# Role of exosomes in cellular communication between tumor cells and the tumor microenvironment (Review)

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Received November 29, 2021; Accepted April 26, 2022

DOI: 10.3892/ol.2022.13360

**Abstract.** Exosomes are nanovesicles secreted by almost all types of cells. They contain RNAs, microRNAs, proteins and other bioactive substances, and can be used as carriers and for communication between cells. They regulate numerous biological processes, such as tumor development, cell proliferation and resistance to chemotherapy. Exosome-mediated communication between tumor cells and the tumor microenvironment (TME) is crucial in the initiation and progression of tumor development. The present review aims to summarize the role of exosomes in mediating the communication between tumor cells and the TME and to suggest the potential use of exosomes as targets for the development of novel therapeutic strategies against cancer.

**Contents**



## 1. Introduction

Exosomes were discovered by Johnstone *et al* in 1987 (1,2). The study found that sheep reticulocytes secrete exosomes to remove the transferrin receptor during their maturation (2). Exosomes are nanoscale extracellular vehicles with a diameter ranging between 50 and 150 nm (3-5) and are located in the density range of 1.13-1.19 g/ml after sucrose gradient centrifugation. Under an electron microscope, exosomes appear as cup-shaped vesicles (6). They are rich in Alix, tumor susceptibility gene 101, heat shock protein 70 (HSP70) (7), tetraspanins (CD63, CD81 and CD9) (7), cytoskeleton proteins, and major histocompatibility complex class II molecules (8). Exosomes contain specific components of the cells from which they originate (9). For example, exosomes deriving from tumor cells contain molecules that suggest their endoplasmic reticulum origin and cell components that can promote tumor development (10), including tyrosine kinase receptors, oncoproteins, phosphorylated proteins and microRNAs (miRNAs/miRs) (11). In addition, exosomes can be detected in a variety of body fluids, including blood, urine and breast milk (12). Therefore, the detection of tumor-related cell components in exosomes can be used as a method for the early diagnosis of some tumors (13).

The biogenesis process of exosomes distinguishes them from apoptotic bodies and other extracellular vesicles. Exosomes originate from the endosomal system and are formed from early endosomes: Inward budding of cellular membranes leads to formation of early endosomes (3,14,15). Early endosomes mature to late endosomes with multiple intraluminal vesicles (ILVs) and late endosomes form multivesicular bodies (MVBs). After the fusion of MVBs with the plasma cell membrane, exosomes are released from the cell into the extracellular environment, carrying the biological information of secretory cells and transmitting biological signals to recipient cells (3,14,15).

During the maturation of ILVs into MVBs, proteins are sorted. Internalized proteins in early endosomes are ubiquitinated and directed to late endosomes (3,14,15). Multiprotein complexes are involved in the sorting and ubiquitination of target proteins (3). The endosomal sorting complexes required for transport (ESCRT) complex regulates endosomal maturation (14). ESCRT complexes are composed of four complexes (ESCRT-0, -I, -II and -III) (14). Ubiquitylated proteins in the endosomal membrane are sequestered by the ESCRT-0 complex (15). The ESCRT-I and ESCRT-II complexes are responsible for the budding of the membrane. For instance, ESCRT induces MVB vesicles to sprout (15,16), while

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*Key words:* exosome, tumor microenvironment, cancer, cellular communication

Rab proteins regulate intracellular vesicle transport (17). Furthermore, there are a variety of proteins involved in this process, including Rab GTPases (Rab11, Rab35, Rab27A and Rab 27b), which are involved in the formation of exosomes (17,18).

## 2. Exosomal nucleic acids

Exosomes can be secreted by reticulocytes (1), dendritic cells (19), macrophages (7) and epithelial cells (7). The double-layered membrane protects exosomal RNAs from being digested by RNA enzymes in the plasma or other body fluids (20). Therefore, exosomes can be used as tumor biomarkers for early diagnosis (20). For example, in gastric cancer, exosomal long noncoding RNA 152 can be used as a potential biological marker (21). Furthermore, miRNAs in circulating exosomes can be used as biomarkers for the screening and diagnosis of lung cancer (22) and several exosomal biomarkers have been reported in a prostate cancer study (23). Therefore, the identification of tumor exosomal RNAs has become a potential diagnostic tool.

