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REVIEW

Volar et al: Circulating miRNAs in prostate cancer

Circulating microRNAs in prostate cancer — non-invasive biomarkers for diagnosis, prognosis and therapy: A review

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ABSTRACT

Prostate cancer (PC) is a common malignancy driven by interacting genetic, environmental, and lifestyle factors, including hereditary mutations (*BRCA1/2, HPC1, AR* variants), premalignant lesions [proliferative inflammatory atrophy (PIA), prostatic intraepithelial neoplasia (PIN)], and Western dietary patterns. This narrative review aims to synthesize evidence on the role of microRNAs (miRNAs) in PC pathogenesis and clinical management across diagnosis, prognosis, therapy, and recurrence prediction. We searched PubMed/MEDLINE (2004–present) using predefined terms, screened reference lists, excluded outdated records, and prioritized biomarker studies with AUC ≥ 0.85. Current diagnostic pathways—digital rectal examination, prostate-specific antigen (PSA) testing, multiparametric MRI, and Gleason-based International Society of Urological Pathology (ISUP) grading—are complemented by molecular tools (4Kscore, PHI, SelectMDx, TMPRSS2–ERG, PCA3, ConfirmMDx). MiRNAs, key post-transcriptional regulators, contribute to PC via dysregulated biogenesis and modulation of androgen receptor signaling within an inflamed, remodeled tumor microenvironment. Circulating and exosomal miRNAs (notably miR-21, miR-375, and miR-182-5p) exhibit greater specificity and stability than PSA, enabling non-invasive diagnosis, risk stratification, treatment monitoring, and recurrence prediction. Therapeutic approaches—antagomirs, sponges, miRNA masks, and CRISPR editing—show preclinical promise, while chemical modifications [peptide nucleic acids (PNAs), locked nucleic acids (LNAs), C2′ modifications] improve stability and delivery but remain limited by biodistribution, tissue penetration, off-target effects, and immunogenicity. In conclusion, standardized workflows and multicenter validation, integrated with clinical and imaging data, are essential to translate miRNA-based tools into precision PC management.

Keywords: Prostate cancer, miRNA, biomarkers, diagnosis, therapy, tumor microenvironment.

INTRODUCTION

Prostate cancer

Prostate cancer (PC) is among the most prevalent malignancies affecting men globally, with approximately one in eight men receiving a diagnosis during their lifetime. It accounts for mortality in roughly one out of every 44 diagnosed cases. According to global estimates, around 1,276,106 new cases of prostate cancer are identified each year, leading to approximately 358,989 deaths annually. These figures are expected to rise in the coming years, driven by demographic shifts such as population aging, increased life expectancy and ongoing advancements in diagnostics and treatment options. By 2030, the global burden of PC is projected to reach 1.7 million new cases, with an estimated 499,000 associated deaths.

Prostate cancer significantly impairs health-related quality of life, especially among middle-aged and older men. Pathological changes in the prostate are most commonly observed after the age of 40 and are often accompanied by a spectrum of urinary and sexual symptoms. These may include increased urinary frequency, dysuria (painful urination), urinary incontinence, haematuria (blood in the urine), haematospermia (blood in the semen), nocturia, and erectile dysfunction. However, these clinical manifestations are not specific to prostate cancer and may also arise from other prostatic conditions, such as benign prostatic hyperplasia (BPH) and various forms of prostatitis— including acute and chronic bacterial prostatitis, chronic pelvic pain syndrome and asymptomatic inflammatory prostatitis. (1)(2)

miRNA

MicroRNAs (miRNAs) are an evolutionarily conserved class of small, non-coding RNA molecules, typically about 22 nucleotides long, that act as critical post-transcriptional regulators of gene expression. (3) They are primarily transcribed by RNA polymerase II, although a subset may be transcribed by RNA polymerase III, reflecting the diversity of their regulatory control. Approximately half of miRNAs are intragenic, arising mostly from intronic regions of protein-coding genes, with a smaller fraction originating from exonic regions. The remaining miRNAs are intergenic, transcribed independently under the control of their own promoter elements.

