Non-coding RNA Research 9 (2024) 1351–1362

Contents lists available at ScienceDirect

Non-coding RNA Research

journal homepage: www.keaipublishing.com/en/journals/non-coding-rna-research

Review Article

Current landscape of exosomal non-coding RNAs in prostate cancer: Modulators and biomarkers

Yongxing Li [a,b,c,1], Xiaoqi Tang [a,1], Binpan Wang [a], Ming Chen [a,**], Ji Zheng [b,c,d,***], Kai Chang [a,d,*]

[a] Department of Clinical Laboratory Medicine, Southwest Hospital, Army Medical University (Third Military Medical University), Chongqing, 400038, PR China
[b] Department of Urology, Urologic Surgery Center, Xinqiao Hospital, Army Medical University (Third Military Medical University), Chongqing, 400037, PR China
[c] School of Medicine, Chongqing University, Chongqing, 400030, PR China
[d] State Key Laboratory of Trauma and Chemical Poisoning, Army Medical University (Third Military Medical University), Chongqing, 400038, PR China

ARTICLE INFO

Keywords:
Biomarkers
Exosomes
Modulators
Non-coding RNAs
Prostate cancer

ABSTRACT

Prostate cancer (PCa) has the highest frequency of diagnosis among solid tumors and ranks second as the primary cause of cancer-related deaths. Non-coding RNAs (ncRNAs), such as microRNAs, long non-coding RNAs and circular RNAs, frequently exhibit dysregulation and substantially impact the biological behavior of PCa. Compared with circulating ncRNAs, ncRNAs loaded into exosomes are more stable because of protection by the lipid bilayer. Furthermore, exosomal ncRNAs facilitate the intercellular transfer of molecules and information. Increasing evidence suggests that exosomal ncRNAs hold promising potential in the progression, diagnosis and prognosis of PCa. This review aims to discuss the functions of exosomal ncRNAs in PCa, evaluate their possible applications as clinical biomarkers and therapeutic targets, and provide a comprehensive overview of the ncRNAs regulatory network in PCa. We also identified ncRNAs that can be utilized as biomarkers for diagnosis, staging, grading and prognosis assessment in PCa. This review offers researchers a fresh perspective on the functions of exosomal ncRNAs in PCa and provides additional options for its diagnosis, progression monitoring, and prognostic prediction.

1. Introduction

Prostate cancer (PCa) has the highest diagnostic rate among male malignancies. Moreover, it ranks second among the leading causes of cancer-associated mortality in the United States [1–3]. Globally, approximately 10 million men have been diagnosed with PCa, and the incidence of metastatic PCa is increasing, leading to over 3.8 million deaths annually [4–6]. By 2040, this number is estimated to be at least twice as high as it is today [7,8]. Since the survival rate of PCa is strongly linked to early diagnosis [9], prostate-specific antigen (PSA) is used for mass screening of suspected patients. However, due to the non-cancer specificity, PSA often leads to unnecessary overdiagnosis and treatment [10]. Given the significant burden of PCa, it is crucial to explore its evolutionary mechanisms and identify potential diagnostic biomarkers and therapeutic tools.

After reticular cells were discovered to secrete vesicles containing biomolecules outside the cell [11], exosomes have emerged as the shining stars of liquid biopsies, displaying profound potential in the realm of cancer diagnosis and treatment. Once considered mere cellular waste bins, exosomes are now recognized as vital vehicles for transporting specific molecules between cells [11]. Exosomes comprise diverse types of biomolecules, including nucleic acids, proteins, lipids, sugars and metabolites [12]. Furthermore, non-coding RNAs (ncRNAs) contained within exosomes, are enriched and more stable than circulating ncRNAs because of the protection provided by the lipid bilayer [13,14]. These exosomal ncRNAs have been found to modulate multiple

* Corresponding author. Department of Clinical Laboratory Medicine, Southwest Hospital, Army Medical University (Third Military Medical University), Chongqing, 400038, PR China.
** Corresponding author.
*** Corresponding author. Department of Urology, Urologic Surgery Center, Xinqiao Hospital, Army Medical University (Third Military Medical University), Chongqing, 400037, PR China.
E-mail addresses: chming1971@126.com (M. Chen), jizheng023@aliyun.com (J. Zheng), changkai0203@tmmu.edu.cn (K. Chang).
[1] Y.L. and X.T. contributed equally to this work.

https://doi.org/10.1016/j.ncrna.2024.07.003
Received 29 February 2024; Received in revised form 12 June 2024; Accepted 18 July 2024
Available online 20 July 2024

cellular processes in malignancies by regulating gene expression [15–17]. In addition, molecular and cellular biological studies of PCa have emphasized the key players in its progression [18,19]. Owing to their unique advantages and functions, exosomal ncRNAs serve as invaluable resources for gaining novel insights into PCa development and potential guides for its diagnosis and treatment.

In this review, we present a brief overview of exosomes and their components. Moreover, we emphasize the modulatory functions of exosomal ncRNAs in the initiation, growth, progression, and therapeutic resistance of PCa, with attention to their possible role as promising biomarkers. We also explore the clinical utilities of exosomal ncRNAs in PCa.

2. Exosomes

Exosomes are the most extensively investigated subset among extracellular vesicles (EVs), varying in size from 30 to 150 nm. They are produced by both eukaryotic cells and prokaryotic cells and can be found in all body fluids [20,21]. These vesicles are generated via an endosomal degradation pathway and cargo inside, on or outside cell can enter exosomes, supporting the essential function of exosomes in intercellular communication [20,22]. While the selective packaging mechanism of exosomes is still unknown, it has been demonstrated that exosomes from different sources or the same cells under different conditions carry a unique content profile [23]. This profile reflects the constituents and current status of the source and may indicate a modulatory selective packaging. Therefore, exosomes have demonstrated potential as modulators and biomarkers of various diseases.

Exosomes contain diverse components including proteins, lipids, nucleic acids, metabolites and small molecules. Proteins, partly originating from the cell membrane, endosomal membrane and cytoskeletal components [24], have been reported to regulate cancer progression [25,26] and serve as biomarkers for diagnostic and prognostic purposes [27,28]. Exosomal lipids are primarily located in the exosomal membrane and play a major role in exosomal formation and homeostasis in recipient cells [27]. They have also been found to modulate cancer and aid diagnosis because of their unique profiles [29–32]. In addition, exosomes also contain nucleic acids such as DNAs and RNAs. It has been demonstrated that the number of DNAs with more bases is relatively higher in larger exosomes than in smaller exosomes [33]. This may indicate that small nucleotides are the most nucleic acids in exosomes. The ncRNAs consisting of dozens to over 200 nucleotides constitute over 98 % of the genome and are abundant in exosomes due to their short length [34]. They regulate gene expression by interacting with mRNAs, remodeling chromatin and cooperating with other biomolecules, thus constructing multiple regulatory networks that modulate the levels of a variety of fundamental protein effectors [35]. The relative abundance and function of ncRNAs in exosomes make them the principal players in cancer modulation [15–17].

The ncRNAs encompass various types of RNA molecules, including microRNAs (miRNAs), long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs) [36]. MiRNAs, serving as short ncRNAs of roughly 22 nucleotides in length, are also the most common ncRNA type transported by exosomes and function by engaging in interactions with mRNAs [37]. LncRNAs are longer than 200 nucleotides and exhibit extensive functional diversity. They can guide chromatin-modifying complexes to target gene promoters and affect transcriptional regulation, as well as bind to miRNAs to modulate molecular functions [38]. CircRNAs are more than 200 nucleotides in length like lncRNAs and are protected from exonuclease degradation due to the closed circular structures and the absence of polyadenylated tail [39]. Therefore, circRNAs in mammalian cells have a longer half-life that is approximately 2.4 times longer than linear RNAs [40] and exosomes exhibit a higher proportion of circRNAs to linear RNAs, with a ratio that is approximately 6 times higher than in cells [41]. Furthermore, circRNAs act as sponges and scaffolds for specific proteins and can be translated to perform specific functions in cancer [17].

Table 1
Molecular mechanisms of exosomal ncRNAs in modulation of prostate cancer.

Process	Types	ncRNAs	Signaling Pathways and Targets
Initiation	miRNAs	miR-27a-3p [48], miR-21 [51–54,121] and let-7b [55]	VEGF [49,56,57], PTEN/AKT [54] and PTEN/ERK [54] pathway
	lncRNAs	/	/
	circRNAs	circRNA HIPK3 [150]	BMI-1 [151]
Growth	miRNAs	miR-183 [65], miR-217 [70], miR-23b-3p [70], miR-143 [141], miR-205 [74], miR-95 [77], miR-153 [85], miR-99b-5p [61], miR-888 cluster [88], miR-1246 [98], miR-26a [99], miR-424 [104], miR-31 [121] and miR-145 [121]	PI3K/AKT [62,63,78,79], NF-κB [62,64], Rho [75,76], STAT3 [86,87,105], TGF-β and mTOR [100] pathway; EZH2 [89]
	lncRNAs	MYU [135], lncAY927529 [139] and PCSEAT [141]	NF-κB [140] and PI3K/AKT [136] pathway; c-Myc [135]
	circRNAs	circRNA HIPK3 [150], circ_0044516 [154] and circ-XIAP [161]	Wnt/β-catenin pathway [155]; BMI-1 [151] and TPD52 [161]
Progression	miRNAs	miR-27a-3p [117], miR-99b-5p [61], miR-183 [65], miR-217 [70], miR-23b-3p [70], miR-143 [141], miR-205 [74], miR-95 [77], miR-153 [85], miR-146a-5p [94], miR-26a [99,117], miR-1246 [98], miR-888 cluster [88], miR-125b [101], miR-130b [101], miR-141-3p [108], miR-155 [101], let-7b [55], miR-424 [104], miR-375 [110], miR-940 [113], miR-1275 [116], miR-92a-1-5p [119], miR-31 [121], miR-145 [121] and miR-21 [55,121]	PI3K/AKT [98,103,120,142], NF-κB [118], Rho [114,115], STAT3 [86,87,105,107], TGF-β [120], EGFR [94,98], mTOR [100], Lats2/YAP [101], MAPK [108], MEK/ERK [120] and Wnt/β-catenin [142] pathway; EZH2 [89], p53 [127], PDCD4 [101], RUNX2 [111,116,117] and FAM134A [113]
	lncRNAs	MYU [135], lncAY927529 [139], PCSEAT [141], HOXD-AS1 [143] and NEAT1 [145]	NF-κB [140], PI3K/AKT [136] and Wnt/β-catenin [142] pathways; c-Myc [135], FOXM1 [143] and PTBP2/SFPQ complex [145]
	circRNAs	circRNA HIPK3 [150], circ_0044516 [154], circ_0081234 [157] and circ-XIAP [161]	Wnt/β-catenin [155] and MAPK [158] pathway; BMI-1 [151] and TPD52 [161]
Therapy resistance	miRNAs	miR-31 [121], miR-145 [121], miR-21 [121], miR-27a [127], miR-423-5p [130] and miR-34a [131,132]	STAT3 [129], TGF-β [130], NF-κB [133] and PI3K/AKT [134] pathway
	lncRNAs	LINC01213 [148]	Wnt/β-catenin pathway [148]
	circRNAs	circ-XIAP [150]	TPD52 [161]

3. Exosomal ncRNAs as modulators in PCa

Exosomes affect initiation, growth, development and treatment of cancer by facilitating cellular communication [42]. There is growing evidence indicating that exosomal ncRNAs are the major contributors to these effects. Exosomal ncRNAs can influence the levels of downstream target mRNAs, genes or proteins, altering various signaling pathways (Table 1). Subsequently, they trigger a range of physiological and

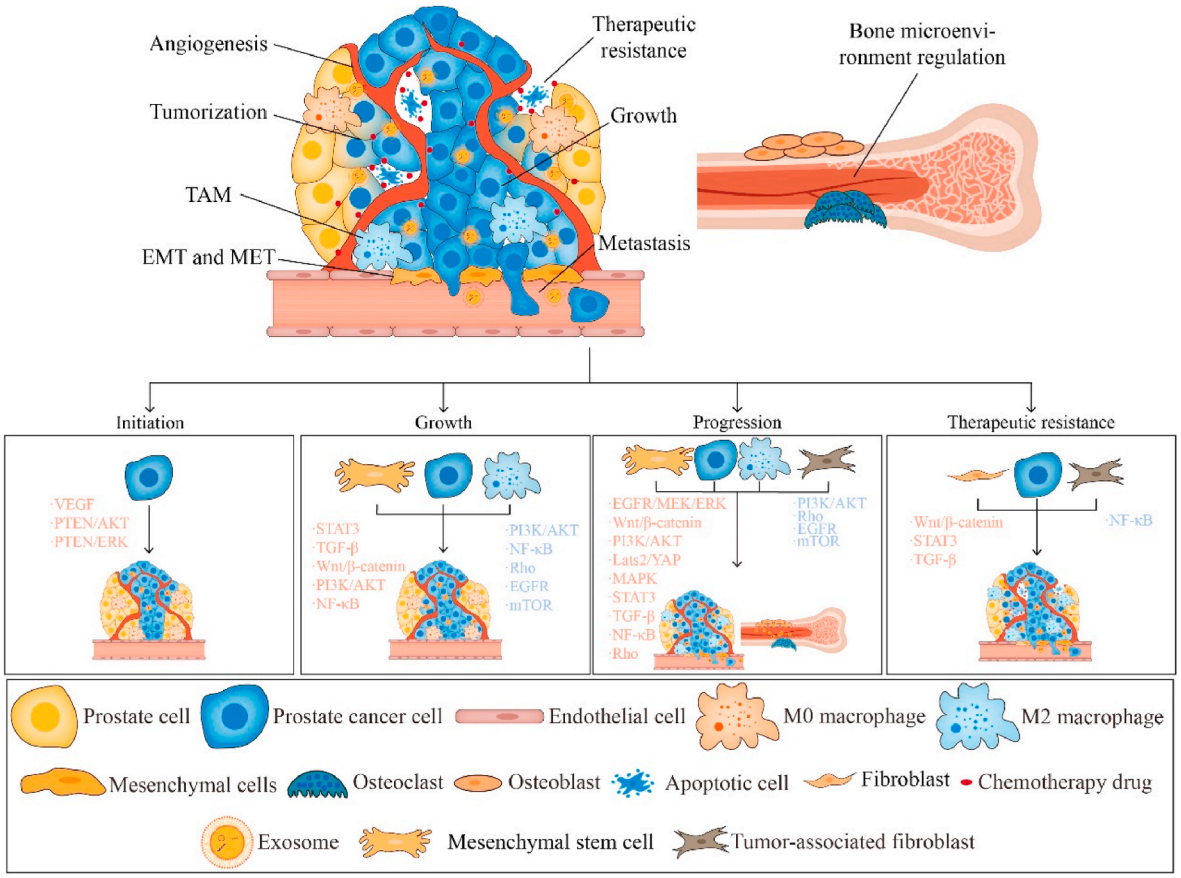

Fig. 1. The modulatory mechanisms of exosomal ncRNAs in PCa. Exosomes derived from diverse cell types transport non-coding RNAs, which in turn modulate the expression of downstream genes, target mRNAs or proteins and alter various signaling pathways. The exosomal ncRNAs trigger a cascade of physiological and pathological events, encompassing angiogenesis, proliferation, apoptosis, migration, invasion, phenotypic transformation, bone microenvironment regulation and therapeutic resistance. Ultimately, these processes affect the occurrence, growth, development and treatment of PCa.

pathological processes, including angiogenesis, proliferation, apoptosis, migration, invasion, phenotypic transformation, bone microenvironment regulation, and therapy resistance (Fig. 1). Therefore, comprehending the role of exosomal ncRNAs could offer a valuable perspective on PCa.

