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REVIEW PAPER

The cellular and molecular role of exosomes in the pathophysiology of cancer

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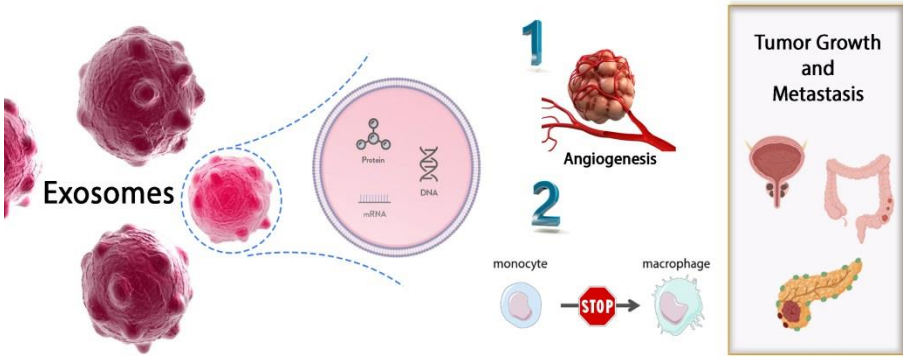
Highlights

- Exosomes are extracellular vesicles containing nucleic acids, proteins, and lipids.
- Exosomes are involved in the process of angiogenesis and tumor metastasis
- Exosomes are involved in the pathology of cancer by interfering in the control of the immune response.

Graphical Abstract



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Abstract

Exosomes are small extracellular particles enclosed in two lipid layers with the endosomal origin that contain nucleic acids, proteins, and lipids, and are secreted by most cell types. They can transmit their contents for the intercellular communication signals and stimulate signaling pathways in target cells. Exosomes might contribute to tumor growth and metastasis by controlling the immune response and promoting angiogenesis. Exosomes are involved in the pathology of many cancers with different mechanisms. It interferes in the development of breast tumors through the process of angiogenesis or for example, exosomal lipids play a special role in the pathology of pancreatic cancer. In addition, the mechanism of epithelial-mesenchymal transition plays a role in colorectal cancer. Activation of matrix metalloproteinases destroys the extracellular matrix in prostate cancer and causes metastasis. Therefore, the detailed understanding of the molecular pathways of exosomes involvement in the pathology of various types of cancers can be a very suitable solution in choosing cancer treatment approaches. The aim of this study was to review the exosomes' role in the progression of cancer.

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Introduction

Extracellular vesicles (EVs) found on the nanoscale contain nucleic acids and proteins and can be released by different cells. These vesicles are categorized into three sets; 1- microvesicles, 2- apoptotic bodies, and exosomes, each of which is different in terms of function, biogenesis, size, and distribution pathway. Exosomes are 40-150 nanometers in size and are released by different types of cells (1-3). They can transmit their contents for communication between cells and stimulate signaling pathways in acceptor cells (4). Exosomes could contribute to cancer development in a variety of ways, for example, they can do so by facilitating the tumor microenvironment, interfering with the immune system, and playing a role in drug resistance (5).

The exosomes derived from cancer cause tumor development, angiogenesis, and metastasis by direct activation of signaling pathways accountable for maintaining the proliferation of tumors, including PI3K/AKT or MAPK/ERK. This has been reported in gastric, bladder, and squamous cell carcinomas (6). Another instance of exosomes that manipulate the microenvironment of a tumor could be observed in the stimulation of the angiogenic procedure which is essential in the progression of cancer due to the provision of oxygen and nutrients and the elimination of waste products (7). Tumor-derived exosomes have noteworthy impacts on the development of cancer by affecting the immune system. On the one hand, tumor-derived exosomes can stimulate the immune response against cancer (8, 9). Tumor-derived exosomes through various mechanisms can increase resistance to treatment. One of the mechanisms is the exosome transport containing miRNA, lncRNA, and protein to the target cell and altering important signaling pathways in drug resistance such as EGFR, PTEN, and mTOR (10). In addition, there is a major mechanism by which tumor-derived exosomes (TEXs) modulate the tumor microenvironment by suppressing an effective cellular immune response and inducing immunosuppressive cells, which can neutralize the drug (11).

In the process of cancer progression, exosomes contributed to angiogenesis with transporting several proangiogenic molecules including matrix metalloproteinases (MMPs), vascular endothelial growth factor (VEGF), and miRNAs. These bodies could elevate angiogenesis via inhibiting the HIF-1 expression. When typical endothelial cells receive tumor-derived exosomes, the angiogenesis paths were activated and induce the formation of new vessels. Interaction of mesenchymal stem cells with cells of immune system through the tumor-derived exosomes may inhibit the anti-tumoral action. Efficient blocking of tumoral angiogenesis could inhibit the progression of tumor. Bevacizumab, a specific antibody of VEGF, was firstly used in clinic as an antiangiogenic molecule. Drug resistance issue is the main problem in cancer treatment with VEGF or its receptor. Immunotherapy in combination with inhibitors of angiogenesis could be effective against several cancers however, more investigations are needed to obtain more effective strategies (12, 13). The aim of this study was to review the cellular and molecular role of exosomes in the pathophysiology of cancer.

