



Review Article

Exosomes: A Promising Tool for Liquid Biopsy in Prostate Cancer



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Abstract

Prostate cancer (PCa) often manifests insidiously, with some patients being diagnosed at an advanced stage, leading to a poor prognosis. Early detection of PCa can significantly prolong overall survival by impeding the progression of metastasis. A commonly utilized screening method for detecting PCa is the prostate-specific antigen test. However, since the prostate-specific antigen lacks specificity and sensitivity for PCa identification, there is a paramount urgency to develop precise diagnostic biomarkers for early detection. Extracellular vesicles, known as exosomes, are released by cells into body fluids. Exosomes derived from cancer cells can carry genetic information about the tumor, including DNA, RNA, and proteins, which play crucial roles in tumor initiation, invasion, metastasis, and drug resistance. Studies have indicated that exosomes (including messenger RNAs, microRNAs, long noncoding RNAs and others) can enhance the sensitivity and specificity of PCa diagnosis, indicating their potential for early detection. This review highlights the biological characteristics and functions of exosomes, as well as recent advancements in their use for the diagnosis, prognosis, and treatment of prostate cancer.

Introduction

Prostate cancer (PCa) is one of the most common cancers in males and a leading cause of cancer-related death globally. It is the most prevalent cancer and the second leading cause of cancer-related death among males in the United States.¹ In recent years, its incidence in China has been steadily increasing, particularly in economically developed coastal regions. Prostate-specific antigen (PSA) is a common tumor marker used for PCa screening, diagnosis, and clinical monitoring. However, since PSA lacks specificity and sensitivity for PCa identification, benign prostate hyperplasia (BPH) or prostate inflammation can also result in elevated PSA levels. This can lead to up to 75% of patients undergoing unnecessary prostate biopsy, which may result in overdiagnosis and overtreatment.² Patients who undergo prostate biopsy often experience severe discomfort from postoperative complications such as hematuria, infection, and pain at the site of the procedure. Some patients with an undetermined diagnosis may even require a second or third biopsy, increasing medical costs,

particularly for patients whose PSA levels fall into the so-called “gray zone” of 4–10 ng/mL.³ Radical prostatectomy and radiotherapy are common treatment options for early-stage, localized prostate cancer. In contrast to traditional open surgery, minimally invasive or robot-assisted radical prostatectomy offers shorter operating times, less tissue trauma, fewer postoperative complications, and significant therapeutic benefits, all of which greatly improve patients’ quality of life in the postoperative period.⁴ Androgen deprivation therapy (ADT) is the primary first-line treatment for PCa, initially leading to tumor regression.⁵ However, despite an initial therapeutic response to ADT, the disease inevitably evolves into castration-resistant prostate cancer (CRPC) within 18 to 24 months.⁶ Once metastasis occurs, patients progress to metastatic castration-resistant prostate cancer, which is associated with a significantly increased mortality rate.⁷ Therefore, the development of novel biomarkers for PCa diagnosis, therapy, and prognosis is urgently needed. The study of exosomes has advanced rapidly in recent years. Exosomes are extracellular vesicles 30–150 nm in diameter that are released by cells. They can carry lipids, proteins, RNA, and DNA. Due to their lipid bilayer structure, exosomes can stably resist external interference, making them potential biomarkers for the diagnosis and treatment of diseases. Exosomes offer several diagnostic advantages, including high sensitivity, minimal invasiveness, low cost, and the ability to provide real-time insights into disease progression.

Keywords: Exosomes; Prostate cancer; Diagnosis; Therapy; Prognosis; Extracellular vesicles.