The biogenesis of miRNAs occurs through two main pathways: the canonical and non-canonical pathways. In the canonical pathway, primary miRNA transcripts (pri-miRNAs) are processed in the nucleus by the microprocessor complex, composed of the RNase III enzyme Drosha and the RNA-binding protein DGCR8, which recognizes conserved motifs (e.g., GGAC) to generate precursor miRNAs (pre-miRNAs) with a characteristic 2-nucleotide 3′ overhang. (3) Pre-miRNAs are exported to the cytoplasm via the Exportin-5/Ran-GTP complex and further processed by Dicer to produce a ~22-nt miRNA duplex. One strand, the guide strand, is incorporated into the RNA-induced silencing complex (RISC) with Argonaute (AGO) proteins, while the passenger strand is typically degraded.

Non-canonical pathways bypass one or more steps of this classical route. Drosha-independent pathways generate miRNAs called mirtrons through mRNA splicing and Exportin-1-mediated export, while Dicer-independent pathways utilize AGO2 to process pre-miRNAs directly, bypassing Dicer cleavage. (4)

MiRNAs are remarkably stable in various biological fluids—including plasma, serum, urine, saliva, synovial fluid, and bile—due to their association with AGO proteins, extracellular vesicles, and high-density lipoproteins. This stability makes them promising non-invasive biomarkers for disease diagnosis, prognosis, and therapeutic monitoring across cancer, cardiovascular, and inflammatory diseases. (5) Functionally, miRNAs regulate gene expression by binding to microRNA-responsive elements (MREs) in the 3′-untranslated regions of target mRNAs. Depending on complementarity, the RISC complex can induce mRNA cleavage or inhibit translation, thereby modulating cell proliferation, differentiation, and development. (6) MiRNA activity is highly context-dependent: the same miRNA may act as an oncogene (oncomir) or tumor suppressor (oncosuppressor) depending on tissue type, target genes, and signaling networks. MiRNAs also mediate cellular responses to stress, including hypoxia, nutrient deprivation, and DNA damage. Compared to small interfering RNAs (siRNAs), miRNAs provide fine-tuned regulation of gene networks, allowing precise adjustment of gene expression in diverse tissues and physiological or pathological conditions. (6)

MATERIALS AND METHODS

For the purpose of this narrative review, we explored the available literature using PubMed/MEDLINE and examined key references from major journals and publishers. Search terms included “prostate carcinoma,” “miRNA,” “PSA,” “tumor microenvironment,” “biomarkers in prostate carcinoma,” “prostate cancer therapy,” and “miRNA therapy.” We focused on studies published after 2004 and studies with outdated records were excluded. For miRNA biomarker studies, only those reporting an AUC of 0.85 or higher were included.

PATHOGENESIS AND ETIOLOGIC FACTORS IN PROSTATE CANCER

A multifactorial disease

PC is a highly heterogeneous malignancy, shaped by a dynamic interplay of genetic, environmental, and racial factors. Among the most influential risk determinant is a positive family history, highlighting the role of hereditary predisposition in the disease’s onset and progression. Genes most implicated in PC pathogenesis are those involved in androgen receptor signalling and testosterone metabolism. These pathways are not only essential for embryonic development of the prostate epithelium but also play a central role in driving tumorigenesis and disease progression later in life. (8) Beyond androgen-related mechanisms, at least seven genetic loci have been implicated in increasing susceptibility to PC. Of particular interest is the hereditary prostate cancer 1 (*HPC1*) gene, located on chromosome 1q24-25 (table 1), which encodes ribonuclease L (RNase L) – a key enzyme in the innate immune response and the interferon-alpha (IFNα) signalling pathway. RNase plays a central role in antiviral defence and regulation of apoptosis. Mutations in RNase L can compromise immune surveillance, increase vulnerability to retroviral infections and contribute to chronic prostatic inflammation—an important driver of malignant transformation in prostatic tissue. (3,9)

Genetic susceptibility and DNA repair pathways in prostate cancer

Another gene of interest is *HPC2/ELAC2*, located on chromosome 17p11, which encodes the enzyme zinc phosphodiesterase ELAC2. This enzyme is involved in the

post-transcriptional processing of *SMAD2* (Mothers against decapentaplegic homolog 2), thereby modulating cell proliferation through activation of the transforming growth factor-beta (TGF-β) signaling cascade. Similarly, the macrophage scavenger receptor 1 (*MSR1*) gene, positioned on chromosome 8p22, has been implicated in susceptibility to PC, however, its precise contribution to tumorigenesis remains poorly understood. (10,11)

