Review Article

Extracellular vesicles and prostate cancer management: a narrative review

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Background and Objective: Prostate cancer (PCa) is the second most common male cancer in the United States. Although new drugs have recently been approved, clinical challenges remain, notably the precise detection and prognostic implications of drug-resistant PCa. Extracellular vesicles (EVs), nanoscale lipid membrane vesicles, are actively secreted into the extracellular milieu by a variety of cell types. Over the past decade, interest in EVs has grown, and emerging evidence suggests that EVs play pivotal roles in cancer biology. In this review, we would like to summarize recent reports on EVs in PCa and discuss the potential clinical applications.

Methods: We performed a non-systematic literature review using the PubMed database to identify articles specifically related to EVs and PCa management.

Key Content and Findings: EVs contain pathogenic components, such as proteins, DNA fragments, mRNA, non-coding RNA, and lipids, all of which can trigger intercellular signaling within tumor microenvironments. Thereby, EVs exert significant effects on several stages of cancer progression, influencing the immune system, angiogenesis, and the establishment of pre-metastatic niches. Furthermore, as EVs are encapsulated, their contents are stable in bodily fluids, and thus EVs have recently attracted attention as a novel kind of liquid biopsy.

Conclusions: We have summarized recent research on how EVs may aid PCa management. To date, we have discovered only the tip of the iceberg. We anticipate that further research will yield innovative therapeutic modalities, thereby aiding all PCa patients.

Keywords: Cancer biology; prostate cancer (PCa); extracellular vesicles (EVs)

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Introduction

Prostate cancer (PCa) is the second leading cause of cancer-related death in males in the United States, and approximately one in eight men are at risk of PCa (1). The age at diagnosis and the clinical severity vary, and the disease is heterogeneous. Localized PCa can often be well-managed via surgical intervention or radiotherapy, but patients with metastatic PCa face a bleak future, with a 5-year survival

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Table 1 Search strategy summary

Items	Specification
Date of search	September 21, 2023
Databases and other sources search	PubMed
Search terms used	"extracellular vesicles", "exosomes", "prostasomes", "cancer progression", "prostate cancer", "prostatic disease"
Timeframe	Between the years 2006 and 2023
Inclusion criteria	Only English language studies were included. While peer-reviewed published manuscripts were prioritized, abstracts and textbook chapters that fit our search criteria (found on google.com) were also included
Selection process	Each author was independently involved in literature search. The primary author (F.U.) reviewed all included articles

rate of 55% (2). Androgen deprivation therapy (ADT) is the cornerstone systemic strategy for locally advanced and metastatic PCa. However, prolonged ADT is often associated with development of castration-resistant PCa (CRPC). Notably, chemotherapy enhances overall survival in patients with metastatic hormone-sensitive PCa (HSPC) and CRPC (3,4). However, a substantial subset of patients who initially respond to chemotherapy eventually become treatment-resistant. The recent regulatory approval of androgen receptor (AR) signaling inhibitors (ARSIs), such as abiraterone acetate and enzalutamide, and olaparib (a poly ADP-ribose polymerase inhibitor) has triggered a paradigm shift in PCa management (5,6). However, clinical challenges remain, including accurate screening of drug-resistant PCa. Thus, the elucidation of PCa pathology and the development of efficacious therapeutic strategies require urgent study.

Extracellular vesicles (EVs) are small lipid-bilayer membrane-bound vesicles released by all living cells. EVs were identified in 1996 (7) but were initially thought to simply remove unwanted components from cells. In 2007, a milestone study from Valadi *et al.* showed that both mRNAs and microRNAs (miRNAs) within EVs are transferred between cells (8). This principle of transferring nucleic acid to other cell was a novel concept, many researchers started to focus on the EV as research topics. EV contents reflect the characteristics of the cells from which the EVs originate. EVs contain bioactive molecules, including miRNAs, mRNAs, proteins, DNA fragments, and lipids, which are transferred to recipient cells. These EV contents then mediate intercellular signaling in the recipient cells and affect both normal physiological processes and the pathogenesis of various diseases (9). As EVs are encapsulated, their contents are stable in bodily fluids, and thus EVs will serve as useful biomarkers (10). In this review, we summarize recent reports on EVs in PCa and discuss the potential clinical applications. We present this article in accordance with the Narrative Review reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-23-533/rc).