Exosome general features

Exosomes are small vesicles with a topology similar to the plasma membrane, which are present in a large number of body fluids such as blood, urine, saliva, semen, serum, etc. Generally, the size of exosomes is 40 to 100 nm, although larger sizes up to 200 nm are also reported. Exosomes include a variety of proteins such as heat shock proteins including hsp70 and hsp90, membrane and binding transporters and tetraspanins. In addition to proteins, exosomes contain lipids involved in cell transport, coding RNAs, and also small RNAs. Among the small RNAs, miRNAs are more present in exosomes (14).

Based on the path of formation and secretion of extracellular vesicles, they are generally classified into two classes. One of these classes, which is called microvesicle, is directly separated from the plasma membrane. Another class is exosomes, and when multivesicles are fused with plasma membranes are secreted by exocytosis. Exosomes are originally formed by endocytosis, first, the cell membrane enters inside as endocytosis, then a large number of vesicles are formed inside the endosome itself, which is called multivesicular bodies, and finally, these bodies are fused with the cell membrane and their internal vesicles secretes into the extracellular space, which is converted into exosomes (15-17).

In general, exosomes can interact with the acceptor cells through three mechanisms. The first mechanism is the membrane proteins of the exosome can directly connect to the signal receptors of the target cell membrane. Second, the exosomes fuse with the plasma membrane of the target cell and release their contents, and thirdly, exosomes can enter the target cell, which themselves have two fates. Exosomes swallowed by the target cell can fuse with endosomes and undergo transcytosis and be transported to neighboring cells, or exosomes enter the endosomes of the target cell and are directed to the lysosome to be degraded there (18-20).

Role in tumorigenesis and facilitation of tumor microenvironment

Tumor cells secrete exosomes known as tumor-derived exosomes (TEXs). The peptides in the TEXs are precisely the same as the peptides in the tumor cells from which the exosome is derived, and they comprise tumor-specific antigens that are existed in the origin cells. The exosomes derived from cancer cause tumor development, angiogenesis, and metastasis by direct activation of signaling pathways accountable for maintaining the proliferation of tumors, including PI3K/AKT or MAPK/ERK. This has been reported in gastric, bladder, and squamous cell carcinomas (6).

Moreover, exosomes derived from tumor cells could change the microenvironment to stimulate the disease invasion and spread. The tumor microenvironment is composed of various cell kinds including endothelial cells, immune cells, and fibroblasts, and the interaction of this microenvironment with the tumor is essential for the growth and development of cancer cells (4). Fibroblast cells are the main elements in cancer tissues and their activated form plays an important role in tumor progression (1). Other instance of manipulation of the cancer microenvironment by exosomes could be observed in the stimulation of the angiogenic procedure. Angiogenesis is essential in the progression of cancer because it provides nutrients and oxygen and removes waste products. Many researches have shown that exosomes have a main role in angiogenesis via the transport of miRNAs, mRNAs, and peptides (Figure 1). For example, exosomes derived from leukemia cells overexpress miR-92a, which enters endothelial cells and leads to increased migration and angiogenesis (7).

Other investigations have revealed that exosomes derived from mesenchymal stem cells stimulate angiogenesis by increasing the production of vascular endothelial growth factor (VEGF) in cancer cells and by inducing the pathways of ERK1/2 and p38 mitogen-activated protein kinase (21). Studies on cancer-derived exosomes have shown important clinical potential for exosome signaling, both as an intervention opinion or biological target in tumor therapy and the inhibition of resistance to chemotherapy and as a possible biomarker for the prognosis of cancer. This issue has been explored and has led to significant research into the study of tumor-induced exosome signaling.

Role of exosome in immune system

Tumor-derived exosomes have significant effects on the immune system in the development of cancer. On the other hand, exosomes derived from tumor could induce the immune response *vs*. tumor, also identified as cancer immune monitoring (8, 9). In addition, exosomes derived from tumor could enable immune suppression and prevent immune monitoring for invasion and proliferation (8, 22). Really, the components of several exosomes derived from tumor have elements from maternal cancer cells that could indirectly or directly affect the progress, activation, and antitumor activity of immune system (23).