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The structure and function of exosomes

Exosomes are extracellular vesicles characterized by lipid bilayer

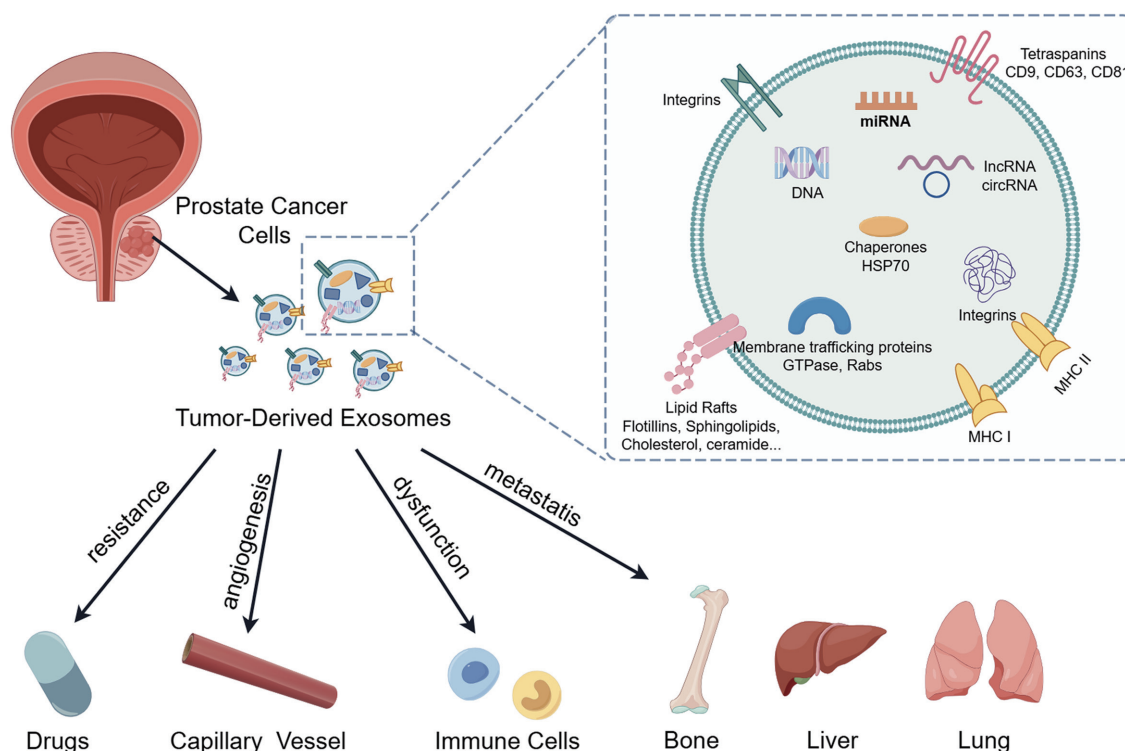


Fig. 1. Role of tumor-derived exosomes in prostate cancer progression. Exosomes participate in drug resistance, vascular remodeling, and antigen presentation. Exosomes not only impair the function of immune cells but also reshape the tumor microenvironment, thereby contributing to tumor growth and facilitating metastasis. (This is made by FigDraw.) circRNA, circular RNA; lncRNA, long noncoding RNA; miRNA, microRNA.

membranes, with a diameter ranging from 30 to 150 nanometers. They are ubiquitously found in diverse bodily fluids, such as blood, urine, ascitic fluid, and saliva.⁸ The primary constituents of exosomes include proteins, lipids, and nucleic acids.⁹ Their composition is influenced by the health status of the originating cells and organisms. Proteins are the predominant components of exosomal contents and can directly impact the invasion and migration capabilities of tumor cells, thereby promoting tumor progression and metastasis. The nucleic acids found in exosomes primarily consist of microRNAs (miRNAs), messenger RNAs, and long noncoding RNAs (lncRNAs). Among these, miRNAs have emerged as a focal point of research in recent years. miRNAs can be transferred to recipient cells via exosome-target cell membrane fusion, thereby modifying the signaling pathways of the recipient cells. The composition of exosomes secreted by different tissues varies significantly. Analysis of relevant studies has revealed that exosomes transport 4,563 proteins, 1,639 messenger RNAs, and 764 miRNAs out of cells, playing a pivotal role in intercellular communication. These molecules can influence target cells through various mechanisms, facilitating intercellular information transfer and participating in numerous physiological and pathological processes, including tumor development, antigen presentation, vascular remodeling, drug resistance, and metastasis (Fig. 1).^{10,11} In summary, exosomes are characterized by diverse and stable contents with multiple biological functions. Analyzing the composition of exosomes provides insights into the physiological and pathological states of their originating cells, establishing exosomes as one of the critical tools for “liquid biopsy.” A growing body of research indicates that exosomes not only serve as molecular markers for diagnosis and prognosis

