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REVIEW ARTICLE

Therapeutic potential of mesenchymal stem cell exosomes for tumors in the digestive system: From bench to bedside

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Abstract

Exosomes are small, bilayer lipid vesicles with diameters ranging from approximately 40–160 nm. These vesicles carry a diverse array of molecular cargo, including DNA, RNA, lipids, and proteins, which play a critical role in intercellular communication. Among the various cell types, mesenchymal stem cells (MSCs) are recognized as highly efficient producers of exosomes. MSC-derived exosomes (MSC-exo) have been demonstrated to play dual roles in cancer progression, either promoting or inhibiting tumor growth, depending on the specific context. This unique ability positions MSC-exo as a promising tool for cancer therapy. This review examines the multifaceted roles of MSC-exo in various types of digestive system tumors. It highlights the exosomes' potential to modulate tumor microenvironments, influence immune responses, and deliver therapeutic molecules, thereby offering new avenues for targeted cancer treatment. In addition, the review explores the clinical application value of MSC-exo as anti-tumor agents, emphasizing the exosomes' potential for drug delivery and personalized medicine. However, despite the exosomes' therapeutic potential, several challenges must be addressed before MSC-exo can be widely adopted in clinical settings. These include issues related to large-scale production, standardization, safety, and regulatory approval. By addressing these challenges, MSC-exo could emerge as a transformative approach in cancer treatment, offering innovative solutions for precision medicine and improved patient outcomes. This review underscores the importance of continued research to fully realize the potential of MSC-exo in oncology.

Keywords: Mesenchymal stem cells; Exosomes; Mesenchymal stem cell-derived exosomes; Intercellular communication regulators; Anti-tumor; Drug delivery

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1. Introduction

The global burden of malignant tumors has been rising continuously. In 2022, an estimated 20 million new cases of malignant tumors were diagnosed globally, and 9.7 million people died from malignant tumors, with digestive system tumors contributing significantly to the global cancer burden. In 2022, digestive system tumors accounted for 23.9% of new global cancer cases and 33.2% of cancer deaths.[1] Treatment for advanced malignant

tumors of the digestive system includes surgical treatment, radiotherapy, and drug therapy. For most patients with metastatic malignant tumors, curative treatment is often no longer a viable option. Palliative chemotherapy has been the main systemic drug treatment, but its clinical application is limited by significant toxicity. In recent years, targeted therapy has further improved treatment efficacy; however, off-target toxicity remains a pressing issue in clinical practice.[2] As research into the mechanisms of mesenchymal stem cells (MSCs) and MSC-derived exosomes (MSC-exo) deepens, growing evidence suggests that both MSCs and MSC-exo hold great potential in treating malignant tumors.[3]

2. MSCs and their exos

2.1. MSCs

MSCs represent a class of pluripotent stem cells (iPSCs) capable of self-renewal and differentiation into various cell types. Under specific induction conditions, MSCs can differentiate into various tissue cells, including adipocytes, muscle cells, tendon cells, ligament cells, nerves cells, liver cells, cardiomyocytes, and endothelial cells, among others. MSCs typically exhibit spindle-shaped or stellate adherent growth, with high expression of CD73, CD90, and CD105, and low expression of CD34, CD45, CD14 or CD11b, CD79a or CD19, and HLA-DR. Even after repeated passage culture and cryopreservation, MSCs retain their multilineage differentiation potential, making them an ideal choice for cell therapy.[4] Clinically, MSCs have achieved significant breakthroughs in treating various diseases, including hematological diseases, cardiovascular diseases, liver cirrhosis, neurological disorders, and autoimmune diseases.[5] More importantly, MSCs can regulate tumor growth through various mechanisms.