In the microenvironment of tumor, exosomes might facilitate the connection between cells and regulate immune cell function. Tumor-derived exosomes (TEXs) and immune cell-derived exosomes (IEXs) can activate the immune response by antigens transporting to antigen-presenting cells (APCs), leading to activation and proliferation of CD4+ and CD8+ T helper cells (Figure 1) (24). Depending on the source of the exosomes, TEXs might comprise certain antigens related to tumor, such as mesothelin, carcinoembryonic antigen, melan A (25). So, TEXs can be employed to form a set of tumor-related antigens to induce the antitumor response as cancer vaccines in immunotherapy (26). Although exosomes have antitumor effects, several investigations have performed on their impacts on cancer development (27). In neuroblastoma tumors, tumor-derived exosomes

enhance the proliferation and migration of tumor by decrease of NEDD4 expression by hsamiR199a-3p (28). Other investigations have shown that the exosomes derived from gastric tumor could stimulate the differentiation of monocytes to tumor-associated macrophages (Figure 1), which could inhibit anticancer responses (29). In addition, miRNAs in TEXs might support the growth and metastasis of tumor. Exosomes secreted by immune cells and other cells have also been reported to facilitate tumor growth and metastasis. Activated CD8+ T helper cells-derived exosomes could facilitate the cancer cell invasion through the pathway of Fas/FasL (30). These studies demonstrate the importance of exosomes in progression of cancer and the appearance of novel patterns in cell biology of tumor. However, exosomes might be a future therapeutic target for cancer because of their significant immune-suppressing function (26).

Role of exosomes in drug resistance

Tumor-derived exosomes through different mechanisms can increase treatment resistance. One of the mechanisms of exosome transport contains miRNA, lncRNA and protein to the target cell and changes in important signaling pathways in drug resistance such as EGFR, PTEN, and mTOR (10). In addition, there is a major mechanism by which TEXs modulate the microenvironment of tumor by suppressing the effective cellular immune response and stimulating immunosuppressive cells, which can neutralize the drug (11). Examples of different mechanisms of exosome-based drug resistance are given in Table 1.

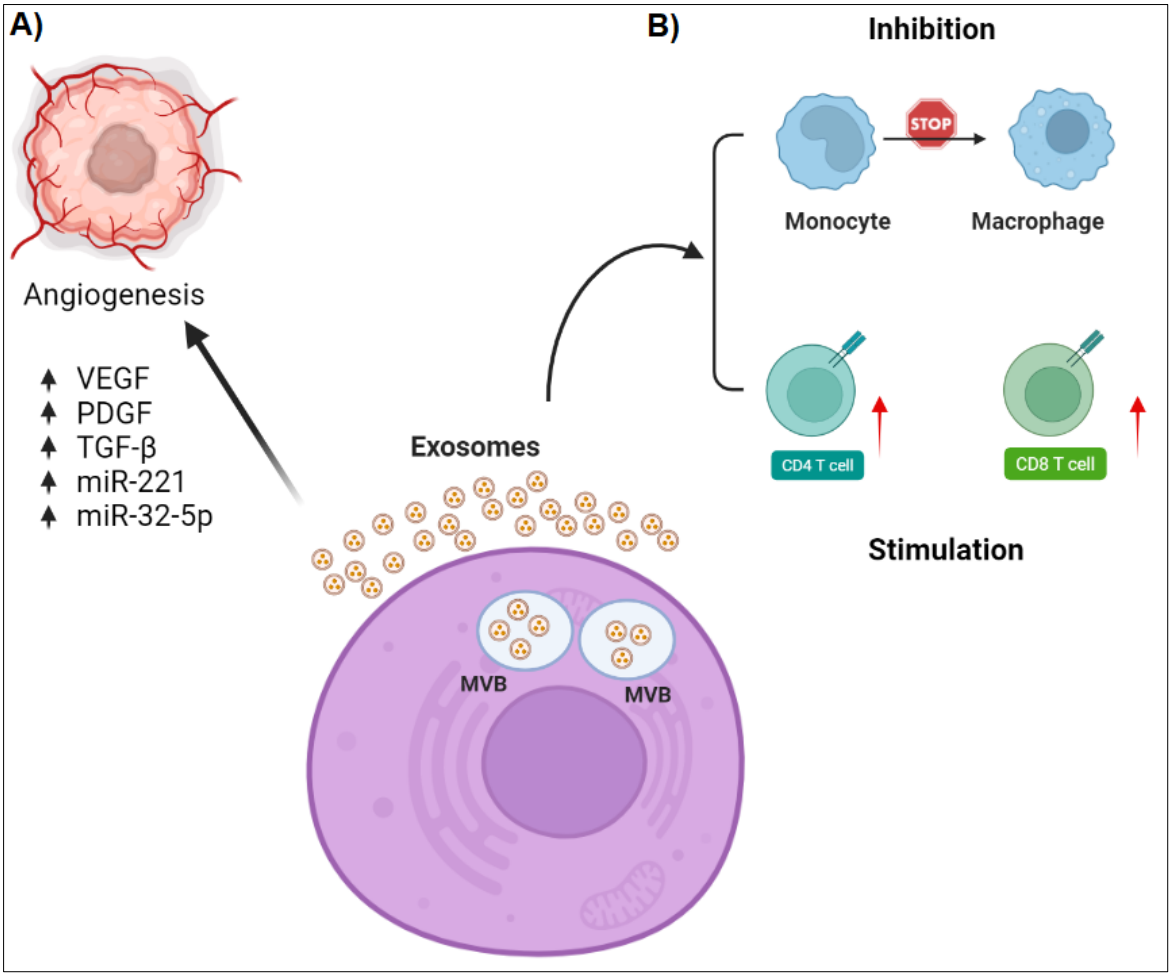

Figure 1. Role of exosomes in cancer development.