3.1. Exosomal miRNAs in PCa

3.1.1. Exosomal miRNAs in PCa initiation

The first step in cancer development is initiation, in which angiogenesis provides oxygen and nutrients and eliminates metabolic waste and carbon dioxide from tumor cells [43]. Angiogenesis, which is the neovascularization from the original ones, is typically activated transiently in response to various stimuli, including wound healing and the female reproductive cycle [44]. However, the angiogenic switch is always activated in cancer to support the growth of cancer cells. Without the support of angiogenesis, the cancer cells would only reside within 100 μm of capillary blood vessels and could not expand [45]. Angiogenesis is regulated by several growth factors and cytokines, such as vascular endothelial growth factor (VEGF) and hypoxia-inducible factor (HIF)-1α [15]. Tumor-derived exosomes can regulate angiogenesis through proangiogenic biomolecules, which induce or inhibit angiogenesis by modulating angiogenic signaling pathways in endothelial cells [46,47].

Exosomal miRNAs are significant modulators of angiogenesis in PCa, involving multiple signaling pathways dominated by VEGF. Exosomal miR-27a-3p is overexpressed in the PC-3 PCa cell line, which induces angiogenesis by enhancing endothelial tube formation [48]. In the proangiogenic process, miR-27a-3p directly targets tissue factor pathway inhibitor (TFPI), inhibits the expression of TFPIα, reduces the phosphorylation of VEGFR2 at residue K951 [49], and then restrains endothelial cell migration [50]. Therefore, miR-27a-3p may induce angiogenesis through the miR-27a-3p/TFPI/VEGF pathway. Additionally, the HIF-1α/VEGF pathway is another common regulatory target. Exosomal miR-21 is upregulated in patients with PCa and DU145 PCa cell line [51–54]. It targets phosphatase and tensin homolog deleted on chromosome ten (PTEN), activates AKT and extracellular regulated kinases (ERK) 1/2, upregulates HIF-1α and VEGF [54], and promotes angiogenesis via HIF-1α/VEGF pathway. Similarly, exosomal let-7b is overexpressed in PC-3 cell-derived exosomes, increased in recipient cells, and promotes tube-like structure formation, which is an essential step during neoangiogenesis in human umbilical vein endothelial cells (HUVEC) [55]. Moreover, let-7b is a hypoxia-responsive miRNA that modulates the expression of VEGF by targeting argonaute 1 (AGO1) [56,57], indicating that the HIF-1α/let-7b/AGO1/VEGF pathway might be the potential mechanism of angiogenesis in PCa. In conclusion, exosomal miRNAs engage in PCa angiogenesis through various signaling pathways dominated by VEGF.

3.1.2. Exosomal miRNAs in PCa growth

With sustained angiogenesis, the tumor acquires sufficient support for growth by regulating cell proliferation and apoptosis. Cell proliferation refers to the controlled growth and division of cells, leading to the generation of new daughter cells and an overall increase in cell population. Apoptosis is an automatic and orderly cell death program that is crucial for cell consumption. Thus, cell proliferation and apoptosis are essential processes in tumor growth and correlate with a rise in the number of malignant cells [45]. These crucial cellular processes are

regulated by various physical and chemical signals. Exosomal miRNAs have been reported to modulate cell proliferation and apoptosis in various cancers, including colorectal [58], gastric [59] and ovarian [60] cancers.

Exosomal miRNAs are involved in modulating cell proliferation as either tumor promoters or suppressors through a series of signaling pathways in PCa. One such tumor suppressor is miR-99b-5p, which is upregulated in exosomes obtained from human bone marrow mesenchymal stem cells (hBMSCs). This elevation significantly inhibited PCa growth *in vivo* and *in vitro* by downregulating insulin-like growth factor-1 receptor (IGF1R) [61]. IGF1R mediates the phosphoinositide 3-kinase (PI3K)/AKT [62,63] and nuclear factor-kappaB (NF-κB) pathways [62], promoting cell proliferation in PCa [62,64]. Another miRNA, miR-183, is upregulated in LNCaP and PC-3 cell-derived exosomes and enhances cell proliferation by downregulating tropomyosin1 (TPM1) [65], which acts as a tumor suppressor in PCa [66,67]. The underlying mechanism of TPM1 in PCa requires further investigation, but the TPM1/mitogen-activated protein kinase kinase (MEK)/ERK pathway and TPM1/NF-κB pathway in colorectal cancer [68] and osteosarcoma [69] may offer possible pathways by which TPM1 functions in PCa.

The modulation of apoptosis by exosomal miRNAs in PCa involves multiple pathways. Exosomal miR-217 is significantly upregulated in the serum of patients with PCa and acts as an oncogenic factor by inhibiting apoptosis, whereas miR-23b-3p is significantly downregulated and acts as a pro-apoptotic factor [70]. However, how miR-217 and miR-23b-3p function in PCa remains unexplored. Notably, miR-217 has oncogenic and anti-tumor effects. MiR-217 significantly promotes apoptosis in chemotherapy-treated PC-3 cells by regulating polo-like kinase 1 (PLK1) and protein tyrosine kinase 2 (PTK2) expression [71]. Other studies have suggested several potential mechanisms, including PLK1/androgen receptor (AR) [72] and PTK2/PI3K/AKT [73] pathways. The dual roles of miR-217 on apoptosis were observed in PC-3 cells, which excluded the possibility of cell line diversity and suggested that the effect of chemotherapy may be the underlying reason. After chemotherapy, intracellular molecules in PC-3 cells may alter, resulting in a reduction in the levels of the miR-217 initial target and an elevation of new targets such as PLK1 and PTK2, or the activation of other complicated mechanisms. This suggests that chemotherapy may trigger the conversion of biomolecules from pro-cancer molecules to anti-cancer molecules.

MiRNAs in exosomes derived from other non-cancerous cells also regulate apoptosis. For instance, hBMSCs-derived exosomes overexpressing miR-205 promote apoptosis *in vivo* and tumor growth *in vitro* by suppressing rhophilin-2 (RHPN2) [74]. By targeting RHPN2, miR-205 indirectly regulates apoptosis via the Rho pathway [75,76]. MiR-95, which is significantly increased in tumor-associated macrophages (TAMs)-derived exosomes, directly targets JunB, thereby inhibiting PCa cell apoptosis [77]. JunB is functionally relevant for increased proliferation and decreased senescence in PCa through interaction with PI3K/AKT pathway [78,79]. Overall, exosomal miRNAs primarily modulate PCa growth via PI3K/AKT, AR and Rho pathways.

3.1.3. Exosomal miRNAs in PCa progression

PCa undergo certain changes as they progress, where cancer cells become more aggressive, non-cancerous cells change their phenotype, and the tumor microenvironment is remodeled. These characteristics enable tumors to alter their microenvironment and grow in distant organs, thereby promoting their survival and development. Invasion and migration increase cell mobility, allowing tumor cells to penetrate the vascular matrix. Recent studies on the new hallmarks of cancer have shown that phenotypic transformation is a crucial factor in neoplastic development [43]. Additionally, the “seed and soil” theory suggests that the emergence of a bone pre-metastasis niche creates favorable conditions for PCa metastasis [80].

Cumulative evidence has revealed that exosomes have emerged as a novel messaging system in organisms, mediating cell-cell and inter-organ communication in tumor progression. Specifically, biologically functional molecules inside exosomes are transferred to recipient cells, facilitating tumor progression by influencing invasion [81], migration [82], phenotypic transformation [83] and bone microenvironment regulation [84].

Cell invasion and migration are hallmark features of aggressive cancer and are significantly influenced by exosomes, particularly exosomal miRNAs. Exosomes facilitate the detachment of tumor cells in situ and their transport to other sites via the bloodstream or lymphatic system [11]. In PCa, exosomal miRNAs have been identified as oncogenic factors that promote cell invasion and migration through multiple pathways. For instance, in the DU145 and PC3 cell lines with high Gleason score (GS $\geq$ 7), miR-153 is overexpressed and transferred through exosomes, promoting cell invasion and migration by regulating kruppel-like factor 5 (KLF5) [85]. KLF5 is deleted and plays a suppressor role by inhibiting the IGF1/signal transducer and activator of the transcription 3 (STAT3) pathway in PCa [86,87]. Exosomal miR-888 and its cluster members are enriched in PC3-ML cells. MiR-888 inhibits KLF5, retinoblastoma-like 1 (RBL1), tissue inhibitor of metalloproteinase 2 (TIMP2) and SMAD4 levels and enhances cell migration and invasion *in vitro* [88]. KLF5 is also a target of exosomal miR-153 [87]. RBL1 interferes with the enhancer of zeste homolog 2 (EZH2) and is involved in oncogenic processes [89]. TIMP2 inhibits cell migration, invasion and cancer cell-mediated tissue remodeling [90], possibly through the PI3K/AKT pathway [91]. SMAD4 regulates cell invasion and motility in PCa [92], likely through the SMAD4/TGF-β pathway [93]. Overall, low levels of KLF5, RBL1, SMAD4, and TIMP2 levels are associated with PCa progression.

Exosomal miRNAs also act as suppressors of cell invasion and migration. Cancer-associated fibroblasts (CAFs) also contribute to PCa progression. CAFs-derived exosomes contain miR-146a-5p, which is taken up by LNCaP and DU145 cells and inhibits epidermal growth factor receptor (EGFR)/ERK pathway [94]. This inhibition results in a decrease in cell migration and invasion of PCa [95]. In addition, EGFR is related to biochemical relapse and high GS in PCa [96]. Therefore, exosomal miRNAs modulate cell invasion and migration in PCa through various pathways, including the IGF/STAT3, RBL1/EZH2, TGF-β, PI3K/AKT and EGFR/ERK pathways.

Moreover, exosomal miRNAs are associated with cellular phenotypic transformations that enhance PCa cell aggressiveness. Epithelial-mesenchymal transition (EMT) is a well-known phenotypic transformation and a conserved developmental program controlled by several signaling pathways. It confers metastatic properties and enhances cancer aggressiveness by regulating cell activity, invasion and apoptosis [97].

Exosomal miRNAs are also involved in PCa EMT. The miR-1246 selectively is secreted into exosomes in PCa. It targets EMT-related genes, inhibits EMT, and regulates other cellular processes via the EGFR and PI3K/AKT pathways [98]. Likewise, Exosomal miR-26a is increased in LNCaP cells and significantly downregulates the expression of EMT-related factors in recipient cells [99] by regulating the la-related proteins 1 (LARP1)/mechanistic target of rapamycin (mTOR) pathway [100].

Other phenotypic transformations such as mesenchymal-epithelial transition (MET) and neoplastic transformations also occur in the tumor microenvironment. Co-culture with C4–2B and PC-3 cell-conditioned media induces phenotypic transformation in stem cells, resulting in the formation of prostate-like neoplastic lesions. This transformation is facilitated by exosomes, which upregulate oncogenic factors (miR-125b, miR-130b, and miR-155) and downregulate tumor suppressors (large tumor suppressor homolog 2 (LATS2) and programmed cell death protein 4 (PDCD4)) [101]. The LATS2/yes associated protein (YAP) pathway is critical for tissue homeostasis in PCa [102], and the PI3K/AKT pathway is associated with the expression of PDCD4 [103]. Additionally, exosomal miRNAs are involved in the acquisition of stem cell-like and tumorigenic properties in prostate epithelial cells. In

patients with metastatic PCa, there is a higher frequency of circulating miR-424-positive exosomes compared to those with primary tumors and benign prostatic hyperplasia (BPH). MiR-424-loaded exosomes promote stem cell-like properties and tumor initiation, contributing to tumorigenesis in recipient cells [104]. Meanwhile, miR-424 promotes tumorigenic traits via the miR-424/constitutive photomorphogenic 1 (COP1)/STAT3 axis [105].

Phenotypic transformation is also present in the immune system, not only in the mesenchymal and epithelial cells. Overexpressed let-7b in PC-3 cell-derived exosomes can be transferred to THP-1 monocytes, inducing TAM-like polarization [55], which facilitates tumor cell growth [106]. These effects of let-7b are attributed to the suppressor of cytokine signaling 1 (SOCS1)/STAT3 pathway [107]. To conclude, exosomal miRNAs modulate the transformation of cell phenotypes and enhance malignant activity through the EGFR, PI3K/AKT, LARP1/mTOR, Lats2/YAP, and STAT3 pathways.