2.2. Exosome formation and components

Exosomes are nanoscale vesicles with a closed membrane structure, typically ranging from 40 to 100 nm in diameter, and are encapsulated by a lipid bilayer. These vesicles contain many biologically functional molecules – such as proteins, nucleic acids, and lipids – and serve as an important medium for transmitting biological signals between cells.[6] In 1983, exosomes were discovered for the 1st time,[7] whereas in 2007, exosomes were found to contain microRNAs (miRNA) and mRNAs, confirming that genetic material can be exchanged between cells through exosomes, thereby altering cellular biological behavior.[8] Exosomal proteins generally encompass a variety of types, such as integral membrane proteins, peripheral membrane proteins, outer membrane proteins anchored by lipids, inner membrane proteins anchored by lipids, surface proteins, and enzymes associated with exosomes. Notably, most of the identified exosomal proteins, such as heat shock proteins and MHC molecules, are also found in other types of extracellular vesicles. However, a series of proteins is relatively specific to exosomes, including CD9, CD63, CD81, TSG101, Alix, HSP70, and HSP90. These proteins are considered markers for identifying exosomes. The lipid composition of exosomes is mainly divided into four categories: sphingolipids, phospholipids, glycolipids, and fatty acids. Thousands of RNA molecules, including miRNAs, long non-coding RNAs (lncRNAs), and circular RNAs, have been identified in exosomes.[9-13] The process of exosome formation (Figure 1) mainly involves the following steps:

(i) Endocytosis: The cell membrane invaginates, forming the endosome.
(ii) Transformation into multivesicular bodies (MVBs): The endosome further transforms into MVBs. During this process, the membrane of the endosome invaginates, forming multiple small vesicles with lipid bilayers.
(iii) Release of exosomes: The MVBs merge with the cell membrane, discharging their internal small vesicles into the extracellular environment as exosomes.[14]

3. Roles of MSC-exo in cancer

Tumor tissues are made up of tumor cells and the tumor microenvironment (TME). Tumor cells, having lost their normal regulatory mechanisms, can grow uncontrollably, invade nearby tissues, and spread to distant parts of the body. The TME includes various components, such as endothelial cells, T cells, natural killer T-cells, myeloid-derived suppressor cells, cancer-associated fibroblasts (CAFs), and tumor-associated stromal cells, among others.[15] MSC-exo plays a crucial role in tumor growth by transporting regulatory molecules. Interestingly, growing evidence suggests that MSC-exo can have dual effects in cancer, acting as a double-edged sword. Some studies indicate that MSC-exo can promote tumor growth. For example, Wang *et al.*[16] demonstrated that exosomes derived from bone marrow mesenchymal stem cells (BMMSC-exo) from both multiple myeloma patients and healthy donors can enhance the growth of multiple myeloma (MM) cells by activating several signaling pathways related to cell proliferation, such as *p38, p53*, and Akt. Further research by Deng *et al.*[17] confirmed that LINC00461 in BMMSC-exo from multiple myeloma patients increases BCL-2 expression by targeting miR-15a/16, thereby preventing apoptosis in multiple myeloma cells. Likewise, studies have also reported that MSC-exo inhibits tumor growth. For instance, BMMSC-exo can release miR-222-3p, which directly targets the *IRF2* gene, thereby negatively regulating the IRF2/INPP4B signaling pathway in THP-1 cells and