Exosomes are known to contain a considerable number of functional messenger RNAs (mRNAs) and miRNAs (24). Exosomes from breast cancer, colorectal cancer and leukemia cells contain human telomerase reverse transcriptase (hTERT) mRNA (25). When these exosomes are absorbed by fibroblasts, they can promote the construction of a tumor metastatic environment by promoting the proliferation and survival of fibroblasts (25). Gutkin *et al* (25) reported that human tumor cells-derived exosomes can transfer hTERT transcriptional mRNA to telomerase-negative fibroblasts. The delivered mRNA can be translated into a protein, which renders the recipient cells telomerase-positive. This was the first study to report that exosomes can transfer the transcriptional mRNA of hTERT.

Exosomes from chronic lymphocytic leukemia (CLL) cells promote the proliferation of stromal cells by secreting miR-202-3p into human bone marrow cells (26). When CLL-exosomes, derived either from CLL cell culture supernatants or plasma from patients with CLL, were co-cultured with human stromal cells, the latter could accept these exosomes, resulting in the promotion of their proliferation associated with the induction of c-Fos expression (26). These exosomes are rich in small RNAs, particularly hsa-mir-202-3p, which can enhance the Hedgehog signal transduction pathway, thus promoting the proliferation of recipient cells (26). miR-9 transported by tumor cell-derived exosomes can promote endothelial cell migration and angiogenesis through the Janus kinase/signal transducer and activator of the transcription signaling pathway (27).

## 3. Role of exosomes in tumor metastasis

Increasing evidence shows that exosomes serve an important role in intercellular communication (28,29). Exosomes transfer proteins, mRNAs and miRNAs to receptive cells, resulting in the regulation of a variety of functions, including immunoregulation, matrix remodeling, growth factor delivery and oncoprotein transfer (28,30-32). The tumor microenvironment (TME) is composed of tumor-associated fibroblasts, osteoblasts and immune cells. The TME can promote the proliferation of tumor cells and confers resistance to chemotherapy (33). Exosomes can regulate multiple biological behaviors of tumor cells, as shown in Fig. 1. Furthermore, exosomal miRNAs, mRNA, proteins and other functional molecules are accepted by the stromal cells in the TME where they exert regulatory effects (34).

Exosomes from the breast cancer microenvironment can promote breast cancer cell metastasis through the Wnt plane cell polarity (PCP) signal (35). During breast cancer cell metastasis, exosomes can promote tumor metastasis via the Wnt PCP pathway, which is different from the classical Wnt signaling pathway (35). Hood *et al* (30) found that exosomes secreted by melanoma cells prepare sentinel lymph nodes for tumor cell metastasis as tumor cells are more likely to metastasize to a site with abundant melanoma exosomes. Bone marrow progenitor cells are permanently 'educated' by exosomes from highly invasive melanoma cells through the receptor tyrosine kinase, MET, to promote the invasion and metastasis of primary tumor cells (36). The receptor tyrosine kinase MET transforms bone marrow precursor cells into an angiogenesis-promoting phenotype, which expresses c-kit, receptor tyrosine kinase EGF-like domains 2 and Met (36). The inhibition of exosomal Met expression can weaken the metastasis that is promoted by bone marrow progenitor cells (36).

Exosomes derived from lung cancer cells can promote epithelial-to-mesenchymal transition (EMT) (37). When serum-derived exosomes from patients with advanced lung cancer are used to treat human bronchial epithelium, they can promote the EMT of the recipient cells (37). Exosomes from pancreatic cancer cells can induce the formation of the metastasis-promoting microenvironment in the liver (38). Exosomes derived from gastric cancer cells can carry EGFR and regulate the microenvironment of the liver to promote the metastasis of gastric cancer cells (39). Exosomes isolated from the serum of patients with gastric cancer contain EGFR, while the exosomes derived from the serum of normal individuals do not (39). This indicates that the levels of the EGFR oncoprotein in the exosomes from the serum of patients with gastric cancer are associated with gastric cancer metastatic stages. The exosomes carrying the EGFR from the gastric cancer can be taken up by liver cells, which will further activate liver hepatocyte growth factor and prepare the premetastatic 'soil' for the gastric cancer (39).