Methods

Using PubMed, a comprehensive literature search was performed. In *Table 1*, the search strategy for articles included is given. Peer-reviewed original articles and reviews published between 2006 and 2023 were analyzed to identify articles of relevance. The keywords searched included: "extracellular vesicles", "exosomes", "prostasomes", "cancer progression", "prostate cancer", and "prostatic disease". Publications that contained information that added to the existing body of literature within the field were included.

Discussion

EVs

EVs are often subclassified into exosomes, microvesicles, and apoptotic bodies based on their secretory origin (11). Exosomes (30–120 nm in diameter) are intraluminal vesicles of multivesicular bodies (MVBs) and are released when MVBs fuse with cellular membranes (12). Microvesicles (100–1,000 nm in diameter) are directly released from cells via outward pinching of the plasma membrane (13). Apoptotic bodies (500–2,000 nm in diameter) are released during the final steps of apoptosis via plasma membrane

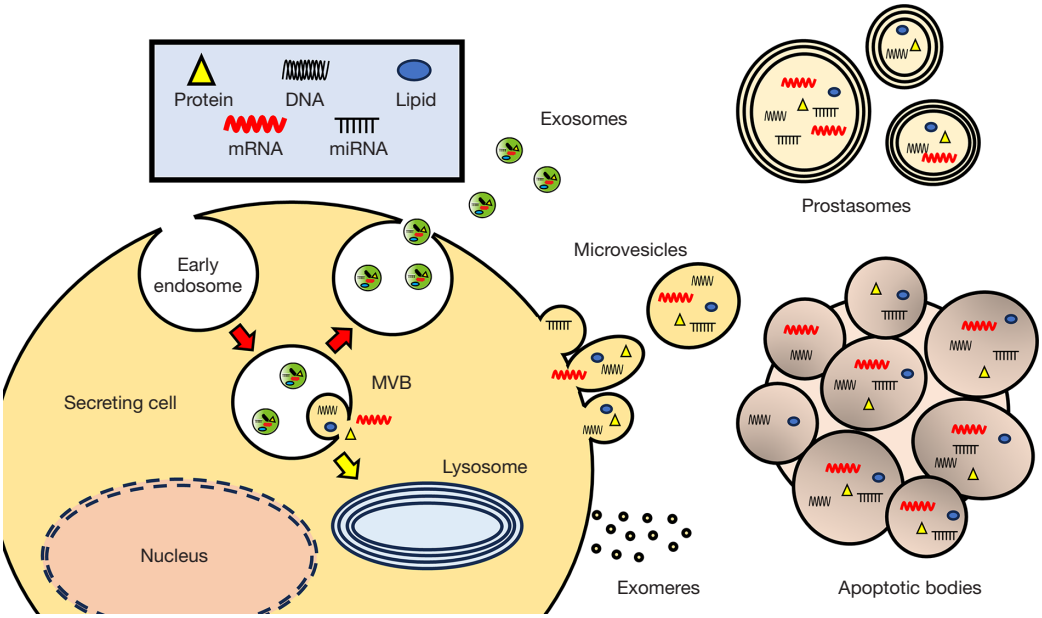

Figure 1 Classification of EVs that contain miRNAs, mRNAs, DNAs, proteins, and lipids. Exosomes are formed via inward budding of MVBs into early endosomes. Then, the MVBs fuse with the limiting plasma membrane to release exosomes into the extracellular space. Microvesicles are directly shed by or bud from plasma membranes. Apoptotic bodies are released from cells undergoing programmed death. miRNA, microRNA; MVB, multivesicular bodies; EVs, extracellular vesicles.

