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REVIEW

Role of exosomal small RNA in prostate cancer metastasis

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Abstract: Prostate cancer (PCa) is the second most common cancer in men worldwide. When the disease becomes metastatic, limited treatment strategies exist, and metastatic disease prognoses are difficult to predict. Recently, evidence has emerged, which indicates that small RNAs are detectable in patient fluids, and exosomal small RNA ectopic expression is correlated with the development, progression, and metastasis of human PCa; however, the role of small RNAs in PCa is only partially understood. In this review, we discuss the research status regarding circulating exosomal small RNAs and applications using these small RNAs in PCa particularly looking at metastatic disease. Exosomal small RNAs could be used as potential biomarkers for the early diagnosis, micrometastasis detection, and prognosis of PCa.

Keywords: prostate cancer, metastases, ncRNA, exosome

Introduction

Prostate cancer (PCa) is the second most commonly diagnosed cancer and the fifth leading cause of cancer death in men worldwide.[1] PCa is a complex disease, with multiple risk factors involving age, ethnicity, heredity, diets, and hormone levels.

PCa occurs as a localized disease in the early stages, at which time the treatment options include prostatectomy or radiotherapy. If the disease progresses as a recurrence or metastasis, androgen deprivation therapy (ADT) becomes the standard treatment. Unfortunately, patients with recurrent or metastatic PCa will inevitably develop castration-resistant PCa (CRPC), an end-stage metastatic disease, after a period of hormone responsiveness. The standard first-line CRPC treatment is docetaxel, but several newer systemic anticancer therapies that have been shown to improve overall survival are available.[2–4] However, most cancer deaths are due to metastatic disease and are resistant to these therapies. Until now, the mechanisms that lead to metastases remain incompletely understood.

Cancer metastasis is a complex process. When tumor cells become motile and invasive during the epithelial–mesenchymal transition (EMT) period, motile cancer cells can enter the blood, where the cells become trapped in capillary beds distant from the primary tumor site. Circulating tumor cells enter secondary metastatic sites by extravasation into unfamiliar microenvironments. After converting to epithelial phenotypes, tumor cells will proliferate and form macrometastases at the second site. Behind this coherent process, the adaptation between tumor cells and the microenvironments plays a crucial role in metastasis regulation. Initially, tumor cells must overcome the extracellular matrix (ECM) barrier, which requires disruption of endothelial cell phenotypes for intravasation and extravasation. Although cancer cells survive in

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circulation, they cannot complete distant metastatic spread without adaptive modulation.[5] The "metastatic niche model" presented below is based on the "Seed and Soil" hypothesis, which suggests that a suitable conducive microenvironment must evolve for tumor cells to engraft and proliferate at secondary sites.[6–8] This model supports the notion that metastatic cells have preferred terminal organs, such as PCa cells that have a higher risk of bone metastasis.[9,10] From the moment that metastasis occurs, cancer and stromal cells secrete molecules that adapt the environment for metastatic spread. Aside from conventional factors such as cytokines and chemokines, noncoding RNAs (ncRNAs) delivered by exosomes have been recently found to play an important role in communications between tumor cells and stromal cells in the tumor microenvironment (Figure 1).[11–13] In this review, we summarize the roles of exosomal ncRNAs in PCa metastases. For comprehensive information about ncRNA-mediated disease, a global network can be found at the mammalian ncRNA-disease repository (www.rna-society.org/mndr/). Besides, miR2Disease (http://www.mir2disease.org/) is a good resource for retrieving miRNA-associated diseases.