but also present novel therapeutic targets to halt the progression of PCa (Table 1).^{12–46}

Exosomes and prostate cancer

Exosomes and early diagnosis of prostate cancer

Early detection and treatment of PCa are crucial for improving patient prognosis and long-term survival rates. Exosomes offer several advantages for the early diagnosis of tumors: (1) Exosomes are produced and secreted by nearly all cells in the body and can be readily obtained from various body fluids, including blood, urine, semen, prostatic fluid, saliva, and ascitic fluid. This makes exosome detection minimally invasive and clinically feasible.⁴⁷ (2) Tumor-derived exosomes are well protected from degradation by nucleases and proteases, preserving their contents, including proteins, lipids, and nucleic acids. The separation and detection of these exosomal contents provide strong indications of tumor development, offering a certain level of sensitivity for tumor diagnosis.⁴⁸ (3) Exosomes carry a variety of specific markers on their membranes that reflect their cellular origin. These markers enhance the specificity of exosome-based tumor detection, improving diagnostic accuracy. Clinically, Gleason scores are well correlated with the biological behavior of PCa. Elevated levels of circTFDP2 are directly linked to an increased Gleason score. Moreover, exosomes containing circTFDP2 play a pivotal role in promoting PCa progression both *in vivo* and *in vitro*. Mechanistically, circTFDP2 promotes PCa cell progression by modulating the PARP1/DNA damage axis, highlighting circTFDP2 as a promising target for PCa.¹² Bertoli *et al.*¹³ demonstrated that miR-153