blebbing (14). Additionally, prostasomes (40–5,000 nm in diameter) feature a cholesterol-rich, multilayered lipid membrane (15). Prostasomes are derived from prostate epithelial cells and are abundant in seminal fluid (16). Notably, prostasomes are ones of the first vesicles to be reported their function between cells. Prostasomes enhance spermatozoal mobility and protect spermatozoa from infection and phagocytosis by immune cells, thus contributing to human reproductive success (17,18). Furthermore, recently, novel small extracellular non-EV particles, termed exomeres, have been reported, complicating our understanding of the compositions and functions of EVs (19,20). Each EV subtype may exert distinct functions, and thus new methods are required to distinguish among the subpopulations. The International Society for Extracellular Vesicles (ISEV) developed standardized terms to be used when analyzing exosomes and other EVs, and it recommends taking great care in the use of terms for the different EVs (21,22). It is essential that scientists involved in EV research should understand the diverse and heterogenous nature of EVs (*Figure 1*). Against this background, here we use "EV" as an umbrella term for all small vesicles secreted into the extracellular space, i.e., exosomes, microvesicles, apoptotic bodies, prostasomes, and exomeres, which will enable the creation of a review that is in accordance with the recommendations of the ISEV (21).

The effects of EVs on PCa progression

Between-cell communication mediated by EVs is pivotal for cancer progression. In the context of tumor initiation, Kosaka *et al.* firstly reported EV-mediated competition between cancer cells and adjacent normal epithelial cells (23). From then, an increasing body of evidence indicates that EVs promote cancer progression including the development of premetastatic niches (24,25), angiogenesis (26), destruction of the blood-brain barrier and the peritoneum (27,28), activation of cancer fibroblasts (29), and induction of drug resistance (30). Furthermore, Ono *et al.* found that EVs from bone marrow mesenchymal stem cells induce breast cancer cell dormancy and contribute to future recurrence (31).

In PCa, EVs from PCa cells enhance cellular proliferation (32), affect the immune milieu (33), and confer resistance to pharmacological interventions (34). Such actions synergistically accelerate the tumorigenic trajectory. Patients with advanced PCa often exhibit skeletal metastases that are not only impervious to treatment but also precipitate skeletal-related incidents, seriously

compromising quality of life. Recently, several articles have suggested that intercellular communication facilitated by EVs contributes to bone metastasis progression (35). Such metastasis in PCa patients is predominantly osteoblastic in nature, but the lesions are the consequence of intricate interactions among disseminated cancer cells, osteoblasts, and osteoclasts (35). This intricate feedback loop is the "vicious cycle" that is postulated to underpin bone metastasis outgrowth (36).

Ito *et al.* were the first to describe EV-facilitated communication between PCa cells and osteoblasts. EVs from the human CRPC cell lines DU-145 and PC-3 (which express the Ets-1 protein) triggered differentiation of murine MC3T3-E1 pre-osteoblastic cells (37). Ye *et al.* showed that EVs from a PCa cell line, MDA-PCa-2b, not only enhanced osteoblastic activity but also regulated the microenvironments of bone metastases. miR-141-3p contained in the EVs from MDA-PCa-2b cells reduced osteoblast DLC1 levels and activated the p38MAPK pathway, in turn enhancing osteoblast proliferation and OPG/RANKL expression. In addition, they also elucidated that the EVs from the PCa cells specifically targeted bone, promoting osteoblastic metastasis *in vivo* (38). Hashimoto *et al.* reported that miR-940 encapsulated in EVs from PCa cells triggered osteogenic differentiation of human mesenchymal stem cells via precise targeting of ARHGP1 and FAM134A, thereby contributing significantly to establishment of an osteoblastic metastatic milieu (39). The cited studies focused on the effects of PCa-derived EVs on osteoblast differentiation (37-39); however, our group recently found that not only PCa-derived EVs but also crosstalk between PCa cells and osteoblasts mediated by EV transfer promoted osteoblastic bone metastases (40). Additionally, we also found that CUB domain-containing protein 1 was present on the EVs of an advanced PCa cell line, PC3M, and promoted osteoclast differentiation (41). Clinically, osteoblastic metastasis is the major form of PCa bone metastasis. However, we sometimes encounter PCa patients, especially advanced-stage patients, with partially osteolytic bone metastasis. Such metastasis is associated with a poorer prognosis compared with the osteoblastic phenotype (42). PC3M is an AR-independent, very aggressive PCa cell line that mirrors advanced-stage PCa. The mechanism by which bone metastasis is induced is complex, and further studies are required. However, reports suggest that the balance of EV-mediated intercellular communication might decide the phenotype of bone metastasis in PCa (*Figure 2*).