In addition to these loci, germline mutations in *BRCA1* and *BRCA2* - genes associated with hereditary breast and ovarian cancers - have also been identified in men with PC. Notably, *BRCA2* mutations confer a significantly elevated risk for developing aggressive and early-onset forms of the disease. Furthermore, the *PALB2* (partner and localizer of *BRCA2*) gene – which encodes a protein integral to BRCA2 function - has been implicated in familial PC cases. (3,10)

The X chromosome also contributes to hereditary risk, particularly through variants in the androgen receptor (AR) gene. (12) Structural alternations, including deletions in the Xq26.3–q27.3 region, have been observed in both familial and sporadic prostate cancer cases, further emphasizing the importance of androgen signaling in the pathogenesis of the disease. (8)

Environmental and lifestyle risk factors

Beyond genetic predisposition, dietary and lifestyle factors exert a substantial influence on the incidence and progression of prostate cancer. The disease is significantly more prevalent in highly industrialized nations, where dietary habits are typically characterized by elevated intake of saturated fats, total caloric content and processed meats. Such nutritional patterns are thought to promote cancer progression through multiple mechanisms, including enhanced androgen activity, increased oxidative stress and the biosynthesis of lipid-derived pro-inflammatory mediators, such as leukotrienes and prostaglandins. These biochemical processes may collectively stimulate basal metabolic activity and create a microenvironment conductive to tumor initiation and progression. Consequently, prostate cancer incidence is higher in Western populations compared to those in Asian and African regions (13), highlighting the potential impact of modifiable lifestyle factors on disease burden. (3)

Morphology and early lesions in prostate carcinogenesis

Proliferative inflammatory atrophy (PIA) and prostatic intraepithelial neoplasia (PIN) represent key premalignant histopathological alterations implicated in the early stages of prostate carcinogenesis. PIA is characterized by regions of epithelial atrophy accompanied by chronic inflammation and increased epithelial cell proliferation. It is hypothesized to arise in response to oxidative stress, infection, or hormonal imbalances, creating a pro-tumorigenic microenvironment through the generation of reactive oxygen species, cytokines, and inflammatory mediators. Over time, PIA lesions may evolve into high-grade PIN (HGPIN), a well-established precursor to invasive prostatic adenocarcinoma. (10)

HGPIN is defined by architectural and cytological atypia within prostatic ducts and acini, including nuclear enlargement, nucleolar prominence, and stratification of luminal cells, while preserving the basal cell layer. Molecular studies have revealed that PIN and prostate cancer often share genetic and epigenetic alterations—such as chromosomal instability, *TMPRSS2-ERG* gene fusion, and loss of *PTEN*—supporting the concept of a progressive neoplastic continuum. Recognition and monitoring of these premalignant lesions are essential, as they provide valuable insight into disease pathogenesis and may serve as targets for early detection and chemopreventive strategies. (9)

MicroRNAs: Biogenesis, function, and role in prostate cancer

Overexpression of certain miRNAs has been observed in a wide range of cancers, including PC. This dysregulation often results from chromosomal mutations, excessive miRNA synthesis, or disturbances in epigenetic regulation. (6) A large-scale genomic study by Calin et al. demonstrated that cancer-associated miRNA genes are specifically distributed across chromosomes, with many located in particular genomic regions that are frequently mutated in tumor cells. These regions are referred to as cancer-associated genomic regions (CAGRs). CAGRs can be classified into several types: tumor suppressor genes, where mutations in both alleles are necessary for cancer development; oncogenes, where a mutation in just one allele is sufficient to trigger tumor formation; breakpoint regions; and fragile sites (FRAs), which facilitate chromosomal recombination, translocation, or integration of plasmids or viral DNA. (14) Excessive miRNA synthesis leads to errors in the maturation of pri-miRNA. (3)

