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MicroRNA in prostate cancer: from biogenesis to applicative potential

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Abstract

Prostate cancer is the most common solid malignant tumor in men, characterized by high morbidity and mortality. While current screening tools, such as prostate-specific antigen (PSA) testing and digital rectal examination, are available for early detection of prostate cancer, their sensitivity and specificity are limited. Tissue puncture biopsy, although capable of offering a definitive diagnosis, has poor positive predictive rates and burdens the patient more. Therefore, more reliable molecular diagnostic tools for prostate cancer urgently need to be developed.

In recent years, microRNAs (miRNAs) have attracted much attention in prostate cancer research. miRNAs are extensively engaged in biological processes such as cell proliferation, differentiation, apoptosis, migration, and invasion by modulating gene expression post-transcriptionally. Dysregulation of miRNA expression in cancer is considered a critical factor in tumorigenesis and progression. This review first briefly introduces the biogenesis of miRNAs and their functions in cancer, then focuses on tumor-promoting miRNAs and tumor-suppressor miRNAs in prostate cancer. Finally, the potential application of miRNAs as multifunctional tools for cancer diagnosis, prognostic assessment, and therapy is discussed in detail. The concluding section summarizes the major points of the review and the challenges ahead.

Keywords Prostate cancer, MicroRNAs, Diagnosis, Prognosis, Therapy, Biomarkers

Introduction

Prostate cancer is the most common solid malignancy in men and the second most prevalent male cancer worldwide, following lung cancer. It is a leading cause of cancer-related deaths in men as well [1, 2]. While the definitive causes remain unclear, age is an essential risk factor [3]. Prostate cancer is rare in men under 40 but becomes increasingly frequent after 50, with approximately 75% of cases occurring in men aged 65 and over [4–6]. Family history and ethnicity also play critical roles; men with a family history of prostate cancer have an increased risk, and higher incidence, disease progression, and mortality rates are observed among men of African descent compared to other racial groups [7–11].

The development and progression of prostate cancer is often coupled with various genetic and chromosomal abnormalities, with breast cancer susceptibility gene 2 (BRCA2) mutation being one of the most critical genetic risk factors [12]. Mutations in the BRCA2 gene, a pivotal tumor suppressor involved in DNA damage repair, result in a loss of DNA reparative function, increasing genomic instability and ultimately promoting tumor development and progression [13]. Studies have shown that BRCA2 mutations not only raise the risk of prostate cancer but are also associated with greater tumor aggressiveness and a poorer prognosis [12, 14]. In addition, altered chromosome structure is a major pathologic feature of prostate

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cancer. Amplification and deletion of chromosome 8 are strongly correlated with prostate cancer occurrence, whereas deletion of the retinoblastoma gene 1 (RB1) on chromosome 13 further promotes tumor development by disrupting cell cycle regulation [15, 16].

Prostate cancer exhibits remarkable heterogeneity in progression risk and prognosis, both globally and within the identical patient populations [17, 18]. Indolent prostate cancer, characterized by slow growth and hypoinvasiveness, is often diagnosed at an early stage and confined to the primary site, allowing for excellent survival rates with timely radical prostatectomy or radiation therapy [19–21]. Despite treatment, about 30% of patients experience biochemical recurrence and metastatic development [22, 23]. Advanced prostate cancer is markedly aggressive, often disseminating to distant organs or bones via the bloodstream or lymphatic system [24]. Androgen deprivation therapy (ADT), which reduces or blocks androgens that promote prostate cancer cell growth, is the preferred treatment for androgen-sensitive recurrent and metastatic cancers but becomes ineffective against further progressive castration-resistant prostate cancers (CRPC) [25, 26].

Early detection of prostate cancer through screening has effectively reduced the advanced cancer diagnosis and mortality rates. This is because early-stage cancers, confined to the prostate gland and potentially curable, are identified before they become aggressive and spread [27–29]. Utilizing advanced diagnostic technologies is crucial for prompt intervention and higher treatment success. Currently, widely used clinical screening tools include prostate-specific antigen (PSA) testing and digital rectal examination, whereas histopathologic analysis of transrectal ultrasound-guided prostate biopsy provides a definitive diagnosis [30, 31]. PSA is a noninvasive biomarker with normal levels ranging from 2.5 to 4 ng/mL [32]. Elevated PSA levels may indicate malignant prostate lesions, but they are more indicative of organ status than cancer specificity, and fluctuations can occur due to prostate trauma or benign conditions (e.g., infection, inflammation, or hyperplasia) [2, 33]. Further prostate biopsy becomes warranted in patients with PSA levels in the "gray zone" of 4 to 10 ng/mL, yet the predictive value for positive prostate cancer is only about 30% [34, 35].

While PSA screening is clinically valuable, its limited accuracy can lead to unnecessary invasive diagnoses and overtreatment of low-risk patients, causing adverse effects. Moreover, PSA testing has limitations in differentiating disease types, assessing metastatic potential, predicting prognosis, and informing preclinical therapeutic decisions [32, 36]. Consequently, researchers are exploring molecular diagnostic tools for prostate cancer with higher accuracy, sensitivity, and reliability to refine risk stratification and tailor personalized treatment plans.

Innovations in the fields of sequencing technology and bioinformatics have recently yielded significant advances in the intensive study of large-scale noncoding RNA expression profiles, including microRNAs (miRNAs), long noncoding RNAs (lncRNAs), and circular RNAs (circRNAs) [37, 38]. miRNAs, a striking member of the noncoding RNA family, are a class of endogenous single-stranded RNA molecules that are highly conserved and have a length of approximately 20 nucleotides [39]. The number of newly discovered miRNAs in various organisms is rapidly increasing by thousands each year. More than 3000 functionally diverse miRNA sequences originating from mammalian genomes have been identified so far, with over half derived from the human genome, and they can modulate up to 30% of protein-coding genes [40, 41]. miRNAs direct the cleavage, translational repression, or destabilization of post-transcriptional messenger RNAs (mRNAs) through complementary pairing of base sequences in the seed region at their 5' end with the 3' untranslated region (3'UTR) of target mRNAs, thereby preventing specific gene expression and protein production [42, 43].