The roles played by EVs in PCa drug resistance

Antiandrogens

Antiandrogenic therapy, which comprises ADT with or without an ARSI, has traditionally been the principal systemic intervention for PCa. However, notwithstanding recent developments in antiandrogen drug development, all patients eventually become resistant to the therapy. It is thus imperative to understand the intricate molecular actions that trigger resistance to antiandrogen therapy.

Lei *et al.* found that let-7a was upregulated in EVs from androgen-independent PCa cells, and that it activated the AR and PI3K/Akt signaling pathways, thus contributing to androgen-independent transformation of androgen-sensitive PCa (43). Lee *et al.* evaluated ARSI resistance, and found that YAP1 and COUP-TFII were upregulated in enzalutamide-resistant PCa cells and EVs from these cells. Notably, after EV-mediated transfer of these components, YAP 1 and COUP-TFII upregulated many genes involved in cancer stemness and lipid metabolism in the recipient PCa cells, which then developed resistance to enzalutamide (44). Martens-Uzunova *et al.* recently reported that androgen manipulation drastically altered the EV RNA profiles (45), supporting the idea that EV communication contributes to the development of antiandrogen drug resistance (*Figure 3A*).

Chemotherapy

Docetaxel is the primary therapeutic modality for patients with high-volume metastatic HSPC and metastatic CRPC (4,46). However, drug resistance always develops with docetaxel treatment. The mechanism of such resistance and a method to overcome it require urgent attention.

Shan *et al.* found that EVs from PCa cancer-associated fibroblasts (CAFs) transfer miR-423-5p to PCa cells, thereby inducing docetaxel resistance by modulating GREM2 expression via the TGF-β signaling pathway (47). Cao *et al.* showed that chemotherapy significantly upregulated miR-27a expression in PCa CAF. EVs from the PCa CAF were rich in miR-27a, which increased chemoresistance by targeting the gene encoding P53 (48). Additionally, Jiang *et al.* reported that lincROR, an oncogenic long noncoding RNA, was packaged into the EVs of docetaxel-resistant PCa cells and then delivered to non-resistant cells, in turn stimulating the β-catenin/hypoxia-inducible factor 1-alpha pathway and contributing to dissemination of the docetaxel-resistant phenotype (49). Furthermore, EVs also enhance chemoresistance in a different approach. Corcoran *et al.* found that docetaxel-resistant PCa cells

