Exosomes are the mediators between the tumor microenvironment and prostate cancer (Review)

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Received April 25, 2023; Accepted May 23, 2024

DOI: 10.3892/etm.2024.12728

Abstract. Prostate cancer poses a serious threat to the well-being of men worldwide, with the leading cause of mortality being primarily through metastasis. Prostate cancer metastasis is dependent on cell communication, which is an essential component of this process; yet its exact mechanism remains obscure. Nonetheless, cell-to-cell communication plays a critical part in prostate cancer metastasis. Exosomes play an indispensable role in the development of metastatic growth by promoting intercellular communication. They are pivotal regulatory agents for both prostate cancer cells as well as their microenvironment. The present study investigated the makeup and function of exosomes in the tumor microenvironment, highlighting their significance to prostate cancer metastasis.

Contents

1. Introduction

In 2020, global cancer statistics reported prostate cancer as the second most widespread cancer in American men, representing 7.3% of all cases. Lung cancer was the most prevalent cancer, accounting for 11.4% of all cases (1,2). These statistics indicate an estimate of 1,141,259 (7.3%) new cases and 375,304 mortalities worldwide attributed to prostate cancer among men (1). Prostate cancer affects a large number of men every year and the incidence and mortality rates can be influenced by various factors, such as age, ethnicity, genetic background and staging (3). Prostate cancer exhibits higher incidence and mortality rates in developed countries compared with developing countries (4). The improvement of prostate cancer treatment and the understanding of its pathogenesis are challenging tasks. Researchers have identified exosomes and the tumor microenvironment (TME) as crucial areas of study and active topics of current literature.

Exosomes are nano-sized organelles encased in a single membrane, typically ranging between 30 to 200 nanometers in diameter. These organelles contain various chemicals, including proteins, lipids, nucleic acids and other substances such as amino acids, and metabolites (5). Exosomes are essential for various cellular activities and have the capacity to transmit information between cells. These single-membrane organelles can be secreted by various cell types and mediate intracellular communication signaling (6). Exosomes are natural nanoparticles that facilitate communication between cells, aiding in the regulation of cancerous growth. These cellular messengers transfer proteins and other biological substances through tissue fluids, affecting the development of cancer (7). Exosomes have the potential to respond to the growth and progression of tumor cells and can also have an impact on the metastasis of tumor cells that are located in a remote location (8). Exosomes have a crucial function in controlling the TME by affecting various processes, such as metastasis, angiogenesis and immunity. These functions are crucial in altering the state of the TME (9). The scientific community and clinical practitioners have shown considerable interest in the mechanism of exosome function in tumors.

The TME encompasses tumor cells, surrounding cells and their cytokine secretions, creating a conducive and abundant environment for tumor survival and proliferation (10). It is important to highlight the intricate and constantly altering nature of the TME, as well as the influence that the type of tumor may have on its individual components (11). However, the essential components of the TME include immune and stromal cells, blood vessels and the extracellular matrix (12). The composition of the TME and its existence are critical for the tumor development, advancement and spread (13). The understanding of the impact of the TME on cancer development

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Key words: exosome, tumor microenvironment, prostate cancer cell

and progression is critical for identifying novel treatment strategies. This relationship can be considered similar to the connection between soil and seeds, with exosomes serving as essential messengers between the tumor and its environment (14). Previous research has revealed a strong interaction between TME and exosomes (15). The interaction between exosomes and TME remains unclear. As a result, the current review aimed to examine the role of exosomes on the regulation of prostate cancer cells within the TME.

2. Composition and role of exosomes in the TME

The structure of exosomes and their inherent biological activity render them significant to intercellular communication. Their discovery and significance first gained prominence in a 1983 article by Pan and Johnstone, which indicated that exosomes released alongside transferrin receptors are involved in sheep reticulocyte formation (16). Subsequent research has uncovered the ability of exosomes to transport various RNA molecules, including but not limited to mRNA, microRNA (miR), transfer RNA, ribosomal RNA, small nuclear RNA, small nucleolar RNA, piwi-interacting RNA and small Cajal body-specific RNA (17). As shown in Fig. 1A, exosomes consist of various components, such as miRs (miR-409, miR-141 and miR-375), mRNAs, DNAs, lipids and functional proteins including cluster of differentiation (CD) 9, CD81, CD82, CD83, actin, myosin and tubulin (18).

These vesicles serve as important players in various physiological and pathological processes, posing challenges for researchers to fully comprehend their functions. Exosome formation encompasses initiation, endocytosis, multivesicular formation and secretion (19). Early endosomes are formed during the initiation stage through the invagination of cell membrane sites that contain ubiquitination surface receptors. This process allows for membrane fusion, which creates a platform for the detection of Fab1-YOTB-Vac1-EEA1 domain-containing proteins, facilitated by the protein Rad5 (20). As multivesicular bodies mature, they can either undergo degradation by lysosomes or be secreted from the cell via Golgi processing or exosomal release. The proteins Rab GTPase (Rab) 6 and Rab7 have significant influence on multivesicular bodies; Rab6 directs them towards lysosomal degradation, while Rab7 guides them towards Golgi processing (21). The involvement of the Rad protein family is crucial in various stages of exosome biogenesis.