Although the expression level and functions of individual miRNAs may be minimal, their ability to regulate multiple mRNA targets in signal transduction pathways and their collective integration enables them to be extensively engaged in regulating a variety of core biological processes such as cell proliferation, differentiation, apoptosis, migration and invasion [44, 45]. Considering that miRNAs play an essential role in maintaining cellular homeostasis and physiological processes, their dysregulated profiles can trigger gene expression alterations that fundamentally affect cellular stability and may contribute to various pathological conditions [46]. Functional studies have revealed an intrinsic correlation between miRNA features and the cancer molecular pathological mechanisms, where genomically amplified oncogenic miRNAs can upregulate oncogenes, whereas oncosuppressor miRNAs with gene deletions may silence tumor suppressor genes, thus triggering the tumorigenesis and metastasis [47, 48]. Moreover, miRNA expression levels vary among different types of cancers, different subtypes of the same cancer, and even among different stages of cancer progression, suggesting that miRNAs exhibit a high degree of tissue specificity and temporal variability [47, 49, 50]. Recently, a series of aberrantly expressed miRNAs found in prostate cancer have been proven to be able to differentiate the malignancy of cancer tissues, identify the invasive intensity of cancer and predict its evolution [51, 52].

miRNAs not only exert critical biological roles intracellularly, but also possess the unique ability to functionally communicate by intercellular signaling [53]. They are secreted by cells into the extracellular environment,

such as serum, urine and other biological fluids, through multiple mechanisms and act as endocrine and paracrine messengers, thereby facilitating communication between the originating cell and the target cell or tissue [42, 54]. In particular, some miRNAs are encapsulated within extracellular vesicles, such as exosomes, microvesicles, or apoptotic bodies, which are capable of delivering miRNAs directly into the target cells through fusion with or uptake by the target cell membrane [55, 56]. Alternatively, miRNAs can bind to specific proteins, such as Argonaute2 (Ago2), or lipoprotein complexes, which can be recognized and utilized by target cells [42, 57]. These encapsulation mechanisms not only make miRNAs resistant to degradation by abundant ribonucleases in body fluids but also enhance their stability in biological samples and their dissemination efficiency in vivo, endowing them with special importance in cancer diagnostic and therapeutic studies [58]. By analyzing miRNAs extracted from biological specimens such as healthy or cancerous prostate tissue and serum, key physiological or pathological information becomes available. Abnormally expressed miRNAs reflect the current cellular status, indicate the malignancy of the tumor, predict the aggressiveness and metastatic tendency of the disease, and may reveal the patient's susceptibility to specific therapeutic regimens [59]. Hence, miRNAs hold the potential to serve as biomarkers for the occurrence and prognostic assessment of prostate cancer.

Therefore, given the complexity and heterogeneity of prostate cancer as a threat to men's health, the limited availability of existing diagnostic and therapeutic tools, and the significance of miRNAs as gene expression regulators, this paper aims to systematically synthesize the roles of miRNAs in prostate cancer and to explore their potential application in clinical settings, including their use as biomarkers for diagnosis and prediction of prostate cancer and as novel therapeutic tools.

miRNA biogenesis

Classical biosynthetic pathways of miRNAs

Typical miRNA biosynthesis is a sequential cleavage containing multiple complicated processing steps involving translocation from nucleus to cytoplasm [60]. The initial stage of this process is dominated by RNA polymerase II, which transcribes miRNA genes into large precursor primary miRNA transcripts (pri-miRNAs). Characterized by their typical secondary hairpin structure, these pri-miRNAs are embedded with mature miRNA sequences, with single-stranded sequences varying in length from hundreds to thousands of nucleotides [61, 62]. Next, in the nucleus, pri-miRNAs are precisely tailored by a microprocessor complex composed of Drosha (a ribonuclease III endonuclease), DiGeorge syndrome critical region 8 (DGCR8, a specialized double-stranded RNA-binding protein), and other partner proteins [63–65]. As a non-catalytic subunit, DGCR8 recognizes the pri-miRNA structure and directs Drosha to cleave approximately 11 bases upstream of the hairpin stem base, releasing a stem-loop intermediate precursor miRNA (pre-miRNA) about 70 nucleotides long [66]. Subsequently, to assist pre-miRNA in the nucleus to translocate into the cytoplasm, the transport protein Exportin-5 (XPO5) binds to Ran-GTP to form a ternary complex, which allows the pre-miRNA to cross the nuclear pore complex into the cytoplasm while avoiding its degradation during translocation [67, 68].

In the cytoplasm, the pre-miRNA is processed by Dicer, another ribonuclease III enzyme that cleaves the loop at its end, producing mature double-stranded miRNAs approximately 22 nucleotides long [69, 70]. These miRNAs are then incorporated into the RNA-induced silencing complex (RISC), where Ago proteins retain the guide strand and degrade the passenger strand. The guide strand miRNA subsequently acts as a navigator to guide the RISC complex to specifically recognize and bind to the complementary sequence in the 3'UTR of the target mRNA. The complementarity of this binding can be partial or complete, where partial complementarity of the seed region (nucleotides 2–8) of the miRNAs to the target sequence typically triggers translational repression of the target mRNA. However, full complementarity activates the direct degradation mechanism of the target mRNA, culminating in post-transcriptional regulation of gene expression [48, 71, 72]. An overview of classical miRNA biogenesis and action mechanisms is shown in Fig. 1 [60].

Alternative biosynthetic pathways of miRNAs

Recent insights into the miRNA biogenesis mechanism have unveiled several alternative pathways to the classical one, a finding that emphasizes the complexity and diversity of miRNA biosynthesis. These alternative pathways permit the production of RNA molecules with structural and functional similarities to conventional miRNAs in the absence of the core processing enzymes Drosha and DGCR8 [73, 74]. Especially, mirtrons, as a remarkable source of non-classical miRNAs, account for about 15% of all miRNA production. They are generated directly from introns by post-transcriptional splicing, forming pre-miRNA-like structures, thus maintaining miRNA production even when Drosha enzyme function is limited or deficient. This process involves the splicing of introns into a linear mirtron by the spliceosome, which is then unwound and rapidly folded by the action of a lariat-debranching enzyme into a morphology with a typical pre-miRNA hairpin structure, and ultimately transferred into the cytoplasm by XPO5, followed by subsequent