PCa frequently results in the development of bone metastasis. Exosomes are essential in the preparation of bone pre-metastatic niches. They contain miRNAs that stimulate the formation of a metastatic microenvironment. Exosomal miR-141-3p is overexpressed in MDA PCa 2b cells. It can enter osteoblasts and stimulate their activity. This can lead to bone metastasis and osteogenic damage in PCa. The underlying mechanism of miR-141-3p involves the inhibition of deletion of liver cancer-1 (DLC1) and the activation of the mitogen-activated protein kinase (MAPK) pathway [108]. DLC1 modulates the Rho pathway and suppresses the invasion of highly metastatic PCa cells [109]. Similarly, exosomal miR-375 is identified to promote osteoblast activity [110] via the miR-375/runt-related transcription factor 2 (RUNX2) pathway [111]. RUNX2 is a major modulator of osteoblast activity and related to the metastatic traits of C4–2B cells [112]. In addition, C4–2B cell-derived exosomal miR-940 enhances osteoblastic differentiation in human mesenchymal stem cells by the modulation of Rho GTPase-activating protein 1 (ARHGAP1) and family with sequence similarity 134 member A (FAM134A) [113]. ARHGAP1 is a potential tumor suppressor that mediates osteoblastic differentiation via the Rho pathway [114,115], whereas FAM134A is an oncogenic factor in tumor metastasis, and its physiological function in osteogenesis remains unclear [113]. The transfer of miR-1275 from PC-3 cells to osteoblasts via exosomes significantly enhances osteoblast proliferation by inhibiting sirtuin 2 (SIRT2) and increasing RUNX2 expression [116]. Collectively, exosomal miRNAs have a critical function in PCa bone metastasis.

In addition to osteoblastic lesions, exosomal ncRNAs have been implicated in osteolytic loss. RM1-BM PCa cell-derived exosomes show increased expression of miR-26a-5p, miR-27a-3p and miR-30e-5p. These miRNAs suppress osteogenesis and osteoblast differentiation [117]. The miR-26a-5p targets bone morphogenetic protein 2 (BMP-2), which was reported to activate NF-κB mediated BMP-2-SMAD signaling cascade [118]. Both miR-26a-5p and miR-27a-3p can rejuvenate the level of t RUNX2 [117]. Exosomes derived from PCa cells regulate bone homeostasis, leading to osteoclastic lesions and the promotion of bone tumor growth. MiR-92a-1-5p is overexpressed in MDA PCa 2b cell exosomes and transferred to osteoclasts, promoting osteoclast differentiation through regulating collagen type I alpha 1 (COL1A1) [119]. COL1A1 might be regulated by TGF-β pathway, EGFR/MEK/ERK pathway and PI3K/AKT pathway [120], which implies the involvement of these pathways in the regulation of osteoclastic lesions.

3.1.4. Exosomal miRNAs in PCa therapy resistance

Therapy resistance inevitably presents a complex challenge in PCa, including resistance to androgen deprivation therapy (ADT) and chemotherapy. ADT is the recommended primary therapy for PCa and can improve patient prognosis to a certain extent. However, almost all androgen-sensitive PCa finally becomes androgen-resistant, leading to castration-resistant PCa (CRPC) that can metastasize to distant organs. Exosomes are pivotal in modulating therapy resistance and promoting PCa progression by conveying anti- and pro-tumor signals [27]. Consequently, exosomes can positively or negatively impact therapy resistance by delivering their cargo, indirectly affecting treatment and prognosis.

Mesenchymal-like PCa cells (Mes-PCa)-derived exosomes are involved in promoting mesenchymal characteristics in recipient cells, resulting in resistance to enzalutamide. Genetic analysis of the recipient cells revealed the downregulation of AR and AR-regulated genes, which may be associated with miR-31, miR-145 and miR-21. Mes-PCa-derived exosomes deliver these miRNAs to recipient cells where they target the AR pathway. The upregulation of these miRNAs is associated with message delivery by Mes-PCa-derived exosomes [121]. MiR-31 and miR-21 act as oncogenic factors in regulating therapeutic resistance [122–124], while miR-145 plays a tumor suppressor role and inhibits chemo-radio-resistance [125,126]. Although these miRNAs are all upregulated in Mes-PCa-derived exosomes, the effect of Mes-PCa-derived exosomes is mainly attributed to miR-31 and miR-21.

Non-cancerous cell-derived exosomes implicate in chemoresistance as well. For example, primary prostate fibroblasts (PSC-27)-derived exosomes carrying miR-27a promote chemoresistance of PC-3 cells by inhibiting p53 [127]. The inhibition of p53 can confer resistance to chemotherapeutic drugs [128], activate the STAT3 pathway, and promote tumor progression [129]. MiR-423-5p is overexpressed in CAF-derived exosomes and modulates drug resistance by targeting gremlin 2 via TGF-β pathway [130].

Moreover, exosomal miRNAs implicate in upregulating chemotherapy sensitivity. For example, exosomes derived from docetaxel-resistant PC-3 and 22Rv1 cells decrease levels of miR-34a, which leads to increased docetaxel resistance by upregulating B-cell lymphoma-2 [131,132]. It is related to NF-κB [133], PI3K/AKT [134] and other pathways. Overall, exosomal miRNAs derived from different cells have a significant impact on regulating therapy resistance via the AR, STAT3, TGF-β, NF-κB and other signaling pathways, contributing to chemoresistance and sensitivity to chemotherapy.

3.2. Exosomal lncRNA in PCa

3.2.1. Exosomal lncRNAs in PCa growth

Exosomal lncRNAs act as miRNA sponges and indirectly regulate PCa growth. They have been shown to exert significant effects on cell proliferation and apoptosis. Exosomal lncRNA MYU complements miR-184, resulting in the upregulation of c-Myc level, which subsequently stimulates the proliferation of PC-3 cells [135]. The c-Myc maintains a high cell proliferation rate and cooperates with the PI3K/AKT pathway [136] to promote PCa cell survival [137,138]. Additionally, the upregulation of exosomal lncAY927529 inhibits apoptosis by positively regulating C-X-C motif chemokine ligand-14 level [139]. It promotes M2 macrophage polarization through the NF-κB pathway and contributes to LNCaP and PC-3 cell proliferation, invasion, colony formation and tumor growth [140].

3.2.2. Exosomal lncRNAs in PCa progression

Exosomal lncRNAs, boasting over 200 nucleotides, possess distinctive nucleotide sequences that allow them to complement and pair with corresponding miRNAs, thereby exerting an indirect influence on gene expression and modulating the progression of PCa. For instance, exosomal lncRNA PCSEAT, which is overexpressed in patients with PCa, is transmitted to promote migration and proliferation of recipient cells via exosomes. PCSEAT modulates EZH2 by interacting with miR-143-3p and miR-24-2-5p [141]. EZH2 plays a crucial role in activating the PI3K/AKT/mTOR and Wnt/β-catenin pathways [142].

Exosomal lncRNAs induce phenotypic transformation in PCa. Exosomal lncRNA HOXD-AS1 is increased in LNCaP-Bic and LNCaP-AI cell-derived exosomes. In recipient cells, HOXD-AS1 competitively binds to miR-361-5p, upregulates forkhead box protein M1 (FOXM1), and induces a metastasis-associated phenotype *in vitro* and *in vivo* [143]. The HIF-1α/FOXM1 pathway is mediated by EMT in PCa [133]. Moreover,

Table 2
Biomarkers of exosomal ncRNAs in prostate cancer.

Biomarker Type	Role	Source		
		Urine	Plasma	Serum
Diagnostic biomarkers	Distinguish PCa from HS	miR-19b [172], miR-21 [51,52], miR-141-5p [52], miR-375 [171], miR-486-5p [171], miR-451a [171], miR-486-3p [171], miR-196a-5p [170], miR-501-3p [170], let-7c [51], miR-574-3p [52] and miR-2909 [174]	miR-125a-5p [175], miR-141-5p [175] and lncAY927529 [139]	miR-141 [52,176,177], miR-212 [150], HIPK3 [150] and circ_0044516 [154]
	Distinguish PCa from BPH	miR-145 [173], miR-1290 [173], miR-2909 [174] and lncRNA-p21 [181]	miR-21-5p [53] and miR-200c-3p [53]	/
	Distinguish PCa from negative prostate biopsy	PCA3 [178] and MALAT1 [178]	/	/
Staging and grading biomarkers	Identify metastatic PCa	miR-375 [171,173] and miR-1290 [171,173]	/	miR-141 [52,176,177] and circ_0081234 [157]
	Distinguish treatment-naïve PCa from CRPC	/	miR-423-3p [183]	/
	Distinguish PCa with different GS	miR-145 [173], PCA3 [178] and MALAT1 [178]	let-7a-5p [53]	/
	Identify metastatic PCa after radical prostatectomy	/	/	miR-141 [52,176,177], miR-375 [177] and miR-1246 [98]
Prognostic biomarkers	Associated with poor overall survival	/	miR-375 [184] and miR-1290 [184]	/

Abbreviation: PCa, prostate cancer; CRPC, castration-resistant prostate cancer; GS, Gleason Score; SM, spine metastasis; HS, healthy subjects; BPH, benign prostatic hyperplasia.

FOXM1 may also be involved in the modulation of the AR pathway through interaction with the AR [144].

In the bone microenvironment, exosomal lncRNAs regulate osteogenic activity. Exosomal lncRNA nuclear-enriched abundant transcript 1 (NEAT1) is transported to hBMSCs, which upregulates RUNX2 level by interacting with miR-205-5p [145]. Additionally, the overexpression of RUNX2 could be partly attributed to the splicing factor proline- and glutamine-rich (SFPQ)/polypyrimidine tract-binding protein 2 (PTBP2) axis [145]. Additionally, exosomal HOXD-AS1 enhances osteolytic loss and tumor metastasis in the microenvironment via the miR-361-5p/FOXM1 axis [143]. FOXM1 is involved in a metastasis-related gene network, including those related to cellular adhesion and bone microenvironment [146].

3.2.3. *Exosomal lncRNAs in PCa therapy resistance*

Exosomal lncRNAs modulate androgen sensitivity in PCa, ultimately influencing the efficacy of ADT. Androgens are key drivers of prostate growth and are known to contribute to tumor progression. As androgen sensitivity changes in tumor cells, PCa can progress to CRPC and become androgen-independent [147]. Androgen-independent PCa cell-derived exosomes enhance the acquisition of androgen independence. This effect is mediated in part by overexpression of the LINC01213, which confers androgen deprivation tolerance by activating the Wnt/β-catenin pathway [148]. Activation of this pathway is more commonly observed in CRPC than in treatment-naïve PCa, and its inhibitors can reduce therapy resistance in PCa [149].

3.3. *Exosomal circRNA in PCa*

3.3.1. *Exosomal circRNAs in PCa initiation*

Exosomal circRNAs modulate angiogenesis in PCa by regulating miRNAs. For example, circHIPK3 interacts with miR-212 [150] and its overexpression leads to upregulation of B-cell-specific Moloney murine leukemia virus integration site 1 (BMI-1) and inhibition of angiogenesis in PCa [151]. BMI-1 significantly affects the initiation and development of PCa [152]. Moreover, BMI-1 has been shown to promote angiogenesis via the NF-κB pathway in gliomas [153], which may be a potential mechanism of BMI-1 in PCa.

3.3.2. *Exosomal circRNAs in PCa growth*

Exosomal circRNAs also implicate in modulating tumor growth by acting as miRNA sponges in PCa. Circ_0044516 overexpression in exosomes downregulates miR-29a-3p and enhances the proliferation as an oncogenic factor in PCa [154]. MiR-29a-3p regulates cell proliferation by mediating the classical Wnt/β-catenin pathway in PCa [155]. Exosomal circHIPK3 reduces apoptosis via the circHIPK3/miR-212/BMI-1 axis [150]. The inhibition of BMI-1 impairs apoptosis-related protein expression via the ubiquitination pathway and promotes apoptosis in PCa [156].

3.3.3. *Exosomal circRNAs in PCa progression*

Exosomal circRNAs modulate PCa progression by acting as miRNA sponges. Exosomes derived from patients with PCa and spinal metastasis (SM) showed higher expression levels of circ_0081234 compared to those without SM. Overexpression of circ_0081234 promoted malignant activity by increasing MAP3K1 levels as a miR-1 sponge [157]. MAP3K1 is part of the MAPK/MEK/ERK pathway, which is a significant signaling pathway in PCa EMT [158]. By the circHIPK3/miR-212/BMI-1 axis, exosomal circHIPK3 enhances cell viability, migration and invasion [150]. BMI-1 also modulates cell migration and invasion in PCa progression [156,159,160].

3.3.4. *Exosomal circRNAs in PCa therapy resistance*

Exosomal circRNAs implicate in the upregulation of chemoresistance via message delivery. Docetaxel (DTX)-resistant PCa cell-derived exosomes enhance DTX resistance, in which circ-XIAP is overexpressed, directly targets miR-1182, and increases TPD52 level [161]. TPD52 avoids apoptosis in response to androgen deprivation by activating the PI3K/AKT and STAT3 pathways [162–164].

Signaling pathways mediated by miRNAs, lncRNAs and circRNAs in exosome-derived PCa cells are not only involved in a single cellular activity. For example, the PI3K/AKT pathway is associated with cellular proliferation, apoptosis, invasion, migration, phenotypic transformation, regulation of the bone microenvironment and therapy resistance in PCa. Therefore, exosomal ncRNAs are delivered and target the same or correlated signaling pathways, which in turn affect cellular activity. This establishes a complicated modulatory network in PCa and sheds new light on the pathogenesis of PCa. Overall, the regulatory mechanisms of PCa are diverse and every cellular process cannot be viewed unilaterally. Additional exploration is necessary to reveal the underlying mechanisms and crosstalk among the aforementioned pathways.