Within the TME, tumor-related fibroblasts represent a prominent cell population (22). The functioning mechanism of fibroblasts associated with tumors remains unknown. Fig. 1B demonstrates the significant role of exosomes in enabling communication between tumor cells and the neighboring microenvironment. A study conducted by Baroni *et al* (23) revealed that exosomes can transport miR-9, which in turn transforms human breast fibroblasts into cells resembling cancer-associated fibroblasts. Zhu *et al* (24) discovered that breast cancer cells can trigger cancer-associated fibroblast-like characteristics in human breast fibroblasts through exosomal miR-425-5p. The TGFβ1/reactive oxygen species (ROS) signaling pathway is the mediator of this process (24). According to Yan *et al* (25), exosomal miR-18b derived from cancer-related fibroblasts can stimulate invasion and metastasis of breast cancer by modulating transcription elongation factor A-like 7.

Exosomes have been identified as significant players in various cancers and diseases, including breast cancer. Kang *et al* (26) reported that exosomes derived from human umbilical cord mesenchymal stem cells (hucMSCs) can boost neural function restoration in rats with spinal cord injuries. According to their findings, exosomes obtained from hucMSCs have potential therapeutic benefits in enhancing motor function through their antiapoptotic and anti-inflammatory properties. It is hypothesized that hucMSC exosomes may exert their protective effects through modulation of the Bcl2/Bax and Wnt/β-catenin signaling pathways, which are implicated in spinal cord injury (26).

Wang *et al* (27) indicated that the application of exosomes sourced from hucMSCs containing miR-326 can alleviate symptoms of bowel disease in mice by inhibiting neural communication. The findings suggest that the therapeutic potential of exosomes derived from hucMSCs are enhanced when they contain high levels of miR-326, as demonstrated by the substantial improvements observed in inflammatory bowel disease mouse models treated with these exosomes in comparison to those treated with regular hucMSC-derived exosomes (27). Zhang *et al* (28) indicated that exosomes obtained from hucMSCs can enhance the development of diabetic cardiomyopathy by adjusting autophagy through the signaling pathway of AMP-activated protein kinase-Unc-51-like autophagy-activating kinase 1. More recent findings have revealed that exosomes obtained from hucMSCs selectively target the miR-138-5p/SRY-related HMG-box-4 pathway for regulation, resulting in the suppression of human melanoma cell survival (29).

Moreover, endometrial cancer is impacted by exosomes, as evidenced by a previous research study (30). Pan *et al* (30) demonstrated that exosomes containing miR-503-3p from hucMSCs can impede the advancement of endometrial cancer cells by suppressing mesoderm-specific transcripts. Exosomes have been shown by numerous studies to enhance the functions of tumor stromal cells in the microenvironment, leading to the promotion of tumor progression (31,32).

3. Interactions between the TME and prostate cancer cells are mediated by exosomes

Earlier studies have suggested that exosomes are involved in the growth of tumors. A previous study conducted by Giovannelli *et al* (33) indicates that exosomes derived from prostate cancer cells can affect the TME, leading to tumor progression. Nevertheless, low oxygen levels and acidic conditions in the TME can influence the production and absorption of exosomes by cancer cells (34,35). Low pH will increase the yield of exosome separation (36,37).

A previous study has shown that an increase in the pH levels in the TME can enhance the therapeutic effects of pharmacological ascorbic acid on castration-resistant prostate cancer cells (38). Xi *et al* (39) have demonstrated that hypoxia-induced activation of ataxia-telangiectasia mutated regulates the secretion of exosomes that are involved in autophagy by cancer-associated fibroblasts, thereby promoting cancer cell invasion. Tumor-derived related exosomes can induce

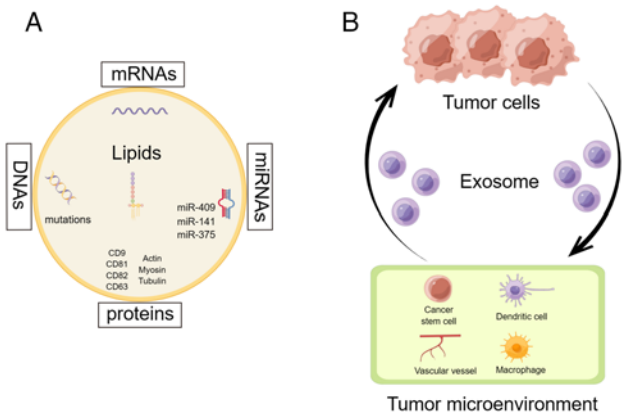

Figure 1. (A) The composition of exosomes. Exosomes include miRs (miR-409, miR-141 and miR-375), mRNAs, DNAs, lipids and relevant functional proteins (CD9, CD81, CD82, CD83, actin, myosin and tubulin). (B) Exosomes act as the mediator between tumor cells and the TME. Exosomes can originate from different types of cells, including cancer stem cells, macrophages and dendritic cells. Exosomes play a crucial role in regulating multiple physiological processes and the pathology of tumor cells. miR, microRNA; CD, cluster of differentiation; TME, tumor microenvironment.

immunosuppressive macrophages to promote the progression of intrahepatic cholangiocarcinoma; however the specific underlying mechanisms have not been fully elucidated (40). The intracellular signaling mechanism of macrophages, the processes involving exosome uptake and the regulatory payload of the TME have not been specifically elucidated.