Table 1. Exosomal biomarkers and functions in prostate cancer

Exosomal bio-markers	Expres-sion level	Exosome source	Role in PCa	References
circTFDP2	↑	Cell	Promotes PCa cell progression via modulating the PARP1/DNA damage axis	12
miR-153	↑	Plasma	Regulates the proliferation, migration, and invasion of prostate cancer cells	13
hsa-miR-19b-3p	↑	Plasma	Discriminate between tumor and NAT	14
hsa-miR-101-3p	↑	Plasma	Discriminate between tumor and NAT	14
miR-20b-5p	↑	Prostatic fluid	Early diagnoses PCa	15
miR-2909	↑	Urine	Promotes tumor cell invasion	16
miR-888	↑	Cell	Promotes proliferation and migration	17
miR-141-3p	↑	Plasma	Early diagnoses PCa	18
miR-125a-5p	↓	Plasma	Early diagnoses PCa	18
PSMA	↑	Plasma	Early diagnoses PCa	19
caveolin-1	↑	Plasma	Early diagnoses PCa	19
lncRNA	↑	Urine	Early diagnoses PCa	20
miR-423-5p	↑	Cell	Inhibits GREM2 through the TGF-β pathway and increases PCa resistance to taxane	21
miR-146a-5p	↓	Cell	Regulates the EGFR/ERK pathway and promotes EMT	22
miR-432-5p	↑	Cell	Increases PCa resistance to DTX by suppressing ferroptosis via targeting CHAC1	23
miR-34a	↓	Urine	Regulates BCL-2 expression and partly modulates the response of cancer cells to docetaxel	24
lincROR	↑	Cell	Initiates a β-catenin/HIF1α positive feedback loop through targeting the MYH9 protein	25
ZNF667-AS1	↓	Cell	Suppresses PCa cell growth, inhibit tumor progression, and reduce DTX resistance	26
miR-222-3p	↑	Cell	Enhances cell proliferation, migration, and invasion ability	27
miR-375	↑	Plasma	Interferes with the expression of PTPN, stabilizes phosphorylated STAT3, and promotes osteoblastic metastasis	28,34,44,45
miR-217	↑	Plasma	Influences the proliferation and invasion of cancer cells	29
miR-23b-3p	↓	Plasma	Influences the proliferation and invasion of cancer cells	29
miR-95	↑	Cell	Combines its downstream gene, JunB, and enhances proliferation, invasion, and EMT	30
HOXD-AS1	↑	Plasma	Promotes PCa cell metastasis	31
PGAM1	↑	Plasma	Promotes angiogenesis	32
hsa-miR-184	↑	Plasma	Promotes angiogenesis	33
miR-21	↑	Plasma	Assesses PCa aggressiveness	34
HSPH1	↑	Cell	Promotes the growth of CD8+ T cells and exerts anti-tumor effects	35
miR-150-5p	↓	Plasma	Regulates the Wnt pathway and bone metastasis	36
miR-500a-3p	↑	Cell	Drives PCa metastasis	37
miR-425-5p	↑	Tissue	Promotes PCa cell bone metastasis	38
miR-196a-5p	↓	Urine	Influences PCa cell proliferation, invasion, and migration	39
miR-501-3p	↓	Urine	Influences the invasion of PCa cells	39
miR-1246	↓	Plasma	Promotes apoptosis of tumor cells, and reduces tumor cell proliferation, invasion, and migration	40
miR-532-5p	↑	Urine	Predicts BCR of PCa	41
hsa-miR-148a-3p	↓	Plasma	Promotes PCa progression	42
miR-1290	↑	Plasma	Predicts the survival prognosis of CRPC patients	43,44
miR-1275	↑	Cell	Enhances osteoblast proliferation and activity via modulation of SIRT2/Runx2 signaling	46

BCL-2, B cell lymphoma-2; BCR, biochemical recurrence; CHAC1, cation transport regulator-like protein 1; CRPC, castration-resistant prostate cancer; DTX, docetaxel; EGFR, epidermal growth factor receptor; EMT, epithelial-mesenchymal transition; ERK, extracellular signal-regulated kinase; GREM2, Gremlin 2; HIF, hypoxia-inducible factor; HOXD-AS1, HOXD cluster antisense RNA 1; lncRNA, long noncoding RNA; miRNA, microRNA; NAT, normal adjacent tissues; PARP1, poly(ADP-ribose) polymerase 1; PCa, prostate cancer; PGAM1, phosphoglycerate mutase 1; PSMA, prostate-specific membrane antigen; PTPN, protein tyrosine phosphatase nonreceptor; Runx2, runt-related protein 2; TGF-β, transforming growth factor β.