## 4. Role of exosomes in drug resistance

Exosomes derived from tumor cells can promote the resistance of tumor cells to chemotherapeutic drugs via multiple mechanisms, such as carrying multidrug resistance (MDR) proteins or by secreting chemotherapeutic drugs (40). For example, exosomes can transfer drug resistance by secreting MDR proteins into recipient cells (41). Exosomes derived from 5T33 bone marrow stromal cells promote the proliferation of multiple myeloma cells and induce their resistance to bortezomib (42). Exosomes can mediate drug resistance by transporting drug resistance proteins. In prostate cancer, docetaxel resistance is associated with an increased secretion of exosomes (43). Exosomes secreted from docetaxel-resistant

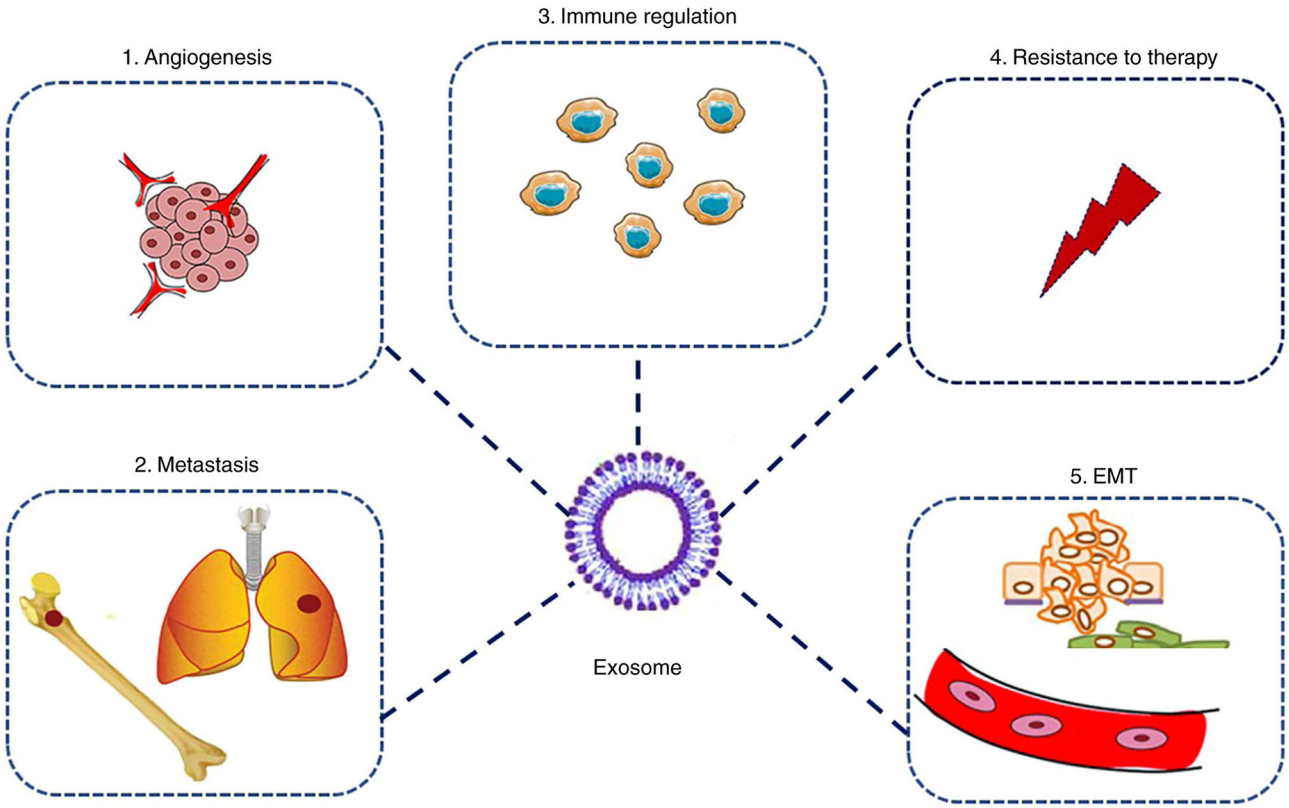


Figure 1. Exosomes can regulate multiple biological behaviors of tumor cells. 1, Exosomes released from tumor cells and the tumor microenvironment can promote angiogenesis. 2, Exosomes can prepare a premetastatic niche and promote cancer cell metastasis. 3, Exosomes can regulate immune responses by presenting antigens, promoting the differentiation of T cells toward T-regulatory cells. 4, Exosomes can regulate resistance to therapy of tumor cells. 5, Exosomes can activate the machinery of the EMT. EMT, Epithelial-to-mesenchymal transition.