4. Exosomal ncRNAs as biomarkers in PCa

Due to their capacity to regulate a wide range of cellular processes, exosomal ncRNAs serve as valuable biomarkers for diagnosis, staging, grading and prognosis assessment. The levels of exosomal ncRNAs reflect the status of donor and recipient cells due to the specific roles of exosomal ncRNAs in PCa. Profiling and quantifying exosomal ncRNAs have shown differential expression levels among healthy individuals, patients with BPH, patients with androgen-sensitive PCa and patients with CRPC [12,165,166]. Therefore, exosomal ncRNAs are of the utmost importance in providing precise diagnostic, staging, grading and prognostic biomarkers for PCa (Table 2).

4.1. Exosomal ncRNAs as diagnostic biomarkers

Exosomal ncRNAs represent reliable and precise biomarkers for PCa diagnosis. At present, PSA screening is the first choice for all patients due to its efficiency. However, it also leads to overdiagnosis and overtreatment because it is prostate-specific, not PCa-specific [10]. Other diagnostic methods, such as tissue biopsy, imaging examination and digital rectal examination (DRE), are not routinely recommended for newly admitted patients because of their limitations, such as invasiveness, high cost, and poor diagnostic performance [167,168]. Exosomes have become a research hotspot and provide a promising alternative to liquid biopsy with better overall diagnostic performance [169]. Particularly, ncRNAs in exosomes are important modulators and biomarkers. Therefore, exosomal ncRNAs may offer a new and valuable choice for PCa diagnosis.

The focus of numerous research has been on exosomal miRNAs as biomarkers for diagnosing PCa. For example, the levels of miR-196a-5p [170], miR-501-3p [170], miR-375 [171] and miR-19b [172] are significantly decreased in urinary exosomes from patients with PCa in comparison to those from non-cancerous subjects. Conversely, the expression levels of miR-451a [171], miR-486-3p [171], miR-486-5p [171], miR-21 [51,52], miR-375 [51], let-7c [51], miR-141-5p [52], miR-574-3p [52], miR-145 [173], miR-1290 [173] and miR-2909 [174] are significantly higher in urinary exosomes from patients with PCa in comparison to those from non-cancerous subjects. In exosomes from plasma, miR-200c-3p [53], miR-21-5p [53] and miR-141-5p [175] are significantly overexpressed and utilized to differentiate between patients with PCa and non-cancerous subjects. Additionally, the decline of miR-125a-5p in plasma exosomes is valuable for diagnosing PCa patients and healthy subjects [175]. Similarly, in exosomes from serum, miR-212 is significantly downregulated [150], whereas miR-141 is significantly upregulated [52,176,177], which is meaningful in PCa diagnosis. Moreover, combining multiple biomarkers, including miR-375, miR-451a, miR-486-3p and miR-486-5p [171], miR-21 and miR-375 [51], miR-125a-5p and miR-141-5p [175], PCA3 and MALAT1 [178], or SChLAP1 and SAP30L-AS1 [179], can increase the diagnostic accuracy.

As a part of ncRNAs, exosomal lncRNAs are also valuable diagnostic biomarkers in PCa. Specific exosomal lncRNAs are enriched or decreased and contain miRNA seeds or RNA-binding protein binding (RBP) motifs [180], which make lncRNAs valuable diagnostic biomarkers. In urinary exosomes, PCA3 [178], MALAT1 [178] and lncRNA-p21 [181] are significantly upregulated and serve for PCa diagnosis. The diagnostic performance of exosomal PCA3 and MALAT1 in combination is superior to that of PCA3 or MALAT1 alone. Moreover, the diagnostic performance is further enhanced by combining urinary exosomal PCA3 and MALAT1, PSA, fPSA/tPSA, and a model that includes age, prostate volume, and DRE status [178]. Similarly, serum exosomes from patients with PCa show significant upregulation of SChLAP1 [179] and lncAY927529 [139], compared to those from normal volunteers.

Exosomal circRNAs can also function for PCa diagnosis. Specifically, exosomal circ_0044516 is increased in the serum of patients with PCa and differentiates them from normal subjects [154]. Similarly, exosomal circHIPK3 is also a diagnostic biomarker found in serum and it is meaningfully increased in patients with PCa in comparison to normal subjects [150]. Both circ_0044516 and circHIPK3 act as miRNA sponges and bind to miR-212 and miR-330-5p, respectively [150,182]. This may explain the decline of miR-212 and miR-330-5p in the exosomes.

4.2. Exosomal ncRNAs as staging and grading biomarkers

In addition to diagnosing PCa, exosomal ncRNAs also function as staging and grading biomarkers. Understanding the stage and grade of PCa is essential as it reveals the current status of the disease and the degree of malignancy. This information can help clinicians make informed therapeutic decisions.

Different PCa stages affect the choice of therapy, making it necessary to determine the disease stage. According to studies, patients with metastatic PCa exhibit overexpression of miR-1290 and decreased levels of miR-375 in urinary exosomes as compared to those with localized PCa [171,173]. Furthermore, overexpression of exosomal miR-141 [176] and miR-1246 [98] in serum can distinguish whether PCa metastasizes or not like miR-1290. Additionally, serum exosomal circ_0081234 is meaningfully overexpressed in patients with PCa SM, suggesting its utility for PCa staging [157]. Plasma exosomal miR-423-3p is meaningfully increased in patients with CRPC than in those with non-CRPC [183]. Additionally, after undergoing radical prostatectomy, serum exosomal miR-375 and miR-141 are meaningfully increased in patients with metastatic PCa compared to those without relapse [177].

The GS of PCa is associated with treatment decisions and risk stratification. Exosomal ncRNAs can help determine GS values. For example, overexpression of urinary exosomal miR-145 can be used to significantly determine GS $\geq$ 8 or GS $\leq$ 7 in patients with PCa [173]. Conversely, the decline of plasma exosomal let-7a-5p is meaningful when distinguishing GS $\geq$ 8 or GS $\leq$ 6 in patients with PCa [53]. PCA3 and MALAT1 are also associated with GS. The levels of these biomarkers are significantly upregulated in urinary exosomes and utilized to distinguish patients with PCa with a high GS (GS $\geq$ 7) from those with other non-aggressive diseases (PCa with a GS $\leq$ 6 and benign disease) [178]. By quantifying these ncRNAs, clinicians can determine the stage and grade of patients without invasive biopsies.

4.3. Exosomal ncRNAs as prognostic biomarkers

Exosomal ncRNAs are also useful for predicting patient survival. For example, patients with CRPC after ADT failure show significant upregulation of plasma exosomal miR-1290 and miR-375, indicating their potential for survival prediction. Moreover, the predictive performance of the prognosis is significantly improved by measuring the ratio of miR-1290/miR-375 [184]. Similarly, circ_14736 and circ_17720 form a part of the circRNA signature model. This model, including eight circRNAs, predicted the biochemical recurrence of PCa [185]. These findings suggest that exosomal ncRNAs have prognostic value and can be used to develop effective predictive models for patients with PCa.

5. Clinical application of exosomal ncRNAs

5.1. Exosomal ncRNAs as biomarkers

Given the roles of exosomal ncRNAs as modulators and biomarkers, they hold promise as novel biomarkers in clinical settings. Based on the apparent differences in exosomal ncRNAs between patients with PCa and others, some studies have used them to diagnose. Wei et al. [186] and Wang et al. [187] designed diverse techniques for the ultrasensitive detection of miR-141. Additionally, Kim et al. [188] successfully measured urinary exosomal miR-6090 and miR-3665 levels in patients with PCa, developed a dual amplification approach, and identified its potential in PCa diagnosis. Moreover, by targeting exosomal miR-21 and

Table 3
The therapeutic potential of exosomal ncRNAs.

ncRNAs	Carrier	Target	Model	Role	Reference
let-7a	Modified exosomes	EGFR-expressing breast cancer	*In vivo and in vitro*	Inhibited tumor growth	[195]
miR-497	Hybrid nanoparticles of liposomes and exosomes	Ovarian cancer	*In vivo and in vitro*	Led to tumor cell death and overcame drug resistance	[196]
anti-miR-21	Anti-exosome antibody–oligonucleotide complexes	Exosome	*In vitro*	Inhibited exosomal miR-21 to prohibit cancer cell growth	[199]
lncRNA MEG3	Modified exosomes	Osteosarcoma	*In vivo and in vitro*	Inhibited proliferation, migration and promoted apoptosis by regulating miR-185-5p	[197]
ciRS-122	Exosome	Colorectal cancer	*In vivo and in vitro*	Suppressed glycolysis and reversed resistance to oxaliplatin by regulating the ciRS-122-miR-122-PKM2 pathway	[198]

surface CD63, Cho et al. [189] could determine whether exosomes derived from cancerous prostate cells or not. The sequence between two lncRNAs or circRNAs has some repeat sites, leading to low efficiency in constructing a system to detect specific sequences of lncRNAs or circRNAs. Hence, real-time fluorescence polymerase chain reaction (PCR) and other methods are commonly used to directly measure the expression of lncRNAs or circRNAs.

Although significant progress has been made in detecting specific biomarkers in the plasma, serum or exosomes, the time-consuming procedures and high technical requirements of some methods make biosensing through exosomal ncRNAs non-mainstream. However, the high enrichment of ncRNAs in exosomes makes it easier to collect the same type of ncRNAs and send signals without acquiring a large volume of body liquid. In addition, some researchers have successfully applied their detection assays from basic research to clinical applications with high diagnostic efficiency [187,188], showing that exosomal ncRNAs have excellent detection performance in PCa. These detection systems not only show compatibility with PCR but also have higher specificity than typical PSA tests.

It is critical to standardize the collection and measurement of exosomal ncRNAs before accurately understanding the relationship between ncRNAs and PCa. Several highly sensitive and specific assays have been developed to determine exosomal miRNAs related to PCa. However, the absence of standardization in the collection and measurement of miRNAs can lead to different conclusions. For instance, Foj et al. [51] found that urinary exosomal miR-141 exhibits no apparent difference in diagnosing PCa upon using differential centrifugation, which differs when comparing urinary exosomal miR-141 by lectin-based exosome agglutination method [52]. Additionally, other potential factors should be explored, such as prostate massage, urine volume, urine concentration, renal function and hemodynamic status [14].

5.2. Exosomal ncRNAs as potential therapeutic tools

Besides as biomarkers, exosomal ncRNAs are hopeful targets for cancer therapy. The ncRNAs encased in exosomes are biocompatible and more prone to evade attacks by the immune system. Exosomal ncRNAs are more stable than ncRNAs in bodily fluids and can cross physiological barriers, because of their biocompatibility. Specific miRNAs in endogenous exosomes derived from stem cells can protect adjacent cells [190,191]. Exogenous ncRNAs can be incorporated into synthetic exosomes using methods like electroporation, lipofection, sonication or calcium chloride treatment [192]. Synthetic exosomes can induce gene silencing with loaded ncRNAs, leading to the knockdown of cancer oncogenes [193,194]. Furthermore, exosomal ncRNAs have been used to breast cancer [195], ovarian cancer [196], osteosarcoma [197], colorectal cancer [198] and other cancers (Table 3). Overall, loading ncRNAs into exosomes is promising for PCa.

6. Conclusions

According to published studies, exosomal ncRNAs have emerged as key regulators of multiple signaling pathways, critically influencing PCa initiation, growth, progression and therapy resistance. The relationship among exosomal ncRNAs, signaling pathways and cellular activities is complex and requires further exploration. Understanding the involvement of exosomal ncRNAs in tumorigenesis, progression and therapeutic response will usher in a new era in PCa diagnosis and treatment. Given their predictive effects in PCa, exosomal ncRNAs can function as innovative biomarkers and construct a professional system that can identify, classify, monitor PCa, predict patient survival, and assist in medical decision-making. Additionally, new therapeutic methods may target exosomal ncRNAs to intervene in oncogene expression, and exosomes can be designed to transport functional ncRNAs to cancer cells. However, the lack of a recognized protocol for obtaining exosomes remains a challenge and researchers must collaborate to determine the best separation and detection techniques based on stability, accuracy and selectivity to facilitate credible research results. Furthermore, exosomal ncRNA expression in various body fluids of patients with PCa at each stage requires reliable average measurements through multiple assessments. With the combined efforts of researchers, exosomal ncRNAs in PCa will be better explored and successfully applied in clinical practice.

Funding

This study was supported by the National Natural Science Foundation of China (82122042), Chongqing Science Fund for Distinguished Young Scholars (CSTB2022NSCQ-JQX0007), Chongqing Medical Scientific Research Project (2023ZDXM021) and Key Project for Clinical Innovation of Army Medical University (CX2019LC107).

CRediT authorship contribution statement

Yongxing Li: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Xiaoqi Tang:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Binpan Wang:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Ming Chen:** Writing – review & editing, Supervision. **Ji Zheng:** Writing – review & editing, Supervision, Funding acquisition. **Kai Chang:** Writing – review & editing, Supervision, Funding acquisition.

Declaration of competing interest

There are no conflicts of interest to declare.

References

[1] R.L. Siegel, K.D. Miller, H.E. Fuchs, A. Jemal, Cancer statistics, Ca-Cancer J. Clin. 72 (1) (2022) 7–33, https://doi.org/10.3322/caac.21708.
[2] C. Xia, X. Dong, H. Li, et al., Cancer statistics in China and United States, 2022: profiles, trends, and determinants, Chinese Med J 135 (5) (2022) 584–590, https://doi.org/10.1097/CM9.0000000000002108.
[3] T.L. Pulliam, P. Goli, D. Awad, et al., Regulation and role of CAMKK2 in prostate cancer, Nat. Rev. Urol. 19 (6) (2022) 367–380, https://doi.org/10.1038/s41585-022-00588-z.