Dendritic cells are an important component present in the TME. A previous study has shown that tumor-derived exosomes can promote tumor metastasis and development by acting on dendritic cells through the heat shock protein (HSP) 72/HSP105-toll-like receptor (TLR) 2/TLR4 pathway (41). Pancreatic cancer is characterized by a reduction in the number and function of dendritic cells, which affects antigen presentation and contributes to immune tolerance (42). Concomitantly, hypoxia-induced exosome secretion promotes the survival of prostate cancer cells in both African-American and native American populations in the USA (43). Three distinct pathways have been elucidated by which exosomes can enter prostate cancer cells (44). One mechanism of prostate cancer cell communication involves direct fusion with the recipient cell membrane (45). The second pathway involves the entrance of several molecules in the prostate cancer cell by binding to its membrane surface (46). The third pathway involves the process of endocytosis of prostate cancer cells that allows exosomes to enter and secrete exosome contents (2). It should be mentioned that p53 has a significant function in enhancing the dispersion of exosomes (47,48). In the following sections, the role of exosomes is examined in regulating intercellular communication between prostate cancer cells and TME, focusing on three crucial perspectives.

4. Cancer metastasis and cancer progression

Prostate cancer-related mortality is predominantly attributed to metastasis (49). Prostate cancer cells detach from the primary tumor during metastasis, navigate in the bloodstream, and eventually establish secondary colonies. During metastasis the prevalent site for colonized prostate cancer cells is the bone (50). Three distinct categories of bone metastasis in cancer have been determined as follows: Osteolytic, osteoblastic and mixed lesions (51,52). A previous investigation has demonstrated that exosomes derived from prostate cancer cells can merge with and transmit signals to the bone stromal cells in the bone tissue. The results indicate that exosomes can have a possible function in promoting prostate cancer metastasis to the bone (53).

Normal prostate epithelial cells secrete exosomes that prevent bone metastasis by failing to transport them to bone stromal cells (54). A study conducted by Karlsson *et al* (55) revealed that exosomes extracted from the TRAMP-C1 mouse prostate cancer cell line can considerably impede the advancement of mononuclear osteoclast precursors by obstructing their maturation, leading to a deceleration in their progression. Zhang *et al* indicated (2) that exosomes play a crucial role in the progression of androgen-independent prostate cancer by activating heme oxygenase 1. Exosomes have multiple functions, which facilitate the spread of prostate cancer and promote the proliferation of prostate cancer cells through the activity of miRs. Therefore, the presence of miRs in exosomes may provide a novel diagnostic method for prostate cancer (56,57). The circ_0044516 exosome is highly promising as a biomarker, as it has the capacity to increase the proliferation and metastasis of prostate cancer cells (58). The contribution of exosomes to prostate cancer metastasis is yet not fully understood, indicating a need for further research in this area.

5. Related regulation of immunity

The immune system plays a crucial role in the growth of cancer. Effective communication between tumors and the immune system is imperative for the development and spread of the tumor, as well as its metastasis. Exosomes present in the environment surrounding the tumor, can cause both chemotherapy resistance, as well as immune system suppression (59). A detailed comprehension of the way by which exosomes mediate immune responses in cancer is essential to further examine the development of exosome-based immunotherapies. Notably, the binding of programmed death-ligand-1 (PD-L1) to programmed cell death protein 1 (PD-1) and the subsequent signaling to $CD8^+$ cells aims to alleviate immunosuppression (60). Numerous research studies have revealed that prostate cancer cells increase PD-1 expression to evade the immune system (61,62). Simultaneously, the findings of Liu *et al* (63) have corroborated this assertion. This study suggests that exosomes originating from gastric cancer cells can elicit immune suppression by altering the gene expression levels in $CD8^+$ cells and the patterns of cytokine secretion (63).

Exosome immunotherapy has gained significant attention in recent years, particularly with regard to the impact of nasopharyngeal carcinoma cell-derived exosome PD-L1 on $CD8^+$ T cell activity and immune evasion (64). The exosome PD-L1 has been identified as a mechanism of immune resistance in non-small cell lung cancer, which promotes the progression of tumors (65). Exosomal miRs serve as mediators in the process of immune evasion in neuroblastoma (66). The immune evasion of breast cancer is facilitated by the increase of exosome miR-27a-3p, which is induced by endoplasmic reticulum stress. These exosomes regulate PD-L1 expression in macrophages, thus reducing immune response (67).

Table I. Role of exosomes in TME and prostate cancer.