Emerging evidence highlights the pivotal role of dysregulated microRNAs (miRNAs) in the pathogenesis and progression of prostate cancer. Aberrations in miRNA expression profiles can disrupt normal cellular homeostasis by suppressing tumour suppressor genes or enhancing oncogenic signalling pathways. Several miRNAs have been identified as direct regulators of androgen receptor (AR) signaling—either by regulating its expression, binding to its transcript, or modulating the activity of AR-associated coregulators. These findings highlight the dual role of miRNAs as both diagnostic and prognostic biomarkers, as well as promising therapeutic targets in the management of PC. (3)

Tumor microenvironment

The tumor microenvironment (TME) plays an essential role in the pathobiology of advanced prostate cancer (PC). It encompasses a dynamic and heterogenous milieu composed of extracellular matrix (ECM) components, neural elements, vasculature, immune infiltrates, mesenchymal-derived stromal cells, and other specialized cellular constituents. These elements interact via intricate networks involving chemokines, cytokines, growth factors, and matrix-remodeling enzymes. Bidirectional communication between tumor and stromal cells is mediated predominantly through autocrine and paracrine signaling pathways.

Preclinical models have demonstrated that early oncogenic events in PC are tightly coupled with stromal remodeling within the TME. Hallmark changes include increased fibroblast proliferation, neovascularization, apoptotic resistance, and the phenotypic transition of myofibroblasts into cancer-associated fibroblasts (CAFs). In this context, myofibroblasts—typically activated during tissue repair—acquire a tumor-promoting phenotype, analogous to the response observed in wound healing. Epithelial-derived transforming growth factor-beta (TGF-β) plays a pivotal role in circumventing myofibroblast apoptosis, establishing a self-sustaining autocrine feedback loop that facilitates persistent TGF-β secretion, enhanced survival signaling, and metabolic reprogramming. This milieu fosters the release of oncogenic mediators such as circulating microRNAs and interleukins, which further potentiate the differentiation of myofibroblasts into CAFs. The resultant desmoplastic stroma—rich in newly generated CAFs—perpetuates tumor progression via a continuous cycle of stromal activation.(15)

Advanced PC, particularly cases exhibiting higher Gleason scores, is frequently associated with a stroma infiltrated by immune effector cells. This immunological infiltration is thought to arise from sustained prostatic tissue irritation caused by factors such as chronic urinary tract infections, intraprostatic urinary reflux, high-fat dietary intake, and elevated estrogenic stimuli. Consequently, there is an increased recruitment of CD3+ T lymphocytes, tumor-associated macrophages, and mast cells into the tumor-adjacent stroma. These immune populations contribute to a chronic inflammatory state characterized by elevated levels of pro-inflammatory cytokines and chemokines, including tumor necrosis factor-alpha (TNF-α) and activation of the nuclear factor kappa B (NF-κB) pathway. These mediators regulate multiple oncogenic processes such as angiogenesis, cellular proliferation, and immune evasion, all of which are instrumental in PC progression. (10)

Ultimately, the reciprocal crosstalk between malignant epithelial cells and the surrounding stroma drives profound molecular and phenotypic changes within the TME. These alterations modulate tumor aggressiveness, metastatic potential, and therapeutic resistance, underscoring the significance of the stromal compartment as a critical determinant of prostate cancer outcomes. (10,15)

DIAGNOSTIC AND PROGNOSTIC ALGORITHMS

Digital rectal examination (DRE) remains a fundamental component of the initial clinical assessment for suspected prostatic pathology, where palpable abnormalities such as glandular enlargement, induration or nodular irregularities may suggest the presence of an underlying neoplastic process. (9)

Prostate-specific antigen testing: Use and limitations

Following DRE, the level of serum prostate-specific antigen (PSA) is routinely performed. PSA, a glycoprotein secreted by the prostatic epithelium, serves as a widely used biomarker for prostate health. Although elevated PSA levels may indicate malignancy, they are not cancer-specific and may also reflect benign conditions such as benign prostatic hyperplasia (BPH) or prostatitis. PSA values exceeding 4 µg/L are typically considered suspicious, with concentrations between 4–10 µg/L associated

with an estimated 25% risk of PC, and levels above 10 µg/L conferring approximately a 50% risk of malignancy (10).