prostate cancer cells can confer docetaxel resistance to docetaxel-sensitive prostate cancer cells by transporting P-glycoprotein in the exosomes (43). Exosomes can have countertherapeutic effects by binding to chemotherapy drugs. In breast cancer, HER-2-overexpressing exosomes can resist the therapeutic effect of trastuzumab. Exosomes secreted by HER2-overexpressing SK-BR-3 and br-474 breast cancer cells can bind to trastuzumab. In the early stage of breast cancer, the binding level of exosomes isolated from the patients is lower than that of patients at late stages of the disease (44). In ovarian cancer cisplatin-resistant cells, cisplatin can promote the development of drug resistance through exosomes (45). When the cells were treated with cisplatin, the exosomes from cisplatin-resistant ovarian cancer cells contained 2.6 times more cisplatin compared with those from cisplatin-sensitive ovarian cancer cells (45). The levels of the cisplatin transporters, multidrug resistance-associated protein 2, ATPase copper transporting α and ATPase copper transporting β, were also higher in the exosomes from the resistant cells compared with those from the sensitive cells (45). Exosomes can induce drug resistance of tumor cells via the efflux of chemotherapeutic drugs. Exosomes released from human ovarian carcinoma cells can export cisplatin via exosomes (45). Exosomes can also mediate chemotherapy resistance through priming cancer stem cells (CSCs) (46). Hu *et al* (46) revealed that cancer-associated fibroblast (CAF)-derived exosomes promote the chemoresistance of colorectal cancer cells by priming CSCs. Drug-sensitive cells can be transformed to drug resistant by acquiring exosomes from chemoresistant cells. In breast cancer, drug resistance can be transferred by glutathione S-transferase P1 (GSTP1)-containing exosomes. GSTP1 can conjugate with glutathione and detoxify chemotherapy drugs (47). Chemosensitive breast cancer cells exhibit increased resistance to anticancer drugs after acquiring the exosomes from chemoresistant breast cancer cells (47). Additionally, the expression levels of GSTP1 in exosomes are associated with the clinical outcomes of patients with breast cancer (47).

## 5. Role of exosomes in the TME

Tumor-related fibroblasts are the most important cells in the TME (48). There are a number of theories regarding the formation of tumor fibroblasts, such as the differentiation from myofibroblasts to fibroblasts, the transdifferentiation of epithelial cells and endothelial cells to fibroblasts via EMT, or the transdifferentiation of mesenchymal stem cells (MSCs) to fibroblasts (49). Exosomes can transfer miR-9 to human breast fibroblasts and transform them into tumor-related fibroblasts (50). Tumor-derived exosomes can increase transforming growth factor-β (TGF-β) expression and signals in mesenchymal cells (50). For example, exosomes from gastric, ovarian and breast cancer can transform MSCs into fibroblast-like cells, which is manifested by the increase in the levels of α-smooth muscle actin (α-SMA) and Smad2 phosphorylation (51-53). Furthermore, exosomes derived from

gastric cancer cells can transform MSCs derived from cord blood into tumor-related fibroblasts (53). These studies demonstrated that exosomes promote tumor stromal cells to acquire tumor-promoting properties (51-53).

As the soil of tumor cell proliferation, the TME regulates the proliferation, metastasis and vascular growth of tumor cells (54). The TME is rich in mesenchymal cells, fibroblasts, endothelial cells, extracellular matrix components, CAFs, and immune cells, including T lymphocytes, B lymphocytes, dendritic cells, macrophages and neutrophils (48). Exosomes can also promote tumor cell proliferation and angiogenesis (4). Vascular endothelial growth factor (VEGF) (55), fibroblast growth factor, TGF (56), platelet-derived growth factor and IL-8 can be used as exosomal proteins to promote the angiogenesis of target cells (57). The exosome-mediated interaction between chronic myeloid leukemia cells and human bone marrow stromal cells can promote the survival of IL-8-dependent leukemia cells (57). Chronic myeloid leukemia cells secrete exosomes to stimulate the secretion of IL-8 from bone marrow stromal cells, resulting in the regulation of angiogenesis and lymphocyte survival (57). Zhu *et al* (58) reported that exosomes from human bone marrow MSCs can promote the expression of tumor VEGF and activate ERK1/2 *in vivo*, enhancing tumor cell proliferation.