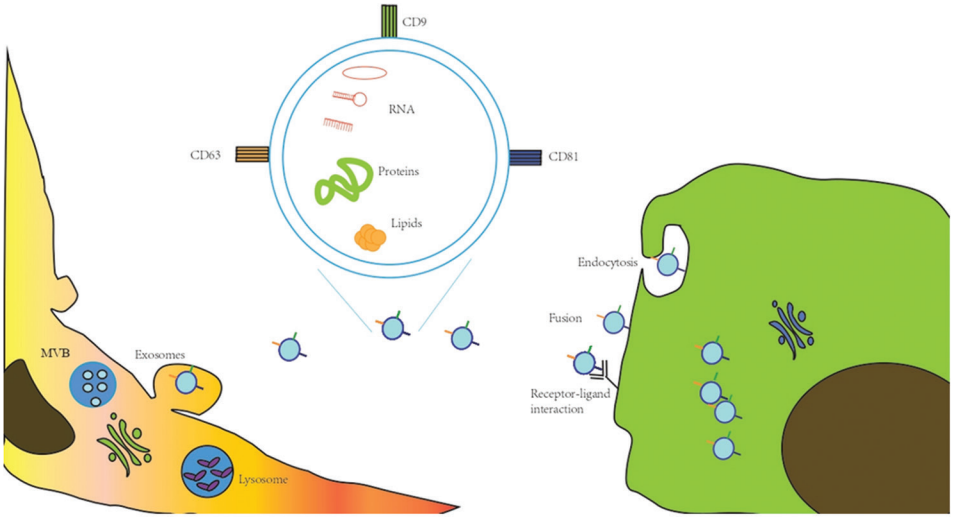

Figure 1. The process of exosome formation. The membrane of the endosome invaginates, forming multiple small vesicles with lipid bilayers. Late endosomes that encapsulate small vesicles are referred to as multivesicular bodies (MVBs). While some MVBs are directed to the Golgi complex or lysosomes for degradation, others fuse with the plasma membrane, releasing their internal small vesicles into the extracellular space, where they are identified as exosomes. MSC-exo can enter cancer cells via various mechanisms, such as membrane fusion, receptor-mediated endocytosis, and phagocytosis. The exosome is composed of three common surface markers (CD9, CD63, and CD81). These exosomes carry a diverse range of biologically active molecules, including proteins, nucleic acids, and lipids.
Abbreviations: MSC: Mesenchymal stem cell; MSC-exo: Mesenchymal stem cell-derived exosomes.

suppressing leukemia cell proliferation.[18] The following sections explore the role of MSC-exo in various types of malignant tumors of the digestive system.

3.1. Liver cancer

The primary pathological type of liver cancer (accounting for 75 – 85%) is hepatocellular carcinoma (HCC). Liver cancer has an insidious onset and a high post-operative recurrence rate, with an overall recurrence rate of up to 70% within 5 years.[19] Recently, MSC-exo has garnered wide attention for its potential in treating liver cancer. Most studies suggest that MSC-exo can inhibit HCC through various pathways, though a few studies indicate that MSC-exo may promote HCC development. Furthermore, MSC-exo may be bioengineered to enhance anti-tumor effects.

Research has demonstrated that exogenous MSC-exo exerts inhibitory effects on liver cancer. For instance, BMMSC-exo containing miR-15a suppressed HCC by downregulating the expression of *SALL4*.[20] Similarly, exosomes derived from umbilical cord mesenchymal stem cells (UCMSC-exo) inhibit HCC proliferation and angiogenesis by reducing the expression of various proteins, such as *SIRT-1, VEGF, SDF-1*, and *CXCR-4*, while simultaneously upregulating *TNF-α* and *caspase-3* levels.[21] UCMSC-exo facilitates the transfer of miRNA-451a from UCMSCs to HCC cells, leading to a reduction in ADAM10 expression. This process reverses the resistance of HCC cells to paclitaxel (PTX). Furthermore, the decreased expression of ADAM10 suppresses epithelial-mesenchymal transition (EMT) and HCC cell proliferation.[22] LncRNAs in MSC-exo also exhibit anti-tumor effects. UCMSC-exo containing lncRNA FAM99B reduces the proliferation, migration, and invasion of MHCC97L and MHCC97H cells. *In vivo*, UCMSC-exo significantly inhibited tumor growth, and exosomes overexpressing lncRNA FAM99B further enhanced this effect.[23] BMMSC-exo, when co-cultured with Hep3B and HuH7 cancer stem cells (CSCs), suppressed the proliferation, invasion, and angiogenesis of these tumor stem cells. *In vivo* experiments demonstrated that these exosomes also inhibited the growth of transplanted tumors. Further investigations revealed that BMMSC-exo facilitated communication between BMMSCs and HCC cells via lncRNA C5orf66-AS1. This lncRNA acted as a sponge, reducing the levels of the oncogenic miR-127-3p in HCC cells, which in turn activated the DUSP1/ERK signaling pathway, thereby curbing the malignant behavior of HCC cells.[24]

However, studies also suggest that MSCs, when stimulated externally, may secrete exosomes that promote HCC progression. For instance, hypoxia-induced BMMSC-exo containing miR-652-3p inhibits TNRC6A, thereby promoting HCC cell proliferation and metastasis[25] (Table 1).

Numerous studies have confirmed that MSC-exo, rich in various non-coding RNAs, can inhibit HCC