Exosomes and exosomal ncRNAs

Exosomes are 40–100 nm vesicles that contain various molecules, including RNA, proteins, and cytokines, which are derived from several different cell types and are shed into extracellular spaces and body fluids.[14] Different from microvesicles that are directly shed from cell membranes, exosomes are released when multivesicular bodies (MVBs) fuse with cell membranes. MVBs, containing intraluminal vesicles, are generated by the inward budding of clathrin-coated domains in the plasma membrane.[15,16] Exosomes facilitate cell–cell communications and RNA transfer between cells and have been found to be useful in cell signaling studies and can impact biological processes in recipient cells.[17–20]

ncRNAs represent about 98% of all transcriptional outputs in human bodies and are classified by size, small ncRNAs (<200 bp) and long ncRNAs (>200 bp).[21] ncRNAs regulate gene expression using several different mechanisms such as RNA interference, cosuppression, transgene silencing, imprinting, methylation, and possibly position-effect variegation, and transvection, although no proteins are encoded.[22] ncRNAs are divided into several categories: microRNAs (miRNAs), PIWI-interacting RNAs (piRNAs), small nucleolar RNAs, long ncRNAs (lncRNAs), and several other types. The most widely described ncRNAs are miRNAs and lncRNAs.[23] miRNAs are single-stranded RNAs and are ~22 nucleotides in length, which play important roles in regulating gene expression. miRNAs are estimated to regulate translation in more than 60% of the protein-coding genes.

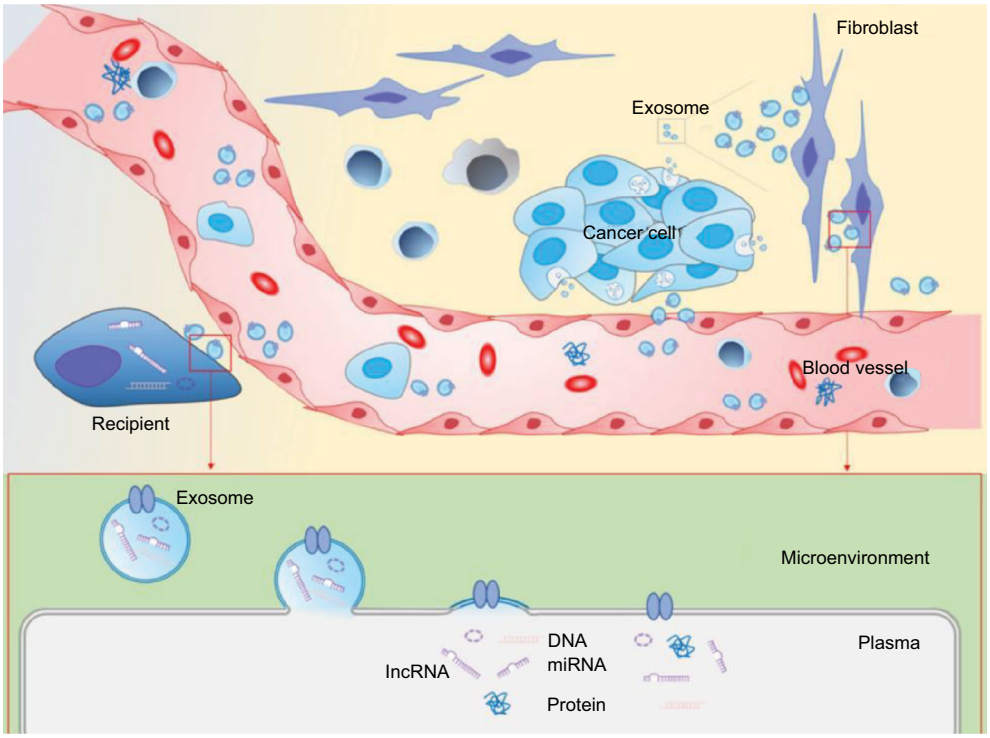

Figure 1 Schematic illustration of the cancer-derived exosome-mediated communication between cancer cell and surrounding or distal recipient.