Exosomes from breast cancer cells can transform adipose tissue-derived MSCs into fibroblast-like cells via the Smad signaling pathway (51). This process is associated with increased expression levels of α-SMA, tumor-promoting factors TGF receptors I and II, stromal cell-derived factor 1 (SDF-1), VEGF, C-C motif chemokine ligand 5, and transglutaminases (51). Exosomes derived from ovarian cancer cells can also induce adipose tissue-derived MSCs to obtain cells with functional characteristics of fibroblasts (52). During this process, the expression levels of α-SMA, tumor-promoting factor SDF-1 and TGF-β in the adipose tissue-derived MSCs also increase, correlating to the increase in the expression levels of TGF-β receptor I and II (52).

Exosomes from the phosphorous cell carcinoma TME can increase the activity of the TGF-β signaling pathway in squamous cell carcinoma (59). TGF-β can activate Smad2 and Smad3 signaling pathways and regulate gene transcription by binding to the TGF-β receptor (59). The exosomes from tumor stromal fibroblasts contain TGF-β type II receptor (TβRII), a receptor component of TGF-β (59). The transferred receptor component increases the TβRII and Smad2 phosphorylation levels in squamous cell carcinoma cells (59).

Exosomes secreted by CLL cells can induce stromal cells to transform into tumor-associated fibroblasts (57). Paggetti *et al* (57) revealed that when PKH67 fluorescence-labeled CLL cells were co-cultured with MSCs and endothelial cells from the bone marrow, the exosomes from the CLL cells were absorbed by the stromal cells. This event was also associated with the transfer of miRNAs and proteins into these recipient cells, resulting in the activation of their inflammatory signals, such as the NF-κB signaling pathway, the transformation of chronic lymphocytic leukemia stromal cells into tumor-related fibroblasts, the upregulation of the expression levels of genes encoding cytokines and chemokines (C-X-C motif chemokine ligand 1, IL6, IL34 and C-C motif chemokine ligand 2) and migration-related factors (intercellular adhesion molecule 1 and MMP1), and the induction of the proliferation and migration of these stromal cells (57). This study not only provided valuable evidence for the regulatory effect of exosomes on the TME but also indicated that tumor cells act on tumor stromal cells and induce the formation of tumor-related fibroblasts (57). Webber *et al* (60) revealed that TGF-β delivery by tumor exosomes was sufficient to transform fibroblasts into myofibroblasts. Myofibroblasts are activated during the process of wound healing and express α-SMA. Myofibroblasts can be activated in the stroma of solid cancer and support the metastasis of cancer cells (61,62).

## 6. EMT regulated by exosomes

EMT is one of the key mechanisms for malignant cells to achieve metastasis (63). When tumor cells undergo EMT, the cells lose epithelial cell traits and acquire a mesenchymal phenotype, especially the hummingbird phenotype (63). Cancer cells that underwent EMT would exhibit downregulated E-cadherin expression and exhibit upregulated expression levels of N-cadherin, twist, snail and vimentin (63). Tumor cells acquire a migratory ability, invade tissues and vessels, and are transported by the circulation, which facilitates the remote colonization of other tissues (63). Exosomes can have robust impacts in the activation of the EMT machinery (64).

Exosomes can deliver oncogenes to the receipt cells to promote EMT and stem cell traits (65). For example, latent membrane protein 1 can be transported to the receipt cells by exosomes (65). Exosomes can also deliver miRNAs to recipient cells (66). For instance, exosomes can deliver miRNA to recipient cells to promote liver cancer EMT and metastasis (66). CAFs can enhance the EMT of oral cancer cells via delivery of miR-34a-5p by exosomes; miR-34a-5p in the exosome will activate EMT by the AKT/GSK-3β/β-catenin signaling pathway (67). By taking up the exosomal miRNA that was secreted in the tumor environment, the oral cancer cells increase their metastatic ability.

Hypoxic bone marrow MSC-derived exosomal miRNAs promote metastasis of lung cancer cells via a STAT3-induced EMT (68). Zhang *et al* (68) reported that exosomes derived from hypoxic bone marrow MSCs can be taken up by lung cancer cells, which activates STAT3 signaling and induces EMT in recipient cells, These plasma exosomes containing miRNA in the patients with lung cancer also showed a diagnostic value (68).