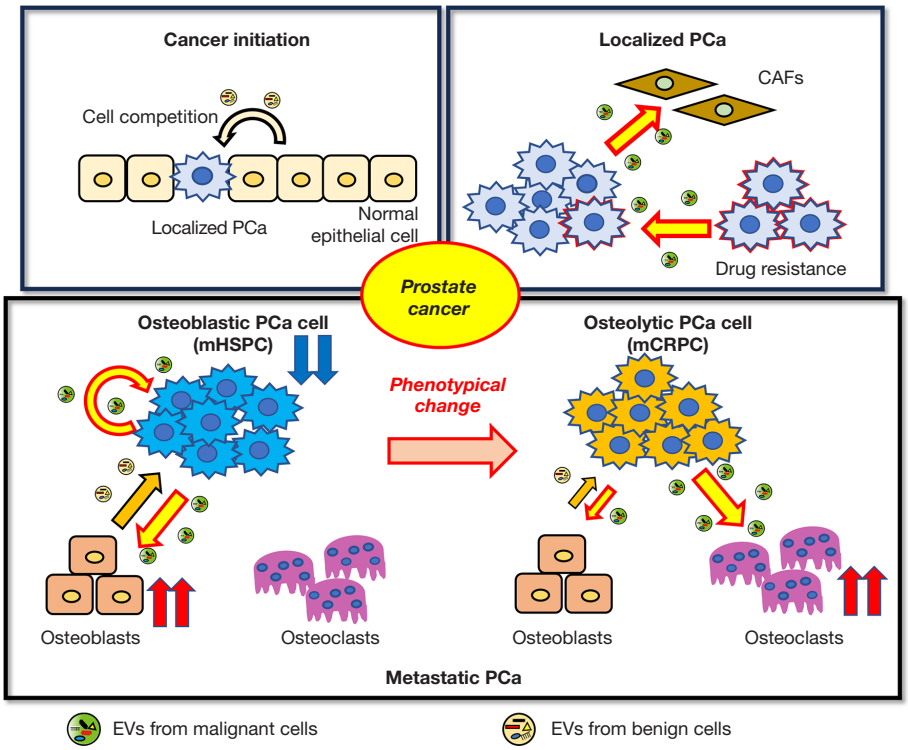

Figure 2 The roles played by EVs in the several phases of PCa progression. Initiation, localized PCa, and metastatic PCa. mHSPC, metastatic hormone sensitive prostate cancer; PCa, prostate cancer; CAFs, cancer-associated fibroblasts; mCRPC, metastatic castration resistant prostate cancer; EVs, extracellular vesicles.

overexpressing MDR-1/P-gp, a transporter protein, discharged docetaxel from the cytoplasm; MDR-1/P-gp was then transferred by EVs from docetaxel-resistant PCa cells to docetaxel-sensitive cells, which contribute to acquired chemoresistance (34). Many EVs play pivotal roles in chemotherapy resistance. Intercellular communication mediated by EVs may serve as a useful therapeutic target in individuals with chemoresistant PCa (*Figure 3B*).

Neuroendocrine differentiation (NED)

Neuroendocrine PCa is an aggressive histological subtype of PCa that usually develops via adenocarcinoma transdifferentiation after treatment resistance is established. The term "lineage plasticity" is often used to describe the phenotypic switch from an epithelial to a neuroendocrine cell.

Quaglia *et al.* reported that EVs derived from PCa cells expressing Vβ3 specifically promote tumor growth and induce NED, as evidenced by increased levels of neuroendocrine markers (50). Enriquez *et al.* reported that crosstalk between PCa and stromal cells triggers NED development. Castration elevated GRP78 expression in PCa cells, eliciting the release of EVs that contained miR-29b, which was then transported to stromal cells, where it downregulated SPARC. This culminated in IL-6 release from stromal cells; IL-6 is a well-established stimulator of NED and acts on PCa cells (51). Extracellular communication via EVs may thus play an important role in NED development (*Figure 3C*).

Immunotherapy

In contrast to the marked effects of immunotherapy on profoundly immunogenic neoplasms such as melanomas, PCa is a poor responder (52,53). The four pivotal KEYNOTE trials evaluated pembrolizumab combined with other agents; no therapeutic effect was noted (54-58). PCa is a "cold" tumor; the cancer does not activate the immune system to an extent that allows tumor eradication. Frequently, the tumor microenvironment exhibits immunosuppressive characteristics, thus abundant regulatory T cells, myeloid-derived suppressor cells, and M2-polarized macrophages, all of which contribute to immune system evasion (59). Some EV studies have explored the mechanisms