Challenges of PSA screening and the need for novel biomarkers

Despite its widespread use, PSA testing is hampered by limited specificity and sensitivity, particularly in distinguishing indolent tumors from clinically significant prostate cancers. Therefore, alternative biomarkers that could improve diagnostic and prognostic approaches are still being intensively investigated. The limitations of PSA testing result in a large number of unnecessary performed biopsies, which are invasive procedures associated with potential complications, including hematuria, urinary retention and infectious sequelae such as urosepsis and prostatitis. To improve diagnostic precision, multiparametric magnetic resonance imaging (mpMRI) is increasingly used to guide targeted biopsies and facilitate histological confirmation (16).

Histopathological diagnosis and tumor grading

Histopathological evaluation most frequently reveals prostatic adenocarcinoma, originating from the glandular epithelium. Tumor grading is performed using the Gleason scoring system, which categorizes prostate cancers based on their architectural differentiation. In 2016, the International Society of Urogenital Pathology (ISUP)
introduced a revised grading system:
ISUP group 1: Gleason ≤6 (3+3); properly formed glands.
ISUP group 2: Gleason 3+4=7; dominantly well-formed glands with a smaller proportion of poorly differentiated ones.
ISUP group 3: Gleason 4+3=7; mostly poorly differentiated glands.
ISUP group 4: Gleason 8 (4+4, 3+5, 5+3); pronounced architectural atypia.
ISUP group 5: Gleason 9–10; absence of glandular structure, frequent necrosis, high aggressiveness.
This classification enhances clinical applicability, thereby improving risk stratification and guiding treatment decisions (17,18).

Biomarkers in prostate cancer: diagnostic and prognostic utility

Biomarkers are integral to the clinical management of prostate cancer (PC), serving critical roles in diagnosis, disease staging, risk stratification, and therapeutic decision-making. While prostate-specific antigen (PSA) remains the cornerstone of initial PC screening, its limited specificity has prompted the development and integration of additional molecular and biochemical markers to improve diagnostic accuracy and reduce overtreatment.

Among these, the four-kallikrein (4K) panel has gained traction in clinical practice, particularly for men presenting with elevated PSA levels. This plasma-based assay quantifies four kallikrein isoforms—total PSA (tPSA), free PSA (fPSA), intact PSA, and human kallikrein 2 (hK2)—and integrates them into a predictive algorithm to estimate the probability of high-grade PC. The 4K score has demonstrated utility in reducing unnecessary biopsies and enhancing the detection of clinically significant disease. (19)

The Prostate Health Index (PHI) is another validated serum-based biomarker that combines tPSA, fPSA, and the [-2]proPSA (p2PSA) isoform into a single numerical value. PHI has been shown to improve specificity over PSA alone, particularly in the diagnostic "grey zone" (PSA 2–10 ng/mL), and may reduce unnecessary biopsies by up to 40%. (20)

Urine-based biomarker assays also offer non-invasive adjuncts to traditional screening. SelectMDx, performed after a digital rectal examination (DRE) to enrich prostate-derived RNA in urine, evaluates mRNA expression of HOXC6, DLX1, and KLK3, in conjunction with PSA density (PSAD). This test stratifies the risk of high-grade PC and has demonstrated the potential to avoid up to 53% of unnecessary biopsies. (21)

The TMPRSS2–ERG gene fusion, a molecular alteration present in approximately 50% of PC cases, can be detected in post-DRE urine samples. This fusion, involving the androgen-regulated transmembrane protease serine 2 (*TMPRSS2*) and the ETS-related gene (*ERG*), is associated with tumor aggressiveness and is under investigation as a prognostic marker and as a tool for monitoring response to androgen deprivation therapy (ADT). (22)

Prostate Cancer Antigen 3 (PCA3), a prostate-specific non-coding RNA overexpressed in more than 95% of primary PCs, represents another urinary

biomarker with enhanced specificity relative to PSA. The PCA3 score, derived from the ratio of PCA3 to PSA mRNA in urine, may guide biopsy decisions and reduce unnecessary procedures. (23)

