



## A Review of The Role of Exosomes in Prostate Cancer

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### Abstract:

Prostate cancer (PCa) is the most common solid tumor in men. While patients with local PCa have better prognostic survival, patients with metastatic PCa have relatively high mortality rates. Exosomes (and other extracellular vesicles) are now part of the cancer research landscape, involved both as players in pathophysiological mechanisms, as biomarkers of the cancer process, and as therapeutic tools. Exosomes contain miRNAs, mRNAs, and proteins with the potential to regulate signaling pathways in recipient cells. Accumulating evidence indicates that exosomes play important roles in cell communication and tumor progression and are suitable for monitoring PCa progression and metastasis. We review the role of exosomes and exosomal microRNAs in biological processes of prostate cancer progression for treatment personalization.

## INTRODUCTION

Prostate cancer (PCa) is the second most frequent tumor in males. PCa is a high prevalence in developing countries. Most individuals with prostate cancer present with locally advanced or metastatic disease at diagnosis thus limiting the effectiveness of conventional therapies. Prostate-specific antigen (PSA) is a widely utilized biomarker for PCa screening, nonetheless, it does not provide precise and accurate diagnostic and prognostic information (1, 2). Importantly, the tumors of many patients with prostate cancer are refractory to androgen therapy and progress to metastatic castration-resistant disease (3). An effective treatment course for prostate cancer patients requires predictive biomarkers in metastatic castration-resistant prostate cancer that support individual therapy (4). Like all epithelial cancers, prostate cancer (PCa) has not escaped the exosomal fever that has affected both researchers and clinicians for the last twenty years with the development of extracellular vesicles (EVs) individualization and counting techniques, and omics characterization techniques (5).

During cancer development, signal transmission

between cells plays a vital role in tumor formation, progression, and metastasis. Exosomes are small extracellular vesicles (EV) ranging from 50 to 150 nm in diameter. Exosomes have a double membrane structure with various cargo contents, such as miRNAs, mRNAs, proteins, lipids, and viral particles (6). Over the last decade, exosome research has rapidly expanded, and the number of coherent publications has gradually increased (7). Exosomes are present in various biological fluids, for instance, blood, urine, milk, semen as well as saliva, and can be purified from the cell growth medium. The biological function of an exosome depends on the contents of the cargo, for instance, miRNAs, viral particles, mRNAs, proteins, or lipids (8). The complex signaling pathway network between exosome-mediated cancer cells and the tumor microenvironment (TME) is considered a key factor in the progression of cancer at all stages (9). It has been shown that urinary markers can aid in the decision-making process regarding whether to carry out a prostate biopsy and in the design of a therapeutic strategy. Urinary exosomes and their cargo, especially miR-21 and miR-375, have become an emerging source of biomarkers in the detection

and prognosis of PCa (10).

The main objective of this review is to describe recent progress in exosome research focusing on the potential role of exosomes as novel biomarkers for PCa.

#### *Exosomes: Structure and Function*

Exosomes are small (from 30 to 120 nm in diameter) extracellular vesicles (EVs). Their lipid bilayer membrane, with a width of 5 nm, protects them from the negative action of RNases and proteases. Exosomes comprise a lipid bilayer membrane and encapsulated molecules. Components of the membrane include lipids and proteins (11). Exosomes have longer retention in circulation in comparison to polymersomes or liposomes (12). According to the International Society of Extracellular Vesicles (ISEV), the term “extracellular vesicles” is the appropriate terminology for heterogeneous populations of vesicles isolated from cell culture supernatants or physiological fluids (13). Exosome shedding is a process with a wide range of important regulatory functions. Their discovery in sheep reticulocyte maturation gave rise to the idea that exosomes may function as a trash bin for unnecessary and redundant proteins and therefore could be an alternative pathway for lysosomal degradation (14). Exosomes are released by the exocytosis of multivesicular bodies (MVBs), developed from early and then late endosomes. Those naturally occurring membrane particles mediate intercellular communication by delivering molecular information between cancer and stromal cells, especially cancer-associated fibroblasts (CAFs) (14, 15). Exosomes are present in body fluids, including the plasma, cerebrospinal fluid, and urine. As a material “transport carrier” in the circulated body fluids, exosomes play an important role in a variety of physiological and pathological processes due to their ability to carry a variety of proteins, nucleic acids, and lipids, transporting the contents to surrounding cells for inter-cell communication (16).