As is commonly known, the way in which messenger RNAs (mRNAs) are silenced depends on the degree of complementarity between the miRNAs and the 3′-untranslated region (3′-URT) of the target mRNA. When perfect base-paring homology exists between the miRNA and the mRNA, the miRNA will cleave the mRNA with the help of Argonaute. Imperfect binding usually occurs that results in target mRNA regulation by suppressed protein translation.[24]

lncRNAs are RNA molecules more than 200 nucleotides in length. With the development of RNA-sequencing techniques, the discovery of novel RNA species including lncRNAs has rapidly expanded. Although many fewer studies have been performed using lncRNAs compared with that of miRNAs, the significance of lncRNA performance in cancer therapy has gained more attention recently. lncRNAs control transcription, translation, and protein function at multiple levels. Possible lncRNA mechanisms are 1) influencing transcription of protein-coding gene upstream promoter regions to interfere with downstream gene expression, 2) inhibiting RNA polymerase II or mediating chromatin remodeling and histone modifications to affect downstream gene expression, 3) disturbing mRNA splicing by complementary binding with protein-coding pre-mRNAs, 4) producing endogenous siRNAs under control of Dicer, 5) combining with specific proteins to modulate corresponding protein activities, 6) being components of nucleic acid–protein complexes, 7) binding to the specific proteins and changing cellular localization of the proteins, and 8) serving as precursors of small RNAs.[25–27] Because of their functional diversity, ncRNAs are involved in the regulation of a variety of biological processes, especially those of cancer progression and metastasis.

Recently, the discovery of stable miRNAs in bodily fluids introduced new insights into ncRNAs and miRNAs that can lead to new diagnostic approaches using less invasive assays.[28] In addition to being packed into exosomes or microvesicles, circulating miRNAs are also combined delivered with high-density lipoproteins[29] or AGO2 proteins[30] to maintain stability. Gallo et al reported that most detectable circulating miRNAs in serum and saliva were concentrated within exosomes,[31] which suggests that exosomes and exosomal ncRNAs are the primary forms of cellular RNA-based communication. Huang et al performed RNA sequencing to annotate the exosomal RNA species from the plasma of 23 CRPC patients following the guideline previously reported.[32] Among the mapped reads, mature miRNAs were the most common and represented 41.72% of reads, followed by piRNAs at 20.92%, lncRNAs at 20.19%, and mRNAs at 6.52%. Collectively, six other RNA species constituted 10.64% of the mappable sequences.[33] During cancer metastases, exosomes can act as delivery vehicles of circulating ncRNAs and transport them from primary to metastatic cancer sites[11,34,35] and mediate adaptations between cancer and stromal cells. This mechanism is similar to that of primary cancer cell motility, which is modulated by EMT processes or establishment of favorable environments at possible metastatic sites to aid in neoplastic cell survival.[36]

Differently expressed circulating miRNAs in PCa patients

Four miRNAs altered in the serum of transgenic adenocarcinoma of mouse prostate mice – miR-141, miR-298, miR-346, and miR-375 – also showed concordant changes in men with metastatic castration-resistant PCa (mCRPC).[37] Yaman Agaoglu et al found that the differences in miRNA plasma levels between the healthy controls and the patients were highly significant for the miR-21 ($P<0.001$) and -221 ($P<0.001$) but not for the miR-141($P=0.23$).[38] An analysis of 742 miRNAs using plasma-derived circulating microvesicles (cMVs) from 78 PCa patients and 28 healthy individuals identified differentially expressed miRNAs that included upregulation of miR-107, -130b, -141, -2110, -301a, -326, -331-3p, -432, -484, -574-3p, and -625 and downregulation of miR-181a-2. In urine samples, miR-107 and miR-574-3p concentrations were also higher in patients compared with controls.[39] These clinical results suggested that circulating miRNAs can assist in the detection of PCa. Moreover, some miRNAs have been identified that are associated with PCa progression, staging, and outcomes, and these miRNAs could be more useful in clinical practice.