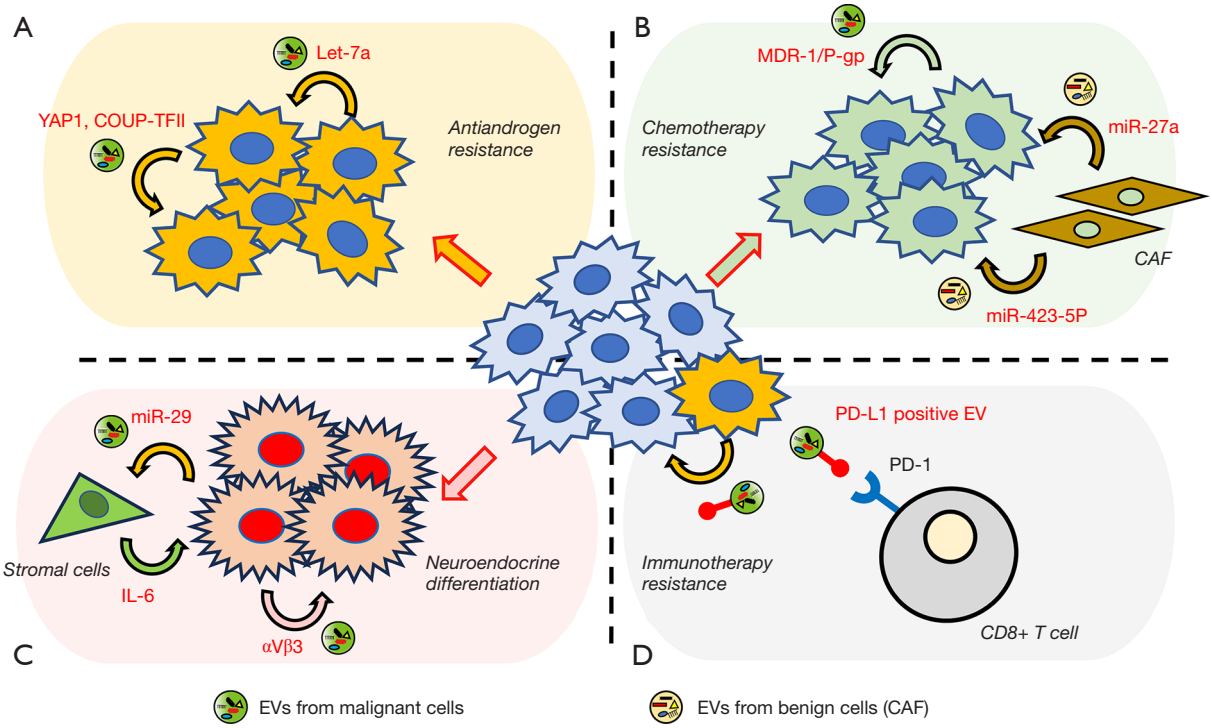

Figure 3 The roles played by EVs in PCa progression. Intercellular communication via EVs increases PCa progression via acquisition of (A) antiandrogen-, (B) chemotherapy-, and (D) immunotherapy resistance and (C) neuroendocrine differentiation. CAF, cancer-associated fibroblast; EVs, extracellular vesicles; PD-1, programmed death-1; PCa, prostate cancer.

by which PCa enables immune system resistance.

In 2019, Poggio *et al.* reported that programmed death-ligand 1 (PD-L1) expressed on the surface of EVs from metastatic PCa cells escalated tumor growth in an immune system-dependent manner. In a syngeneic PCa model, resistance to anti-PD-L1 therapy appeared to be triggered by PD-L1, and therefore targeting PD-L1 might be a valuable therapeutic strategy (60). Li *et al.* found that PD-L1 was transferred via EVs from PCa cells expressing high levels of PD-L1 to PCa cells expressing lower levels, thus aiding the ability of PCa to evade immune cells (61) (*Figure 3D*).

Bone-targeting radium-223 therapy prolongs survival in a fraction of bone metastatic PCa patients (62). Vardaki *et al.* recently found that the levels of immune checkpoint modulators in plasma derived-EVs were increased in patients who received radium-223 treatment (63). Using a mouse model, they also revealed that radium-223 treatment increased the levels of immune checkpoint modulators both *in vitro* and *in vivo*. Consequently, they tested the significance of the findings by combining Ra-223 with immune checkpoint blockade therapy and found that the combination had greater efficacy than Ra-223 alone (63), suggesting that the combination therapy may warrant a clinical trial. Although the PCa immune microenvironment is very complex, EVs may not only contribute to treatment resistance but also serve as potential markers of treatment efficacy.

The clinical significance of EVs in PCa liquid biopsies

EV contents reflect the cellular origin of the EVs and may thus serve as valuable PCa biomarkers. Unlike conventional tissue biopsy, liquid biopsy is minimally invasive and allows real-time detection of actionable anomalies. In light of each facet of PCa management, liquid biopsy presents itself as a more compelling option. Thus, we next summarize recent clinical studies that investigated whether EVs are diagnostic or prognostic in the PCa context.