The exosomes could transport some specific molecules to target cells and trigger angiogenesis (A). exosomes could also interfere with immune functions. For example, they could inhibit monocyte to macrophage differentiation and stimulate the activation and proliferation of CD4+ and CD8+ T helper cells (B).

Table 1. Drug resistance of different tumors by exosomes through different mechanisms (31-36).

Cancer cell type	Exosome cargo	Mechanism	Target genes	Drug resistance
Breast Cancer	miR-155	Epithelial-to-mesenchymal transition (EMT) induction	TGF-β	Chemical resistance
Ovarian cancer		EMT induction	TGF-β/SMAD	Resistance to platinum
Gastric cancer	miR-155-5p	EMT induction	GATA3, TP53	Resistance to paclitaxel
Glioblastoma	PTPRZ1-MET	EMT induction		Resistance to temozolomide
Breast cancer	LncRNA-SNHG14	Inhibition of apoptosis	Bcl-2/BAX	Resistance to trastuzumab
Oral squamous cell carcinoma		Inhibition of apoptosis	PTEN	Resistant to cisplatin
Hepatocellular carcinoma	miR-221	Inhibition of apoptosis	Caspase 3	Resistance to sorafenib
Human lung adenocarcinoma		Induction of the mTOR pathway	Upregulation of mTOR expression	Resistance to cisplatin
Chronic lymphocytic leukemia	CD20	Attenuation of antibody deposition on the target cell		Resistance to rituximab

Role of exosome in breast cancer

Cancer stem cells may be the origin of cancers. Because these cells have the ability of self-renewal and can cause tumor development. Breast tumors may also originate from these types of cells. Differentiated breast tumor cells have some abilities such as disruption of the cell cycle and resistance to apoptosis (37). Exosomes induced by some factors such as heparanase or by hypoxia are related to angiogenesis in breast tumor. In fact, this angiogenesis is one of the main parts of breast tumorigenesis. Evidence shows that exosome derived from breast cancer (Exo-BCa) induce apoptosis resistance of normal cells around the breast tumor. These exosomes can regulate the expression of the NKG2D receptor and thereby inhibit the immune responses against breast cancer cells (38, 39). Most deaths by breast cancer are because of invasion and metastasis of tumor cells. It proposed that the exosomes may participate to metastasis and invasion of theses tumor cells. One of the mechanisms by which exosomes can increase breast cancer metastasis is the transfer of miR-10b to cancer cells, which is found in malignant breast cancers (40). Schematic of exosome and four breast, pancreatic, colorectal and prostate cancers are shown in Figure 2.

Role of exosomes in pancreatic cancer

Pancreatic cancer is characterized by invasion. This problem causes ineffectiveness of pancreatic cancer treatments, because metastatic lesions from this cancer show resistance to chemotherapy. The process of metastasis is very complex and is observed in malignant cancers. Metastatic cells can be transported to different parts of the body through body fluids. In the next new environment, these cells can resist chemotherapy and cause cancer recurrence (41). It is known that exosomes play a role in some pathological processes such as initiation and metastasis of cancer cells. These bodies can turn normal cells into prostate and breast cancer cells. The contents of exosomes, such as oncogene proteins, adhesion molecules, cytokines, some specific mRNA and miRNAs, promote the proliferation of cancer cells (42). For example, miR-200, which is a tumor suppressor, can promote breast tumor metastasis (43). Exosomes derived from cancer cells can facilitate the proliferation of gastric cancer cells by inducing cellular kinase cascades (44).

However, in the case of pancreatic cancer, different results were obtained and exosomes inhibit the Notch-1 pathway through lipids and induce apoptosis (45). Exosomal lipids also activate NF-κB in MiaPaCa-2, a

pancreatic cancer cell line, and as a result induce the expression of SDF-1α and finally block cell death (46). According to the mentioned cases, it is clear that exosomal lipids play a special role in the pathology of pancreatic cancer. Also, some exosomes derived from the pancreas can cause the proliferation of pancreatic tumor cells through the mediation of some special miRNAs (47). In one study, it was found that exosomes from pancreatic cancer induce metastasis in animal models. The said exosomes prepare the liver for the implantation of pancreatic cancer cells (48).