Metastasis-associated circulating miRNAs in PCa patients

The first report to evaluate the utility of circulating miRNAs to distinguish PCa patients with metastasis from those with advanced, but localized disease revealed that miRNA-21, -221, and -141 plasma levels were significantly higher in the metastatic cohort.[38] Circulating miRNAs were also reported to be significantly upregulated in the serum of metastatic PCa patients, and miR-375 was the most prominent and the only miRNA that showed greater serum concentrations in PCa patients with distant metastases compared with that of PCa patients with localized PCa. This study also confirmed that circulating miR-375 and miR-141 correlated with the risk of disease progression.[40] An analysis using plasma samples from 16 PCa patients with metastatic disease and 55 PCa patients with localized disease found 16 miRNAs that were

differently expressed in cMVs. Among these 16 miRNAs, 15 had significantly greater concentrations and one (miR-572) had significantly lower concentrations in PCa patients with metastatic disease compared with those of PCa patients with localized disease. In a subsequent study, cMVs and exosomes were separated in the serum of 47 PCa patients with metastatic disease and 72 PCa patients in remission. This study showed that miR-375 and miR-141 were significantly increased in both the cMVs and the exosomes.[39] Another study demonstrated that miR-375, -141, and -378 expression was significantly upregulated and miR-409-3p expression was significantly downregulated in the serum of CRPC patients compared with patients who had a low risk of developing CRPC.[41] Overall, over 30 differentially expressed circulating miRNAs have been identified. A summary of differentially circulating ncRNAs found in PCa patients with metastatic disease compared with those with localized disease is presented in Table 1. Only miR-375 and miR-141 have higher repetition rates. Some deviations in the compiled data could be due to the different study designs, cohort selections, treatment strategies, methods of sample collection, and the sensitivity and specificity of platforms used.[42]

Table 2 illustrates miRNA and lncRNA targets that regulate the development of PCa metastases and that are involved in signaling pathways. Overall, the mechanisms behind how miRNAs function in PCa metastases have not been substantially studied; however, a few preclinical studies have been reported. miR-375 has been shown to have multiple functions in several different types of cancer. In most cancer cases, miR-375 plays a role in tumor suppression of several cancer types, such as head and neck squamous cell carcinoma,[43,44] esophageal cancer,[45] gastric cancer,[46] pancreatic cancer,[47] and hepatocellular carcinoma.[48,49] However, some studies implicate miR-375 upregulation in the propagation of PCa.[50,51] miR-375 might play a dual role in prostate carcinogenesis.[52] The reason for the antagonistic roles of miR-375 in different study toward PCa could be attributed to PCa heterogeneity. Circulating miR-375 expression is considered a prognostic biomarker for PCa.[33,53] Higher miRNA-375 expression in circulation is the most confirmed miRNA that is related to metastatic PCa.[37,40,41,50,54,55] However, scant information regarding the mechanism of circulating miR-375 in regulating metastatic spread of PCa has been discovered. A couple of studies showed that miR-375 promotes cell growth by targeting Sec23A.[56,57] This was validated by a recent study, which demonstrated that miR-375 exerts its oncogenic effects by targeting CBX7 and thus regulates critical cancer pathways such as the EMT and Wnt/β-catenin signaling pathways.[58] More details on these processes remain to be determined.

miR-200 family including miR-200a, -200b, miR-200c, -141, and -429 was found to be associated with several cancer types. Members of this family directly target the metastasis-promoting protein, WAVE3, to inhibit PCa cell invasion.[59] These miRNAs also target the E-cadherin transcriptional repressors, ZEB1 and ZEB2, and were identified as determining factors in the development of cancer cell epithelial phenotypes.[60–64] Moreover, miR-200b negatively regulates vascular endothelial growth factor (VEGF) signaling by targeting the VEGF and the VEGF receptor and could have therapeutic potential as an angiogenic inhibitor.[65] However, the miR-200 family has been associated with Sec23-mediated inhibition of metastasis-suppressing proteins[66] and adhesion improvements at distant sites to promote EMT and increased colonization.[67] Therefore, the miR-200 family was found to have different roles in various stages of metastasis.[36]