exhibits elevated expression levels in patients with high Gleason score PCa, playing a critical role in regulating the proliferation, migration, and invasion of PCa cells. Notably, miR-153 is secreted by exosomes within the tumor microenvironment, and upon entering peritumoral tissues, it significantly impacts tumor cell growth. Exosomal miRNAs have the potential to predict invasive versus localized metastasis and can distinguish between normal tissue, BPH, and aggressive prostate cancers. Duca *et al.*¹⁴ reported that both hsa-miR-19b-3p and hsa-miR-101-3p were significantly elevated in the bloodstream of PCa patients compared to the control group, and were markedly increased in prostate tumors compared with normal adjacent tissues. Further receiver operating characteristic analysis demonstrated that hsa-miR-19b-3p could reliably differentiate tumor tissues from normal adjacent tissues, whereas hsa-miR-101-3p was effective in distinguishing metastatic prostate cancer from nonmetastatic prostate cancer.¹⁴ Zhai *et al.*¹⁵ utilized reverse transcription-quantitative PCR (RT-qPCR) to evaluate the expression of miR-20b-5p in PCa and BPH tissues. Their findings revealed significantly increased expression levels of miR-20b-5p in PCa, which suppressed the expression of RB1, suggesting that RB1 may serve as a crucial target gene for miR-20b-5p.¹⁵ Exosomal miR-2909 is upregulated in the urine of PCa patients compared to healthy individuals, promoting tumor cell invasion.¹⁶ Additionally, miR-888 has emerged as a novel oncogenic factor in PCa, stimulating migration and proliferation that drive tumor progression. Mouse xenograft studies further confirmed that miR-888 functions as a pro-oncogenic factor, enhancing prostate tumor growth *in vivo*.¹⁷ Moreover, elevated plasma exosomal miR-141-3p expression and reduced miR-125a-5p expression in PCa patients may serve as potential biomarkers for specific tumor traits associated with PCa.¹⁸ These findings suggest that miRNAs in exosomes extracted from PCa patients' bodily fluids hold significant potential as diagnostic markers for PCa and as promising tools to guide prostate biopsy decisions. Nucleic acids and proteins are the primary targets for exosome content detection. Nucleic acid markers such as miR-375, PCA3, TMPRSS2: ERG, and miR-107 are elevated in the exosomes of prostate cancer patients.^{49,50} Biomarkers such as FOLH1, XPO1, SFN, and GDF15 indicate that both receptors and transmembrane proteins have the potential to serve as effective indicators of PCa at the protein level.⁵¹ Prostate-specific membrane antigen (PSMA) and caveolin-1, which are membrane proteins overexpressed in PCa, are integral to tumor growth and contribute significantly to increased tumor aggressiveness.^{52,53} Compared to exosomes from men with BPH, investigations show that the plasma of PCa patients contains more PSMA and caveolin-1 exosomes.¹⁹ Li *et al.*²⁰ reported that a lncRNA assay showed superior diagnostic performance compared to PSA, detecting clinically significant PCa. Thus, in addition to exosomal miRNAs, urinary exosomal lncRNAs also exhibit strong potential for the early diagnosis of PCa. The combination of various exosomal biomarkers in body fluids can enhance diagnostic accuracy, thereby assisting physicians in formulating more effective treatment plans.

Exosomes and the treatment of prostate cancer

Targeted therapy

Exosomes are playing an increasingly significant role in PCa therapy. They can deliver various substances, including proteins and nucleic acids, while effectively crossing biological barriers with minimal immunogenicity, making them highly promising as natural vectors for drug or gene delivery. Currently, ultracentrifugation is the primary method for exosome extraction; however,