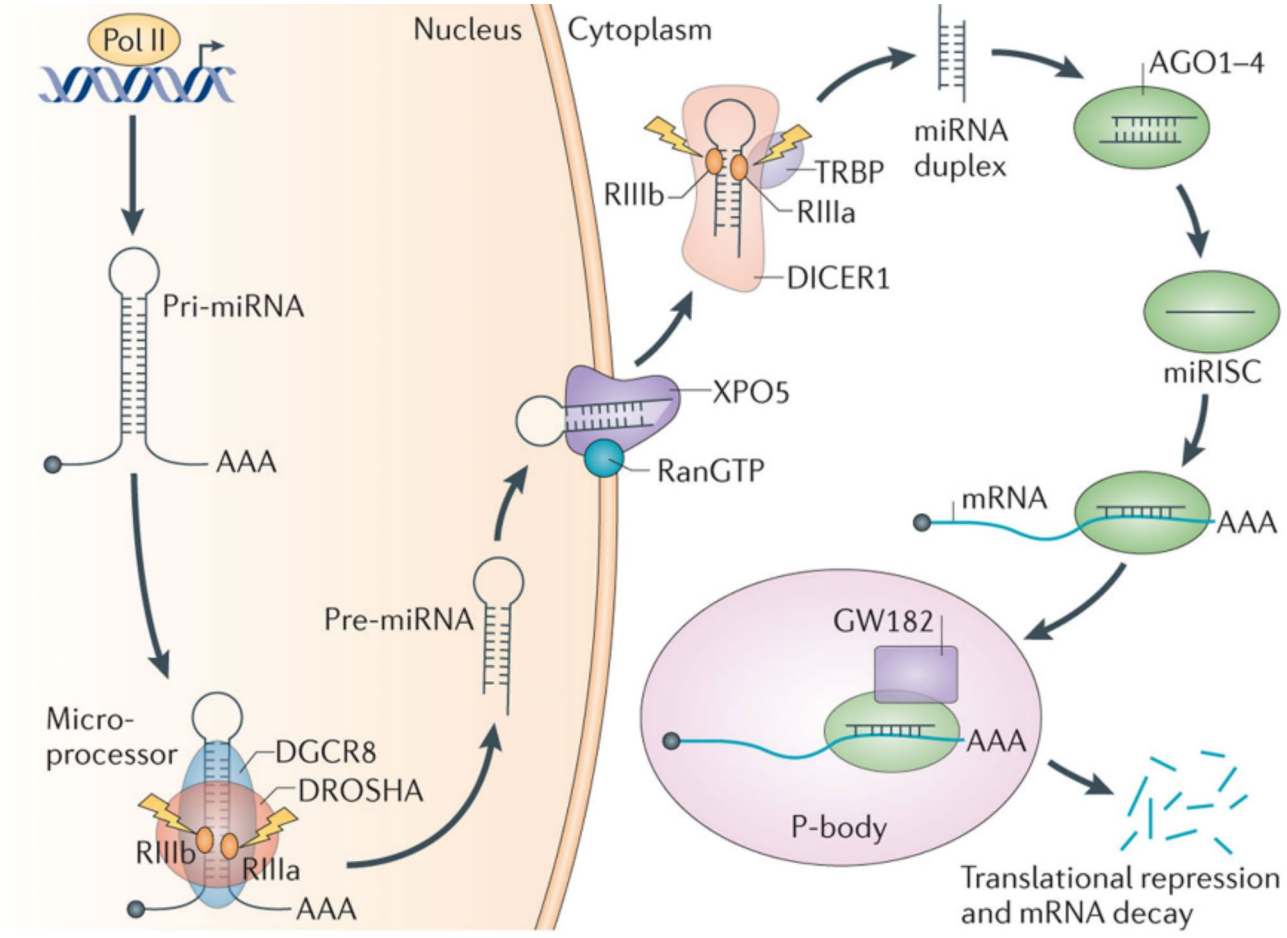

Fig. 1 Schematic illustration of intracellular miRNA biogenesis and action mechanisms. Reproduced with permission from Ref [60]. copyright 2015, Springer Nature

processing according to the conventional miRNA maturation pathway [75–77].

There are also multiple Drosha-independent pathways, mainly including small nucleolar RNA (snoRNA), transfer RNA (tRNA), small hairpin RNA (shRNA), and tRNase Z pathways. These pathways initiate the processing of various types of RNA precursors into miRNA-like molecules in situations where Drosha enzyme action is bypassed. Meanwhile, pathways such as the Ago2-dependent pathway which do not require the intervention of Dicer tailoring at the miRNA maturation stage, have also been identified [78–80].

miRNA functions in cancer

Prior to the discovery of miRNAs, molecular biology research focused primarily on protein-coding genes. Although the existence of non-coding RNAs was known to scientists, these RNA molecules were initially regarded as "genomic noise" without biological function [81]. In 1993, Lee et al. first discovered a small RNA molecule, lin-4 miRNA, which inhibits the lin-14 protein translation by complementary binding to the lin-14 gene, thereby regulating the developmental time sequence of *Caenorhabditis elegans* [82]. This mechanism demonstrated, for the first time, the role and function of miRNAs in gene expression regulation, laying the foundation for investigation of their impact in biological processes and diseases. In 2002, Calin and his team found that miR-15 and miR-16 expression levels in chronic lymphocytic leukemia patients were notably inferior to those in healthy individuals [83]. This discovery was the first to confirm that aberrant miRNA expression is closely associated with human tumorigenesis, sparking a boom in research toward miRNAs in cancer. Along with the advances in high-throughput sequencing technology and bioinformatics, increasingly more studies have reported the versatile functions of miRNAs in cancer, covering various aspects ranged from regulatory mechanisms to clinical applications [84, 85].

As previously mentioned, miRNAs regulate the target mRNA expression post-transcriptionally through a complementary pairing mechanism. miRNAs have short seed sequences and are not strictly complementary, therefore a single miRNA can target hundreds of different mRNAs

simultaneously. Furthermore, the 3'UTR of mRNAs is often long and complex, and contains multiple miRNA-pairing sites, which makes a single mRNA potentially regulated by multiple miRNAs. This multi-targeting ability renders miRNAs central molecules in the complex regulation of gene networks, thus exerting pivotal roles in a broad range of biological processes and signaling pathways including cell proliferation, differentiation, apoptosis, cell migration, invasion, metabolism, and immune responses [72, 86, 87]. Consequently, dysregulation of miRNA expression may lead to disorders in gene regulatory networks and abnormalities in cell function, contributing to the occurrence and progression of various diseases, including cancer.

Mechanisms of miRNA dysregulation in cancer include mutations, amplifications, deletions, and errors in the biogenesis process. Cancerous miRNA biogenesis is often disrupted due to disturbances in the expression and function of key enzymes and protein components, leading to altered miRNA processing mechanisms and abnormal miRNA expression. In prostate cancer, abnormal elevation of Dicer1 and DGCR8 has been found to be closely associated with miRNA dysregulation [65, 88]. In addition, epigenetic alterations, such as histone modifications and DNA methylation, could influence the expression status of miRNA genes [89–91]. These factors result in increased expression of cancer-favoring miRNAs and diminished expression of anti-tumor miRNAs.

Dysregulated miRNAs in prostate cancer

The first miRNAs associated with prostate cancer were reported by Volinia et al. in 2006. A large-scale miRNA profile study was conducted by analyzing 363 tumor samples and 177 normal control samples from six solid tumors, including prostate tumors. They found that 137 of the 228 miRNAs were expressed in at least 90% of the samples. Among these miRNAs, 39 were upregulated in prostate cancer samples, while 6 were downregulated [92]. Nevertheless, in 2007, Porkka et al. utilized oligonucleotide array hybridization technique to analyze 13 clinical prostate tissue samples (5 untreated samples, 4 hormone-refractory tumors, and 4 prostate hyperplasia control samples), 6 cell lines, and 9 xenografts, and observed that the trend of expression of miRNAs in prostate cancer was contrary to the previous results. 51 miRNAs in prostate cancer were aberrantly expressed, of which 37 were downregulated and 14 were upregulated. Besides, this study performed hierarchical clustering of tumors based on differences in miRNA expression levels, highlighting the potential importance of miRNAs in the diagnosis and prognosis of prostate cancer [93].

