http://pmjournal.ir Review Article

Winter 2022, Volume7, Issue 24 (28-32)

A Review of The Role of Exosomes in Prostate Cancer

Rafid A Abdulkareem[1], Seyed Majid Hashemi Fard[2*], Masoomeh Kohandani[2]

[1]Genetic engineering and biotechnology Institute, Baghdad University, Iraq.
[2]Department of Biology, Payame Noor University, Tehran, Iran.
[3] Master of Science in Cellular and Molecular Biology, Department of cell and Molecular Biology, Karazmi University, Tehran, Iran.

Corresponding author: Seyed Majid Hashemi Fard, AmitisGen Lab, Food and Drug Administration of Iran Ministry of Health and Medical Education. Tehran, Iran. Email: majidhf65@gmail.com.

DOI: 10.22034/pmj.2022.252442

Submitted: 2022-01-10
Accepted: 2022-02-15

Keywords:
Exosomes
Prostate Cancer
Extracellular Vesicles
Biomarker
PCa

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-β 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 avb3 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).

REFERENCES

1. Sasaki T, Sugimura Y. The importance of time to prostate-specific antigen (PSA) nadir after primary androgen deprivation therapy in hormone-naïve prostate cancer patients. Journal of clinical medicine. 2018 Dec;7(12):565.
2. Siegel Rebecca L, Miller Kimberly D. Jemal Ahmedin. Cancer statistics, 2019. CA: a cancer journal for clinicians. 2019;69(1):7-34.
3. Ye Y, Deng M, Zhao D, Jiang L, Chen D, Wu Z, Wang Y, Li Z, Yang Z, Li J, Zhou F. Prostate cryoablation combined with androgen deprivation therapy for newly diagnosed metastatic prostate cancer: a propensity score-based study. Prostate cancer and prostatic diseases. 2021 Sep;24(3):837-44.
4. Ingrosso G, Detti B, Scartoni D, Lancia A, Giacomelli I, Baki M, Carta G, Livi L, Santoni R. Current therapeutic options in metastatic castration-resistant prostate cancer. InSeminars in Oncology 2018 Oct 1 (Vol. 45, No. 5-6, pp. 303-315). WB Saunders.
5. Kretschmer A, Tilki D. Biomarkers in prostate cancer–current clinical utility and future perspectives. Critical reviews in oncology/hematology. 2017 Dec 1;120:180-93.
6. Fujita K, Nonomura N. Urinary biomarkers of prostate cancer. International Journal of Urology. 2018 Sep;25(9):770-9.
7. Foj L, Ferrer F, Serra M, Arévalo A, Gavagnach M, Giménez N, Filella X. Exosomal and non-exosomal urinary miRNAs in prostate cancer detection and prognosis. The Prostate. 2017 May;77(6):573-83.
8. Mathivanan S, Fahner CJ, Reid GE, Simpson RJ. ExoCarta 2012: database of exosomal proteins, RNA and lipids. Nucleic acids research. 2012 Jan 1;40(D1):D1241-4.
9. Fujita Y, Yoshioka Y, Ochiya T. Extracellular vesicle transfer of cancer pathogenic components. Cancer science. 2016 Apr;107(4):385-90.
10. Kumar S, Lombard DB. Functions of the sirtuin deacylase SIRT5 in normal physiology and pathobiology. Critical reviews in biochemistry and molecular biology. 2018 May 4;53(3):311-34.
11. Pullan JE, Confeld MI, Osborn JK, Kim J, Sarkar K, Mallik S. Exosomes as drug carriers for cancer therapy. Molecular pharmaceutics. 2019 Apr 5;16(5):1789-98.
12. Di C, Zhang Q, Wang Y, Wang F, Chen Y, Gan L, Zhou R, Sun C, Li H, Zhang X, Yang H. Exosomes as drug carriers for clinical application. Artificial Cells, Nanomedicine, and Biotechnology. 2018 Nov 12;46(sup3):S564-70.
13. Qin J, Xu Q. Functions and application of exosomes. Acta Pol Pharm. 2014 Mar;71(4):537-43.