Table 1 ncRNAs proven to be differently expressed in the circulation of prostate cancer patients with metastatic disease compared with those with localized disease

ncRNAs	Sample	Regulation	Standard	References
miR-141, miR-21, miR-221	Plasma	Up	RNU1A	38
miRNA-375 and miRNA-141	Serum	Up	cel-miRNA-39, cel-miRNA-54, cel-miRNA-238	40
miRNA-375, miRNA-200b and miRNA-141	Plasma	Up	cel-miRNA-39	39
miRNA-375, miRNA-378 and miRNA-141	Serum	Up	RNU6B, cel-miRNA-39, cel-miRNA-54, cel-miRNA-238	41
miRNA-409-3p		Down		
miRNA-375, miRNA-141, miRNA-200c, miRNA-152, miRNA-126, miRNA-21, miRNA-151-3p, and miRNA-423-3p	Plasma	Up	miR-30e	55
miRNA-16 and miRNA-205		Down		
miRNA-141	Serum	Up	cel-miRNA-39	76
miRNA-141	Serum	Up	U6 snRNA	77
PCAT18	Plasma	Up	GAPDH	101

Abbreviations: ncRNA, noncoding RNA; PCAT18, prostate cancer-associated noncoding RNA transcript 18.

Table 2 Proven targets and signal pathways of ncRNAs in prostate cancer patients with metastatic disease

ncRNAs	Target	Involved signaling pathways	References
miRNA-375	Sec23A		56
	CBX7	EMT and Wnt/β-catenin signaling pathways	58
miRNA-141	Shp	AR-signaling axis	78
miRNA-200	WAVE3	EMT-signaling pathway	59
	ZEB1 and ZEB2		60
	ZEB1 and SIP1		61
miR-126	Protein		90
miRNA-21	RECK	MMP-related pathways	87
miRNA-152	TGFα		93
miRNA-205	ZEB1 and SIP1	EMT-signaling pathway	61
PCAT18		AR-signaling	101

Abbreviations: AR, androgen receptor; EMT, epithelial–mesenchymal transition; MMP, matrix metalloproteinase; ncRNA, noncoding RNA; PCAT18, prostate cancer-associated noncoding RNA transcript 18.

miR-141, a special member of the miR-200 family, has been reported to be a tumor suppressor in several malignancies, such as gastric cancer,[68,69] pancreatic cancer,[70] breast cancer,[71,72] renal cell carcinoma,[73,74] and hepatocellular carcinoma.[75] Recently, circulating miR-141 was positively upregulated in the blood of metastatic PCa patients.[37–39,41,76,77] miR-141 targeted the small heterodimer partner protein to modulate androgen receptor (AR)-regulated transcriptional activity in AR-responsive LNCaP cells,[78] and AR signaling was closely related to PCa formation,[79] progression,[80] and metastasis.[81] miR-141 inhibits cell migration and invasion by targeting transforming growth factor (TGF)-β2[82] and insulin receptor substrate 2.[83] miR-141 was also reported to regulate the transcriptional coactivator, PDZ-binding motif (TAZ), a transcription cofactor that plays pivotal roles in the EMT.[84]

miR-21 is one of the most widely studied metastasis-related miRNAs, which have been shown to be at significantly higher levels in the blood of PCa patients with metastases compared with those who had localized or advanced disease.[38] This molecule was also shown to promote cancer metastasis by regulating several aspects of the metastatic cascade. miR-21 promotes tumor cell invasion by targeting the tumor suppressor PDCD4, an inhibitor of the urokinase receptor, prometastatic factor.[85] miR-21 also modulates the expression of matrix metalloproteinases (MMPs) by directly targeting the MMP inhibitors, such as PTEN,[86] RECK,[87] and TIMP3[88] to degrade the ECM and promote cancer metastasis. Exosomal miR-21 can also regulate tumor microenvironments by binding to Toll-like receptors (TLRs) in immune cells, which triggers a TLR-mediated prometastatic inflammatory response that can ultimately lead to tumor growth and metastasis.[89]