The role of exosomes on colorectal cancer

Epithelial-mesenchymal transition (EMT) is hypothesized to be the first event in cancer development. This phenomenon is related to some factors such as changing the expression of cell surface proteins, extracellular matrix proteins, intracellular skeleton and MMPs (49). Tumor exosomes can contribute to EMT. The presence of EpCAM in colorectal cancer, which is associated with Claudine-7, can play a role in cancer development through the mechanism of Epithelial-mesenchymal transition (24, 50). In a research, it was found that a type of colorectal cell line grows in suspension after some time, which indicates the occurrence of metastasis, and this phenomenon was confirmed after analyzing the expression of E-cadherin and vimentin. Electron microscope studies also showed that adherent cells produce exosomes that are received by metastatic cells. The presence of miR-210 in the mentioned exosomes causes the process of EMT and eventually metastasis (51).

The role of exosomes on prostate cancer

Various cancer cells produce exosomes and can cause cancer to develop. These effects are due to the content of exosomes including DNA, RNA (especially miRNAs), and special proteins. Chemokine receptor CXCR1, which is present in the membrane of exosomes from prostate tumor, can cause the expansion of prostate cancer niche. Metalloprotein 9 increases expression in fibroblasts under the influence of tumor exosomes and activates them. These molecules can destroy the extracellular matrix and promote the metastasis of cancer cells. Increased expression of metalloprotein 9 in fibroblasts activates fibroblasts in the secretion of exosomes and metastasis of tumor cells. Communicating between cancer cells and fibroblasts through exosomes provides a suitable environment for tumor expansion (52). Also, some miRNAs, including miR-100, increase the expression of some metalloproteins and cause the migration of fibroblasts (53).

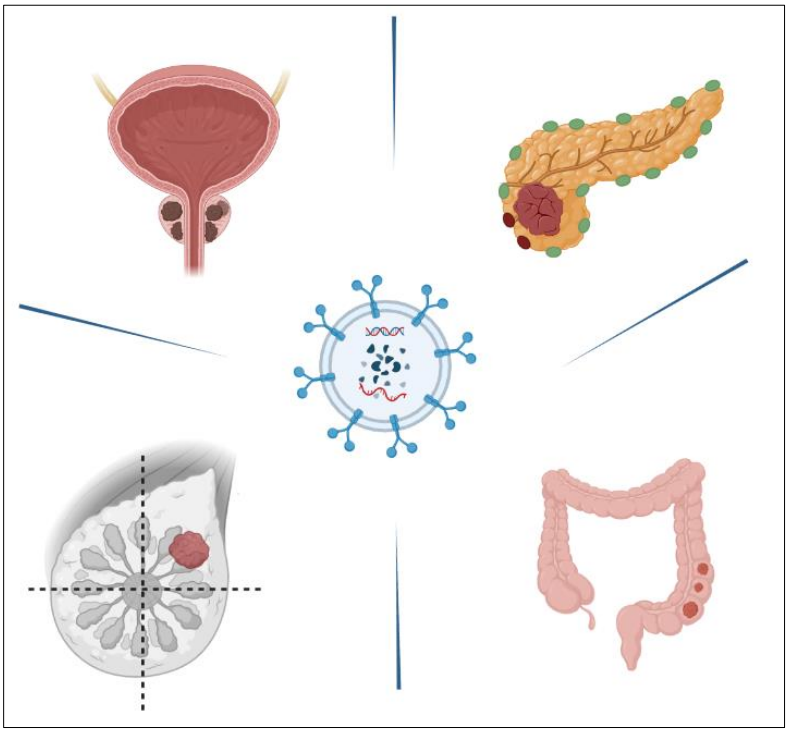

Figure 2. Exosomes and cancers.

Exosomes are involved in the pathology of many cancers with different mechanisms. It interferes in the development of breast tumors through the process of angiogenesis or for example, exosomal lipids play a special role in the pathology of pancreatic cancer. In addition, the mechanism of epithelial-mesenchymal transition plays a role in colorectal cancer. Activation of matrix metalloproteinases destroys the extracellular matrix in prostate cancer and causes metastasis.

Conclusion

Exosomes are vesicles that can act as mediators of intercellular communication. They are usually secreted by most cells and have specific properties depending on the type of source cell. Sometimes these exosomes can carry signals that trigger the onset and progression of cancer. Cargoes trapped inside the exosome sometimes interfere with biological processes such as angiogenesis, immune system reactions, and the maintenance of tumor microenvironment homeostasis, causing tumorigenesis. Of course, the role of exosomes in cancer can be considered dual-purpose. Knowing the exact mechanisms involved in exosomes in cancer progression can be an appropriate way to provide effective therapeutic strategies against many types of cancers.