14. Guo W, Gao Y, Li N, Shao F, Wang C, Wang P, Yang Z, Li R, He J. Exosomes: New players in cancer. Oncology reports. 2017 Aug 1;38(2):665-75.
15. Witwer KW, Buzás EI, Bemis LT, Bora A, Lässer C, Lötvall J, Nolte-'t Hoen EN, Piper MG, Sivaraman S, Skog J, Théry C. Standardization of sample collection, isolation and analysis methods in extracellular vesicle research. Journal of extracellular vesicles. 2013 Jan 1;2(1):20360.
16. Théry C, Zitvogel L, Amigorena S. Exosomes: composition, biogenesis and function. Nature reviews immunology. 2002 Aug;2(8):569-79.
17. Raposo G, Nijman HW, Stoorvogel W, Liejendekker R, Harding CV, Melief CJ, Geuze HJ. B lymphocytes secrete antigen-presenting vesicles. The Journal of experimental medicine. 1996 Mar 1;183(3):1161-72.
18. Clayton A, Mason MD. Exosomes in tumour immunity. Current oncology. 2009 May;16(3):46-9.
19. Lynch S, Santos SG, Campbell EC, Nimmo AM, Botting C, Prescott A, Antoniou AN, Powis SJ. Novel MHC class I structures on exosomes. The Journal of Immunology. 2009 Aug 1;183(3):1884-91.
20. Sharrow SO, Mathieson BJ, Singer A. Cell surface appearance of unexpected host MHC determinants on thymocytes from radiation bone marrow chimeras. The Journal of Immunology. 1981 Apr 1;126(4):1327-35.
21. Huang T, Deng CX. Current progresses of exosomes as cancer diagnostic and prognostic biomarkers. International journal of biological sciences. 2019;15(1):1.
22. Soung YH, Ford S, Zhang V, Chung J. Exosomes in cancer diagnostics. Cancers. 2017 Jan;9(1):8.
23. Makler A, Narayanan R. Mining exosomal genes for pancreatic cancer targets. Cancer genomics & proteomics. 2017 May 1;14(3):161-72.
24. Boukouris S, Mathivanan S. Exosomes in bodily fluids are a highly stable resource of disease biomarkers. Proteomics–Clinical Applications. 2015 Apr;9(3-4):358-67.
25. Falcon-Perez J. Exosome profiling: potential in cancer diagnosis and stratification. InEndocrine Abstracts 2017 May 3 (Vol. 49). Bioscientifica.
26. Zhai LY, Li MX, Pan WL, Chen Y, Li MM, Pang JX, Zheng L, Chen JX, Duan WJ. In situ detection of plasma exosomal microRNA-1246 for breast cancer diagnostics by a Au nanoflare probe. ACS applied materials & interfaces. 2018 Oct 23;10(46):39478-86.
27. Villarroya-Beltri C, Baixauli F, Gutiérrez-Vázquez C, Sánchez-Madrid F, Mittelbrunn M. Sorting it out: regulation of exosome loading. InSeminars in cancer biology 2014 Oct 1 (Vol. 28, pp. 3-13). Academic Press.
28. Lázaro-Ibáñez E, Neuvonen M, Takatalo M, Thanigai Arasu U, Capasso C, Cerullo V, Rhim JS, Rilla K, Yliperttula M, Siljander PR. Metastatic state of parent cells influences the uptake and functionality of prostate cancer cell-derived extracellular vesicles. Journal of extracellular vesicles. 2017 Dec 1;6(1):1354645.
29. Kharmate G, Hosseini-Beheshti E, Caradec J, Chin MY, Tomlinson Guns ES. Epidermal growth factor receptor in prostate cancer derived exosomes. PLoS One. 2016 May 6;11(5):e0154967.
30. Vlaeminck-Guillem V. Extracellular vesicles in prostate cancer carcinogenesis, diagnosis, and management. Frontiers in oncology. 2018 Jun 13;8:222.
31. Huang X, Yuan T, Tschannen M, Sun Z, Jacob H, Du M, Liang M, Dittmar RL, Liu Y, Liang M, Kohli M. Characterization of human plasma-derived exosomal RNAs by deep sequencing. BMC genomics. 2013 Dec;14(1):1-4.
32. Wang X, Wang X, Zhu Z, Li W, Yu G, Jia Z, Wang X. Prostate carcinoma cell-derived exosomal MicroRNA-26a modulates the