Author	TME	Exosomes	Mechanism	(Refs.)
Li *et al*	Low PH	Exosomal proteins	Acidic microenvironment may facilitate exosomes to fuse with prostate cancer cells.	(27)
Panigrahi *et al*	Hypoxia	Unique proteins and triglycerides	Hypoxic microenvironment can promote the secretion of exosomes in prostate cancer cells.	(31)
Li *et al*	Hypoxia	Circ0044516	Promote bone metastasis of prostate cancer.	(58)
Hosseini *et al*	Myeloid suppressor and dendritic cells	PD-L1	PD-L1 in exosomes inhibits immune cells in TME and promotes the progression of prostate cancer.	(71)
Alcayaga *et al*	Hypoxia	VEGF and FGF	VEGF and FGF carried by exosomes promote angiogenesis in a hypoxic microenvironment and accelerate the spread of prostate cancer cells.	(82)

TME, tumor microenvironment; PD-L1, programmed death-ligand-1; FGF, fibroblast growth factors.

In patients with prostate cancer, myeloid suppressor and dendritic cells have been observed in the TME and are known to exhibit immunosuppressive effects. A previous study has indicated that these cells may contribute significantly to the proliferation and metastasis of cancer cells (68). Previous studies have indicated that a large quantity of PD-L1 within exosomes can potentially signify the advanced stages of prostate cancer, leading to a lower rate of survival and negative outcome (69,70). It should be emphasized that exosomes originating from prostate cancer cells have the potential to alter the behavior of macrophages and adjust the immune response (71).

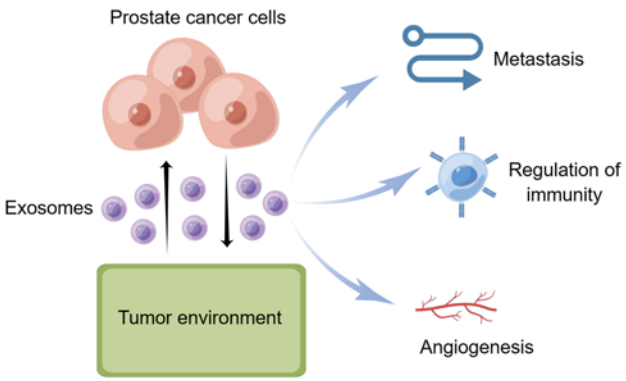

Figure 2. Exosomes play an important role in the communication between the TME and prostate cancer cells. Exosomes mainly play a role in cancer metastasis, related immune regulation and angiogenesis. TME, tumor microenvironment.

6. Angiogenesis

Hypoxia-induced angiogenesis is a critical process that drives the advancement and dissemination of prostate cancer (72). Three stages of angiogenesis have been identified: i) The formation of blood vessels; ii) the angiogenesis stage; iii) and the maturation stage (73). Angiogenesis requires the synchronization of regulatory factors and activating signals (74). Exosomes are known to carry angiogenic factors, including VEGF and fibroblast growth factors, which promote the growth of new blood vessels (75,76). Early detection of prostate cancer is possible by utilizing biomarkers that are derived from proteins present in plasma exosomes associated with survival (77).

The Src tyrosine kinase is crucial for the development and growth of prostate cancer (78). Src tyrosine kinases impact the process of angiogenesis by activating signaling pathways through integrin (79). Earlier investigations have indicated that exosomes can contain Src tyrosine kinases and facilitate the progression of prostate cancer (80,81). Alcayaga-Miranda *et al* (82) revealed that exosomes extracted from menstrual stem cells have the ability to effectively suppress angiogenesis caused by prostate cancer. A previous study has indicated that exosomes can decrease ROS production and promote VEGF release, while also lowering NF-κB activity (83). Exosomes have been shown to possess an impact on the formation of blood vessels and as a result influence the multiplication of cells in prostate cancer. However, the precise mechanisms responsible for this effect require further investigation. The in-depth understanding of the angiogenesis mechanisms can be beneficial in improving prostate cancer treatment and prognosis.

7. Conclusion

Exosomes have been found to impact cancer metastasis and progression and regulate immunity and angiogenesis, which are involved in the spread of prostate cancer cells (Fig. 2). Nonetheless, the specific mechanisms underlying this correlation are currently uncertain. Further analysis of these mechanisms has the potential to advance the management and prediction of prostate cancer outcomes (Table I). Exosomes play a key inhibitory role in the progression of

androgen-independent prostate cancer by activating heme oxygenase-1 (2). Effective communication between tumors and the immune system is essential for tumor development and spread, as well as metastasis. Exosomes in the tumor microenvironment promote the progression of prostate cancer by secreting PD-L1, but macrophages in the immune system are able to slow this process. Exosomes in the prostate cancer microenvironment can promote the release of VEGF by reducing the production of ROS, and at the same time reduce the activity of NF-κB, inhibit angiogenesis, and effectively reduce the proliferation of prostate cancer.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