ConfirmMDx is a tissue-based epigenetic assay used post-biopsy to assess DNA hypermethylation in genes associated with tumorigenesis, including GSTP1, APC, and RASSF1. This test is particularly valuable in patients with histologically negative biopsies but persistent clinical suspicion of PC, as it detects field effects suggestive of occult malignancy. ConfirmMDx has been shown to improve diagnostic accuracy, reduce repeat biopsy rates, and identify patients at increased risk for clinically significant disease. (13)

Collectively, these biomarkers, when used in conjunction with PSA and clinical parameters, enhance diagnostic precision, optimize patient selection for prostate biopsy, and provide critical prognostic insights, particularly in the context of personalized medicine in prostate cancer care.

Circulating miRNA as biomarker in prostate cancer

Circulating microRNAs (miRNAs) in plasma have emerged as highly promising non-invasive biomarkers for the diagnosis and prognosis of (PC) (5). Unlike messenger RNAs, miRNAs exhibit exceptional physicochemical stability in body fluids, including plasma, serum, and seminal fluid. They are inherently resistant to endogenous RNases, extreme pH shifts, temperature fluctuations, and repeated freeze–thaw cycles, enabling reliable detection even under suboptimal storage conditions.

Origin and stability of circulating miRNAs are explained by multiple mechanisms:

1. Passive Release: miRNAs can enter circulation through cell lysis during apoptosis, necrosis, or tumor-associated cellular turnover, reflecting the intracellular miRNA of damaged or malignant cells.
2. Active Secretion via Extracellular Vesicles (EVs): Prostate cells actively secrete miRNAs within exosomes (30–150 nm) and microvesicles. These vesicles facilitate intercellular communication, influence tumor microenvironment remodeling, angiogenesis, and immune evasion, and are

remarkably stable in circulation. Notably, prostate-derived EVs can enter urine, allowing non-invasive detection (24).

3. Non-Vesicular Secretion: miRNAs may also be released independently of vesicles, often in complex with RNA-binding proteins (RBPs) such as Argonaute 2 (AGO2) and Nucleophosmin 1 (NPM1), which protect them from enzymatic degradation. The AGO2–miRNA complex accounts for over 90% of plasma miRNAs, highlighting the importance of non-vesicular transport (25).

A subset of miRNAs, termed oncomiRs, are upregulated in tumors and promote proliferation, invasion, angiogenesis, and metastasis. For example, miR-21 is consistently overexpressed in prostate and other cancers, with elevated serum levels correlating with disease presence and progression. Advances in high-throughput miRNA profiling, including microRNAome sequencing, qRT-PCR, and antisense-based detection, have enhanced the sensitivity and specificity of miRNA-based diagnostics (26).

1. Clinical utility in prostate cancer: Numerous studies have identified circulating miRNAs with potential as diagnostic and prognostic biomarkers for PC.
2. Diagnostic panels: Moya et al. reported a four-miRNA panel—miR-98-5p, miR-152-3p, miR-326, and miR-4289—that distinguished PC patients from healthy controls with an AUC of 0.88 (27). Liu et al. proposed a panel of miR-223, miR-24, and miR-375 to differentiate indolent from progressive disease (AUC = 0.690) (28).
3. Prognostic biomarkers: Brase et al. identified miR-141 and miR-375 as markers associated with metastatic PC (29). Shen et al. demonstrated a serum panel including miR-20a, miR-21, miR-145, and miR-221 could discriminate high- from low-risk disease (AUC = 0.824) (30). Wood et al. highlighted miR-218-5p as a predictor of bone metastases (AUC = 0.86) (31). Hoey et al. developed a panel of miR-20a, miR-17, miR-20b, and miR-106a predictive of high-risk post-prostatectomy patients (32). Biddara et al. showed miR-182-5p and miR-375-3p were associated with advanced disease stages (33). Alhasan et al. proposed a five-miRNA signature (miR-106a, miR-135a, miR-200c,

miR-433, and miR-605) capable of distinguishing aggressive from indolent PC with 89% accuracy (34).