Table 1. The role of MSC-exo in HCC

MSC-exo	Loaded small molecule	Cell line	Animal model	Mechanism of action	Effect	References
BMMSCs	miR-15a	Hep3B; Huh7	Hep3B cell xenograft in BALB/c nude mice	Downregulated SALL4 expression	Inhibited HCC progression	[20]
UCMSCs	lncRNA FAM99B	MHCC97L; MHCC97H	MHCC97L cell xenograft in BALB/c nude mice	-	Enhanced cell cycle arrest and cell apoptosis while suppressing cell viability, migration, and invasion in HCC	[23]
BMMSCs	lncRNA C5orf66-AS1	Hep3B-CSCs; HuH7-CSCs	Hep3B-CSCs cell xenograft in BALB/c nude mice	Downregulated miR-127-3p; upregulated the DUSP1/ERK axis	Blocked malignant behaviors of HCC-sourced CSCs	[24]
BMMSCs	miR-652-3p	SMMC-7721; hepG2	-	Downregulated the TNRC6A expression	Promoted the proliferation and metastasis of HCC	[25]
AMSCs	miR-199a-3p	Huh7; SMMC-7721; PLC/PRF/5	PLC/PRF/5 cell xenograft in BALB/c nude mice	Downregulated the mTOR pathway	Increased the sensitivity of HCC cells to chemotherapeutic agents	[27]
BMMSCs	miR-338-3p	HepG2	-	Downregulated EST1 expression	Inhibited HCC cell proliferation, invasion, and migration; induced cell apoptosis	[28]

Abbreviations: AMSCs: Adipose mesenchymal stem cells; BMMSCs: Bone marrow mesenchymal stem cells; CSCs: Cancer stem cells; HCC: Hepatocellular carcinoma; UCMSCs: Umbilical cord mesenchymal stem cells; MSC-exo: mesenchymal stem cell-derived exosomes; HCC: Hepatocellular carcinoma.

cells through different mechanisms, suggesting their therapeutic potential for HCC. MSC-exo, in combination with other anti-tumor drugs, has also demonstrated more significant efficacy. Research indicates that miR-125a and miR-125b inhibit HCC cell growth and stemness via the CD90 pathway.[26] Adipose MSC-exo (AMSC-exo) can mediate the transfer of miR-199a-3p, miR-374c-5p, and miR-338-3p between AMSCs and HCC cells.[27-29] Overexpression of miR-199a-3p and miR-122 in AMSC-exo can alter downstream gene expression, enhancing HCC cell sensitivity to chemotherapy.[27] MiR-338-3p-overexpressing BMMSC-exo inhibits HCC cell proliferation, invasion, and migration by downregulating ETS1 and inducing apoptosis.[28] In addition, MSC-exo can serve as effective drug carriers for CSC-targeted therapy. For instance, BMMSC-exo delivering norcantharidin (NCTD) demonstrated greater anti-tumor effects compared to NCTD alone, promoting NCTD uptake by tumor cells, inducing cell cycle arrest, and enhancing apoptosis. BMMSC-exo-NCTD exhibited tumor-targeting effects at liver cancer sites and repaired liver cells without inducing systemic toxicity.[30] Moreover, BMMSC-exo modified with siGRP78, combined with sorafenib, targeted GRP78 in HCC cells, inhibiting cancer cell growth. The exosomal transfer of siGRP78 enhanced sorafenib sensitivity in chemoresistant HCC cells.[31]

3.2. Gastric cancer (GC)

East Asia is a hotspot for GC. In regions where routine early screening for GC has not been widely implemented, the early diagnosis rate is low. Most patients are diagnosed at advanced stages, often missing the optimal window for treatment. Therefore, there is an urgent need to explore novel therapeutic strategies for GC.

Research has demonstrated that MSC-exo has a certain inhibitory effect on GC. *In vitro*, UCMSC-exo co-cultured with the GC cell line BGC-823 significantly inhibited tumor cell activity.[32] In addition, BMMSC-exo can deliver miR-200a to TGF-β-treated AGS cells, reversing EMT, normalizing the expression of *ZEB1*, vimentin, and Snail1, and inhibiting tumor progression.[33] MiR-1228 is inversely correlated with the survival of GC patients, with lower levels observed in those diagnosed with stage III and IV GC. When BMMSC-exo, loaded with miR-1228, were co-cultured with GC cells, miR-1228 was found to function as a tumor suppressor by targeting and downregulating *MMP-14*, effectively inhibiting GC cell metastasis.[34]