YQW and XHL wrote the manuscript and made substantial contributions to conception and design. XW and YZ drew the pictures and analyzed and interpretated the data. YQW revised the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71: 209-249, 2021.
2. Zhang Y, Chen B, Xu N, Xu P, Lin W, Liu C and Huang P: Exosomes promote the transition of androgen-dependent prostate cancer cells into androgen-independent manner through up-regulating the heme oxygenase-1. Int J Nanomedicine 16: 315-327, 2021.
3. Rebello RJ, Oing C, Knudsen KE, Loeb S, Johnson DC, Reiter RE, Gillessen S, Van der Kwast T and Bristow RG: Prostate cancer. Nat Rev Dis Primers 7: 9, 2021.
4. Sandhu S, Moore CM, Chiong E, Beltran H, Bristow RG and Williams SG: Prostate cancer. Lancet 398: 1075-1090, 2021.
5. Pegtel DM and Gould SJ: Exosomes. Annu Rev Biochem 88: 487-514, 2019.
6. Beit-Yannai E, Tabak S and Stamer WD: Physical exosome:Exosome interactions. J Cell Mol Med 22: 2001-2006, 2018.
7. Terrasini N and Lionetti V: Exosomes in critical illness. Crit Care Med 45: 1054-1060, 2017.
8. Soung YH, Ford S, Zhang V and Chung J: Exosomes in cancer diagnostics. Cancers (Basel) 9: 8, 2017.
9. No authors listed: Exosomes. Nat Biotechnol 38: 1150, 2020.
10. Yang L: Tumor microenvironment and metabolism. Int J Mol Sci 18: 2729, 2017.
11. Anderson NM and Simon MC: The tumor microenvironment. Curr Biol 30: R921-R925, 2020.
12. Jiang X, Wang J, Deng X, Xiong F, Zhang S, Gong Z, Li X, Cao K, Deng H, He Y, *et al*: The role of microenvironment in tumor angiogenesis. J Exp Clin Cancer Res 39: 204, 2020.
13. Hu C, Chen M, Jiang R, Guo Y, Wu M and Zhang X: Exosome-related tumor microenvironment. J Cancer 9: 3084-3092, 2018.
14. Lau AN and Vander Heiden MG: Metabolism in the tumor microenvironment. Annu Rev Cancer Biol 4: 17-40, 2020.
15. Ugel S, Canè S, De Sanctis F and Bronte V: Monocytes in the tumor microenvironment. Annu Rev Pathol 16: 93-122, 2021.
16. Pan BT and Johnstone RM: Fate of the transferrin receptor during maturation of sheep reticulocytes in vitro: Selective externalization of the receptor. Cell 33: 967-978, 1983.
17. Wróblewska JP, Lach MS, Kulcenty K, Galus Ł, Suchorska WM, Rösel D, Brábek J and Marszałek A: The analysis of inflammation-related proteins in a cargo of exosomes derived from the serum of uveal melanoma patients reveals potential biomarkers of disease progression. Cancers (Basel) 13: 3334, 2021.
18. Javed A, Kong N, Mathesh M, Duan W and Yang W: Nanoarchitectonics-based electrochemical aptasensors for highly efficient exosome detection. Sci Technol Adv Mater 25: 2345041, 2024.
19. Kakarla R, Hur J, Kim YJ, Kim J and Chwae YJ: Apoptotic cell-derived exosomes: Messages from dying cells. Exp Mol Med 52: 1-6, 2020.
20. Kiral FR, Kohrs FE, Jin EJ and Hiesinger PR: Rab GTPases and membrane trafficking in neurodegeneration. Curr Biol 28: R471-R486, 2018.
21. Shikanai M, Yuzaki M and Kawauchi T: Rab family small GTPases-mediated regulation of intracellular logistics in neural development. Histol Histopathol 33: 765-771, 2018.
22. Vitale I, Manic G, Coussens LM, Kroemer G and Galluzzi L: Macrophages and metabolism in the tumor microenvironment. Cell Metab 30: 36-50, 2019.
23. Baroni S, Romero-Cordoba S, Plantamura I, Dugo M, D'Ippolito E, Cataldo A, Cosentino G, Angeloni V, Rossini A, Daidone MG and Iorio MV: Exosome-mediated delivery of miR-9 induces cancer-associated fibroblast-like properties in human breast fibroblasts. Cell Death Dis 7: e2312, 2016.
24. Zhu Y, Dou H, Liu Y, Yu P, Li F, Wang Y and Xiao M: Breast cancer exosome-derived miR-425-5p Induces cancer-associated fibroblast-like properties in human mammary fibroblasts by TGF β 1/ROS signaling pathway. Oxid Med Cell Longev 2022: 5266627, 2022.
25. Yan Z, Sheng Z, Zheng Y, Feng R, Xiao Q, Shi L, Li H, Yin C, Luo H, Hao C, *et al*: Cancer-associated fibroblast-derived exosomal miR-18b promotes breast cancer invasion and metastasis by regulating TCEAL7. Cell Death Dis 12: 1120, 2021.
26. Kang J and Guo Y: Human umbilical cord mesenchymal stem cells derived exosomes promote neurological function recovery in a rat spinal cord injury model. Neurochem Res 47: 1532-1540, 2022.
27. Wang G, Yuan J, Cai X, Xu Z, Wang J, Ocansey DKW, Yan Y, Qian H, Zhang X, Xu W and Mao F: HucMSC-exosomes carrying miR-326 inhibit neddylation to relieve inflammatory bowel disease in mice. Clin Transl Med 10: e113, 2020.
28. Zhang Z, Chen L, Chen X, Qin Y, Tian C, Dai X, Meng R, Zhong Y, Liang W, Shen C, *et al*: Exosomes derived from human umbilical cord mesenchymal stem cells (HUCMSC-EXO) regulate autophagy through AMPK-ULK1 signaling pathway to ameliorate diabetic cardiomyopathy. Biochem Biophys Res Commun 632: 195-203, 2022.
29. Wang X, Cui Z, Zeng B, Qiong Z and Long Z: Human mesenchymal stem cell derived exosomes inhibit the survival of human melanoma cells through modulating miR-138-5p/SOX4 pathway. Cancer Biomark 34: 533-543, 2022.
30. Pan Y, Wang X, Li Y, Yan P and Zhang H: Human umbilical cord blood mesenchymal stem cells-derived exosomal microRNA-503-3p inhibits progression of human endometrial cancer cells through downregulating MEST. Cancer Gene Ther 29: 1130-1139, 2022.