References

1. Kalluri R. The biology and function of exosomes in cancer. J Clin Invest 2016; 126(4): 1208-1215. https://doi.org/10.1172/JCI81135
2. Colombo M, Raposo G, Théry C. Biogenesis, secretion, and intercellular interactions of exosomes and other extracellular vesicles. Ann Rev Cell Develop Biol 2014; 30: 255-289. https://doi.org/10.1146/annurev-cellbio-101512-122326
3. Liu Y, Shi K, Chen Y, Wu X, Chen Z, Cao K, Tao Y, Chen X, Liao J, Zhou J. Exosomes and their role in cancer progression. Front Oncol 2021; 11: 639159. https://doi.org/10.3389/fonc.2021.639159
4. Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes. Science 2020; 367(6478): eaau6977. https://doi.org/10.1126/science.aau6977
5. Zhou Y, Zhang Y, Gong H, Luo S, Cui Y. The role of exosomes and their applications in cancer. Int J Mole Sci 2021; 22(22): 12204. https://doi.org/10.3390/ijms222212204
6. Meehan K, Vella LJ. The contribution of tumour-derived exosomes to the hallmarks of cancer. Crit Rev Clin Labor Sci 2016; 53(2): 121-131. https://doi.org/10.3109/10408363.2015.1092496
7. Fernandes Ribeiro M, Zhu H, W Millard R, Fan GC. Exosomes function in pro-and anti-angiogenesis. Curr Angiogen 2013; 2(1): 54-59. https://doi.org/10.2174/2211552811302002000l
8. Barros FM, Carneiro F, Machado JC, Melo SA. Exosomes and immune response in cancer: friends or foes? Front. Immunol 2018; 9: 730. https://doi.org/10.3389/fimmu.2018.00730
9. Romagnoli GG, Zelante BB, Toniolo PA, Migliori IK, Barbuto JAM. Dendritic cell-derived exosomes may be a tool for cancer immunotherapy by converting tumor cells into immunogenic targets. Front Immunol 2015; 5: 692. https://doi.org/10.3389/fimmu.2014.00692
10. Liu J, Ren L, Li S, Li W, Zheng X, Yang Y, et al. The biology, function, and applications of exosomes in cancer. Acta Pharmaceu Sinica 2021; 11(9): 2783-2797. https://doi.org/10.1016/j.apsb.2021.01.001
11. Hellwinkel JE, Redzic JS, Harland TA, Gunaydin D, Anchordoquy TJ, Graner MW. Glioma-derived extracellular vesicles selectively suppress immune responses. Neuro Oncol 2015; 18(4): 497-506. https://doi.org/10.1093/neuonc/nov170
12. Olejarz W, Kubiak-Tomaszewska G, Chrzanowska A, Lorenc T. Exosomes in Angiogenesis and Anti-angiogenic Therapy in Cancers. Int J Mole Sci 2020; 21(16): 5840. https://doi.org/10.3390/ijms21165840
13. Quintero-Fabián S, Arreola R, Becerril-Villanueva E, Torres-Romero JC, Arana-Argáez V, Lara-Riegos J, Ramírez-Camacho MA, Alvarez-Sánchez ME. Role of Matrix Metalloproteinases in Angiogenesis and Cancer. Front Oncol 2019; 9: 1370. https://doi.org/10.3389/fonc.2019.01370