it is costly, requires large sample volumes, and has a low yield. Alternative methods, such as exosome sedimentation, immunoaffinity capture, and ultrafiltration, are also available, but further development of efficient and reliable isolation techniques is necessary. Additionally, elucidating the composition and mechanisms of substances within exosomes is essential, as well as establishing methods for obtaining high-purity exosomes and determining appropriate dosages for clinical application.⁵⁴ Current treatment approaches for PCa include endocrine therapy, chemotherapy, radiation therapy, and surgery. While these approaches can substantially delay or suppress disease progression, chemoresistance remains a major challenge, often leading to patient mortality.⁵⁵ Shan *et al.*²¹ demonstrated that exosomes derived from cancer-associated fibroblasts (CAFs) reduce the chemosensitivity of PCa cells and enhance the chemoresistance of drug-resistant cells. They also reported that PCa resistance to taxanes is increased by exosomes from PCa-associated fibroblasts carrying miR-423-5p, which inhibit Gremlin 2 (GREM2) via the transforming growth factor β (TGF- β) pathway.²¹ Interestingly, this mechanism was found to partially increase drug sensitivity *in vivo*. ADT remains the primary treatment for advanced prostate cancer. Zhang *et al.*²² reported that miR-146a-5p expression levels were substantially reduced in exosomes derived from ethanol-treated CAFs (to mimic the castration level of the PCa microenvironment after ADT), potentially accelerating tumor metastasis by regulating the EGFR/ERK pathway and promoting epithelial-mesenchymal transition (EMT). A major challenge in the treatment of CRPC is the resistance of PCa cells to drugs such as docetaxel (DTX). miR-432-5p, originating from CAF exosomes, increases PCa resistance to DTX by suppressing ferroptosis via targeting CHAC1.²³ Additionally, miR-34a in prostate cancer cells can modulate BCL-2 expression, potentially influencing the sensitivity of cancer cells to DTX.²⁴ In DTX-resistant PCa cell lines, lincROR has been shown to be significantly expressed and linked to a poor response to DTX treatment. Mechanistically, targeting the MYH9 protein, exosome-mediated lincROR initiates a β -catenin/HIF1 α positive feedback loop.²⁵ Notably, ZNF667-AS1 was shown to suppress PCa cell growth, inhibit tumor progression in mice, and reduce DTX resistance. Furthermore, increased exogenous expression of ZNF667-AS1 in tumor-derived exosomes interacts with U2AF1 to reduce the expression of TGFBR1, leading to attenuated Treg expansion associated with DTX resistance.²⁶ Moreover, miR-222-3p is elevated in CRPC cells, significantly enhancing cell proliferation, migration, and invasion.²⁷ Gan *et al.*²⁸ demonstrated that miR-375 interferes with the expression of PTPN4, thereby stabilizing phosphorylated STAT3. Compared to plasma exosomes from healthy controls, the level of miR-217 expression was significantly upregulated, while miR-23b-3p expression was significantly downregulated in PCa patients.²⁹ These miRNAs are thought to influence the proliferation and invasion of cancer cells. In the tumor microenvironment (TME), tumor-associated macrophages are essential for mediating intercellular communication. Guan *et al.*³⁰ analyzed microRNA sequences in exosomes derived from macrophages and reported that miR-95 expression in exosomes derived from tumor-associated macrophages was significantly increased, indicating that recipient PCa cells directly take up miR-95. *In vitro* and *in vivo* assays further demonstrated that miR-95 directly interacts with its downstream gene JunB, thereby increasing proliferation, invasion, and EMT in PCa cells. These findings suggest that detecting exosomal miRNAs could provide novel therapeutic strategies and lay the groundwork for developing personalized treatments for PCa patients. However, these studies are still in the experimental stage,

and the role of exosomes in PCa treatment requires further clinical studies with larger cohorts. In recent years, scholars have proposed the innovative concept of “radiolabeled exosomes”, which involves the use of radiation and nuclear medicine technologies to study the distribution of exosomes *in vivo*.⁵⁶ This approach has the potential to visualize responses to PCa therapy, offering clinicians effective tools for the treatment of the disease.

Exosome-mediated drug delivery

Extracellular vesicles can deliver multiple therapeutic molecules to tumor cells, enhancing drug accumulation in tumor tissues and thereby improving therapeutic efficacy while reducing systemic toxicity.^{57,58} PCa cell-derived extracellular vesicles function as efficient delivery vehicles for paclitaxel to their parental cells, facilitating intracellular drug delivery via an endocytic mechanism.⁵⁹ Interestingly, fluorescence lifetime imaging microscopy investigates the interaction attributes of extracellular vesicles (EVs) and living cells.⁶⁰ The study used fluorescence lifetime imaging microscopy to explore how microvesicles and exosomes loaded with the chemotherapeutic agent paclitaxel are taken up by cells, revealing differences in their uptake mechanisms. Exosomes primarily facilitate drug delivery through endocytosis, whereas microvesicles gain access to cells via both direct fusion with the cellular membrane and endocytosis.⁶¹ miR-let-7c has been identified as a tumor suppressor in PCa, and exogenous let-7c therapy inhibits the growth and spread of CRPC by targeting both cancer cells and mesenchymal stem cells.⁶² Exosomes from mesenchymal stem cells could function as a therapeutic delivery system for let-7c to target CRPC.⁶³ Berbamine, derived from the root of *Berberis amurensis*, has demonstrated antitumor activities in various cancers.^{64,65} In PCa, berbamine increased the exosomal levels of let-7 family members and miR-26b, indicating that it may modulate their expression via exosome delivery.⁶⁶ Additionally, exosome-mediated delivery of TGF β R1 kinase inhibitors and TLR7/8 agonists may be a potential treatment option for PCa.⁶⁷ EV-based drug delivery systems not only offer novel strategies to overcome tumor drug resistance but also hold significant potential for broader clinical applications. Despite their promising therapeutic prospects, the clinical translation of EV-based therapies still requires further research and appropriate regulatory frameworks to ensure their safety and efficacy.