31. Zhang Y, Huo M, Li W, Zhang H, Liu Q, Jiang J, Fu Y and Huang C: Exosomes in tumor-stroma crosstalk: Shaping the immune microenvironment in colorectal cancer. FASEB J 38: e23548, 2024.
32. Chen XJ, Guo CH, Wang ZC, Yang Y, Pan YH, Liang JY, Sun MG, Fan LS, Liang L and Wang W: Hypoxia-induced ZEB1 promotes cervical cancer immune evasion by strengthening the CD47-SIRPα axis. Cell Commun Signal 22: 15, 2024.
33. Giovannelli P, Di Donato M, Galasso G, Monaco A, Licitra F, Perillo B, Migliaccio A and Castoria G: Communication between cells: Exosomes as a delivery system in prostate cancer. Cell Commun Signal 19: 110, 2021.
34. Parolini I, Federici C, Raggi C, Lugini L, Palleschi S, De Milito A, Coscia C, Iessi E, Logozzi M, Molinari A, *et al*: Microenvironmental pH is a key factor for exosome traffic in tumor cells. J Biol Chem 284: 34211-3422, 2009.
35. Wang X, Sun C, Huang X, Li J, Fu Z, Li W and Yin Y: The advancing roles of exosomes in breast cancer. Front Cell Dev Biol 9: 731062, 2021.
36. Ban JJ, Lee M, Im W and Kim M: Low pH increases the yield of exosome isolation. Biochem Biophys Res Commun 461: 76-79, 2015.
37. Saber SH, Ali HEA, Gaballa R, Gaballah M, Ali HI, Zerfaoui M and Abd Elmageed ZY: Exosomes are the driving force in preparing the soil for the metastatic seeds: Lessons from the prostate cancer. Cells 9: 564, 2020.
38. Li Z, He P, Luo G, Shi X, Yuan G, Zhang B, Seidl C, Gewies A, Wang Y, Zou Y, *et al*: Increased tumoral microenvironmental pH improves cytotoxic effect of pharmacologic ascorbic acid in castration-resistant prostate cancer cells. Front Pharmacol 11: 570939, 2020.
39. Xi L, Peng M, Liu S, Liu Y, Wan X, Hou Y, Qin Y, Yang L, Chen S, Zeng H, *et al*: Hypoxia-stimulated ATM activation regulates autophagy-associated exosome release from cancer-associated fibroblasts to promote cancer cell invasion. J Extracell Vesicles 10: e12146, 2021.
40. Luo C, Xin H, Zhou Z, Hu Z, Sun R, Yao N, Sun Q, Borjigin U, Wu X, Fan J, *et al*: Tumor-derived exosomes induce immunosuppressive macrophages to foster intrahepatic cholangiocarcinoma progression. Hepatology 76: 982-999, 2022.
41. Shen Y, Guo D, Weng L, Wang S, Ma Z, Yang Y, Wang P, Wang J and Cai Z: Tumor-derived exosomes educate dendritic cells to promote tumor metastasis via HSP72/HSP105-TLR2/TLR4 pathway. OncoImmunology 6: e1362527, 2017.
42. Deicher A, Andersson R, Tingstedt B, Lindell G, Bauden M and Ansari D: Targeting dendritic cells in pancreatic ductal adenocarcinoma. Cancer Cell Int 18: 85, 2018.
43. Panigrahi GK, Praharaj PP, Peak TC, Long J, Singh R, Rhim JS, Abd Elmageed ZY and Deep G: Hypoxia-induced exosome secretion promotes survival of African-American and Caucasian prostate cancer cells. Sci Rep 8: 3853, 2018.
44. Llorente A, Skotland T, Sylvänne T, Kauhanen D, Róg T, Orłowski A, Vattulainen I, Ekroos K and Sandvig K: Molecular lipidomics of exosomes released by PC-3 prostate cancer cells. Biochim Biophys Acta 1831: 1302-1309, 2013.
45. Bertokova A, Svecova N, Kozics K, Gabelova A, Vikartovska A, Jane E, Hires M, Bertok T and Tkac J: Exosomes from prostate cancer cell lines: Isolation optimisation and characterisation. Biomed Pharmacother 151: 113093, 2022.
46. Spetzler D, Pawlowski TL, Tinder T, Kimbrough J, Deng T, Kim J, Moran B, Conrad A, Esmay P and Kuslich C: The molecular evolution of prostate cancer cell line exosomes with passage number. J Clin Oncol 28 (15 Suppl): e21071, 2010.
47. Müller JS, Burns DT, Griffin H, Wells GR, Zendah RA, Munro B, Schneider C and Horvath R: RNA exosome mutations in pontocerebellar hypoplasia alter ribosome biogenesis and p53 levels. Life Sci Alliance 3: e202000678, 2020.
48. Ogawa K, Lin Q, Li L, Bai X, Chen X, Chen H, Kong R, Wang Y, Zhu H, He F, *et al*: Aspartate β-hydroxylase promotes pancreatic ductal adenocarcinoma metastasis through activation of SRC signaling pathway. J Hematol Oncol 12: 144, 2019.
49. Adekoya TO and Richardson RM: Cytokines and chemokines as mediators of prostate cancer metastasis. Int J Mol Sci 21: 4449, 2020.
50. Dann J, Castronovo FP, McKusick KA, Griffin PP, Strauss HW and Prout GR Jr: Total bone uptake in management of metastatic carcinoma of the prostate. J Urol 137: 444-448, 1987.
51. Chau CH and Figg WD: Molecular and phenotypic heterogeneity of metastatic prostate cancer. Cancer Biol Ther 4: 166-167, 2005.