metastasis and tumor growth of prostate carcinoma. Biomedicine & Pharmacotherapy. 2019 Sep 1;117:109109.
33.Krishn SR, Singh A, Bowler N, Duffy AN, Friedman A, Fedele C, Kurtoglu S, Tripathi SK, Wang K, Hawkins A, Sayeed A. Prostate cancer sheds the αvβ3 integrin in vivo through exosomes. Matrix Biology. 2019 Apr 1;77:41-57.
34.Dai J, Escara-Wilke J, Keller JM, Jung Y, Taichman RS, Pienta KJ, Keller ET. Primary prostate cancer educates bone stroma through exosomal pyruvate kinase M2 to promote bone metastasis. Journal of Experimental Medicine. 2019 Dec 2;216(12):2883-99.
35.Osaki M, Okada F. Exosomes and their role in cancer progression. Yonago acta medica. 2019;62(2):182-90.
36.Liu CM, Hsieh CL, Shen CN, Lin CC, Shigemura K, Sung SY. Exosomes from the tumor microenvironment as reciprocal regulators that enhance prostate cancer progression. International Journal of Urology. 2016 Sep;23(9):734-44.
37.Huang X, Yuan T, Tschannen M, Sun Z, Jacob H, Du M, Liang M, Dittmar RL, Liu Y, Liang M, Kohli M. Characterization of human plasma-derived exosomal RNAs by deep sequencing. BMC genomics. 2013 Dec;14(1):1-4.
38.Steinbichler TB, Dudás J, Riechelmann H, Skvortsova II. The role of exosomes in cancer metastasis. InSeminars in cancer biology 2017 Jun 1 (Vol. 44, pp. 170-181). Academic Press.
39.Sánchez CA, Andahur EI, Valenzuela R, Castellón EA, Fullá JA, Ramos CG, Triviño JC. Exosomes from bulk and stem cells from human prostate cancer have a differential microRNA content that contributes cooperatively over local and pre-metastatic niche. Oncotarget. 2016 Jan 26;7(4):3993.
40.Lorenc T, Klimczyk K, Michalczewska I, Słomka M, Kubiak-Tomaszewska G, Olejarz W. Exosomes in prostate cancer diagnosis, prognosis and therapy. International Journal of Molecular Sciences. 2020 Jan;21(6):2118.
41.Sugatani T, Vacher J, Hruska KA. A microRNA expression signature of osteoclastogenesis. Blood, The Journal of the American Society of Hematology. 2011 Mar 31;117(13):3648-57.
42.Zhang HL, Qin XJ, Cao DL, Zhu Y, Yao XD, Zhang SL, Dai B, Ye DW. An elevated serum miR-141 level in patients with bone-metastatic prostate cancer is correlated with more bone lesions. Asian journal of andrology. 2013 Mar;15(2):231.
43.Chaffer CL, Weinberg RA. A perspective on cancer cell metastasis. science. 2011 Mar 25;331(6024):1559-64.
44.Saber SH, Ali HE, Gaballa R, Gaballah M, Ali HI, Zerfaoui M, Abd Elmageed ZY. Exosomes are the driving force in preparing the soil for the metastatic seeds: lessons from the prostate cancer. Cells. 2020 Mar;9(3):564.
45.Bijnsdorp IV, Geldof AA, Lavaei M, Piersma SR, van Moorselaar RJ, Jimenez CR. Exosomal ITGA3 interferes with non-cancerous prostate cell functions and is increased in urine exosomes of metastatic prostate cancer patients. Journal of extracellular vesicles. 2013 Jan 1;2(1):22097.
46.Yim N, Ryu SW, Choi K, Lee KR, Lee S, Choi H, Kim J, Shaker MR, Sun W, Park JH, Kim D. Exosome engineering for efficient intracellular delivery of soluble proteins using optically reversible protein–protein interaction module. Nature Communications. 2016 Jul 22;7(1):1-9.
47.Takahara K, Ii M, Inamoto T, Nakagawa T, Ibuki N, Yoshikawa Y, Tsujino T, Uchimoto T, Saito K, Takai T, Tanda N. microRNA-145 mediates the inhibitory effect of adipose tissue-derived stromal cells on prostate cancer. Stem cells and development. 2016 Sep 1;25(17):1290-8.
48.Wolfers J, Lozier A, Raposo G, Regnault A, Thery C, Masurier C, Flament C, Pouzieux S, Faure F, Tursz T, Angevin E. Tumor-derived exosomes are a source of shared tumor rejection antigens for CTL cross-priming. Nature medicine. 2001 Mar;7(3):297-303.
49.Qi H, Liu C, Long L, Ren Y, Zhang S, Chang X, Qian X, Jia H, Zhao J, Sun J, Hou X. Blood exosomes endowed with magnetic and targeting properties for cancer therapy. ACS nano. 2016 Mar 22;10(3):3323-33.
50.Saari H, Lázaro-Ibáñez E, Viitala T, Vuorimaa-Laukkanen E, Siljander P, Yliperttula M. Microvesicle-and exosome-mediated drug delivery enhances the cytotoxicity of Paclitaxel in autologous prostate cancer cells. Journal of Controlled Release. 2015 Dec 28;220:727-37.
51.Chaput N, Taïeb J, Schartz N, Flament C, Novault S, André F, Zitvogel L. The potential of exosomes in immunotherapy of cancer. Blood Cells, Molecules, and Diseases. 2005 Sep 1;35(2):111-5.
52.Viaud S, Théry C, Ploix S, Tursz T, Lapierre V, Lantz O, Zitvogel L, Chaput N. Dendritic cell-derived exosomes for cancer immunotherapy: what's next?. Cancer research. 2010 Feb 15;70(4):1281-5.
53.Gerlinger M, Rowan AJ, Horswell S, Larkin J, Endesfelder D, Gronroos E et al. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. N Engl J Med. 2012; 366: 883–92.
54.van der Pol E, Boing AN, Harrison P, Sturk A, Nieuwland R. Classification, functions, and clinical relevance of extracellular vesicles. Pharmacol Rev. 2012; 64: 676–705.
55.Pan J, Ding M, Xu K, Yang C, Mao LJ. Exosomes in diagnosis and therapy of prostate cancer. Oncotarget. 2017 Nov 14;8(57):97693.
56.Duijvesz D, Luider T, Bangma CH, Jenster G. Exosomes as biomarker treasure chests for prostate cancer. European urology. 2011 May 1;59(5):823-31.