Significant progress has been made over the past decade in researching miRNA function in prostate cancer, especially in revealing their biological roles in tumorigenesis, progression and metastasis. Studies have verified that specific miRNAs regulate key cellular processes and signaling pathways at different stages of prostate cancer, from formation to organ metastasis, extensively affecting cell proliferation, apoptosis, cell cycle, epithelial-mesenchymal transition (EMT), angiogenesis and metastasis [94–96]. In accordance with the nature and expression environment of miRNAs in the malignant behavior of prostate tumors, miRNAs that inhibit the expression of tumor suppressors are termed oncogenic miRNAs, with tumor-promoting properties, Conversely, miRNAs that inhibit the expression of pro-carcinogenic genes are termed tumor-suppressor miRNAs, contributing to the prevention of tumorigenesis [97]. Therefore, an in-depth exploration of miRNAs participating in different tumorigenic processes and their acting mechanisms is crucial for fully understanding prostate carcinogenesis and malignant progression from the molecular perspective. This includes not only the study of individual miRNA functions, but also a thorough analysis of the miRNA regulatory network to reveal the intricate interactions among diverse miRNAs and also among miRNAs together with their target genes.

Oncogenic miRNAs in prostate cancer

The collaborative action of cell cycle proteins (Cyclins) and cyclin-dependent kinases (CDKs) ensures the normal progression of the cell cycle [98]. Yet, dysregulation of cell cycle regulation induced by tumor-associated miRNAs can accelerate cell cycle progression and inhibit apoptosis, thus propelling prostate carcinogenesis and progression. This malfunction is characterized by increased expression of cyclin D and reduced abundance of the CDKs inhibitors p21 and p27 [99, 100]. Wu et al. observed that overexpression of miR-153 in prostate cancer cells caused an increase in the expression level of the cyclin D1 and a decrease in the expression of the CDK inhibitor p21 [101]. Moreover, some miRNAs can affect the expression of the tumor suppressor gene p27. miR-21 downregulates the gene expression of p27 via targeting its coding region, thus impairing the function mediated by p57 [102]. In addition, the miR-221/miR-222 gene cluster located on the X-chromosome possesses seed sequences consistent with its target genes. These miRNAs display carcinogenic activity in prostate cancer, impacting cell cycle distribution and cell proliferation by suppressing p27. Specifically, miR-221/miR-222 overexpression lifts cell cycle repression by targeted inhibition of p27. These miRNAs further promote p27 degradation by upregulating S-phase kinase-related protein 2 (SKP2). Besides, they facilitate cell transition from G1 to S phase by elevating cyclin A. At the same time, increased cyclin D1 enhances the cell proliferation ability. Thus, the miR-221/miR-222 gene cluster is able to strengthen in vitro

clonogenic formation and in vivo tumorigenicity [103]. In addition, miR-429 is also involved in the regulation of p27. Reduced miR-429 expression could inhibit the proliferation of prostate cancer cell lines IF11 and IA8 and caused their arrest in G1 phase [104].

Apoptosis is a physiological cell death mode controlled by genes that functions to eliminate senescent, impaired, or abnormal cells in order to maintain tissue stability, support development and organ formation, and modulate the immune system [105, 106]. In normal cells, cells self-destruct through the apoptotic pathway upon DNA damage, preventing cancerous transformation by halting the accumulation of mutations. However, in prostate cancer, overexpression of certain miRNAs helps cells evade death by interfering with multiple apoptotic signaling pathways, thereby fostering cell proliferation and tumor growth [107]. Hsu et al. observed that miR-18a expression was upregulated in prostate cancer specimens and cell lines. By conducting bioinformatics analysis and luciferase reporter assays, they confirmed the direct action of miR-18a on serine/threonine protein kinase 4 (STK4). miR-18a decreased AKT dephosphorylation by reducing STK4 protein levels, which in turn resisted apoptosis and promoted cell proliferation [108]. Another study found that miR-32 expression levels in patients with castration-resistant prostate cancer were dramatically higher than in those with benign prostatic hyperplasia. miR-32 possessed the capacity to simultaneously target and repress B-cell translocation gene 2 (BTG-2) and phosphoinositide-3-kinase interacting protein 1 (PIK3IP1), both of which play important roles in cell apoptosis and tumor suppression. Overexpression of miR-32 in LNCaP cell lines significantly facilitated cell proliferation and reduced apoptosis, resulting in promoting cell growth [109]. As a tumorigenic miRNA known to be overexpressed in most malignant tumors, miR-21 governs widely various target genes and signaling pathways, and exerts an essential role in cancer development [110]. Of these, one of the tumor suppressor genes repressed by miR-21 is FBXO11, which belongs to the F-box subfamily without a unique uniform structural domain. In prostate cancer, F-box protein 11 (FBXO11) mediates the degradation of the oncogenic protein B cell lymphoma 6 (BCL6), leading to the promotion of apoptosis. However, miR-21 confers anti-apoptotic property on cells by reducing the expression of FBXO11, making it an oncogenic miRNA that regulates apoptosis in prostate cancer [111].

EMT is a biochemical process where epithelial cells lose their original phenotype and obtain mesenchymal properties. During this process, E-cadherin, which keeps epithelial cells tightly connected, is inhibited, causing the loss of intercellular adhesion between epithelial cells; concomitantly, the expression of mesenchymal markers, such as N-cadherin and vimentin, is enhanced, which endows cells with invasive and migratory capabilities as well as stem cell properties. Physiological EMT plays a key role in embryonic development and wound healing, whilst pathological EMT contributes to tumor cell proliferation and ectopic survival [112–114]. In metastatic prostate cancer, dysregulated EMT encourages primary tumor cells to invade peripheral tissues through the blood or lymphatic system and colonize distant sites, allowing metastatic cells to restore epithelial features similar to the primary host tumor via the MET pathway [115]. Many miRNAs are thought to modulate the expression of key genes and proteins during EMT, thereby promoting cancer metastasis. Studies have indicated that miR-181a expression was upregulated in metastatic prostate tumor samples and dramatically promoted the migration and metastasis of prostate cancer cells. TGFB-induced factor homeobox 2 (TGIF2) acts as a repressor in the Smad pathway and prevents the formation of Smad complexes by bounding directly to Smad2/3. miR-181a decreases the repression of Smad2/3 by targeting TGIF2 specifically and increases its phosphorylation and intranuclear translocation, which consequently induces the EMT process in prostate cancer [116]. StAR-related lipid transfer domain containing 13 (StarD13) is a tumor suppressor gene that exerts anti-cancer effects by reinforcing intercellular adhesion and inhibiting cell migration. However, Chen et al. demonstrated that miR-9 promoted the EMT process in prostate cancer cells DU145 and PC-3 by downregulating StarD13. Inhibiting miR-9 expression could notably reduce the levels of N-cadherin and vimentin while increasing E-cadherin, thus reversing the progression of prostate cancer cells towards a mesenchymal phenotype [117]. Not only that, some miRNAs in the delta-like 1 homolog-deiodinase, iodothyronine 3 (DLK1-DIO3) cluster such as miR-154, miR-379, and miR-409 are highly expressed in bone metastatic prostate cancer cell lines and tissues, and are considered pivotal elements in promoting prostate tumor induction, EMT, and bone metastasis [118, 119].