52. Bilen MA, Pan T, Lee YC, Lin SC, Yu G, Pan J, Hawke D, Pan BF, Vykoukal J, Gray K, *et al*: Proteomics profiling of exosomes from primary mouse osteoblasts under proliferation versus mineralization conditions and characterization of their uptake into prostate cancer cells. J Proteome Res 16: 2709-2728, 2017.
53. Renzulli JF II, Del Tatto M, Dooner G, Aliotta J, Goldstein L, Dooner M, Colvin G, Chatterjee D and Quesenberry P: Microvesicle induction of prostate specific gene expression in normal human bone marrow cells. J Urol 184: 2165-2171, 2010.
54. Duan Y, Tan Z, Yang M, Li J, Liu C, Wang C, Zhang F, Jin Y, Wang Y and Zhu L: PC-3-derived exosomes inhibit osteoclast differentiation by downregulating miR-214 and blocking NF-κB signaling pathway. Biomed Res Int 2019: 8650846, 2019.
55. Karlsson T, Lundholm M, Widmark A and Persson E: Tumor cell-derived exosomes from the prostate cancer cell line TRAMP-C1 impair osteoclast formation and differentiation. PLoS One 11: e0166284, 2016.
56. Lee J, Kwon MH, Kim JA and Rhee WJ: Detection of exosome miRNAs using molecular beacons for diagnosing prostate cancer. Artif Cells Nanomed Biotechnol 46 (Suppl 3): S52-S63, 2018.
57. Che Y, Shi X, Shi Y, Jiang X, Ai Q, Shi Y, Gong F and Jiang W: Exosomes derived from miR-143-Overexpressing MSCs inhibit cell migration and invasion in human prostate cancer by down-regulating TFF3. Mol Ther Nucleic Acids 18: 232-244, 2019.
58. Li T, Sun X and Chen L: Exosome circ_0044516 promotes prostate cancer cell proliferation and metastasis as a potential biomarker. J Cell Biochem 121: 2118-2126, 2019.
59. Petanidis S, Domvri K, Porpodis K, Anestakis D, Freitag L, Hohenforst-Schmidt W, Tsavlis D and Zarogoulidis K: Inhibition of kras-derived exosomes downregulates immunosuppressive BACH2/GATA-3 expression via RIP-3 dependent necroptosis and miR-146/miR-210 modulation. Biomed Pharmacother 122: 109461, 2020.
60. Ayala-Mar S, Donoso-Quezada J and González-Valdez J: Clinical implications of exosomal PD-L1 in cancer immunotherapy. J Immunol Res 2021: 8839978, 2021.
61. Wang J, Zeng H, Zhang H and Han Y: The role of exosomal PD-L1 in tumor immunotherapy. Transl Oncol 14: 101047, 2021.
62. Bai W, Tang X, Xiao T, Qiao Y, Tian X, Zhu B, Chen J, Chen C, Li Y, Lin X, *et al*: Enhancing antitumor efficacy of oncolytic virus M1 via albendazole-sustained $CD8^+$ T cell activation. Mol Ther Oncol 32: 200813, 2024.
63. Liu J, Wu S, Zheng X, Zheng P, Fu Y, Wu C, Lu B, Ju J and Jiang J: Immune suppressed tumor microenvironment by exosomes derived from gastric cancer cells via modulating immune functions. Sci Rep 10: 14749, 2020.
64. Yang J, Chen J, Liang H and Yu Y: Nasopharyngeal cancer cell-derived exosomal PD-L1 inhibits CD8+ T-cell activity and promotes immune escape. Cancer Sci 113: 3044-3054, 2022.
65. Kim DH, Kim H, Choi YJ, Kim SY, Lee JE, Sung KJ, Sung YH, Pack CG, Jung MK, Han B, *et al*: Exosomal PD-L1 promotes tumor growth through immune escape in non-small cell lung cancer. Exp Mol Med 51: 1-13, 2019.
66. Schmittgen TD: Exosomal miRNA cargo as mediator of immune escape mechanisms in neuroblastoma. Cancer Res 79: 1293-1294, 2019.
67. Yao X, Tu Y, Xu Y, Guo Y, Yao F and Zhang X: Endoplasmic reticulum stress-induced exosomal miR-27a-3p promotes immune escape in breast cancer via regulating PD-L1 expression in macrophages. J Cell Mol Med 24: 9560-9573, 2020.
68. Palicelli A, Bonacini M, Croci S, Bisagni A, Zanetti E, De Biase D, Sanguedolce F, Ragazzi M, Zanelli M, Chaux A, *et al*: What do we have to know about PD-L1 expression in prostate cancer? A systematic literature review. Part 7: PD-L1 expression in liquid biopsy. J Pers Med 11: 1312, 2021.
69. Xu W, Lu M, Xie S, Zhou D, Zhu M and Liang C: Endoplasmic reticulum stress promotes prostate cancer cells to release exosome and up-regulate PD-L1 expression via PI3K/Akt signaling pathway in macrophages. J Cancer 14: 1062-1074, 2023.
70. Li D, Zhou X, Xu W, Chen Y, Mu C, Zhao X, Yang T, Wang G, Wei L and Ma B: Prostate cancer cells synergistically defend against $CD8^+$ T cells by secreting exosomal PD-L1. Cancer Med 12: 16405-16415, 2023.
71. Hosseini R, Asef-Kabiri L, Yousefi H, Sarvnaz H, Salehi M, Akbari ME and Eskandari N: The roles of tumor-derived exosomes in altered differentiation, maturation and function of dendritic cells. Mol Cancer 20: 83, 2021.
72. Felmeden DC, Blann AD and Lip GYH: Angiogenesis: Basic pathophysiology and implications for disease. Eur Heart J 24: 586-603, 2003.