14. Raposo G, Stoorvogel W. Extracellular vesicles: exosomes, microvesicles, and friends. J Cell Biol 2013; 200(4): 373-383. https://doi.org/10.1083/jcb.201211138
15. Subra C, Laulagnier K, Perret B, Record M. Exosome lipidomics unravels lipid sorting at the level of multivesicular bodies. Biochimie 2007; 89(2): 205-212. https://doi.org/10.1016/j.biochi.2006.10.014
16. Gruenberg J, van der Goot FG. Mechanisms of pathogen entry through the endosomal compartments. Nat Rev Mole Cell Biol 2006; 7(7): 495-504. https://doi.org/10.1038/nrm1959
17. Conner SD, Schmid SL. Regulated portals of entry into the cell. Nature 2003; 422(6927): 37-44. https://doi.org/10.1038/nature01451
18. Munich S, Sobo-Vujanovic A, Buchser WJ, Beer-Stolz D, Vujanovic NL. Dendritic cell exosomes directly kill tumor cells and activate natural killer cells via TNF superfamily ligands. Oncoimmunology 2012; 1(7): 1074-1083. https://doi.org/10.4161/onci.20897
19. Mulcahy LA, Pink RC, Carter DR. Routes and mechanisms of extracellular vesicle uptake. J Extracell Vesicles 2014; 3(1): 24641. https://doi.org/10.3402/jev.v3.24641
20. Tian T, Zhu YL, Hu FH, Wang YY, Huang NP, Xiao ZD. Dynamics of exosome internalization and trafficking. J Cell Physiol 2013; 228(7): 1487-1495. https://doi.org/10.1002/jcp.24304
21. Vakhshiteh F, Atyabi F, Ostad SN. Mesenchymal stem cell exosomes: a two-edged sword in cancer therapy. Int J Nanomedicine 2019; 14: 2847. https://doi.org/10.2147/IJN.S200036
22. Théry C, Ostrowski M, Segura E. Membrane vesicles as conveyors of immune responses. Nat Rev Immunol 2009; 9(8): 581-593. https://doi.org/10.1038/nri2567
23. Li X, Corbett AL, Taatizadeh E, Tasnim N, Little JP, Garnis C, Daugaard M, Guns E, Hoorfar M, Li IT. Challenges and opportunities in exosome research—Perspectives from biology, engineering, and cancer therapy. APL Bioengin 2019; 3(1): 011503. https://doi.org/10.1063/1.5087122
24. Greening DW, Gopal SK, Mathias RA, Liu L, Sheng J, Zhu HJ, Simpson RJ. Emerging roles of exosomes during epithelial–mesenchymal transition and cancer progression. Seminars Cell Develop Biol 2015; 40: 60-71. https://doi.org/10.1016/j.semcdb.2015.02.008
25. Andre F, Schartz NE, Movassagh M, Flament C, Pautier P, Morice P, Pomel C, Lhomme C, Escudier B, Le Chevalier T, Tursz T. Malignant effusions and immunogenic tumour-derived exosomes. Lancet 2002; 360(9329): 295-305. https://doi.org/10.1016/S0140-6736(02)09552-1
26. Xie F, Xu M, Lu J, Mao L, Wang S. The role of exosomal PD-L1 in tumor progression and immunotherapy. Mole Cancer 2019; 18(1): 1-10. https://doi.org/10.1186/s12943-019-1074-3
27. Tung KH, Ernstoff MS, Allen C, La Shu S. A Review of Exosomes and their Role in The Tumor Microenvironment and Host–Tumor "Macroenvironment". J Immunolog Sci 2019; 3(1): 4. https://doi.org/10.29245/2578-3009/2019/1.1165
28. Ma J, Xu M, Yin M, Hong J, Chen H, Gao Y, Xie C, Shen N, Gu S, Mo X. Exosomal hsa-miR199a-3p promotes proliferation and migration in neuroblastoma. Front Oncol 2019; 9: 459. https://doi.org/10.3389/fonc.2019.00459
29. Harada K, Dong X, Estrella JS, Correa AM, Xu Y, Hofstetter WL, Sudo K, Onodera H, Suzuki K, Suzuki A, Johnson RL. Tumor-associated macrophage infiltration is highly associated with PD-L1 expression in gastric adenocarcinoma. Gastric Cancer 2018; 21(1): 31-40. https://doi.org/10.1007/s10120-017-0760-3
30. Cai Z, Yang F, Yu L, Yu Z, Jiang L, Wang Q, Yang Y, Wang L, Cao X, Wang J. Activated T cell exosomes promote tumor invasion via Fas signaling pathway. J Immunol 2012; 188(12): 5954-5961. https://doi.org/10.4049/jimmunol.1103466
31. Crow J, Atay S, Banskota S, Artale B, Schmitt S, Godwin AK. Exosomes as mediators of platinum resistance in ovarian cancer. Oncotarget 2017; 8(7): 11917. https://doi.org/10.18632/oncotarget.14440
32. Santos JC, Lima NdS, Sarian LO, Matheu A, Ribeiro ML, Derchain SFM. Exosome-mediated breast cancer chemoresistance via miR-155 transfer. Sci Rep 2018; 8(1): 1-11. https://doi.org/10.1038/s41598-018-19339-5