miR-126 was also found to be upregulated in the plasma of metastatic PCa patients,[55] and miR-126* regulates protein translation and invasion of PCa LNCaP cells.[90] Moreover, miR-126 has a suppressor role in cancer cell invasion through direct repression of a disintegrin and metalloprotease 9 (ADAM9).[91] Another study identified that when miR-126 partnered with another miR-126, the combination repressed mesenchymal stem cell and monocyte recruitment into the tumor stroma, which effectively inhibited tumor cell invasion and metastasis.[92]

miR-152 upregulation in plasma samples from mCRPC patients was confirmed compared with those that had localized PCa.[55] miR-152 could also control PCa cell migration and invasive potential by directly targeting TGFα.[93] In other types of cancer, miR-152 was shown to inhibit non-small-cell lung cancer cell metastasis by targeting neuropilin-1.[94] Elevated levels of circulating miR-221 were detected in PCa patients with metastases.[38] miR-221 promotes the EMT by targeting PTEN in extrahepatic cholangiocarcinoma, which forms a positive feedback loop with the β-catenin/c-Jun signaling pathway[95] and whose inhibition led to reduced cell migration in PCa cells that was partly mediated by Sirtuin 1 (SIRT1) activation.[96] miR-221 also promoted cancer invasion and angiogenesis by targeting TIMP2,[97] TIMP3, and PTEN.[98] miR-205 and miR-409-3p were downregulated in the circulation of metastatic PCa patients, and it was confirmed that miR-409-3p regulated the EMT process.[61,99,100] In summary, circulating miRNAs are present and have diverse roles throughout the entire metastatic process of PCa. In one stage of metastasis, multiple miRNAs have roles in regulating the process.

Metastasis-related circulating lncRNA in PCa

As seen in Table 2, there are many fewer reports about circulating lncRNAs than miRNAs. For many years, studies mainly

focused on differential lncRNA expression in PCa tissues. Recently, significant differential expression of circulating lncRNAs in metastatic PCa compared with localized PCa has been disclosed. Prostate cancer-associated noncoding RNA transcript 18 (PCAT18) was detected in PCa patient plasma, and its expression was shown to be increased as PCa progresses from localized to metastatic disease, which suggests that PCAT18 is a potential biomarker for metastatic PCa. PCAT18 expression was significantly associated with AR signaling, and PCAT18 silencing was shown to inhibit PCa cell proliferation, migration, and invasion: however, the molecular mechanisms behind its actions remain unclear.[101] A few other lncRNAs were reported to be involved with PCa metastatic disease, but the differential expression in the blood of PCa patients with metastatic disease compared with PCa patients with localized disease remains uncovered. The prostate cancer antigen 3 lncRNA (PCA3; also referred to as DD3) was initially found to be significantly overexpressed in more than 95% of primary and metastatic PCa tissue sections.[102] PCA3 can be detected in urine and used as a noninvasive method for PCa diagnoses.[103,104] Moreover, higher PCA3 scores were associated with greater tumor aggressiveness.[105]

Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is the most studied metastatic-associated lncRNA and has been shown to be overexpressed during PCa progression.[106] In early studies, MALAT1 transcript fragments were higher in the plasma of PCa patients compared with that of non-PCa patients.[107] MALAT1 is associated with EMT; loss of MALAT1 results in reduced LPHN2 and ABCA1 levels, which are important factors of EMT.[108] MALAT1 knockdown in PCa cell lines abrogates cell growth, migration, and invasion and induces G0/G1 cell cycle arrest.[109] HOX transcript antisense RNA (HOTAIR) expression increases in PCa cells during growth and invasion.[110] HOTAIR is also connected with both EMT and ECM remodeling. Therefore, the regulation of MMP expression partially mediates HOTAIR functions in cancer metastasis. Moreover, HOTAIR could affect EMT processes by modulating specific EMT-related genes.[111–113] A recent study demonstrated that lncRNA CCAT2 knockdown stimulated EMT by abrogating N-cadherin and vimentin expression and by intensifying E-cadherin expression in PCa.[114]