In vivo studies in mice have shown that some exosomes can directly deliver mRNA to recipient cells, especially under the stimulation of acute or chronic infections (17). Exosomes also have immunoregulatory activities including antigen presentation and immune tolerance. Exosomes carrying MHC class II complexes that bind to tumor-specific antigens were able to significantly inhibit tumor growth in mice (18). These exosomes may indirectly activate naïve T cells and B cells by interacting with antigen-presenting cells, and may also promote the proliferation of CD4+ T cells (19). Recent studies point out that exosomes released from the tumor microenvironment can regulate (also by tethering TGF) a proliferation, a reduction of apoptosis, promotion of angiogenesis, and, finally, evasion of immune surveillance. Moreover, exosomes

can provide candidate biomarkers for prostate cancer, contribute to tumor progression and, after a loss of environment homeostasis, promote tumor metastasis (19, 20).

#### *Role of Exosomes in Cancer*

In recent years, research has focused on the usefulness of exosomes in diagnosing cancer patients as well as monitoring their responses to therapy (21). Because of stability, exosomes are easily harvested from a variety of accessible body fluids. This makes them attractive targets for developing new methods for detecting cancer (22). The use of exosomes and exosomal cargo for cancer diagnostics requires the identification of the most commonly deregulated genes for a specific cancer type (23). Among the different types of exosomes, tumor cell-derived exosomes play an essential role in the invasion and metastasis of cancer cells. Tumor cell-derived exosomes can transmit tumor metastasis signals, determine the direction of cancer cell metastasis, and promote epithelial-mesenchymal transformation (EMT) and angiogenesis. In some tumors, cells may release higher quantities of exosomes/microvesicles when compared to normal cells. This increase in exosomes release may be caused by enhanced proliferation rates of cancer cells or cell damage triggered by chemotherapy (24). Moreover, changes in the environmental conditions, like hypoxia, also accelerate this release and can increase invasiveness. Exosomes favor cancer progression by modulating different processes, like the immune response and angiogenesis stimulation, invasion, and resistance (25). Some exosomes also have immunomodulatory functions and cancer treatment potential (22, 26, and 27).

Prostate cells release diverse types of membrane vesicles into extracellular environment. These vesicles released from prostate epithelial cells at times described as ‘prostasomes’ correspond to bigger sized (30-200nm) vesicles as compared to the exosomes. PCa exosomes are thought to favor the microenvironment for the cellular transformation into tumors, and a large part of such exosomes are also released to prostatic secretions like urine and blood (28). The release of exosomes in biofluids could have major advantages to shed light on complex mechanisms of tumor progression and treatment response. The intercellular exchange of genetic and non-genetic signals via extracellular vesicles (herein, named exosomes) is an emergent tool in personalized cancer medicine (29).

#### *Exosome Functions in Prostate Cancer*

Most deaths of advanced prostate cancer patients are due to the metastasis of prostate cancer. Exosomes derived from tumors can be taken by the cells of specific organs and assist in the formation of the pre-metastatic niche. Prostate cancer has metastatic organotropism of

the bone (30). Bone metastasis is the most common type of metastasis from advanced prostate cancer (PCa). Pyruvate kinase M2 (PKM2) is transported through exosomes from PCa cells into BMSCs (bone marrow stromal cells) (31). This feature is a novel mechanism via which primary tumor-originated exosomes enhance premetastatic niche formation (32). PCa-derived exosomes upregulate PKM2 expression, which ultimately upregulates CXCL12 expression (C-X-C motif chemokine ligand-12) in BMSCs thus inducing a pre-metastatic niche. Targeting the exosome-triggered CXCL12 axis abrogates exosome-stimulated bone metastasis indicating the therapeutic potential of targeting exosome-derived PKM2 (33, 34). Exosomes are key biomarkers for the early diagnosis of PCa, personalized treatment, and prognosis of patients (35). Exosomes in the blood and urine of PCa patients were reported to contain unique PCa-specific components, which are the source of biomarkers for PCa metastasis identified 36 exosomal miRNAs and proteins as candidate biomarkers for PCa in clinical studies (36). In prostate cancer, plasma vesicles, isolated using the precipitation-based ExoQuick method identified miR-1290 and miR-375 as potential prognostic biomarkers in castration-resistant prostate cancer (CRPC), since their level correlates with poorer overall survival ( $p < 0.004$ ) (37). Prostate cancer-derived exosomes contained TGF- $\beta$  which induced the conversion from bone marrow mesenchymal stem cells to fibroblasts. Exosomes can prepare a pre-metastatic niche. For example, exosomal miR-21, miR-375, and miR-141 help cancer cells overcome the low-androgen conditions in distant metastatic organs (38).