Angiogenesis is the process by which new blood vessels are generated from existing ones, providing the tumor with essential oxygen and nutrients while assisting in the elimination of metabolic waste products. In addition, angiogenesis promotes the formation of metastatic foci by supplying channels for cancer cells to enter the blood circulation and spread to distant organs [120]. Recent findings have shown that a variety of miRNAs induce angiogenesis in prostate cancer through different mechanisms. Liu et al. investigated the effect of miR-21 overexpression on angiogenesis in human prostate cancer cells DU145, and noted that the upregulation of miR-21 directly enhanced the expression of the pro-angiogenic factors hypoxia-inducible factor-1α (HIF-1α)

and vascular endothelial growth factor (VEGF). This was mainly achieved by miR-21 targeting the inhibition of phosphatase and tensin homolog (PTEN), and then activating the AKT and ERK signaling pathways [121]. Furthermore, Li et al. demonstrated a positive correlation between HIF-1α and miR-182 expression levels in a mouse prostate cancer model. miR-182 leads to sustained activation of the HIF-1α pathway through modulating negative regulators of HIF-1 signaling, including prolyl hydroxylase domain enzymes (PHDs) and factors inhibiting HIF-1 (FIH1), thereby enhancing angiogenesis and an increase in tumor volume [122]. Adiponectin is capable of inhibiting neovascularization mediated by VEGF-A and functions as an inhibitor in prostate tumor cell proliferation. miR-323, however, promotes the expression of VEGF-A in prostate cancer cells by targeting Adiponectin receptor 1 (AdipoR1), which further increases cancer angiogenesis [123].

Owing to the multi-targeting nature of miRNAs, a single oncogenic miRNA can simultaneously regulate multiple cytological processes that contribute to the development and progression of prostate cancer. For example, bioinformatics analysis revealed that miR-93 is predominantly enriched in the transforming growth factor-β (TGF-β), phosphatidylinositol 3-kinase (PI3K)/AKT, and mitogen-activated protein kinase (MAPK) signaling pathways [124]. In vitro studies further verified that reduced expression of miR-93 suppresses the proliferation, migration, and invasion of prostate cancer cells while eliciting cell cycle dysfunction and promoting early apoptosis [125]. Liu et al. found that miR-93 could enhance the proliferation, invasion and metastasis of cancer cells by upregulating the expression of genes including TGF-β receptor 2 (TGF-βR2), integrin subunit β 8 (ITGβ8) and large tumor suppressor kinase 2 (LATS2) [126]. Another study demonstrated that miR-93 inhibits disabled homolog 2 (DAB2), thereby constitutively activating the AKT and ERK1/2 signaling pathways, eventually promoting prostate cancer cell growth and migration [127].

Tumor suppressor miRNAs in prostate cancer

As described earlier, the anti-cancer miRNAs exert their effects by negatively regulating oncogenes and related signaling pathways to restrict the tumor formation and growth. Within the carcinogenic environment, however, the expression of these tumor-suppressor miRNAs is often downregulated, which attenuates their inhibitory capacity on oncogenes, resulting in the expression of these genes being up-regulated and driving tumor progression. This altered miRNA expression triggers multiple consequences affecting tumor behavior, including aberrant cell proliferation induced by imbalanced cell cycle regulation, obstruction of the apoptotic process, and loss of suppression on EMT-related factors. This facilitates the EMT process, a critical step for tumor cells to acquire invasiveness and metastatic capacity [89, 94, 128].

In many types of cancers, including prostate cancer, the miR-34 family has been demonstrated to have extensive tumor-suppressive effects [129]. The family members, miR-34a, miR-34b and miR-34c, exert their tumor-suppressive functions by targeting prostate cancer genes at different stages of the disease. To be specific, overexpression of miR-34a significantly inhibited the proliferation and colony formation of DU145 and PC-3 prostate cancer cells in metastatic prostate cancer models. Mechanistically, miR-34a reduced the downstream expression of growth differentiation factor 15 (GDF15) by downregulating stathmin 1, a key protein involved in cell proliferation, motility and tumor metastasis, thereby achieving negative regulation of tumorigenesis and invasion [130]. Moreover, miR-34a could also regulate the Wnt signaling pathway and inhibit the EMT of cells by downregulating the key transcription factor in the pathway, lymphoid enhancer factor 1 (LEF1), which reduces the migration and invasion of prostate cancer cells [131]. Interestingly, a study conducted by Dong et al. showed that by transfecting miR-34a into PC-3 cells, overexpressed miR-34a modulated the Wnt/β-catenin pathway by decreasing Wnt1 transcriptional activity, resulting in the inhibition of PC-3 cell proliferation and migration while favoring apoptosis [132]. Likewise, miR-34b and miR-34c engage in the critical pathways controlling the proliferation, migration and invasion of prostate cancer cells. In particular, miR-34b influences the TGF-β/small mother against decapentaplegic 3 (SMAD3) signaling pathway in association with the downregulation of TGF-βR1 and phosphorylation of SMAD3 [133]. Cancer stem cells are a special subpopulation of tumor cells with the potential for self-renewal and differentiation. Cancer stem cells expressing cluster of differentiation 44 (CD44) display particularly strong clonogenic, tumor-inducing, and metastatic abilities, enabling them to perform key functions in cancer development and metastasis [134]. Liu et al. found that miR-34a, a p53 target, was underexpressed in purified CD44-positive prostate cancer cells. Enforced expression of miR-34a in these cells reduced the expression of its target CD44, which in turn inhibited prostate cancer regeneration and metastasis [135].

Studies have demonstrated that the activation of the tumor suppressor miR-145 is strongly related to p53, which is involved in the regulation of prostate cancer cell stemness and EMT. Wild-type p53 upregulated miR-145 expression, which in turn inhibited the mesenchymal markers vimentin and fibronectin in PC-3 cells, as well as the cancer stem cell markers CD44 and c-Myc, whereas anti-miR-145 could reverse this inhibitory effect [136].