Exosomes and the prognosis of prostate cancer

Exosomes, which carry diverse lipids, proteins, and RNAs, play a major role in the survival, angiogenesis, and proliferation of cancer cells, as well as their capacity to evade immune surveillance.⁶⁸ Exosomes are closely linked to the invasion of PCa and the formation of micrometastases. Metastasis is responsible for approximately 50% of PCa-related deaths. The five-year overall survival (OS) rate for distant metastatic prostate cancer (mPCa) is only 31%, indicating a poor prognosis.⁶⁹ Through the miR-361-5p/FOXO1 axis, exosomal lncRNA HOXD-AS1 induces metastasis-associated phenotypes both *in vitro* and *in vivo*, thereby driving PCa metastasis.³¹ TME is essential for cancer metastasis. Podosome development, a crucial element of neovascularization, and cancer metastasis are both significantly influenced by angiogenesis in the TME.⁷⁰ Notably, exosomal PGAM1 may attach to γ -actin, promoting neovascular sprouting and facilitating podosome formation. In the *in vivo* study, exosomal PGAM1 was found to significantly enhance lung metastasis.³² Moreover, hsa-miR-184 has been identified as a promising regulator associated with the proangiogenic effects of PCa exosomes.³³ The TME also facilitates the transport of miR-

NAs by exosomes. One study analyzed the expression of exosomal miR-21 and miR-375, revealing that exosomal miR-21 levels were elevated in PCa patients with high PSA levels and those with invasive prostate cancer.³⁴ Furthermore, heat shock protein family genes are highly expressed in the T cell stress response state, a distinct stress response state.⁷¹ HSPH1, a gene associated with extracellular vesicles and a member of the heat shock protein family, may contribute to T cell stress response state in PCa. Through the IL2-MYC-IL2RA pathway, HSPH1 stimulates the differentiation of conventional T cells, thereby promoting CD8⁺ T cell proliferation and exerting anti-tumor effects.³⁵ Exosomes exhibit differential expression levels across various samples. Cruz-Burgos *et al.*³⁶ identified differences in the expression of miRNAs (miR-140-3p, miR-23b-3p, and miR-150-5p) in tissues and plasma. Moreover, these miRNAs were evaluated in exosomes from PCa cells and plasma samples. Notably, the expression of miR-150-5p was lower in high Gleason score samples compared to control samples. In a hypoxic microenvironment, exosomes from CAFs drive PCa metastasis via the miR-500a-3p/FBXW7/HSF1 pathway.³⁷ Exosomes are also strongly associated with PCa metastasis. Rode *et al.*³⁸ reported the expression profiles of exosomal miRNAs in mPCa cell lines (LNCaP and PC-3), identifying fourteen miRNAs as potential noninvasive biomarkers for mPCa. They confirmed the differential expression of five miRNAs—miR-205-5p, miR-148a-3p, miR-125b-5p, miR-183-5p, and miR-425-5p—in mPCa exosomes.³⁸ Rodríguez *et al.*³⁹ demonstrated that the expression levels of miR-196a-5p and miR-501-3p were both downregulated in PCa. Similarly, miR-1246 was downregulated in PCa tissues and cell lines and released into exosomes.⁴⁰ Notably, high expression of miR-1246 inhibited xenograft tumor growth, promoted tumor cell apoptosis, and reduced cell proliferation, invasion, and migration. Additionally, miR-1246 inhibited the activity of N-cadherin and vimentin, thereby suppressing EMT. Biochemical recurrence is a marker of poor prognosis in patients with intermediate-risk prostate cancer. Kim *et al.*⁴¹ reported that miR-532-5p expression was elevated in biochemical recurrence patients based on RT-PCR analysis. With the inevitable progression of mPCa to CRPC, CRPC represents the terminal stage of the disease, characterized by a median survival of less than two years and resistance to treatments targeting the androgen signaling pathway. In CRPC, biochemical and radiological progression are the primary indicators for diagnosis. High-throughput miRNA sequencing of plasma samples collected from CRPC patients during treatment revealed downregulation of hsa-miR-148a-3p expression.