73. Kargozar S, Baino F, Hamzehlou S, Hamblin MR and Mozafari M: Nanotechnology for angiogenesis: Opportunities and challenges. Chem Soc Rev 49: 5008-5057, 2020.
74. Jin Y, Xing J, Xu K, Liu D and Zhuo Y: Exosomes in the tumor microenvironment: Promoting cancer progression. Front Immunol 13: 1025218, 2022.
75. Yu L, Gui S, Liu Y, Qiu X, Zhang G, Zhang X, Pan J, Fan J, Qi S and Qiu B: Exosomes derived from microRNA-199a-over-expressing mesenchymal stem cells inhibit glioma progression by down-regulating AGAP2. Aging (Albany NY) 11: 5300-5318, 2019.
76. Zhang C, Ji Q, Yang Y, Li Q and Wang Z: Exosome: Function and role in cancer metastasis and drug resistance. Technol Cancer Res Treat 17: 1533033818763450, 2018.
77. Khan S, Jutzy JMS, Valenzuela MMA, Turay D, Aspe JR, Ashok A, Mirshahidi S, Mercola D, Lilly MB and Wall NR: Plasma-derived exosomal survivin, a plausible biomarker for early detection of prostate cancer. PLoS One 7: e46737, 2012.
78. Bagnato G, Leopizzi M, Urciuoli E and Peruzzi B: Nuclear functions of the tyrosine kinase Src. Int J Mol Sci 21: 2675, 2020.
79. Rivera-Torres J and San José E: Src tyrosine kinase inhibitors: New perspectives on their immune, antiviral, and senotherapeutic potential. Front Pharmacol 10: 1011, 2019.
80. DeRita RM, Zerlanko B, Singh A, Lu H, Iozzo RV, Benovic JL and Languino RL: c-Src, insulin-like growth factor I receptor, G-protein-coupled receptor kinases and focal adhesion kinase are enriched into prostate cancer cell exosomes. J Cell Biochem 118: 66-73, 2016.
81. Larssen P, Wik L, Czarnewski P, Eldh M, Löf L, Ronquist KG, Dubois L, Freyhult E, Gallant CJ, Oelrich J, *et al*: Tracing cellular origin of human exosomes using multiplex proximity extension assays. Mol Cell Proteomics 16: 502-511, 2017.
82. Alcayaga-Miranda F, González PL, Lopez-Verrilli A, Varas-Godoy M, Aguila-Díaz C, Contreras L and Khoury M: Prostate tumor-induced angiogenesis is blocked by exosomes derived from menstrual stem cells through the inhibition of reactive oxygen species. Oncotarget 7: 44462-44477, 2016.
83. Maisto R, Oltra M, Vidal-Gil L, Martínez-Gil N, Sancho-Pellúz J, Filippo CD, Rossi S, D Amico M, Barcia JM and Romero FJ: ARPE-19-derived VEGF-containing exosomes promote neovascularization in HUVEC: The role of the melanocortin receptor 5. Cell Cycle 18: 413-424, 2019.