Besides, the reduced expression of miR-145 in prostate cancer had a tight relationship with DNA methylation and p53 mutation pathway [137]. miR-145 could also regulate EMT negatively via inhibiting the expression of various growth factors and matrix metalloproteinases 2 (MMP-2) and 9 (MMP-9) in PC-3 cells, along with the enhancement of E-cadherin expression. These actions collectively suppress bone metastasis of prostate cancer and facilitate cancer cell apoptosis [138]. Not only that, Zeng et al. proved that miR-145 decreased the invasive phenotype and motility of PC-3 cells by targeting the post-transcriptional expression of cadherin-2 [139]. Furthermore, several researches reported that miR-145 inhibited neuroendocrine differentiation and proliferation of LNCaP cells through its targeted SRY-box transcription factor 11 (SOX11). Simultaneously, it reduced the growth and migration of LNCaP cells by targeting SOX2 [140, 141]. During EMT, miR-145 maintained the epithelial property of cells and prevented cancer cell invasion and metastasis, which was achieved by targeting a key activator of EMT, zinc finger E-box binding protein 2 (ZEB2) [142].

The work by Zhang et al. indicated that miR-382 exerted its anti-tumor effect by attacking Snail and MMP-2, the downstream genes of chicken ovalbumin upstream promoter-transcription factor II (COUP-TFII), and reducing the proliferation and metastasis of prostate cancer cells [143]. Park et al. demonstrated that overexpressing miR-122 notably represses the proliferative and migratory capacities of prostate cancer cells in vitro and inhibits in vivo tumor formation in a xenograft mouse model. This inhibitory effect was mainly attributed to miR-122 reducing the accumulation of δ-catenin, which subsequently downregulated the expression of key gene c-Myc in the downstream oncogenic signaling pathway and cyclin D1 [144]. Wan et al. found that the downregulation of miR-224 resulted in increased expression of apoptosis protein apelin (APLN) in prostate cancer tissues with advanced pathologic stage, metastatic features, and PSA failure. A significant decrease in the invasive and migratory abilities of prostate cancer cells was observed when APLN was inhibited by miR-224 [145]. In addition, insufficient expression of miR-224 contributed to losing inhibition towards tribbles pseudokinase 1 (TRIB1) and tumor protein D52 (TPD52), which are considered to potentiate proliferation, invasion, and migration of prostate cancer cells [146, 147]. Several studies have pointed to the inhibitory role of miR-372 in tumor modulation. As a tumor suppressor, miR-372 can suppress the proliferation, migration and invasion of DU145 cells by regulating the transcriptional activity of the target p65 and affecting CDK8, MMP-9 and PSA [148]. Contradictorily, another study revealed that miR-372 reduced its mediated tumor-suppressive signals and promoted cancer cell proliferation and invasion by targeting and reducing the expression of PR domain containing 16 (PRDM16) [149]. In addition, a study by Cao and colleagues showed that overexpression of miR-372 enhanced cell proliferation and migration in prostate cancer cells [150]. Accordingly, further studies are still needed to elucidate the specific regulatory mechanism of miR-372 in prostate cancer.

Diagnostic miRNAs in prostate cancer

Clinically, the initial suspicion of prostate cancer usually relies on elevated PSA levels and abnormalities detected during digital rectal examination, whereas final diagnosis requires prostate biopsy [30, 31]. Although serum PSA has been extensively used as a noninvasive biomarker for prostate cancer screening, its inadequacy in differentiating benign from malignant lesions may lead to overdiagnosis and false-positive results, and thus presenting some limitations in diagnostic applications. Variable disease course and long-term surveillance represent major challenges in the clinical management of patients with prostate cancer. The repeated performance of biopsies aggravates the burden on the patient and often lacks sufficient sensitivity to precisely locate the cancerous lesion and to determine the tumor characteristics in detail. In addition, bias in sampling for multifocal prostate cancer leads to inadequate disease assessment and affects therapeutic decisions [151]. Therefore, there is an urgent need to address these issues through development of diagnostic tools with high specificity and sensitivity.

In the past two decades, researchers have put considerable effort into developing miRNA analysis systems for patient body fluids as an ideal alternative to minimally invasive surgery for prostate diagnosis. This is largely due to the distinct tissue and pathology specificity of miRNA expression profiles, which can reflect variations in different cancer stages, and the fact that circulating miRNAs are easily accessible and have very high biochemical stability even under harsh temperature and pH conditions [58, 59, 152]. Several advanced molecular biology and genomics techniques have been employed to enrich the diagnosis of specific miRNA expression profiles, including quantitative reverse transcription PCR, miRNA microarrays, next-generation sequencing, single-cell RNA sequencing, bioinformatics analysis, and in situ hybridization. All of these approaches help to identify and validate miRNAs relevant to specific diseases [153–156].

The potential practicality of miRNAs in the multifaceted diagnosis of prostate cancer has been broadly demonstrated. In addition, the diagnostic accuracy of prostate cancer could be further improved by multiple miRNA screening. A study by Lin et al. found that miRNAs such as miR-34b-3p, miR-361-5p, and miR-200c-3p were abnormally expressed by comparing serum samples from

112 prostate cancer patients with those from 112 healthy controls, and that a combination of these three miRNAs may serve as serum markers for identifying prostate cancer (AUC 0.916, 95% CI 0.864, 0.953) [157]. Gilyazova et al. compared the differences in expression of 754 miRNAs by analyzing microarray data from patients with early and advanced prostate cancer (46 cases). They observed that miR-324-3p, miR-429, miR-570, and miR-616 levels were lower in early-stage cancer patients in comparison to advanced-stage patients, while miR-423-5p was elevated. The low expression of these miRNAs was confirmed in a further validation with 39 independent samples, pointing to the potential of these miRNAs as diagnostic markers for prostate cancer staging (AUC 0.958, SN 86%, SP 94%) [158]. In addition, miRNAs including miR-141 and miR-375 have been repeatedly reported as reliable biomarkers of prostate disease. Foj et al. observed that the expression of miR-141, miR-375, and miR-21 in urinary particles of patients with prostate cancer was markedly greater than that of healthy controls (p 0.033, 0.038, and 0.001, respectively) [159]. Besides, Abramovic's team noted that the abundance of miR-375-3p and miR-182-5p was substantially higher in the plasma of the prostate cancer patients than in those of prostate hyperplasia patients, and the positive predictive specificity of the combination of these two miRNAs was as high as 90.2%, significantly superior to the PSA cutoff value of just 1.7% at 4 μg/L (p 0.0226, 0.0363) [160]. Brase et al. compared serum samples from patients with localized and metastatic prostate cancer and showed that among the 667 analyzed miRNAs, circulating miR-375 and miR-141 proved to be the most typical signatures of high-risk prostate cancers, and the levels of these miRNAs were also correlated with Gleason scores or positive lymph node results (p 0.0028, 0.039) [161]. Furthermore, five miRNAs, miR-200c, miR-605, miR-135a, miR-433, and miR-106a, reported by Alhasan et al., were able to differentiate between indolent and aggressive features of prostate cancer with an accuracy of at least 89% (AUC 1.0, 0.92, 0.98, 0.98, 0.89, respectively) [162]. Therefore, miR-141 and miR-375 displayed significant value in the diagnosis of prostate cancer and its metastatic changes.