[4] K.J. Foreman, N. Marquez, A. Dolgert, et al., Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016-40 for 195 countries and territories, Lancet 392 (10159) (2018) 2052–2090, https://doi.org/10.1016/S0140-6736(18)31694-5.
[5] C. Arenas-Gallo, J. Owiredu, I. Weinstein, et al., Race and prostate cancer: genomic landscape, Nat. Rev. Urol. 19 (9) (2022) 547–561, https://doi.org/10.1038/s41585-022-00622-0.
[6] H. Van Poppel, T. Albreht, P. Basu, et al., Serum PSA-based early detection of prostate cancer in Europe and globally: past, present and future, Nat. Rev. Urol. 19 (9) (2022) 562–572, https://doi.org/10.1038/s41585-022-00638-6.
[7] S. Sandhu, C.M. Moore, E. Chiong, et al., Prostate cancer, Lancet 398 (10305) (2021) 1075–1090, https://doi.org/10.1016/S0140-6736(21)00950-8.
[8] G.B.D. Disease, Incidence Injury and Collaborators Prevalence, Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017, Lancet 392 (10159) (2018) 1789–1858, https://doi.org/10.1016/S0140-6736(18)32279-7.
[9] P.F. Pinsky, A. Black, S.E. Daugherty, et al., Metastatic prostate cancer at diagnosis and through progression in the prostate, lung, colorectal, and ovarian cancer screening trial, Cancer 125 (17) (2019) 2965–2974, https://doi.org/10.1002/cncr.32176.
[10] Kishor Mistry, Greg Cable, Meta-analysis of prostate-specific antigen and digital rectal examination as screening tests for prostate carcinoma, J. Am. Board Fam. Pract. 16 (2) (2003) 95–101.
[11] L. Zhang, D. Yu, Exosomes in cancer development, metastasis, and immunity, Biochim. Biophys. Acta Rev. Canc 1871 (2) (2019) 455–468, https://doi.org/10.1016/j.bbcan.2019.04.004.
[12] X. Filella, L. Foj, Prostate cancer detection and prognosis: from prostate specific antigen (PSA) to exosomal biomarkers, Int. J. Mol. Sci. 17 (11) (2016), https://doi.org/10.3390/ijms17111784.
[13] X. Tang, Y. Wang, L. Zhou, et al., Strand displacement-triggered G-quadruplex/rolling circle amplification strategy for the ultra-sensitive electrochemical sensing of exosomal microRNAs, Mikrochim. Acta 187 (3) (2020) 172, https://doi.org/10.1007/s00604-020-4143-9.
[14] Jingpu Wang, Jie Ni, Julia Beretov, et al., Exosomal microRNAs as liquid biopsy biomarkers in prostate cancer, Crit. Rev. Oncol. Hematol. 145 (2020) 102860, https://doi.org/10.1016/j.critrevonc.2019.102860.
[15] Z. Sun, K. Shi, S. Yang, et al., Effect of exosomal miRNA on cancer biology and clinical applications, Mol. Cancer 17 (1) (2018) 147, https://doi.org/10.1186/s12943-018-0897-7.
[16] Z. Sun, S. Yang, Q. Zhou, et al., Emerging role of exosome-derived long non-coding RNAs in tumor microenvironment, Mol. Cancer 17 (1) (2018) 82, https://doi.org/10.1186/s12943-018-0831-z.
[17] Y. Wang, J. Liu, J. Ma, et al., Exosomal circRNAs: biogenesis, effect and application in human diseases, Mol. Cancer 18 (1) (2019) 116, https://doi.org/10.1186/s12943-019-1041-z.
[18] A. Ali, A. Du Feu, P. Oliveira, et al., Prostate zones and cancer: lost in transition? Nat. Rev. Urol. 19 (2) (2022) 101–115, https://doi.org/10.1038/s41585-021-00524-7.
[19] M. Baures, C. Dariane, E. Tika, et al., Prostate luminal progenitor cells: from mouse to human, from health to disease, Nat. Rev. Urol. 19 (4) (2022) 201–218, https://doi.org/10.1038/s41585-021-00561-2.
[20] F. Teng, M. Fussenegger, Shedding light on extracellular vesicle biogenesis and bioengineering, Adv. Sci. 8 (1) (2020) 2003505, https://doi.org/10.1002/advs.202003505.
[21] A. Thakur, D.C. Parra, P. Motallebnejad, M. Brocchi, H.J. Chen, Exosomes: small vesicles with big roles in cancer, vaccine development, and therapeutics, Bioact. Mater. (2022), https://doi.org/10.1016/j.bioactmat.2021.08.029.
[22] R. Kalluri, V.S. LeBleu, The biology, function, and biomedical applications of exosomes, Science 367 (6478) (2020), https://doi.org/10.1126/science.aau6977.
[23] S. Mathivanan, C.J. Fahner, G.E. Reid, R.J. Simpson, ExoCarta 2012: database of exosomal proteins, RNA and lipids, Nucleic Acids Res. 40 (Database issue) (2012) D1241–D1244, https://doi.org/10.1093/nar/gkr828.
[24] V. Vlaeminck-Guillem, Extracellular vesicles in prostate cancer carcinogenesis, diagnosis, and management, Front. Oncol. 8 (2018) 222, https://doi.org/10.3389/fonc.2018.00222.
[25] C. Fedele, A. Singh, B.J. Zerlanko, R.V. Iozzo, L.R. Languino, The alphavbeta6 integrin is transferred intercellularly via exosomes, J. Biol. Chem. 290 (8) (2015) 4545–4551, https://doi.org/10.1074/jbc.C114.617662.
[26] J.S. Brzozowski, D.R. Bond, H. Jankowski, et al., Extracellular vesicles with altered tetraspanin CD9 and CD151 levels confer increased prostate cell motility and invasion, Sci. Rep. 8 (1) (2018) 8822, https://doi.org/10.1038/s41598-018-27180-z.
[27] L. Mashouri, H. Yousefi, A.R. Aref, et al., Exosomes: composition, biogenesis, and mechanisms in cancer metastasis and drug resistance, Mol. Cancer 18 (1) (2019) 75, https://doi.org/10.1186/s12943-019-0991-5.
[28] Yaron Vinik, Francisco Gabriel Ortega, Gordon B. Mills, et al., Proteomic analysis of circulating extracellular vesicles, Sci. Adv. 6 (2020).
[29] A. Llorente, T. Skotland, T. Sylvanne, et al., Molecular lipidomics of exosomes released by PC-3 prostate cancer cells, Biochim. Biophys. Acta 1831 (7) (2013) 1302–1309, https://doi.org/10.1016/j.bbalip.2013.04.011.
[30] X. Luo, X. Zhao, C. Cheng, et al., The implications of signaling lipids in cancer metastasis, Exp. Mol. Med. 50 (9) (2018) 1–10, https://doi.org/10.1038/s12276-018-0150-x.
[31] L. Cheng, K. Zhang, Y. Qing, et al., Proteomic and lipidomic analysis of exosomes derived from ovarian cancer cells and ovarian surface epithelial cells, J. Ovarian Res. 13 (1) (2020) 9, https://doi.org/10.1186/s13048-020-0609-y.
[32] L. Tao, J. Zhou, C. Yuan, et al., Metabolomics identifies serum and exosomes metabolite markers of pancreatic cancer, Metabolomics 15 (6) (2019) 86, https://doi.org/10.1007/s11306-019-1550-1.
[33] H. Zhang, D. Freitas, H.S. Kim, et al., Identification of distinct nanoparticles and subsets of extracellular vesicles by asymmetric flow field-flow fractionation, Nat. Cell Biol. 20 (3) (2018) 332–343, https://doi.org/10.1038/s41556-018-0040-4.
[34] J. Wang, S. Zhu, N. Meng, et al., ncRNA-encoded peptides or proteins and cancer, Mol. Ther. 27 (10) (2019) 1718–1725, https://doi.org/10.1016/j.ymthe.2019.09.001.
[35] E. Anastasiadou, L.S. Jacob, F.J. Slack, Non-coding RNA networks in cancer, Nat. Rev. Cancer 18 (1) (2018) 5–18, https://doi.org/10.1038/nrc.2017.99.
[36] M.D. Bullock, A.M. Silva, P. Kanlikilicer-Unaldi, et al., Exosomal non-coding RNAs: diagnostic, prognostic and therapeutic applications in cancer, Noncoding RNA 1 (1) (2015) 53–68, https://doi.org/10.3390/ncrna1010053.
[37] Z. Wei, A.O. Batagov, S. Schinelli, et al., Coding and noncoding landscape of extracellular RNA released by human glioma stem cells, Nat. Commun. 8 (1) (2017) 1145, https://doi.org/10.1038/s41467-017-01196-x.
[38] F.J. Slack, A.M. Chinnaiyan, The role of non-coding RNAs in oncology, Cell 179 (5) (2019) 1033–1055, https://doi.org/10.1016/j.cell.2019.10.017.
[39] M. Su, Y. Xiao, J. Ma, et al., Circular RNAs in Cancer: emerging functions in hallmarks, stemness, resistance and roles as potential biomarkers, Mol. Cancer 18 (1) (2019) 90, https://doi.org/10.1186/s12943-019-1002-6.
[40] W.R. Jeck, J.A. Sorrentino, K. Wang, et al., Circular RNAs are abundant, conserved, and associated with ALU repeats, RNA 19 (2) (2013) 141–157, https://doi.org/10.1261/rna.035667.112.
[41] Y. Li, Q. Zheng, C. Bao, et al., Circular RNA is enriched and stable in exosomes: a promising biomarker for cancer diagnosis, Cell Res. 25 (8) (2015) 981–984, https://doi.org/10.1038/cr.2015.82.
[42] X.H. Tang, T. Guo, X.Y. Gao, et al., Exosome-derived noncoding RNAs in gastric cancer: functions and clinical applications, Mol. Cancer 20 (1) (2021) 99, https://doi.org/10.1186/s12943-021-01396-6.
[43] D. Hanahan, Hallmarks of cancer: new dimensions, Cancer Discov. 12 (1) (2022) 31–46, https://doi.org/10.1158/2159-8290.CD-21-1059.
[44] D. Hanahan, R.A. Weinberg, Hallmarks of cancer: the next generation, Cell 144 (5) (2011) 646–674, https://doi.org/10.1016/j.cell.2011.02.013.
[45] D. Hanahan, R.A. Weinberg, The hallmarks of cancer, Cell 100 (1) (2000) 57–70, https://doi.org/10.1016/s0092-8674(00)81683-9.
[46] C. Aslan, S. Maralbashi, F. Salari, et al., Tumor-derived exosomes: implication in angiogenesis and antiangiogenesis cancer therapy, J. Cell. Physiol. 234 (10) (2019) 16885–16903, https://doi.org/10.1002/jcp.28374.
[47] W. Olejarz, G. Kubiak-Tomaszewska, A. Chrzanowska, T. Lorenc, Exosomes in angiogenesis and anti-angiogenic therapy in cancers, Int. J. Mol. Sci. 21 (16) (2020), https://doi.org/10.3390/ijms21165840.
[48] A.N. Prigol, M.P. Rode, A.H. Silva, J. Cisilotto, T.B. Creczynski-Pasa, Pro-angiogenic effect of PC-3 exosomes in endothelial cells in vitro, Cell. Signal. 87 (2021) 110126, https://doi.org/10.1016/j.cellsig.2021.110126.
[49] B. Arroyo A, S. Salloum-Asfar, C. Perez-Sanchez, et al., Regulation of TFPIalpha expression by miR-27a/b-3p in human endothelial cells under normal conditions and in response to androgens, Sci. Rep. 7 (1) (2017) 43500, https://doi.org/10.1038/srep43500.
[50] E.W. Holroyd, S. Delacroix, K. Larsen, et al., Tissue factor pathway inhibitor blocks angiogenesis via its carboxyl terminus, Arterioscler. Thromb. Vasc. Biol. 32 (3) (2012) 704–711, https://doi.org/10.1161/ATVBAHA.111.243733.
[51] L. Foj, F. Ferrer, M. Serra, et al., Exosomal and non-exosomal urinary miRNAs in prostate cancer detection and prognosis, Prostate 77 (6) (2017) 573–583, https://doi.org/10.1002/pros.23295.
[52] R. Samsonov, T. Shtam, V. Burdakov, et al., Lectin-induced agglutination method of urinary exosomes isolation followed by mi-RNA analysis: application for prostate cancer diagnostic, Prostate 76 (1) (2016) 68–79, https://doi.org/10.1002/pros.23101.
[53] E. Endzelins, A. Berger, V. Melne, et al., Detection of circulating miRNAs: comparative analysis of extracellular vesicle-incorporated miRNAs and cell-free miRNAs in whole plasma of prostate cancer patients, BMC Cancer 17 (1) (2017) 730, https://doi.org/10.1186/s12885-017-3737-z.
[54] L.Z. Liu, C. Li, Q. Chen, et al., MiR-21 induced angiogenesis through AKT and ERK activation and HIF-1alpha expression, PLoS One 6 (4) (2011) e19139, https://doi.org/10.1371/journal.pone.0019139.
[55] E. Costanzi, R. Romani, P. Scarpelli, I. Bellezza, Extracellular vesicles-mediated transfer of miRNA let-7b from PC3 cells to macrophages, Genes 11 (12) (2020), https://doi.org/10.3390/genes11121495.
[56] Z. Chen, T.C. Lai, Y.H. Jan, et al., Hypoxia-responsive miRNAs target argonaute 1 to promote angiogenesis, J. Clin. Invest. 123 (3) (2013) 1057–1067, https://doi.org/10.1172/JCI65344.
[57] Y. Zhu, J. Zhang, X. Hu, et al., Extracellular vesicles derived from human adipose-derived stem cells promote the exogenous angiogenesis of fat grafts via the let-7/AGO1/VEGF signalling pathway, Sci. Rep. 10 (1) (2020) 5313, https://doi.org/10.1038/s41598-020-62140-6.
[58] A. Shang, C. Gu, W. Wang, et al., Exosomal circPACRGL promotes progression of colorectal cancer via the miR-142-3p/miR-506-3p- TGF-beta1 axis, Mol. Cancer 19 (1) (2020) 117, https://doi.org/10.1186/s12943-020-01235-0.
[59] P. Zheng, L. Chen, X. Yuan, et al., Exosomal transfer of tumor-associated macrophage-derived miR-21 confers cisplatin resistance in gastric cancer cells,