Therapeutic monitoring: Certain miRNAs correlate with treatment response. miR-21 has been linked to enhanced radiosensitivity, while miR-146a and miR-155 are associated with post-radiotherapy inflammatory responses. Abramovic et al. quantified miR-375-3p, miR-182-5p, miR-21-5p, and miR-148a-3p in blood and seminal plasma from PC and BPH patients, showing miR-182-5p and miR-375-3p were significantly overexpressed in PC with combined specificity of 90.2%, markedly outperforming PSA (specificity = 25% at 4 μg/L) (10,35).

In summary, these findings underscore the potential of circulating and exosomal miRNAs as robust, minimally invasive biomarkers for early detection, risk stratification, prognosis, and therapeutic monitoring in prostate cancer. Despite their promise, translation into clinical practice requires standardized isolation protocols, larger multi-center validation studies, and systematic evaluation of prostate-specific miRNAs.

THERAPEUTIC CHALLENGES AND FUTURE DIRECTIONS

While miRNA-based therapies have shown promise in treating tumors, several challenges hinder their clinical application. Unmodified miRNAs are rapidly degraded by serum nucleases and excreted by the kidneys, limiting their serum half-life. Additionally, they can activate the immune system, leading to immunotoxicity. One of the primary obstacles is the effective delivery of miRNAs to tumor tissues while ensuring sufficient tissue penetration and minimizing side effects. Chemical modifications—such as peptide nucleic acids (PNAs), locked nucleic acids (LNAs), and C2' modifications—can improve resistance to degradation, reduce immunotoxicity, and enhance target tissue binding. However, the development of both viral and non-viral miRNA carriers remains crucial. While viral vectors provide high delivery efficiency, they often induce immunotoxic responses. In contrast, non-viral carriers are safer but generally less efficient. (36,37)

miRNA therapies

In prostate cancer (PC) therapy, inhibition of oncogenic microRNAs (miRNAs) can be effectively achieved through synthetic anti-miRNA oligonucleotides (AMOs),

which are typically 17–22 nucleotides in length and function by annealing to complementary miRNA sequences. This binding impairs the RNA-induced silencing complex (RISC), preventing the miRNA from targeting tumor suppressor transcripts, thereby mitigating tumor proliferation and metastatic potential. A notable subclass of chemically engineered AMOs, termed antagomirs, has demonstrated in vivo efficacy in miRNA silencing within PC models. For example, direct intratumoral administration of antagomirs against miR-221 and miR-222 led to downregulation of these oncogenic miRNAs and reactivation of tumor suppressor pathways, significantly impeding tumor growth in murine subcutaneous xenograft models. (38)

Innovative approaches in AMO design include the use of crosslinked 2′-O-methyl (2′-OMe) RNA duplexes incorporating 2-amino-6-vinylpurine (AVP) to achieve selective interstrand crosslinking with uracil residues. A recent study developed such crosslinked duplexes targeting miR-21 and demonstrated superior inhibitory activity relative to commercially available locked nucleic acid (LNA)-modified inhibitors, suggesting enhanced target affinity and stability. (39) Further optimization of AMO constructs through incorporation of LNA or peptide nucleic acid (PNA) modifications has been explored, particularly against miR-21. LNA-modified anti-miR-21 oligonucleotides have been shown to suppress PC cell viability and tumor burden in xenograft models. Likewise, systemic administration of PNA-based anti-miR-21 significantly reduced bone metastases in vivo. (40)

Beyond direct miRNA antagonism, alternative strategies include miRNA sponges—vector-encoded RNA transcripts harboring multiple tandem miRNA response elements. These constructs sequester miRNAs, thereby attenuating their regulatory activity on tumor suppressor gene targets. (37) Another method involves miRNA masks—antisense oligonucleotides designed to hybridize with miRNA binding sites on target mRNAs rather than the miRNAs themselves. This sterically hinders RISC binding and permits normal translation of tumor suppressor genes, circumventing oncogenic miRNA interference. (41) Additionally, genome editing technologies such as CRISPR/Cas9 are being explored for their capacity to delete or mutate oncogenic miRNA loci. This

approach offers a potentially durable method to silence miRNAs implicated in PC progression and metastasis. (3)