Although the diagnostic performance of miRNAs existing in serum and urine has been widely recognized, variations in their expression across different biological sample types, along with the lack of standardization in detection methods, may affect diagnostic accuracy. For example, miR-141 is significantly elevated in the serum of patients with metastatic prostate cancer, especially in the early stage of aggressive disease [163]. Interestingly, miR-141 can also be detected in various body fluids, including urine, where its expression may be higher due to its release from exosomes or other extracellular vesicles. This variation may be correlated with the stability and secretion pathways of miRNAs in different body fluids, suggesting that the selection of the appropriate sample type for miRNA analysis needs to be considered in light of specific clinical needs [164, 165]. Serum miRNAs may be better suited for broad screening, whereas urine miRNAs may offer higher sensitivity and specificity for early prostate cancer diagnosis. However, the use of different detection methods potentially leads to inconsistent clinical results. Therefore, subsequent efforts should strive to standardize miRNA detection processes to enhance the consistency of results in different clinical settings.

Beyond sample type and technical issues, patient age, race, and co-morbidities may also influence the diagnostic accuracy of miRNA [166]. As an example, miRNA expression levels in older patients may fluctuate with increased prostate size or inflammation [167]. These external factors could impact the sensitivity and specificity of miRNA-based diagnostics. Therefore, future studies should account for these external factors in miRNA detection and focus on developing more robust diagnostic models.

Prognostic miRNAs in prostate cancer

The prognostic evaluation of prostate cancer is the foundation for developing individualized treatment plans and managing the disease. It not only provides assistance in clarifying the severity of the disease and the risk of progression, but also guides the selection and modification of the treatment program, thereby improving the therapeutic outcome and patient survivability. The leading clinical and pathological indicators of prostate cancer prognosis include Gleason score, tumor-node-metastasis staging and PSA level, but these indicators have limitations, such as high subjectivity, tissue heterogeneity, insufficient specificity and lack of molecular features [168, 169]. These limitations emphasize the importance of developing highly specific prognostic biomarkers that contribute to the improvement of accuracy and reliability of prognostic assessment.

Numerous investigations to date have suggested the great potential of various miRNAs in the prognostic prediction of prostate cancer. A recent study was conducted to compare serum circulating miR-20a and miR-26a levels in 40 prostate cancer patients preoperatively and one week postoperatively. It was noticed that there was a decrease in both of these miRNA levels, with the reduction in miR-20a being more statistically significant. This indicated that decreased miR-20a and miR-26a levels may be reflecting their tumor origin, and this alteration could be used to monitor residual tumors after prostate cancer surgery [170]. Peng et al. analyzed the differences in the levels of miR-218-5p in tissues and serum of 38 patients with bone metastasis and 115 patients with non-bone metastasis of prostate cancer, finding a

Table 1 A summary of diagnostic and prognostic miRNAs in prostate cancer

Author (year)	Identified miRNAs	Sample source	Clinical application	Ref.
Lin (2024)	miR-34b-3p, miR-361-5p, miR-200c-3p	Serum	Diagnostic	157
Gilyazova (2023)	miR-324-3p, miR-429, miR-570, miR-616	Tissue	Diagnostic	158
Foj (2017)	miR-141, miR-375, miR-21	Urine	Diagnostic	159
Abramovic (2021)	miR-375-3p, miR-182-5p	Plasma	Diagnostic	160
Brase (2011)	miR-375, miR-141	Serum	Diagnostic	161
Alhasan (2016)	miR-200c, miR-605, miR-135a, miR-433, miR-106a	Serum	Diagnostic	162
Torbati (2019)	miR-20a, miR-26a	Serum	Prognostic	170
Peng (2019)	miR-218-5p	Serum	Prognostic	171
Wa (2020)	miR-532-3p	Tissue	Prognostic	172
Larne (2013)	miR-96-5p, miR-183-5p, miR-145-5p, miR-221-5p	Tissue	Prognostic	173
Suer (2019)	miR-424, miR-572	Tissue	Prognostic	176
Guo (2021)	miR-423-3p	Plasma	Prognostic	177
Huang (2015)	miR-375, miR-1290	Plasma	Prognostic	178

significant decrease in its expression in the presence of bone metastasis of prostate cancer, which implied that the decrease in miR-218-5p may mark bone metastasis of prostate cancer and is positively related to poor prognosis in patients with metastatic prostate cancer [171]. Furthermore, Wa et al. stated that downregulated miR-532-3p induced sustained activation of the NF-κB pathway, which has significant clinical value in the prediction of bone metastasis in prostate cancer [172]. Larne and his team performed differential expression analysis of miRNAs in tissue samples from 49 prostate cancer patients versus 25 healthy controls, and developed a prognostic tool termed the miRNA index quote (miQ) which is used to assess tumor invasion, metastasis, and overall survival. This tool introduced the expression of upregulated miR-96-5p and miR-183-5p, as well as downregulated miR-145-5p and miR-221-5p, exhibiting higher efficacy in distinguishing prostate cancer from non-cancer samples compared with PSA testing [173].

CRPC is a form of prostate cancer that continues its progression following androgen deprivation therapy and is characterized by a persistent rise in PSA levels and a deterioration of clinical symptoms. While advances have been made in the treatment of CRPC, it persists as the leading cause of death from prostate cancer [174]. Diverse miRNAs have been confirmed to reflect the molecular features and biological behaviors of CRPC cells. With dynamic monitoring of changes in miRNA levels, it is feasible to deliver early warnings of disease progression, predict the probability of CRPC transformation, and evaluate therapeutic efficacy and drug resistance in real time [175]. By carrying out microarray analysis on 20 recurrent and 20 non-recurrent prostate cancer patients, Suer et al. observed that downregulation of miR-424 and upregulation of miR-572 were remarkably relevant to prostate cancer recurrence, suggesting that these miRNAs could be applied for predicting the disease progression [176]. A study by Guo et al., on the other hand, demonstrated that high expression of miR-423-3p in plasma was strongly associated with the development of CRPC, indicating its potential as a biomarker for early prediction of castration resistance [177]. Moreover, a study revealed that miR-375 and miR-1290 had a negative correlation with the overall survival rate of CRPC patients, which was helpful in predicting the prognosis of patients [178]. Table 1 provides a detailed list of miRNAs identified as diagnostic and prognostic biomarkers for prostate cancer.

Therapeutic miRNAs in prostate cancer

Regarding the critical regulatory role of miRNAs in disease progression and metastasis, new therapeutic strategies aiming at miRNAs have shown promise in medical and pharmaceutical research and development. These strategies mainly encompass the introduction of miRNA mimics to restore lost tumor-suppressive miRNAs and the application of miRNA antagonists to suppress overexpressed tumor-promoting miRNAs [179]. Although miRNA-based therapeutics outperform conventional drugs in terms of molecular precision, low off-target effects, flexibility, and low toxicity, their susceptibility to degradation, cell membrane barriers, poor targeting capabilities, and low bioavailability have limited their clinical applications [179, 180].