Cancer-derived exosomes can transfer miRNAs to macrophages to induce their M2 polarization and activate EMT in recipient cells (69). In colon cancer, exosomes derived from colon cancer cells can promote the polarization of macrophages into an M2 phenotype (69). Colorectal cancer cells deliver exosomes to macrophages and promote the upregulation of miRNA-106b-5p (miR-106b) in macrophages (69). This process further activates the PI3Kγ/AKT/mTOR signaling cascade in macrophages, prompting them to polarize into an M2 phenotype (69). The polarized M2 macrophages will further promote the EMT and metastasis of colorectal cancer cells (69). CSCs of clear cell renal cell carcinoma (CCRCC) contain integrin CD103, which can be transported to cancer cells by activating EMT through PTEN targeting (70). Bioactive miR-19b-3p is transported to recipient cells by cancer stem cell-derived exosomes, where miR-19b-3p activates CCRCC EMT by targeting PTEN (70). miRNAs are

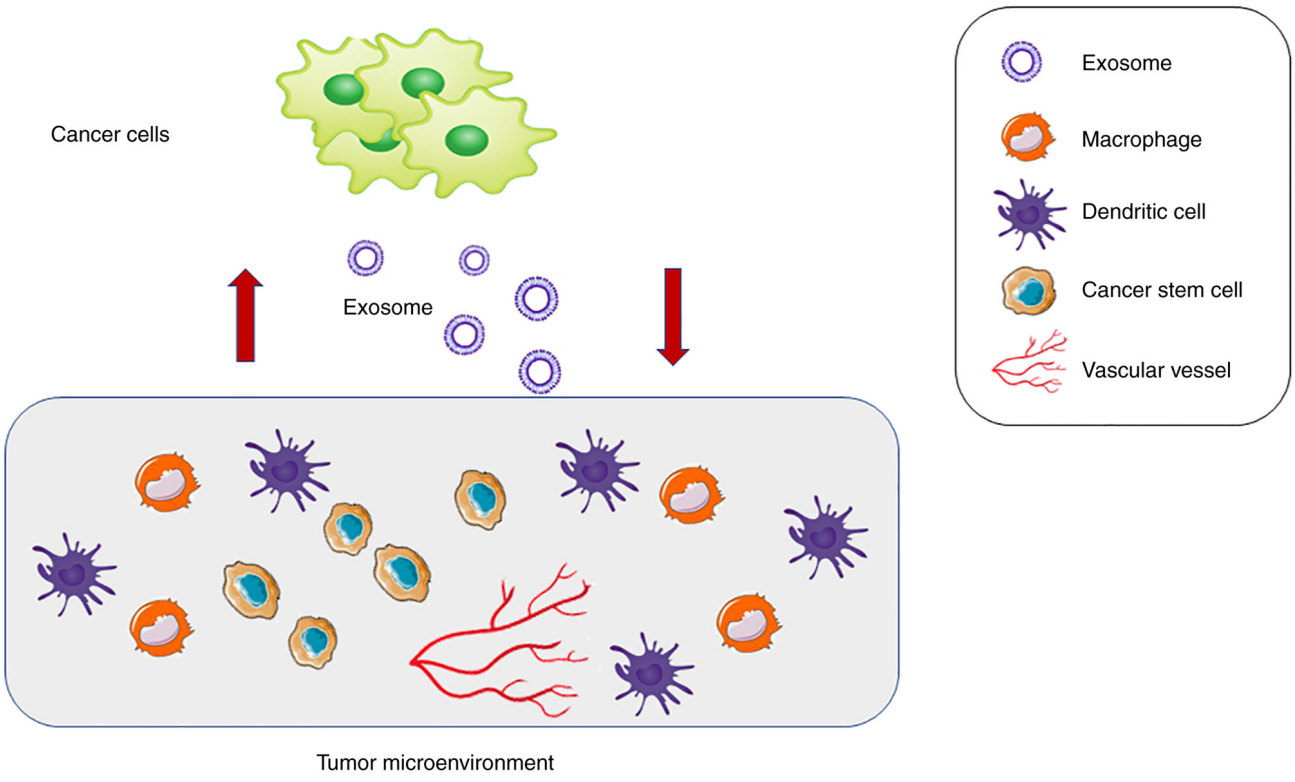


Figure 2. Exosomes as communicators between cancer cells and the tumor environment. Exosomes derived from cells in the tumor microenvironment, including macrophages, dendritic cells and cancer stem cells, can regulate the multiple functions of cancer cells.