Diagnostic EVs

Given the location of the prostate, urinary EVs may elucidate aspects of prostate carcinogenesis. Many authors have explored whether urinary EVs serve as useful

diagnostic indicators (64-68). McKiernan *et al.* pioneered an FDA-endorsed non-invasive assay: the ExoDx Prostate IntelliScore urine exosome assay. The PCA3, ERG, and SPDEF levels in urine specimens are used to calculate the ExoDx Prostate IntelliScore. The method distinguishes high-grade PCa (Gleason score ≥7) from low-grade PCa, reducing the number of unnecessary prostate biopsies (69). EVs from plasma contain PCa-specific proteins including PTEN and survivin (70,71). Aggressive PCa is characterized by little or no PTEN expression; PTEN molecules have been detected in the EVs of PCa patients but not healthy controls (70). Furthermore, elevated EV survivin levels were more common in PCa patients than in those with benign prostatic hyperplasia or healthy controls (71).

Prognostic EVs

Several studies have shown that certain EVs predict the outcomes of PCa. In recent years, many new pharmaceutical agents have been developed to address the therapeutic needs of patients with CRPC, including enzalutamide and abiraterone acetate. However, 20–40% of CRPC patients do not respond to such agents (72). The discovery that AR-V7 is key in conferring resistance to enzalutamide and abiraterone among metastatic CRPC patients has garnered substantial attention (72,73). Del Re *et al.* examined the role played by AR-V7-encoding RNA in plasma-derived EVs in terms of predicting resistance to hormonal therapy in patients with metastatic CRPC (74). miRNAs encapsulated in serum or plasma EVs may be used to diagnose PCa and/or predict its prognosis. Notably, the miR-141 and miR-375 levels within serum EVs have been linked to the risk of metastatic PCa (75,76). Huang *et al.* found that the miR-1290 and miR-375 levels in plasma EVs serve as prognostic biomarkers of metastatic PCa (77). A comprehensive RNA sequencing strategy confirmed substantial associations between the levels of these miRNAs and the overall survival of CRPC patients.

Despite that EV data has aided PCa management, only the ExoDx system is used in clinical practice, because the supposedly useful EV components differ across the various investigations, partly due to variations in the assays employed and EV storage conditions. Although cell-free DNA status is applied in guiding PCa treatment selection, in the present era of precision medicine, further advances will be anticipated. As EV-centered liquid biopsies become more informative, a large prospective validation study followed by the development of pragmatic hospital-friendly protocols is key for clinical implementation.

Future clinical applications

Cells in tumor microenvironments engage in intercellular communication principally via secretion of cytokines, chemokines, and growth factors (78). The communication within such microenvironments is mediated by EVs released from all cell types. Many studies have revealed pivotal roles played by EVs in tumor progression (79). As the tumor microenvironment matures, EV production increases exponentially, contributing to tumor progression. It is possible that therapeutic reduction in the level of tumor-derived EVs might impede cancer development. To date, three distinct approaches targeting EVs have been proposed: elimination of circulating EVs, inhibition of EV secretion, and disruption of EV uptake (10) (*Figure 4A*). Although we previously reported the potential of the inhibition of EV secretion in PCa (80,81), to date elimination of circulating EVs might be the optimal clinical choice. Marleau *et al.* (82) pioneered a therapeutic paradigm to eradicate circulating EVs, in which a sophisticated hemofiltration system selectively removes circulating EVs derived from breast cancer cells via precise targeting of the human epidermal growth factor receptor 2 (HER2) on the surfaces of such EVs (82). Notably, HER2 located on EV reduces the efficacy of cancer therapies (including trastuzumab) and contributes to cancer progression (83). Hence, selective removal of cancer-derived EVs via specific HER2 targeting will be an exceptionally promising approach for cancer treatment. Additionally, in PCa, as we referred above, PD-L1 on EVs may contribute to resistance to immunotherapy (60,61), thus, targeting PD-L1 positive EVs might be a good approach for PCa treatment.