To tackle these challenges, substantial research has been devoted to developing more stable and efficient miRNA delivery systems with enhanced performance through chemical modification and specific targeting strategies. Takeshita and his group successfully delivered miR-16 into the bone metastatic cells of prostate cancer in a model mouse by injecting an atelocollagen vector into the tail vein, which significantly inhibited tumor growth as the intervention downregulated CDK1 and CDK2 genes [181]. Gauer et al. developed a chitosan

Table 2 miRNA nanoparticle delivery system for prostate cancer

Vehicle	Modify	miRNA	Outcome	Stage	Ref.
Atelocollagen	-	miR-16	Inhibited bone-metastatic human prostate tumor growth	Tumor in mice bones	181
Chitosan NPs	-	miR-34a	Decreased established prostate tumor growth in the bone	Tumor in nude mice bones	182
ZIF-8 NPs	FA	miR-491	Inhibited growth of CRPC solid tumor	Solid tumor in nude mice	183
PHB NPs	PEI	miR-124	Inhibited cell proliferation, motility and colony formation	PC-3 prostate cancer cells	184
SSPEI	R11	miR-145	Inhibited peritoneal tumor growth	Intraperitoneal tumor in nude mice	185
Magnetic NPs	PEI-PEG	miR-205	Induced apoptosis and enhanced chemosensitivity	C4-2 and PC-3 prostate cancer cells	186
PEG-PAMAM	PSMA aptamer	miR-15a/16–1	Suppression of tumor growth	Intraperitoneal tumor in nude mice	187
pRNA-3WJ	PSMA aptamer	miR-17/21	Stunted tumor growth and proliferation	Subcutaneous xenograft tumor in nude mice	188

PAMAM: polyamidoamine

nanoparticle (NP) platform specifically designed for the delivery of miR-34a, which inhibits tumor growth and preserves skeletal integrity in a bone metastasis xenograft model of prostate cancer by inducing autophagy and apoptosis [182]. Ju et al. selected pH-sensitive zeolite imidazolate framework-8 (ZIF-8) nanocarriers for miR-491 loading, leveraging the acidic microenvironmental property of prostate tumor tissues, and modified the surface with folic acid (FA) to enhance nanoparticle internalization by targeting the overexpressed FA receptor in cancer cells. The FA@miR-491 -5p@ZIF-8 composite vector could accumulate rapidly at tumor site, reduce the proliferation and migration of C4-2 cells by acting on the targeted epoxide hydrolase 1 (EPHX1), as well as inhibit the growth of CRPC in nude mice [183].

Polyethyleneimine (PEI), a widely used polymer carrier, could electrostatically bind to miRNAs to form stable nanocomplexes, featuring excellent miRNA delivery capabilities. Conte et al. synthesized a cationic polymer carrier consisting of PEI and biodegradable polyhydroxybutyrate (PHB) via an aminolysis method, which delivered miR-124 in PC-3 cells with 30% higher efficiency compared to commercially available lipofectamine. This PHB-PEI NPs/miR-124 complex inhibited tumorigenic features such as cell proliferation, motility and colony formation by regulating carnitine palmitoyltransferase 1 A (CPT1A) [184]. In order to avoid the non-specific tissue toxicity associated with PEI polymers as nanocarriers, Zhang et al. modified the cell-penetrating peptide polyarginine (R11), specifically absorbed in prostate cancer, to polyethyleneimine (PEI) to produce the R11-SSPEI nanocomplex, which could efficiently deliver miR-145 into peritoneal mouse prostate tumors to restrain tumor growth and prolong survival time [185]. Nagesh et al. developed a PEI-polyethylene glycol (PEG)-conjugated magnetic nanoparticle platform by coating with PEI and PEG, where PEI enhanced miR-205 binding efficiency, and PEG ensured NP stability while reducing aggregation. This platform effectively transfected miR-205 into chemotherapy-resistant prostate cancer cells, restoring their sensitivity to chemotherapeutic agents [186]. However, the study did not explore the in vivo tumor-targeting potential of the magnetic NPs, where an external magnetic field could guide the NPs to accumulate precisely at the tumor site, increasing their concentration in the therapeutic area while minimizing side effects on normal tissues.

Some studies have integrated prostate-specific membrane antigen (PSMA) antibodies or aptamers with NPs to achieve specific recognition of cancer cells and precise targeted delivery of miRNAs by capitalizing on the highly expressive properties of PSMA proteins on the surface of prostate cancer cells [187, 188]. Additionally, advanced delivery systems, such as liposomal NPs, polymeric NPs, electroporation technology and viral vectors, in combination with targeted modifications, have greatly boosted the precision of miRNA delivery [179, 180, 189]. In preclinical studies, miRNA-based therapies have demonstrated tremendous therapeutic potential in a variety of cancer models. However, many bottlenecks remain to be overcome for miRNA-based therapies to be one of the mainstream means of cancer treatment. Therefore, it becomes particularly important to accelerate the development and innovation of nanotechnology aimed at miRNA delivery. A detailed summary of miRNA-based nanoparticle delivery systems for prostate cancer therapy is provided in Table 2.

Conclusion

As the most common type of cancer in men, prostate cancer usually has insidious early symptoms and is frequently diagnosed at the metastatic stage, leading to a

high mortality rate. Existing screening and diagnostic methods, such as PSA testing and direct rectal examination, have insufficient accuracy and reliability, and usually necessitate reliance on prostate biopsy to validate the diagnosis, which may carry risks such as false-negative results and infection. Confronted with this situation, there is an urgent clinical need to develop non-invasive biomarkers to enhance the diagnostic value of early detection and improve patient prognosis, thereby reducing cancer mortality. Since miRNA was discovered in 1993, researchers have gained plenty of achievements in the exploration of its biogenesis, function and cancer regulatory mechanisms, which enormously offers a broad potential for the versatile application of miRNAs in cancer therapy. A number of miRNAs display dysregulation during prostate cancer occurrence, progression and metastasis, and these miRNAs can be classified as either tumorigenic or tumor suppressor properties regarding their effects on cellular behaviors. Upon the basis of the differential expression of these miRNAs at different stages of cancer, they could be employed for the differential diagnosis of benign prostate lesions and tumors, distinguishing the grading and staging of cancer, and prognostic assessment.

It should also be emphasized that anti-tumor approaches, such as inhibiting overexpressed pro-oncogenic miRNAs and restoring lowly expressed anti-tumor miRNAs, offer a promising outlook for cancer therapy, and relevant research still continues. However, the fragile and off-target nature of miRNAs makes their precise delivery to cancer cells extremely challenging.

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