CONCLUSION

Prostate cancer remains a major global health concern due to its high incidence, heterogeneous progression, and limited therapeutic efficacy in a substantial subset of patients. The integration of molecular biomarkers, particularly microRNAs (miRNAs), holds significant promise for improving early detection, risk stratification, and personalized therapy. Emerging evidence highlights the dual utility of circulating and exosomal miRNAs as non-invasive diagnostic and prognostic tools, as well as potential therapeutic agents capable of modulating oncogenic pathways. Still there are several limitations concerning the clinical translation of miRNA-based applications. Preanalytical variability—including differences in sample collection, processing, storage, and miRNA isolation methods—contributes to inconsistencies in assay performance and comparability across studies. Additionally, many studies are constrained by small cohort sizes, retrospective designs, or single-center analyses, limiting its findings. Variability in miRNA expression due to patient heterogeneity, comorbidities, or concurrent medications further complicates interpretation.

To address these challenges, standardization of detection platforms and protocols is essential, alongside rigorous validation across diverse populations. Furthermore, the development of safe and effective miRNA delivery systems, including chemical modifications, nanocarrier technologies, and genome-editing approaches, is crucial to realizing the therapeutic potential of miRNAs.

Future research should concentrate on large-scale, multi-center clinical trials, integrated biomarker panels, and longitudinal studies to assess the predictive and therapeutic utility of miRNAs in prostate cancer. Interdisciplinary collaboration between molecular biologists, clinicians, and bioengineers will be vital to translate these insights into clinically actionable strategies, ultimately enabling more precise, less invasive, and more effective management of prostate cancer.

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TABLES WITH LEGENDS

Table 1. Genes involved in the development of PC

Gene locus	Mutated genes	Protein/enzyme encoded by the genome	Role in the development of cancer
1q24-25	HPC1 gen	Ribonuclease L (RNASEL)	virus defence and apoptosis regulation
17p11	HPC2/ELAC2 gen	ELAC2 protein	regulation of proliferation by activation of the TGF- β signaling pathway
8p22	MSR1	Macrophage receptor 1	unknown
17q21	BRCA 1	Breast cancer type 1 susceptibility protein	a more aggressive form of PC
13q13	BRCA 2	Breast cancer type 2 susceptibility protein	increased risk of developing PC
16p12	PALB 2	Partner and localizer of BRCA2 protein	familial PC
Xq26.3-q27.3	AR	Androgen receptor	sporadic and hereditary PC

Abbreviations: AR: Androgen receptor; BRCA1: Breast cancer type 1 susceptibility protein; BRCA2: Breast cancer type 2 susceptibility protein; ELAC2: ELAC2 protein;

HPC1: Hereditary prostate cancer 1; HPC2: Hereditary prostate cancer 2; MSR1: Macrophage scavenger receptor 1; PALB2: Partner and localizer of BRCA2; PC: Prostate cancer; RNASEL: Ribonuclease L; TGF-β: Transforming growth factor beta.

Table 2. miRNA panels used for the diagnosis and prediction of PC treatment

Panel	*miRNA*	Purpose
Moya et al.	miR-98-5p, miR152-3p, miR-326 and miR-4289	Isolation of patients who have PC
Liu et al.	miR-223, miR-24 and miR-375	Distinguishing indolent from progressive disease course
Brase et al .	miR-141 and miR- 375	Predictors of tumour metastatic potential
Shen et al.	miR-20a, miR-21, miR-145, and miR-221	Distinguishing high-risk and low-risk PC
Hoey et al.	miR-20a, miR-17, miR-20b and miR-106a	Distinguishing high-risk and low-risk PC
Biddara et al.	miR-182-5p and miR-375-3p	Prediction of advanced PC
Alhasan et al.	miR-106a, miR-135a, miR-200c, miR-433, and miR-605	Prediction of high-risk PC
Abramovic et al.	miR-375-3p, miR-182-5p	Distinguishing PC from BPH, comparison of miRNA and PSA as biomarkers

Abbreviations: PC: Prostate cancer; BPH: Benign prostatic hyperplasia; PSA: Prostate-specific antigen; miRNA: microRNA; miR: mature microRNA; 5p/3p: derived from the 5-prime or 3-prime arm of the pre-miRNA.

GRAPHICAL ABSTRACT