J. Exp. Clin. Cancer Res. 36 (1) (2017) 53, https://doi.org/10.1186/s13046-017-0528-y.
[60] C.L. Au Yeung, N.N. Co, T. Tsuruga, et al., Exosomal transfer of stroma-derived miR21 confers paclitaxel resistance in ovarian cancer cells through targeting APAF1, Nat. Commun. 7 (2016) 11150, https://doi.org/10.1038/ncomms11150.
[61] S. Jiang, H. Chen, K. He, J. Wang, Human bone marrow mesenchymal stem cells-derived exosomes attenuated prostate cancer progression via the miR-99b-5p/IGF1R axis, Bioengineered 13 (2) (2022) 2004–2016, https://doi.org/10.1080/21655979.2021.2009416.
[62] C. Lang, C. Yin, K. Lin, et al., m(6) A modification of lncRNA PCAT6 promotes bone metastasis in prostate cancer through IGF2BP2-mediated IGF1R mRNA stabilization, Clin. Transl. Med. 11 (6) (2021) e426, https://doi.org/10.1002/ctm2.426.
[63] Y. Ding, M. Wang, J. Yang, Circular RNA midline-1 (circMID1) promotes proliferation, migration, invasion and glycolysis in prostate cancer, Bioengineered 13 (3) (2022) 6293–6308, https://doi.org/10.1080/21655979.2022.2037367.
[64] Isabel Heidegger, Johann Kern, Philipp Ofer, Helmut Klocker, Petra Massoner, Oncogenic functions of IGF1R and INSR in prostate cancer include enhanced tumor growth, cell migration and angiogenesis, Oncotarget 5 (9) (2014) 2723–2735.
[65] Y. Dai, X. Gao, Inhibition of cancer cell-derived exosomal microRNA-183 suppresses cell growth and metastasis in prostate cancer by upregulating TPM1, Cancer Cell Int. 21 (1) (2021) 145, https://doi.org/10.1186/s12935-020-01686-x.
[66] R. Wang, Y. Xiao, M. Pan, Z. Chen, P. Yang, Integrative analysis of bulk RNA-Seq and single-cell RNA-Seq unveils the characteristics of the immune microenvironment and prognosis signature in prostate cancer, J. Oncol. 2022 (2022) 6768139, https://doi.org/10.1155/2022/6768139.
[67] T. Li, D. Li, J. Sha, P. Sun, Y. Huang, MicroRNA-21 directly targets MARCKS and promotes apoptosis resistance and invasion in prostate cancer cells, Biochem. Biophys. Res. Commun. 383 (3) (2009) 280–285, https://doi.org/10.1016/j.bbrc.2009.03.077.
[68] W. Zhang, W. Li, X. Han, Skullcapflavone I inhibits proliferation of human colorectal cancer cells via down-regulation of miR-107 expression, Neoplasma 66 (2) (2019) 203–210, https://doi.org/10.4149/neo_2018_180427N279.
[69] R. Jiang, C. Zhang, G. Liu, R. Gu, H. Wu, MicroRNA-107 promotes proliferation, migration, and invasion of osteosarcoma cells by targeting tropomyosin 1, Oncol. Res. 25 (8) (2017) 1409–1419, https://doi.org/10.3727/096504017X14882829077237.
[70] C. Zhou, Y. Chen, X. He, Z. Zheng, D. Xue, Functional implication of exosomal miR-217 and miR-23b-3p in the progression of prostate cancer, OncoTargets Ther. 13 (2020) 11595–11606, https://doi.org/10.2147/OTT.S272869.
[71] H.M. Lin, I. Nikolic, J. Yang, et al., MicroRNAs as potential therapeutics to enhance chemosensitivity in advanced prostate cancer, Sci. Rep. 8 (1) (2018) 7820, https://doi.org/10.1038/s41598-018-26050-y.
[72] Z. Zhang, L. Chen, H. Wang, N. Ahmad, X. Liu, Inhibition of Plk1 represses androgen signaling pathway in castration-resistant prostate cancer, Cell Cycle 14 (13) (2015) 2142–2148, https://doi.org/10.1080/15384101.2015.1041689.
[73] F.J. Sulzmaier, C. Jean, D.D. Schlaepfer, FAK in cancer: mechanistic findings and clinical applications, Nat. Rev. Cancer 14 (9) (2014) 598–610, https://doi.org/10.1038/nrc3792.
[74] S. Jiang, C. Mo, S. Guo, et al., Human bone marrow mesenchymal stem cells-derived microRNA-205-containing exosomes impede the progression of prostate cancer through suppression of RHPN2, J. Exp. Clin. Cancer Res. 38 (1) (2019) 495, https://doi.org/10.1186/s13046-019-1488-1.
[75] J.W. Peck, M. Oberst, K.B. Bouker, E. Bowden, P.D. Burbelo, The RhoA-binding protein, rhophilin-2, regulates actin cytoskeleton organization, J. Biol. Chem. 277 (46) (2002) 43924–43932, https://doi.org/10.1074/jbc.M203569200.
[76] W.Y. Hu, P. Afradiasbagharani, R. Lu, et al., Morphometric analysis of rat prostate development: roles of MEK/ERK and Rho signaling pathways in prostatic morphogenesis, Biomolecules 11 (12) (2021), https://doi.org/10.3390/biom11121829.
[77] H. Guan, R. Peng, F. Fang, et al., Tumor-associated macrophages promote prostate cancer progression via exosome-mediated miR-95 transfer, J. Cell. Physiol. 235 (12) (2020) 9729–9742, https://doi.org/10.1002/jcp.29784.
[78] M.K. Thomsen, L. Bakiri, S.C. Hasenfuss, et al., Loss of JUNB/AP-1 promotes invasive prostate cancer, Cell Death Differ. 22 (4) (2015) 574–582, https://doi.org/10.1038/cdd.2014.213.
[79] P. Birner, G. Egger, O. Merkel, L. Kenner, JunB and PTEN in prostate cancer: 'loss is nothing else than change', Cell Death Differ. 22 (4) (2015) 522–523, https://doi.org/10.1038/cdd.2014.232.
[80] Q. Liu, H. Zhang, X. Jiang, et al., Factors involved in cancer metastasis: a better understanding to "seed and soil" hypothesis, Mol. Cancer 16 (1) (2017) 176, https://doi.org/10.1186/s12943-017-0742-4.
[81] Q. Wu, L. Zhou, D. Lv, X. Zhu, H. Tang, Exosome-mediated communication in the tumor microenvironment contributes to hepatocellular carcinoma development and progression, J. Hematol. Oncol. 12 (1) (2019) 53, https://doi.org/10.1186/s13045-019-0739-0.
[82] B.H. Sung, C.A. Parent, A.M. Weaver, Extracellular vesicles: critical players during cell migration, Dev. Cell 56 (13) (2021) 1861–1874, https://doi.org/10.1016/j.devcel.2021.03.020.
[83] F. Pardo, R. Villalobos-Labra, B. Sobrevia, F. Toledo, L. Sobrevia, Extracellular vesicles in obesity and diabetes mellitus, Mol. Aspect. Med. 60 (2018) 81–91, https://doi.org/10.1016/j.mam.2017.11.010.
[84] E. Yang, X. Wang, Z. Gong, et al., Exosome-mediated metabolic reprogramming: the emerging role in tumor microenvironment remodeling and its influence on cancer progression, Signal Transduct. Targeted Ther. 5 (1) (2020) 242, https://doi.org/10.1038/s41392-020-00359-5.
[85] G. Bertoli, A. Panio, C. Cava, et al., Secreted miR-153 controls proliferation and invasion of higher Gleason score prostate cancer, Int. J. Mol. Sci. 23 (11) (2022), https://doi.org/10.3390/ijms23116339.
[86] J.B. Ma, J.Y. Bai, H.B. Zhang, et al., KLF5 inhibits STAT3 activity and tumor metastasis in prostate cancer by suppressing IGF1 transcription cooperatively with HDAC1, Cell Death Dis. 11 (6) (2020) 466, https://doi.org/10.1038/s41419-020-2671-1.
[87] C. Nan, Y. Wang, S. Yang, Y. Chen, circCRKL suppresses the progression of prostate cancer cells by regulating the miR-141/KLF5 axis, Pathol. Res. Pract. 216 (11) (2020) 153182, https://doi.org/10.1016/j.prp.2020.153182.
[88] T. Hasegawa, G.J. Glavich, M. Pahuski, et al., Characterization and evidence of the miR-888 cluster as a novel cancer network in prostate, Mol. Cancer Res. 16 (4) (2018) 669–681, https://doi.org/10.1158/1541-7786.MCR-17-0321.
[89] T. Tonini, G. D'Andrilli, A. Fucito, L. Gaspa, L. Bagella, Importance of Ezh2 polycomb protein in tumorigenesis process interfering with the pathway of growth suppressive key elements, J. Cell. Physiol. 214 (2) (2008) 295–300, https://doi.org/10.1002/jcp.21241.
[90] K. Wang, Z. Chen, J. Shi, et al., Resveratrol inhibits the tumor migration and invasion by upregulating TET1 and reducing TIMP2/3 methylation in prostate carcinoma cells, Prostate 80 (12) (2020) 977–985, https://doi.org/10.1002/pros.24029.
[91] J.W. Jeong, C.Y. Jin, C. Park, et al., Inhibition of migration and invasion of LNCaP human prostate carcinoma cells by cordycepin through inactivation of Akt, Int. J. Oncol. 40 (5) (2012) 1697–1704, https://doi.org/10.3892/ijo.2012.1332.
[92] Z. Ding, C.J. Wu, G.C. Chu, et al., SMAD4-dependent barrier constrains prostate cancer growth and metastatic progression, Nature 470 (7333) (2011) 269–273, https://doi.org/10.1038/nature09677.
[93] Q. Wa, L. Li, H. Lin, et al., Downregulation of miR-19a-3p promotes invasion, migration and bone metastasis via activating TGF-beta signaling in prostate cancer, Oncol. Rep. 39 (1) (2018) 81–90, https://doi.org/10.3892/or.2017.6096.
[94] Y. Zhang, J. Zhao, M. Ding, et al., Loss of exosomal miR-146a-5p from cancer-associated fibroblasts after androgen deprivation therapy contributes to prostate cancer metastasis, J. Exp. Clin. Cancer Res. 39 (1) (2020) 282, https://doi.org/10.1186/s13046-020-01761-1.
[95] H. Zhang, F. Liang, J. Yue, et al., MicroRNA-137 regulates hypoxia-mediated migration and epithelial-mesenchymal transition in prostate cancer by targeting LGR4 via the EGFR/ERK signaling pathway, Int. J. Oncol. 57 (2) (2020) 540–549, https://doi.org/10.3892/ijo.2020.5064.
[96] C. Peraldo-Neia, G. Migliardi, M. Mello-Grand, et al., Epidermal Growth Factor Receptor (EGFR) mutation analysis, gene expression profiling and EGFR protein expression in primary prostate cancer, BMC Cancer 11 (2011) 31, https://doi.org/10.1186/1471-2407-11-31.
[97] V. Mittal, Epithelial mesenchymal transition in tumor metastasis, Annu. Rev. Pathol. 13 (2018) 395–412, https://doi.org/10.1146/annurev-pathol-020117-043854.
[98] D. Bhagirath, T.L. Yang, N. Bucay, et al., microRNA-1246 is an exosomal biomarker for aggressive prostate cancer, Cancer Res. 78 (7) (2018) 1833–1844, https://doi.org/10.1158/0008-5472.CAN-17-2069.
[99] X. Wang, X. Wang, Z. Zhu, et al., Prostate carcinoma cell-derived exosomal MicroRNA-26a modulates the metastasis and tumor growth of prostate carcinoma, Biomed. Pharmacother. 117 (2019) 109109, https://doi.org/10.1016/j.biopha.2019.109109.
[100] M. Kato, Y. Goto, R. Matsushita, et al., MicroRNA-26a/b directly regulate La-related protein 1 and inhibit cancer cell invasion in prostate cancer, Int. J. Oncol. 47 (2) (2015) 710–718, https://doi.org/10.3892/ijo.2015.3043.
[101] Z.Y. Abd Elmageed, Y. Yang, R. Thomas, et al., Neoplastic reprogramming of patient-derived adipose stem cells by prostate cancer cell-associated exosomes, Stem Cell. 32 (4) (2014) 983–997, https://doi.org/10.1002/stem.1619.
[102] Y. Guo, J. Cui, Z. Ji, et al., miR-302/367/LATS2/YAP pathway is essential for prostate tumor-propagating cells and promotes the development of castration resistance, Oncogene 36 (45) (2017) 6336–6347, https://doi.org/10.1038/onc.2017.240.
[103] S. Sheth, S. Jajoo, T. Kaur, et al., Resveratrol reduces prostate cancer growth and metastasis by inhibiting the Akt/MicroRNA-21 pathway, PLoS One 7 (12) (2012) e51655, https://doi.org/10.1371/journal.pone.0051655.
[104] D. Albino, M. Falcione, V. Uboldi, et al., Circulating extracellular vesicles release oncogenic miR-424 in experimental models and patients with aggressive prostate cancer, Commun. Biol. 4 (1) (2021) 119, https://doi.org/10.1038/s42003-020-01642-5.
[105] C. Dallavalle, D. Albino, G. Civenni, et al., MicroRNA-424 impairs ubiquitination to activate STAT3 and promote prostate tumor progression, J. Clin. Invest. 126 (12) (2016) 4585–4602, https://doi.org/10.1172/JCI86505.
[106] L. Mezzasoma, E. Costanzi, P. Scarpelli, V.N. Talesa, I. Bellezza, Extracellular vesicles from human advanced-stage prostate cancer cells modify the inflammatory response of microenvironment-residing cells, Cancers 11 (9) (2019), https://doi.org/10.3390/cancers11091276.
[107] J. Rong, L. Xu, Y. Hu, et al., Inhibition of let-7b-5p contributes to an anti-tumorigenic macrophage phenotype through the SOCS1/STAT pathway in prostate cancer, Cancer Cell Int. 20 (2020) 470, https://doi.org/10.1186/s12935-020-01563-7.