RNA expression analysis of urine-derived and PCa cell line-derived exosomes revealed that the known RNA markers for PCa, such as the TMPRSS2:ERG fusion gene and prostate cancer antigen 3 (PCA3), can be detected in exosomes by reverse transcriptase-polymerase chain reaction (39). The TMPRSS2:ERG fusion transcripts were detected in urinary exosomes from two patients with high Gleason scores but not in those from two patients with low Gleason scores. PCA3 mRNA was detected in exosomes derived from all patients (40). exosomal miR-26a derived from PCa cells significantly changed the expression of epithelial-mesenchymal transition (EMT)- related factors and inhibited the metastasis and tumor growth of PCa. Exosomal integrin  $\alpha v\beta 3$  can also increase PCa aggressiveness. These biologically active molecules in exosomes are promising key biomarkers for PCa diagnosis, metastasis detection, individualized treatment, and patient prognosis (41, 42).

#### *Invasion and Metastasis of Prostate Cancer*

Tumor metastasis is a complicated process, including vascular leakiness and an alteration of

the microenvironment, in which exosomes are also involved (42). Initially, exosomes begin an epithelial-mesenchymal transition (EMT) via miRNAs by losing their junction and adhesion ability. Thus, epithelial tumor cells obtain mesenchymal cell properties and are responsive to malignancy (43). The tumor microenvironment contributes to the regulation of prostate cancer progression through proliferation, angiogenesis, and metastasis, and it also regulates immunity (44). Exosomes released from the TME regulate proliferation, reduce apoptosis, promote angiogenesis, and regulate immune escape, thus promoting the invasion and metastasis of PCa (45).

#### *Exosomes in prostate cancer therapy*

EVs can be used as carriers to deliver therapeutic agents to tumor cells, leading to an effective tumor cell killing, while minimizing the side effects of the drugs (46). Exosomes can be used as a delivery vector to target cancer cells and the contents can escape the attack by the immune system (47). Adipose-derived stromal cells (ASCs) derived exosomal miR-145 could reduce the activity of Bcl-xL and promote prostate cancer cell apoptosis via the caspase-3/7 pathway. Therefore, ASCs-derived exosomes can be used in prostate cancer therapy (48). Qi et al. confirmed that drug-loaded exosomes enhanced cancer cell targeting under an external magnetic field and suppressed tumor growth (49). Saari et al. confirmed that cancer cell-derived EVs can be used as effective carriers of Paclitaxel to autologous prostate cancer cells by increasing its cytotoxicity (50).

The simultaneous application of either radiation technology or nuclear medicine with exosomes are promising tools for the realization of the enhancement of targeting strategies using radiation technology (51). Exosomes are also utilized in tumor vaccination. Tumor-derived exosomes often contain tumor-specific antigens to activate dendritic cells which induce the antitumor response of T lymphocytes (52).

In personalized medicine, customized treatment depends on information about the molecular characteristics of the cancer signature, namely personalized diagnostics. Biomarkers in personalized diagnostics can be divided into several subgroups according to their application: screening, early diagnosis, prognosis, prediction, monitoring, and companion diagnostics (53). In contrast to invasive tissue biopsy, exosomes are effective biomarkers in the diversified diagnosis of personalized medicine. Secondly, exosomes are akin to vessels enriched with much information about the parental cells, and the cargoes in exosomes are protected by the phospholipid bilayer from degradation by proteinases and nucleases. Consequently, biomarkers at a relatively low expression are much easier to be detected through

isolating exosomes. For instance, some biomarkers such as PCA3 and TMPRSS2 are mRNAs not easily detected in body fluids but appear in exosomes in prostate cancer (54).

## CONCLUSIONS

Exosomes are small vesicles (50–100 nm) secreted by almost all tissues, representing their tissue origin. By isolating these exosomes, several problems of biomarker discovery from complex body fluids can be largely solved. Many biological molecules are encapsulated in the exosomes from prostate cancer such as miRNAs, lncRNAs, and proteins and their expression levels differ from those of normal prostate cells. The unique characteristics of exosomes such as high stability and high biocompatibility imply that they are potential effective drug delivery systems. However, further studies on the translation of EVs into clinical therapies should be conducted to design standards for exosome classification and manipulation. In summary, exosomes are prospective tools for the development of diagnosis, as well as therapy of PCa, however, further studies should explore the clinical application of exosomes (55, 56).

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