [142], we reviewed the expression profiles in PCa of the miRNAs identified in this review as possible regulators of the *AR* gene (Table 3). We observed that 13 of these miRNAs are underexpressed, while 11 are overexpressed in PCa. These dysregulations in the miRNAs that regulate *AR* can lead to either the suppression or overactivation of AR signaling pathways. Additionally, these miRNAs may play a pivotal role in the regulation of other genes that interact with *AR*, forming intricate signaling pathways crucial in PCa biology.

Table 3. Expression profiles of AR-targeting miRNAs in PCa.

miRNA	Status in PCa	Design	LogFC	Reference
hsa-miR-129-5p	Downregulated	Cancer (n = 99) vs. normal (n = 28)	−0.53	[143]
hsa-miR-4668-5p	Upregulated	Blood from PCa (n = 809) vs. normal blood (n = 41)	0.71	[144]
hsa-miR-6124	Upregulated	Cancer (n = 60) vs. normal (n = 27)	0.31	[145]
hsa-miR-553	Downregulated	Cancer (n = 7) vs. normal (n = 5)	−0.12	[146]
hsa-miR-5581-5p	Downregulated	Blood from PCa (n = 40) vs. normal blood (n = 100)	−2.40	[147]
hsa-miR-219b-5p	Downregulated	Blood from PCa (n = 40) vs. normal blood (n = 100)	−1.02	[147]
hsa-miR-6740-3p	Downregulated	Blood from PCa (n = 40) vs. normal blood (n = 100)	−2.59	[147]
hsa-miR-3912-5p	Upregulated	Blood from PCa (n = 809) vs. normal blood (n = 41)	0.54	[144]
hsa-miR-3620-3p	Downregulated	Blood from PCa (n = 809) vs. normal blood (n = 41)	−1.29	[144]
hsa-miR-3945	Downregulated	Blood from PCa (n = 40) vs. normal blood (n = 100)	−1.96	[147]
hsa-miR-4761-3p	Downregulated	Blood from PCa (n = 809) vs. normal blood (n = 41)	−0.84	[144]
hsa-miR-513a-3p	Downregulated	Blood from PCa (n = 40) vs. normal blood (n = 100)	−3.57	[147]
hsa-miR-4257	Upregulated	Cancer (n = 60) vs. normal (n = 27)	0.09	[145]
hsa-miR-483-5p	Upregulated	Cancer (n = 99) vs. normal (n = 28)	0.76	[143]
hsa-miR-5692a	Upregulated	Blood from PCa (n = 40) vs. normal blood (n = 100)	1.53	[147]
hsa-miR-5586-3p	Upregulated	Blood from PCa (n = 25) vs. normal blood (n = 969)	1.93	[148]
hsa-miR-636	Downregulated	Blood from PCa (n = 25) vs. normal blood (n = 969)	−1.25	[148]
hsa-miR-219a-2-3p	Upregulated	Blood from PCa (n = 23) vs. normal blood (n = 70)	1.72	[149]
hsa-miR-6830-3p	Downregulated	Blood from PCa (n = 40) vs. normal blood (n = 100)	−1.82	[147]
hsa-miR-130b-5p	Upregulated	Blood from PCa (n = 23) vs. normal blood (n = 70)	1.75	[149]
hsa-miR-6809-3p	Downregulated	Blood from PCa (n = 40) vs. normal blood (n = 100)	−1.08	[147]
hsa-miR-1225-3p	Downregulated	Blood from PCa (n = 40) vs. normal blood (n = 100)	−0.37	[147]

Table 3 illustrates that among the 45 miRNAs identified as potential regulators of *AR* (as presented in Table 1), only 22 have been experimentally linked to dysregulation in PCa. This disparity underscores significant gaps in our understanding of how miRNAs modulate *AR* activity and their functional implications in PCa. Investigating the dysregulation of these miRNAs could yield crucial insights into the molecular mechanisms driving PCa progression and offer opportunities for developing new therapeutic strategies, such as miRNA inhibitors or mimics targeting *AR*-regulated pathways. Further research is imperative to unravel the intricate regulatory networks involving miRNAs and *AR* in PCa, which holds promise for enhancing both diagnostic capabilities and therapeutic interventions in clinical settings.

6. Conclusions

miRNAs hold significant clinical promise in oncology, particularly in the realms of diagnosis, prognosis, and therapeutic development for PCa. They have demonstrated utility as biomarkers for early disease detection, as well as predictors of therapeutic response, disease progression, metastasis, and age at onset.

This review underscores the dysregulation of numerous miRNAs in PCa, emphasizing their potential as markers for various clinical aspects of the disease. However, our analysis reveals that many of these miRNA–*AR* interactions lack experimental validation or have not been adequately studied in the context of PCa, highlighting a significant research gap that warrants exploration. Understanding these interactions could not only shed light on the molecular underpinnings of PCa progression but also pave the way for novel therapeutic strategies, such as miRNA inhibitors or mimics targeting *AR*-regulated pathways. Addressing these gaps through further research is crucial for advancing both diagnostic approaches and therapeutic interventions in clinical practice.

Our analysis reveals that a multitude of miRNAs exert regulatory control over *AR* at multiple levels: directly, indirectly, and through co-regulation. The extensive 3′UTR region of *AR* appears to contribute significantly to this regulatory complexity. Furthermore, our database searches have identified numerous variants in the 3′UTR region of *AR* that potentially alter miRNA binding, thereby impacting *AR* regulation. Notably, none of these variants have been studied in association with PCa, and only two variants in the seed region have been associated with PCa. This gap presents a significant opportunity for molecular investigation into PCa. Understanding the implications of these genetic variations in the context of PCa is imperative for discerning their associations with the disease and could significantly enhance our grasp of its molecular and genetic underpinnings.

Research into miRNAs and their interactions with *AR*, alongside genetic variants, represents a promising avenue for enhancing PCa management. Integrating these findings into clinical practice not only promises to refine disease diagnosis and prognosis but also to advance personalized treatment strategies.

Further exploration of miRNAs as biomarkers and therapeutic targets in PCa is warranted. This endeavor holds the potential to catalyze transformative advancements in both research and clinical care, offering new insights into disease mechanisms and paving the way for more effective therapeutic interventions.

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