[108] Y. Ye, S.L. Li, Y.Y. Ma, et al., Exosomal miR-141-3p regulates osteoblast activity to promote the osteoblastic metastasis of prostate cancer, Oncotarget 8 (55) (2017) 94834–94849, https://doi.org/10.18632/oncotarget.22014.
[109] V. Tripathi, N.C. Popescu, D.B. Zimonjic, DLC1 induces expression of E-cadherin in prostate cancer cells through Rho pathway and suppresses invasion, Oncogene 33 (6) (2014) 724–733, https://doi.org/10.1038/onc.2013.7.
[110] S.L. Li, N. An, B. Liu, et al., Exosomes from LNCaP cells promote osteoblast activity through miR-375 transfer, Oncol. Lett. 17 (5) (2019) 4463–4473, https://doi.org/10.3892/ol.2019.10110.
[111] N.B. Lei, X. Liang, P. Wang, Q. Liu, W.G. Wang, Teriparatide alleviates osteoporosis by promoting osteogenic differentiation of hMSCs via miR-375/RUNX2 axis, Eur. Rev. Med. Pharmacol. Sci. 23 (24) (2019) 11043–11050, https://doi.org/10.26355/eurrev_201912_19812.
[112] S.K. Baniwal, O. Khalid, Y. Gabet, et al., Runx2 transcriptome of prostate cancer cells: insights into invasiveness and bone metastasis, Mol. Cancer 9 (1) (2010) 258, https://doi.org/10.1186/1476-4598-9-258.
[113] K. Hashimoto, H. Ochi, S. Sunamura, et al., Cancer-secreted hsa-miR-940 induces an osteoblastic phenotype in the bone metastatic microenvironment via targeting ARHGAP1 and FAM134A, Proc. Natl. Acad. Sci. U.S.A. 115 (9) (2018) 2204–2209, https://doi.org/10.1073/pnas.1717363115.
[114] McBeath Rowena, Dana M. Pirone, Celeste M. Nelson, Kiran Bhadriraju, Christopher S. Chen, Cell shape, cytoskeletal tension, and RhoA regulate stem cell lineage commitment, Dev. Cell 6 (4) (2004) 483–495.
[115] M.R. Clay, M.C. Halloran, Rho activation is apically restricted by Arhgap1 in neural crest cells and drives epithelial-to-mesenchymal transition, Development 140 (15) (2013) 3198–3209, https://doi.org/10.1242/dev.095448.
[116] Z. Zou, R. Dai, N. Deng, W. Su, P. Liu, Exosomal miR-1275 secreted by prostate cancer cells modulates osteoblast proliferation and activity by targeting the SIRT2/RUNX2 cascade, Cell Transplant. 30 (2021) 9636897211052977, https://doi.org/10.1177/09636897211052977.
[117] G. Furesi, A.M. de Jesus Domingues, D. Alexopoulou, et al., Exosomal miRNAs from prostate cancer impair osteoblast function in mice, Int. J. Mol. Sci. 23 (3) (2022), https://doi.org/10.3390/ijms23031285.
[118] T.R. Graham, V.A. Odero-Marah, L.W. Chung, et al., PI3K/Akt-dependent transcriptional regulation and activation of BMP-2-Smad signaling by NF-kappaB in metastatic prostate cancer cells, Prostate 69 (2) (2009) 168–180, https://doi.org/10.1002/pros.20870.
[119] L. Yu, B. Sui, W. Fan, et al., Exosomes derived from osteogenic tumor activate osteoclast differentiation and concurrently inhibit osteogenesis by transferring COL1A1-targeting miRNA-92a-1-5p, J. Extracell. Vesicles 10 (3) (2021) e12056, https://doi.org/10.1002/jev2.12056.
[120] J.A. Rodriguez-Nieves, S.C. Patalano, D. Almanza, M. Gharaee-Kermani, J. A. Macoska, CXCL12/CXCR4 Axis activation mediates prostate myofibroblast phenoconversion through non-canonical EGFR/MEK/ERK signaling, PLoS One 11 (7) (2016) e0159490, https://doi.org/10.1371/journal.pone.0159490.
[121] I.Y. El-Sayed, A. Daher, D. Destouches, et al., Extracellular vesicles released by mesenchymal-like prostate carcinoma cells modulate EMT state of recipient epithelial-like carcinoma cells through regulation of AR signaling, Cancer Lett. 410 (2017) 100–111, https://doi.org/10.1016/j.canlet.2017.09.010.
[122] P.C. Lin, Y.L. Chiu, S. Banerjee, et al., Epigenetic repression of miR-31 disrupts androgen receptor homeostasis and contributes to prostate cancer progression, Cancer Res. 73 (3) (2013) 1232–1244, https://doi.org/10.1158/0008-5472.CAN-12-2968.
[123] N. Bhatnagar, X. Li, S.K. Padi, et al., Downregulation of miR-205 and miR-31 confers resistance to chemotherapy-induced apoptosis in prostate cancer cells, Cell Death Dis. 1 (12) (2010) e105, https://doi.org/10.1038/cddis.2010.85.
[124] J. Ribas, X. Ni, M. Haffner, et al., miR-21: an androgen receptor-regulated microRNA that promotes hormone-dependent and hormone-independent prostate cancer growth, Cancer Res. 69 (18) (2009) 7165–7169, https://doi.org/10.1158/0008-5472.CAN-09-1448.
[125] D. Coradduzza, S. Cruciani, C. Arru, et al., Role of miRNA-145, 148, and 185 and stem cells in prostate cancer, Int. J. Mol. Sci. 23 (3) (2022), https://doi.org/10.3390/ijms23031626.
[126] J.H. He, J.Z. Zhang, Z.P. Han, et al., Reciprocal regulation of PCGEM1 and miR-145 promote proliferation of LNCaP prostate cancer cells, J. Exp. Clin. Cancer Res. 33 (1) (2014) 72, https://doi.org/10.1186/s13046-014-0072-y.
[127] Z. Cao, L. Xu, S. Zhao, Exosome-derived miR-27a produced by PSC-27 cells contributes to prostate cancer chemoresistance through p53, Biochem. Biophys. Res. Commun. 515 (2) (2019) 345–351, https://doi.org/10.1016/j.bbrc.2019.05.120.
[128] W.H. Chappell, S. Candido, S.L. Abrams, et al., Influences of TP53 and the anti-aging DDR1 receptor in controlling Raf/MEK/ERK and PI3K/Akt expression and chemotherapeutic drug sensitivity in prostate cancer cell lines, Aging (Albany NY) 12 (11) (2020) 10194–10210, https://doi.org/10.18632/aging.103377.
[129] L.E. Pascal, Y. Wang, M. Zhong, et al., EAF2 and p53 Co-regulate STAT3 activation in prostate cancer, Neoplasia 20 (4) (2018) 351–363, https://doi.org/10.1016/j.neo.2018.01.011.
[130] G. Shan, J. Gu, D. Zhou, et al., Cancer-associated fibroblast-secreted exosomal miR-423-5p promotes chemotherapy resistance in prostate cancer by targeting GREM2 through the TGF-beta signaling pathway, Exp. Mol. Med. 52 (11) (2020) 1809–1822, https://doi.org/10.1038/s12276-020-0431-z.
[131] C. Corcoran, S. Rani, L. O'Driscoll, miR-34a is an intracellular and exosomal predictive biomarker for response to docetaxel with clinical relevance to prostate cancer progression, Prostate 74 (13) (2014) 1320–1334, https://doi.org/10.1002/pros.22848.
[132] Y. Li, B. Zhang, L. Xiang, et al., TGF-Beta causes docetaxel resistance in prostate cancer via the induction of Bcl-2 by acetylated KLF5 and protein stabilization, Theranostics 10 (17) (2020) 7656–7670, https://doi.org/10.7150/thno.44567.
[133] C. Tang, T. Liu, K. Wang, et al., Transcriptional regulation of FoxM1 by HIF-1alpha mediates hypoxia-induced EMT in prostate cancer, Oncol. Rep. 42 (4) (2019) 1307–1318, https://doi.org/10.3892/or.2019.7248.
[134] J.H. Kim, H. Lee, E.A. Shin, et al., Implications of Bcl-2 and its interplay with other molecules and signaling pathways in prostate cancer progression, Expert Opin. Ther. Targets 21 (9) (2017) 911–920, https://doi.org/10.1080/14728222.2017.1369044.
[135] J. Wang, X. Yang, R. Li, et al., Long non-coding RNA MYU promotes prostate cancer proliferation by mediating the miR-184/c-Myc axis, Oncol. Rep. 40 (5) (2018) 2814–2825, https://doi.org/10.3892/or.2018.6661.
[136] R.J. Rebello, R.B. Pearson, R.D. Hannan, L. Furic, Therapeutic approaches targeting MYC-driven prostate cancer, Genes 8 (2) (2017) 71, https://doi.org/10.3390/genes8020071.
[137] J. Ge, W. Yu, J. Li, et al., USP16 regulates castration-resistant prostate cancer cell proliferation by deubiquitinating and stablizing c-Myc, J. Exp. Clin. Cancer Res. 40 (1) (2021) 59, https://doi.org/10.1186/s13046-021-01843-8.
[138] T. Ding, Y. Zhu, H. Jin, et al., Circular RNA circ_0057558 controls prostate cancer cell proliferation through regulating miR-206/USP33/c-Myc Axis, Front. Cell Dev. Biol. 9 (2021) 644397, https://doi.org/10.3389/fcell.2021.644397.
[139] Q. Li, J. Hu, Y. Shi, et al., Exosomal lncAY927529 enhances prostate cancer cell proliferation and invasion through regulating bone microenvironment, Cell Cycle 20 (23) (2021) 2531–2546, https://doi.org/10.1080/15384101.2021.1992853.
[140] H.Y. Tian, Q. Liang, Z. Shi, H. Zhao, Exosomal CXCL14 contributes to M2 macrophage polarization through NF-kappaB signaling in prostate cancer, Oxid. Med. Cell. Longev. 2022 (2022) 7616696, https://doi.org/10.1155/2022/7616696.
[141] X. Yang, L. Wang, R. Li, et al., The long non-coding RNA PCSEAT exhibits an oncogenic property in prostate cancer and functions as a competing endogenous RNA that associates with EZH2, Biochem. Biophys. Res. Commun. 502 (2) (2018) 262–268, https://doi.org/10.1016/j.bbrc.2018.05.157.
[142] J. Chen, F. Wang, H. Xu, et al., Long non-coding RNA SNHG1 regulates the Wnt/beta-catenin and PI3K/AKT/mTOR signaling pathways via EZH2 to affect the proliferation, apoptosis, and autophagy of prostate cancer cell, Front. Oncol. 10 (2020) 552907, https://doi.org/10.3389/fonc.2020.552907.
[143] Y. Jiang, H. Zhao, Y. Chen, et al., Exosomal long noncoding RNA HOXD-AS1 promotes prostate cancer metastasis via miR-361-5p/FOXM1 axis, Cell Death Dis. 12 (12) (2021) 1129, https://doi.org/10.1038/s41419-021-04421-0.
[144] Y. Liu, Z. Gong, L. Sun, X. Li, FOXM1 and androgen receptor co-regulate CDC6 gene transcription and DNA replication in prostate cancer cells, Biochim. Biophys. Acta 1839 (4) (2014) 297–305, https://doi.org/10.1016/j.bbagrm.2014.02.016.
[145] C. Mo, B. Huang, J. Zhuang, et al., LncRNA nuclear-enriched abundant transcript 1 shuttled by prostate cancer cells-secreted exosomes initiates osteoblastic phenotypes in the bone metastatic microenvironment via miR-205-5p/runt-related transcription factor 2/splicing factor proline- and glutamine-rich/polypyrimidine tract-binding protein 2 axis, Clin. Transl. Med. 11 (8) (2021) e493, https://doi.org/10.1002/ctm2.493.
[146] U.R. Chandran, C. Ma, R. Dhir, et al., Gene expression profiles of prostate cancer reveal involvement of multiple molecular pathways in the metastatic process, BMC Cancer 7 (2007) 64, https://doi.org/10.1186/1471-2407-7-64.
[147] K. Desai, J.M. McManus, N. Sharifi, Hormonal therapy for prostate cancer, Endocr. Rev. 42 (3) (2021) 354–373, https://doi.org/10.1210/endrev/bnab002.
[148] Z. Guo, X. Lu, F. Yang, et al., Exosomal LINC01213 plays a role in the transition of androgen-dependent prostate cancer cells into androgen-independent manners, J. Oncol. 2022 (2022) 8058770, https://doi.org/10.1155/2022/8058770.
[149] V. Murillo-Garzon, R. Kypta, WNT signalling in prostate cancer, Nat. Rev. Urol. 14 (11) (2017) 683–696, https://doi.org/10.1038/nrurol.2017.144.
[150] Y. Tang, J. Liu, X. Li, W. Wang, Exosomal circRNA HIPK3 knockdown inhibited cell proliferation and metastasis in prostate cancer by regulating miR-212/BMI-1 pathway, J. Biosci. 46 (3) (2021) 69, https://doi.org/10.1007/s12038-021-00190-2.
[151] Malathi Ramalinga, Arpita Roy, Anvesha Srivastava, et al., MicroRNA-212 negatively regulates starvation induced autophagy in prostate cancer cells by inhibiting SIRT1 and is a modulator of angiogenesis and cellular senescence, Oncotarget 6 (33) (2015) 34446–34457.
[152] R.U. Lukacs, S. Memarzadeh, H. Wu, O.N. Witte, Bmi-1 is a crucial regulator of prostate stem cell self-renewal and malignant transformation, Cell Stem Cell 7 (6) (2010) 682–693, https://doi.org/10.1016/j.stem.2010.11.013.
[153] L. Jiang, L. Song, J. Wu, et al., Bmi-1 promotes glioma angiogenesis by activating NF-kappaB signaling, PLoS One 8 (1) (2013) e55527, https://doi.org/10.1371/journal.pone.0055527.
[154] T. Li, X. Sun, L. Chen, Exosome circ_0044516 promotes prostate cancer cell proliferation and metastasis as a potential biomarker, J. Cell. Biochem. 121 (3) (2020) 2118–2126, https://doi.org/10.1002/jcb.28239.
[155] B. Liao, S. Chen, Y. Li, et al., LncRNA BLACAT1 promotes proliferation, migration and invasion of prostate cancer cells via regulating miR-29a-3p/DVL3 Axis, Technol. Cancer Res. Treat. 20 (2021) 1533033820972342, https://doi.org/10.1177/1533033820972342.
[156] K. Wu, S.M. Woo, S.U. Seo, T.K. Kwon, Inhibition of BMI-1 induces apoptosis through downregulation of DUB3-mediated Mcl-1 stabilization, Int. J. Mol. Sci. 22 (18) (2021) 10107, https://doi.org/10.3390/ijms221810107.
[157] G. Zhang, Y. Liu, J. Yang, H. Wang, Z. Xing, Inhibition of circ_0081234 reduces prostate cancer tumor growth and metastasis via the miR-1/MAP 3 K1 axis, J. Gene Med. 24 (8) (2022) e3376, https://doi.org/10.1002/jgm.3376.