A multi-institutional high-throughput analysis of PCa tissue samples from 1,008 patients confirmed the prognostic value of measuring lncRNA, SChLAP1 (second chromosome locus associated with prostate-1) levels to detect metastatic progression.[115] SChLAP1 impairs the SNF5-mediated regulation of gene expression and genomic binding to coordinate cancer cell invasion.[116] A study recently identified the lncRNA, Linc00963, which regulates the epidermal growth factor receptor (EGFR) signaling pathway to promote PCa cell growth, migration, and invasion.[117]

Ongoing PCa clinical trials

With the accumulating evidence from preclinical studies, clinical trials have recently been launched. The Medical College of Wisconsin (Milwaukee, Wisconsin) sponsored a study in June 2017 that is recruiting PCa patients (estimated to 60), with aims to identify exosomal miRNAs that can predict responses to ADT. Patients who were intermediate to high risk at diagnosis, those who were treated but now have recurrent disease, and those with metastatic disease are recruited to the study. Blood samples will be collected at the time of pretreatment, 3 months' posttreatment, and during disease progression. Exosomal RNA markers that predict responses to ADT will be validated.

Another observational study in 2016 sponsored by the Assuta Medical Center (Israel) and enrolling as many as 120 PCa patients is aiming to find correlations among circulating miRNAs associated with PCa metastases to bones and lymph nodes using PET imaging.

In another study sponsored by the Hospital of Ghent University (Belgium), blood from PCa patients with lymph node metastases will be collected to examine the role of circulating miRNAs as a biomarker to diagnose and predict relapse-free survival rates. The sample size is expected to be 330. None of the clinical trials mentioned have posted results, which we eagerly await.

Conclusion and prospects

The identification of circulating ncRNA provides novel biomarkers and therapeutic targets for mCRPC. Several molecules have been proven to serve as predictors of PCa metastases. Exosomes protect the stability of circulating ncRNAs in body fluids and can be easily quantified. Exosomal ncRNA expression is related to cancer progression and the microenvironments during cancer metastasis. It is well accepted that the communication between cancer cells and the extracellular environments begin in the early stage of metastasis before the cancer cells move to their colonized sites. Therefore, more studies have shown that circulating ncRNAs are associated with the PCa stages.[101,118,119] The results of these studies suggest that circulating ncRNAs could be promising as biomarkers to predict cancer metastases.

Further understanding of ncRNAs has provided novel insights into PCa therapeutics. In the last few years, ncRNA-based cancer therapeutics inspire the interest of researchers.[120–122] However, the methods needed to deliver miRNA mimics or inhibitors to target cells steadily and effectively remain a crucial obstacle. Exosomes have been studied as vehicle transporting molecules that can deliver genetic materials to target sites with high efficiency.[123,124] Ohno et al performed a study using exosomes to deliver let-7a to EGFR-expressing breast cancer tissues.[125] Exosomal ncRNAs for clinical use require more research to resolve problems, such as enhancing exosome production and reducing immunogenicity. Emerging evidence suggests that exosomal ncRNA could eventually play an essential role in metastatic PCa treatment.

In summary, abundant research on exosomal miRNAs is present, while much less evidence exists that determines if lncRNAs may play an essential role in PCa metastases. With new technologies evolving at a rapid pace, lncRNA studies will overcome limitations and more promising lncRNAs will be discovered. However, in the field of ncRNAs, many challenges and opportunities still exist.

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Disclosure

The authors report no conflicts of interest in this work.

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