33. Santos MF, Rappa G, Karbanová J, Kurth T, Corbeil D, Lorico A. VAMP-associated protein-A and oxysterol-binding protein–related protein 3 promote the entry of late endosomes into the nucleoplasmic reticulum. J Biol Chem 2018; 293(36): 13834-13848. https://doi.org/10.1074/jbc.RA118.003725
34. Wang M, Qiu R, Yu S, Xu X, Li G, Gu R, Tan C, Zhu W, Shen B. Paclitaxel-resistant gastric cancer MGC-803 cells promote epithelial-to-mesenchymal transition and chemoresistance in paclitaxel-sensitive cells via exosomal delivery of miR-155-5p. Int J Oncol 2019; 54(1): 326-338. https://doi.org/10.3892/ijo.2018.4601
35. Wang F, Li L, Piontek K, Sakaguchi M, Selaru FM. Exosome miR-335 as a novel therapeutic strategy in hepatocellular carcinoma. Hepatology 2018; 67(3): 940-954. https://doi.org/10.1002/hep.29586
36. Zeng AL, Yan W, Liu YW, Wang Z, Hu Q, Nie E, Zhou X, Li R, Wang XF, Jiang T, You YP. Tumour exosomes from cells harbouring PTPRZ1–MET fusion contribute to a malignant phenotype and temozolomide chemoresistance in glioblastoma. Oncogene 2017; 36(38): 5369-5381. https://doi.org/10.1038/onc.2017.134
37. Al-Hajj M, Clarke MF. Self-renewal and solid tumor stem cells. Oncogene 2004; 23(43): 7274-7282. https://doi.org/10.1038/sj.onc.1207947
38. Thompson CA, Purushothaman A, Ramani VC, Vlodavsky I, Sanderson RD. Heparanase regulates secretion, composition, and function of tumor cell-derived exosomes. J Biol Chem 2013; 288(14): 10093-10099. https://doi.org/10.1074/jbc.C112.444562
39. Yu DD, Wu Y, Shen HY, Lv MM, Chen WX, Zhang XH, Zhong SL, Tang JH, Zhao JH. Exosomes in development, metastasis and drug resistance of breast cancer. Cancer Sci 2015; 106(8): 959-964. https://doi.org/10.1111/cas.12715
40. Singh R, Pochampally R, Watabe K, Lu Z, Mo YY. Exosome-mediated transfer of miR-10b promotes cell invasion in breast cancer. Mole Cancer 2014; 13(1): 256. https://doi.org/10.1186/1476-4598-13-256
41. Mohme M, Riethdorf S, Pantel K. Circulating and disseminated tumour cells - mechanisms of immune surveillance and escape. Nat Rev Clin Oncol 2017; 14(3): 155-167. https://doi.org/10.1038/nrclinonc.2016.144
42. Yan Y, Fu G, Ming L. Role of exosomes in pancreatic cancer. Oncol Lett 2018; 15(5): 7479-7488. https://doi.org/10.3892/ol.2018.8348
43. Le MT, Hamar P, Guo C, Basar E, Perdigão-Henriques R, Balaj L, Lieberman J. miR-200–containing extracellular vesicles promote breast cancer cell metastasis. J Clin Invest 2014; 124(12): 5109-5128. https://doi.org/10.1172/JCI75695
44. Qu JL, Qu XJ, Zhao MF, Teng YE, Zhang Y, Hou KZ, Jiang YH, Yang XH, Liu YP. Gastric cancer exosomes promote tumour cell proliferation through PI3K/Akt and MAPK/ERK activation. Digest Liver Dis 2009; 41(12): 875-880. https://doi.org/10.1016/j.dld.2009.04.006
45. Beloribi S, Ristorcelli E, Breuzard G, Silvy F, Bertrand-Michel J, Beraud E, Verine A, Lombardo D. Exosomal lipids impact notch signaling and induce death of human pancreatic tumoral SOJ-6 cells. PloS One 2012; 7(10): e47480. https://doi.org/10.1371/journal.pone.0047480
46. Beloribi-Djefaflia S, Siret C, Lombardo D. Exosomal lipids induce human pancreatic tumoral MiaPaCa-2 cells resistance through the CXCR4-SDF-1α signaling axis. Oncoscience 2015; 2(1): 15-30. https://doi.org/10.18632/oncoscience.96
47. Takikawa T, Masamune A, Yoshida N, Hamada S, Kogure T, Shimosegawa T. Exosomes derived from pancreatic stellate cells: MicroRNA signature and effects on pancreatic cancer cells. Pancreas 2017; 46(1): 19-27.
48. Costa-Silva B, Aiello NM, Ocean AJ, Singh S, Zhang H, Thakur BK, Becker A, Hoshino A, Mark MT, Molina H, Xiang J. Pancreatic cancer exosomes initiate pre-metastatic niche formation in the liver. Nat Cell Biol 2015; 17(6): 816-826. https://doi.org/10.1038/ncb3169
49. De Wever O, Pauwels P, De Craene B, Sabbah M, Emami S, Redeuilh G, Gespach C, Bracke M, Berx G. Molecular and pathological signatures of epithelial–mesenchymal transitions at the cancer invasion front. Histochem Cell Biol 2008; 130(3): 481-494. https://doi.org/10.1007/s00418-008-0464-1

50. Philip R, Heiler S, Mu W, Büchler MW, Zöller M, Thuma F. Claudin-7 promotes the epithelial-mesenchymal transition in human colorectal cancer. Oncotarget 2015; 6(4): 2046-2063. https://doi.org/10.18632/oncotarget.2858
51. Bigagli E, Luceri C, Guasti D, Cinci L. Exosomes secreted from human colon cancer cells influence the adhesion of neighboring metastatic cells: Role of microRNA-210. Cancer Biol Therap 2016; 17(10): 1062-1069. https://doi.org/10.1080/15384047.2016.1219815
52. Osaki M, Okada F. Exosomes and Their Role in Cancer Progression. Yonago Acta Medica 2019; 62(2): 182-190. https://doi.org/10.33160/yam.2019.06.002
53. Shimoda M, Khokha R. Metalloproteinases in extracellular vesicles. Biochim Biophys Acta Mole Cell Res 2017; 1864(11 Pt A): 1989-2000. https://doi.org/10.1016/j.bbamcr.2017.05.027

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