Prostate-specific membrane antigen (PSMA) is a type 2 transmembrane protein, and its expression is transcriptionally repressed by AR. Therefore, antiandrogen therapy reduces AR signaling, which increases the expression of PSMA in advanced PCa (84). According to the increasing the expression level of PSMA in PCa tissue, CD9 and PSMA double-positive plasma derived EVs are increased in patients with metastatic PCa (45). The biological function of PSMA on EVs remains unclear; one recent study proposed that EVs targeting PSMA can be used to deliver drugs. Severic *et al.* developed genetically engineered EVs expressing anti-PSMA antibodies that were internalized by PSMA-positive PCa cell lines both *in vitro* and *in vivo* (85). siRNA loading of the EVs expressing anti-PSMA antibody reduced the target gene expression in the recipient cells (PSMA-positive PCa cells) (86). Thus, EV-

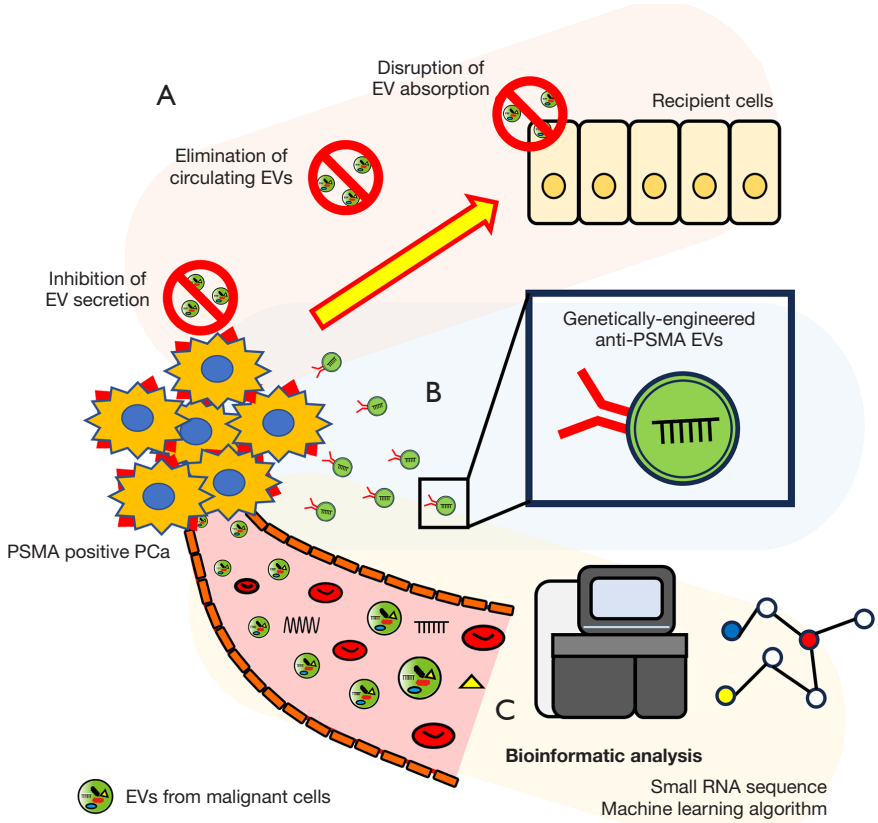

Figure 4 Future clinical applications of EVs. If EVs are to aid targeting therapies (A), the optimal administration/delivery route(s), dose(s), and pharmacokinetics must be investigated thoroughly (B). In terms of biomarkers that aid screening, methods that detect EV components are essential (C). EVs, extracellular vesicles; PSMA, prostate specific membrane antigen; PCa, prostate cancer.

based drug carriers may greatly aid clinical drug delivery (*Figure 4B*).

Efforts have been made to enhance the cancer detection and prediction of liquid biopsy. Machine learning has been employed to analyze EV proteomic profiles. Hoshino *et al.* meticulously amassed 426 human tissue explants, and plasma and other bodily fluid samples, from patients with seven distinct cancers and from healthy individuals (87). Exhaustive proteomic profiles obtained via low- and high-resolution/high-mass-accuracy nano-liquid chromatography-tandem mass spectrometry data were subjected to rigorous evaluation by machine learning algorithms (87). A set of tumor-type-specific EV proteins in both tissue explants and plasma were identified and were able to categorize malignancies of enigmatic primary provenance (87). EV proteins may thus serve as useful biomarkers of cancer and specific cancer subtypes. Of course, further work will be required for clinical application (*Figure 4C*).

Conclusions

We have summarized recent research on how EVs may aid PCa management. To date, we have discovered only the tip of the iceberg. We anticipate that further research will yield innovative therapeutic modalities, thereby aiding all PCa patients.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-23-533/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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