small non-coding single-stranded RNA molecules with a length of 22 nucleotides; miRNAs can regulate gene expression at the post-transcriptional level (71). Sun *et al* (72) reported that exosomes derived from colorectal cancer cells express high levels of miR-335-5p, which is transported to colorectal cells to promote EMT and migration of the recipient cells by the RAS p21 protein activator 1.

## 7. Immunoregulatory roles of exosomes

Exosomes from the TME can serve immunoregulatory roles in the communication of cancer cells (73) Exosomes can circumvent immune defenses to cancer cells through multiple mechanisms (74). Exosomes can promote an immunosuppressive environment through expanding the pool of $CD4^+/CD25^+$ regulatory T cells (75). They can also inhibit the proliferation of immune cells (53). For example, tumor-derived exosomes can induce the apoptosis of tumor activated $CD8^+$ T lymphocytes (76). Exosomes derived from dendritic cells can directly present antigen to T cells (77,78). Exosomes derived from dendritic cells contain functional major histocompatibility complex (MHC)-peptide complexes, which can be presented on their surface and transferred to recipient cells (79). Exosomes carrying MHC-peptide complexes can be captured, processed and presented by antigen-presenting cells (APCs) (79).

Tumor antigens can be transferred by exosomes to antigen presenting cells, including macrophages and dendritic cells, after phagocytosis of exosomes by APCs and release of the exosomal antigens into the cytoplasm of APCs (80). For example, HSPs (HSP70-80) can be transferred to dendritic cells by exosomes and induces $CD8^+$ T cell activation (81).

Exosomal antigen presentation to T cells can also occur indirectly. For instance, 'cross-dressing' involves the delivery of MHC-peptide complexes to antigen presenting cells through the fusion of antigen-presenting cells with exosomes derived from dendritic cells (82). This study has demonstrated the activation of $CD4^+$ T cells *in vivo* following injection of exosomes carrying antigens (82). With the presence of MHC class II-negative but T cell costimulatory molecules-positive dendritic cells, antigen-bearing exosomes can activate T cells *in vitro* (82). This indicates that peptide-MHC complexes can be exchanged by exosomes, and presented to T cells to initiate an adaptive immune response (82).

## 8. Conclusion

The interaction between tumor cells and the TME is mediated by exosomes. The role of tumor cells and the TME is not a one-way information transfer but a two-way information exchange (29). Exosomes as communicators between cancer cells and the tumor environment are shown in Fig. 2. The targeted killing of tumor cells is not sufficient for the treatment of tumors. The TME is vital in tumor occurrence, and thus, has gained attention. Exosomes are messengers between tumor cells and the TME. Therefore, exosomes can be used as tools for the development of novel therapeutic strategies (83).

At present, researchers can trace exosomes, for example through the use of labeling tetraspanins, including CD63, CD9 and CD82, which can also help visualize the interaction between exosomes and tumor stromal cells. Researchers can use a technique based on the Cre recombinase-locus of X (cross)-over in P1 system to label exosome transportation

by immunofluorescent signals (84). When the exosomes are released by cells expressing the Cre recombinase, they are absorbed by Cre reporter cells, and the latter can display fluorescence signals. Based on this technique, researchers can track exosomes *in vivo* and *in vitro* (84).

The interaction between exosomes and the TME regulates all aspects of tumor development, including the promotion of tumor cell proliferation, the enhancement of stromal cell transformation, the induction of tolerance of tumor cells to chemotherapeutic drugs and the promotion of distant metastasis (54). Participation of exosomes in all aspects of tumor biological mechanisms makes them good targets for antitumor treatment. Blocking the production and release of exosomes and their uptake by receptor cells may be an alternative treatment strategy for the development of an antitumor treatment that targets exosomes.

**Acknowledgements**

Not applicable.

**Funding**

No funding was received.

**Availability of data and materials**

Not applicable.

**Authors' contributions**

QL wrote, 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.

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