[158] V. Odero-Marah, O. Hawsawi, V. Henderson, J. Sweeney, Epithelial-mesenchymal transition (EMT) and prostate cancer, Adv. Exp. Med. Biol. 1095 (2018) 101–110, https://doi.org/10.1007/978-3-319-95693-0_6.
[159] M. Jin, T. Zhang, C. Liu, et al., miRNA-128 suppresses prostate cancer by inhibiting BMI-1 to inhibit tumor-initiating cells, Cancer Res. 74 (15) (2014) 4183–4195, https://doi.org/10.1158/0008-5472.CAN-14-0404.
[160] N. Bansal, M. Bartucci, S. Yusuff, et al., BMI-1 targeting interferes with patient-derived tumor-initiating cell survival and tumor growth in prostate cancer, Clin. Cancer Res. 22 (24) (2016) 6176–6191, https://doi.org/10.1158/1078-0432.CCR-15-3107.
[161] H. Zhang, M. Li, J. Zhang, Y. Shen, Q. Gui, Exosomal circ-XIAP promotes docetaxel resistance in prostate cancer by regulating miR-1182/TPD52 Axis, Drug Des. Dev. Ther. 15 (2021) 1835–1849, https://doi.org/10.2147/DDDT.S300376.
[162] J.A. Byrne, S. Frost, Y. Chen, R.K. Bright, Tumor protein D52 (TPD52) and cancer-oncogene understudy or understudied oncogene? Tumour Biol. 35 (8) (2014) 7369–7382, https://doi.org/10.1007/s13277-014-2006-x.
[163] R. Ummanni, S. Teller, H. Junker, et al., Altered expression of tumor protein D52 regulates apoptosis and migration of prostate cancer cells, FEBS J. 275 (22) (2008) 5703–5713, https://doi.org/10.1111/j.1742-4658.2008.06697.x.
[164] D. Zhang, D. He, Y. Xue, et al., PrLZ protects prostate cancer cells from apoptosis induced by androgen deprivation via the activation of Stat3/Bcl-2 pathway, Cancer Res. 71 (6) (2011) 2193–2202, https://doi.org/10.1158/0008-5472.CAN-10-1791.
[165] Y. Yang, K.Y. Liu, Q. Liu, Q. Cao, Androgen receptor-related non-coding RNAs in prostate cancer, Front. Cell Dev. Biol. 9 (2021) 660853, https://doi.org/10.3389/fcell.2021.660853.
[166] M.Y. Konoshenko, O.E. Bryzgunova, P.P. Laktionov, miRNAs and androgen deprivation therapy for prostate cancer, Biochim. Biophys. Acta Rev. Canc 1876 (2) (2021) 188625, https://doi.org/10.1016/j.bbcan.2021.188625.
[167] R.K. Ghosh, T. Pandey, P. Dey, Liquid biopsy: a new avenue in pathology, Cytopathology 30 (2) (2019) 138–143, https://doi.org/10.1111/cyt.12661.
[168] L. Naji, H. Randhawa, Z. Sohani, et al., Digital rectal examination for prostate cancer screening in primary care: a systematic review and meta-analysis, Ann. Fam. Med. 16 (2) (2018) 149–154, https://doi.org/10.1370/afm.2205.
[169] Y. Li, X. Tang, R. Deng, et al., Dumbbell dual-hairpin triggered DNA nanonet assembly for cascade-amplified sensing of exosomal MicroRNA, ACS Omega 9 (17) (2024) 19723–19731, https://doi.org/10.1021/acsomega.4c02652.
[170] M. Rodriguez, C. Bajo-Santos, N.P. Hessvik, et al., Identification of non-invasive miRNAs biomarkers for prostate cancer by deep sequencing analysis of urinary exosomes, Mol. Cancer 16 (1) (2017) 156, https://doi.org/10.1186/s12943-017-0726-4.
[171] Z. Li, L.X. Li, Y.J. Diao, et al., Identification of urinary exosomal miRNAs for the non-invasive diagnosis of prostate cancer, Cancer Manag. Res. 13 (2021) 25–35, https://doi.org/10.2147/CMAR.S272140.
[172] O.E. Bryzgunova, M.M. Zaripov, T.E. Skvortsova, et al., Comparative study of extracellular vesicles from the urine of healthy individuals and prostate cancer patients, PLoS One 11 (6) (2016) e0157566, https://doi.org/10.1371/journal.pone.0157566.
[173] Y. Xu, S. Qin, T. An, et al., MiR-145 detection in urinary extracellular vesicles increase diagnostic efficiency of prostate cancer based on hydrostatic filtration dialysis method, Prostate 77 (10) (2017) 1167–1175, https://doi.org/10.1002/pros.23376.
[174] S. Wani, D. Kaul, R.S. Mavuduru, N. Kakkar, A. Bhatia, Urinary-exosomal miR-2909: a novel pathognomonic trait of prostate cancer severity, J. Biotechnol. 259 (2017) 135–139, https://doi.org/10.1016/j.jbiotec.2017.07.029.
[175] W. Li, Y. Dong, K.J. Wang, et al., Plasma exosomal miR-125a-5p and miR-141-5p as non-invasive biomarkers for prostate cancer, Neoplasma 67 (6) (2020) 1314–1318, https://doi.org/10.4149/neo_2020_191130N1234.
[176] Z. Li, Y.Y. Ma, J. Wang, et al., Exosomal microRNA-141 is upregulated in the serum of prostate cancer patients, OncoTargets Ther. 9 (2016) 139–148, https://doi.org/10.2147/OTT.S95565.
[177] R.J. Bryant, T. Pawlowski, J.W. Catto, et al., Changes in circulating microRNA levels associated with prostate cancer, Br. J. Cancer 106 (4) (2012) 768–774, https://doi.org/10.1038/bjc.2011.595.
[178] Y. Li, J. Ji, J. Lyu, et al., A novel urine exosomal lncRNA assay to improve the detection of prostate cancer at initial biopsy: a retrospective multicenter diagnostic feasibility study, Cancers 13 (16) (2021), https://doi.org/10.3390/cancers13164075.
[179] Y.H. Wang, J. Ji, B.C. Wang, et al., Tumor-derived exosomal long noncoding RNAs as promising diagnostic biomarkers for prostate cancer, Cell. Physiol. Biochem. 46 (2) (2018) 532–545, https://doi.org/10.1159/000488620.
[180] A. Ahadi, S. Brennan, P.J. Kennedy, G. Hutvagner, N. Tran, Long non-coding RNAs harboring miRNA seed regions are enriched in prostate cancer exosomes, Sci. Rep. 6 (2016) 24922, https://doi.org/10.1038/srep24922.
[181] M. Isin, E. Uysaler, E. Ozgur, et al., Exosomal lncRNA-p21 levels may help to distinguish prostate cancer from benign disease, Front. Genet. 6 (2015) 168, https://doi.org/10.3389/fgene.2015.00168.
[182] Y. Wu, Circ_0044516 enriches the level of SARM1 as a miR-330-5p sponge to regulate cell malignant behaviors and tumorigenesis of prostate cancer, Biochem. Genet. 60 (4) (2022) 1346–1361, https://doi.org/10.1007/s10528-021-10160-w.
[183] T. Guo, Y. Wang, J. Jia, et al., The identification of plasma exosomal miR-423-3p as a potential predictive biomarker for prostate cancer castration-resistance development by plasma exosomal miRNA sequencing, Front. Cell Dev. Biol. 8 (2020) 602493, https://doi.org/10.3389/fcell.2020.602493.
[184] X. Huang, T. Yuan, M. Liang, et al., Exosomal miR-1290 and miR-375 as prognostic markers in castration-resistant prostate cancer, Eur. Urol. 67 (1) (2015) 33–41, https://doi.org/10.1016/j.eururo.2014.07.035.
[185] S. Wang, W. Su, C. Zhong, et al., An eight-CircRNA assessment model for predicting biochemical recurrence in prostate cancer, Front. Cell Dev. Biol. 8 (2020) 599494, https://doi.org/10.3389/fcell.2020.599494.
[186] Y. Wei, W. Zhou, X. Li, et al., Coupling hybridization chain reaction with catalytic hairpin assembly enables non-enzymatic and sensitive fluorescent detection of microRNA cancer biomarkers, Biosens. Bioelectron. 77 (2016) 416–420, https://doi.org/10.1016/j.bios.2015.09.053.
[187] Q. Wang, J. Liu, J. Zeng, et al., Determination of miRNA derived from exosomes of prostate cancer via toehold-aided cyclic amplification combined with HRP enzyme catalysis and magnetic nanoparticles, Anal. Biochem. 630 (2021) 114336, https://doi.org/10.1016/j.ab.2021.114336.
[188] J. Kim, J.S. Shim, B.H. Han, et al., Hydrogel-based hybridization chain reaction (HCR) for detection of urinary exosomal miRNAs as a diagnostic tool of prostate cancer, Biosens. Bioelectron. 192 (2021) 113504, https://doi.org/10.1016/j.bios.2021.113504.
[189] S. Cho, H.C. Yang, W.J. Rhee, Simultaneous multiplexed detection of exosomal microRNAs and surface proteins for prostate cancer diagnosis, Biosens. Bioelectron. 146 (2019) 111749, https://doi.org/10.1016/j.bios.2019.111749.
[190] G.Y. Xiao, C.C. Cheng, Y.S. Chiang, et al., Exosomal miR-10a derived from amniotic fluid stem cells preserves ovarian follicles after chemotherapy, Sci. Rep. 6 (2016) 23120, https://doi.org/10.1038/srep23120.
[191] M. Khan, E. Nickoloff, T. Abramova, et al., Embryonic stem cell-derived exosomes promote endogenous repair mechanisms and enhance cardiac function following myocardial infarction, Circ. Res. 117 (1) (2015) 52–64, https://doi.org/10.1161/CIRCRESAHA.117.305990.
[192] S.P. Li, Z.X. Lin, X.Y. Jiang, X.Y. Yu, Exosomal cargo-loading and synthetic exosome-mimics as potential therapeutic tools, Acta Pharmacol. Sin. 39 (4) (2018) 542–551, https://doi.org/10.1038/aps.2017.178.
[193] T.A. Shtam, R.A. Kovalev, E.Y. Varfolomeeva, et al., Exosomes are natural carriers of exogenous siRNA to human cells in vitro, Cell Commun. Signal. 11 (2013) 88, https://doi.org/10.1186/1478-811X-11-88.
[194] T.N. Lamichhane, A. Jeyaram, D.B. Patel, et al., Oncogene knockdown via active loading of small RNAs into extracellular vesicles by sonication, Cell. Mol. Bioeng. 9 (3) (2016) 315–324, https://doi.org/10.1007/s12195-016-0457-4.
[195] S. Ohno, M. Takanashi, K. Sudo, et al., Systemically injected exosomes targeted to EGFR deliver antitumor microRNA to breast cancer cells, Mol. Ther. 21 (1) (2013) 185–191, https://doi.org/10.1038/mt.2012.180.
[196] L. Li, D. He, Q. Guo, et al., Exosome-liposome hybrid nanoparticle codelivery of TP and miR497 conspicuously overcomes chemoresistant ovarian cancer, J. Nanobiotechnol. 20 (1) (2022) 50, https://doi.org/10.1186/s12951-022-01264-5.
[197] X. Huang, W. Wu, D. Jing, et al., Engineered exosome as targeted lncRNA MEG3 delivery vehicles for osteosarcoma therapy, J. Contr. Release 343 (2022) 107–117, https://doi.org/10.1016/j.jconrel.2022.01.026.
[198] L. Yang, B. Han, Z. Zhang, et al., Extracellular vesicle-mediated delivery of circular RNA SCMH1 promotes functional recovery in rodent and nonhuman primate ischemic stroke models, Circulation 142 (6) (2020) 556–574, https://doi.org/10.1161/CIRCULATIONAHA.120.045765.
[199] A. Yamayoshi, S. Oyama, Y. Kishimoto, et al., Development of antibody-oligonucleotide complexes for targeting exosomal MicroRNA, Pharmaceutics 12 (6) (2020), https://doi.org/10.3390/pharmaceutics12060545.