⁴² Furthermore, miR-375 and miR-1290 have been identified as prognostic markers for survival in CRPC patients.⁴³ Huang *et al.*⁴⁴ demonstrated associations between miR-1290, miR-1246, and miR-375 with OS through Cox regression analysis in a cohort of 100 CRPC patients. Higher expression levels of miR-1290 and miR-375 were significantly associated with lower OS in this cohort.⁴⁴ Bone metastasis is the most common, occurring in approximately 90% of patients with mPCa and primarily of the osteoblastic bone-forming type.^{72,73} Notably, exosomal miR-375 from PCa cells specifically targets DIP2C, which activates the Wnt signaling pathway, thereby facilitating osteoblastic metastasis and promoting PCa progression.⁴⁵ Additionally, exosomal miR-1275 from PCa patients enhances osteoblast proliferation by modulating SIRT2/Runx2 signaling.⁴⁶ In summary, detecting the relevant components of miRNAs in exosomes derived from PCa patients can effectively indicate the biological behavior of tumors and provide valuable insights into patient prognosis. These findings are important for guiding the development of treatment strategies for PCa.

Limitations

The clinical application of exosome-based biomarkers in prostate cancer remains limited by heterogeneity in exosome isolation, detection, and normalization methods. In addition, many reported biomarkers have been evaluated in relatively limited cohorts, and their diagnostic, prognostic, and therapeutic value requires further validation in larger, prospective, and clinically diverse populations.

Conclusions and future directions

Through research on prostate cancer-derived exosomes, we have gained new insights into the mechanisms of prostate cancer progression and metastasis from a novel perspective. All cells within tumors and the surrounding microenvironment can secrete exosomes. These exosomes provide valuable information about tumor heterogeneity. As a result, exosomes can serve as diagnostic biomarkers for prostate cancer screening, monitoring progression, assessing treatment response, and predicting survival prognosis. Notably, exosomes exhibit high sensitivity, specificity, and tissue specificity. Their detection is minimally invasive, cost-effective, and provides real-time insights into disease progression. These attributes position exosomes as promising noninvasive biomarkers for detecting tumors in the urinary and male reproductive systems, including PCa, kidney cancer,⁷⁴ and bladder cancer.⁷⁵ Emerging studies have confirmed the involvement of exosomes in the pathogenesis of PCa and highlighted their significant potential in its diagnosis, treatment, and prognosis. However, higher-level evidence is needed to establish the clinical value of this novel biomarker. Currently, exosome-related research is limited by relatively small sample sizes. Future studies should aim to expand both the quantity and diversity of research samples to substantiate the positive roles of these newly identified exosome biomarkers in the early diagnosis, treatment, and prognostic evaluation of PCa. These advancements have the potential to reduce treatment costs and mortality rates among patients.

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Conflict of interest

The authors have no conflicts of interest related to this publication.

Author contributions

Conceptualization (AQ, YY, YZ), literature search and analysis (YX), drafting of the manuscript (AQ, ZL), and critical revision of the manuscript (XL, XH). All authors have approved the final version and publication of the manuscript.

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