However, some studies have indicated that MSC-exo may contribute to GC progression. BMMSC-exo promotes EMT in GC by upregulating *RHOXF2*. After oxaliplatin (OXA) treatment, the upregulation of miR-424-3p in BMMSC-exo inhibits *RHOXF2* expression in GC cells, thereby suppressing their proliferation, migration, and

invasion. This suggests that delivering miR-424-3p through BMMSC-exo is a promising therapeutic approach for GC.[35] In addition, MSC-exo conferred drug resistance to GC cells, primarily through their protein content. These proteins activate the *CaM-Ks/Raf/MEK/ERK* signaling pathway, increase multidrug resistance protein expression, and protect GC cells from chemotherapy-induced apoptosis.[36] Another study found that exosomes from p53-deficient BMMSCs enhance the proliferation and migration of GC cells and p53 wild-type BMMSCs.[37] Research has also reported that BMMSC-exo can transfer miR-374a-5p to GC cells, enhancing the expression of adhesion molecules in these cells by targeting *HAPLN1*, which in turn facilitates the migration of GC cells.[38] BMMSC-exo has been proposed to secrete miR-221, which acts as a tumor-promoting molecule by activating the Hedgehog and *PTEN/P27* signaling pathways, thereby promoting GC proliferation and progression.[39] Moreover, BMMSC-exo can promote tumor growth by triggering the Hedgehog signaling pathway[40] (Table 2).

3.3. Colorectal cancer (CRC)

For advanced-stage CRC, enhancing the efficacy of drug therapy is crucial. Most studies suggest that MSC-exo can inhibit CRC. AMSC-exo has been reported to suppress the expression of aquaporin 5 (*AQP5*) and *EGFR* genes, which are key molecules in tumor progression, within the HCT-116 tumor cell line.[41] BMMSC-exo can also deliver miR-100 into CRC cells, downregulating the mTOR/miR-143 axis and inhibiting CRC cell proliferation, migration, and invasion.[42] In addition, BMMSC-exo can inhibit tumor-associated macrophage activity. Research has demonstrated that UCMSC-exo mediates miR-1827, inhibiting *SUCNR1* in CRC cells. Furthermore, UCMSC-exo also suppresses M2 macrophage polarization and liver metastasis.[43]

Studies have confirmed that MSC-exo significantly inhibits overexpressed integrin family proteins in CRC cells. Xu *et al.*[44] demonstrated that integrin α2 (*ITGA2*) is overexpressed in CRC cells. It is indicated that miR-16-5p derived from BMMSC-exo inhibits CRC cells by downregulating *ITGA2*.[44] Some studies have reported that MSC-exo may promote CRC. AMSC-exo promotes the advancement of CRC by triggering the transformation of MSCs into CAFs (MSC-CAFs) via the *TRPC3/NF-KB* signaling pathway[45] (Table 3).

In recent years, MSC-exo-based therapies have become a key focus of research for treating CRC. Studies have reported that UCMSC-exo upregulates miR-431-5p, consequently inhibiting CRC progression by suppressing

Table 2. The role of MSC-exo in GC

MSC-exo	Loaded small molecule	Cell line	Animal model	Mechanism of action	Effect	References
UCMSCs	-	BGC-823	-	-	Enhanced GC cell proliferation, invasion, and migration	[32]
BMMSCs	miR-200a	TGF-β-treated AGS	-	Inhibited mesenchymal-epithelial transition	Inhibited GC cell proliferation and migration	[33]
BMMSCs	miR-1228	SGC-7901; MGC-823	-	Downregulated MMP-14 expression	Inhibited GC cell metastasis	[34]
BMMSCs	miR-424-3p	SGC-7901	SGC-7901 cell xenograft in BALB/c nude mice	Inhibited RHOXF2 expression	Inhibited GC cell proliferation, invasion, and migration	[35]
UCMSCs	-	HGC-27; MGC-803; SGC-7901	HGC-27 cell xenograft in BALB/c nude mice	Inhibited the CaM-Ks/Raf/MEK/ERK pathway	Enhanced drug resistance	[36]
$p53^{-/-}$ mBMMSCs	-	MFC	MFC cell xenograft in BALB/c nude mice	Inhibited the Wnt/β-catenin pathway	Enhanced GC progression	[37]
BMMSCs	miR-374a-5p	SGC-7901; MGC-823	SGC-7901 cell xenograft in BALB/c nude mice	Upregulated HAPLN1 expression	Enhanced GC cell proliferation and migration	[38]
BMMSCs	miR-221	SGC-7901; BGC-823	SGC-7901 cell xenograft in BALB/c nude mice	Activated the Hedgehog and PTEN/P27 pathways	Enhanced the oncogenic activity of GC cells	[39]
BMMSCs	-	MG63; SGC7901	-	Activated the Hedgehog pathway	Enhanced GC progression	[40]

Abbreviations: AMSCs: Adipose mesenchymal stem cells; BMMSCs: bone marrow mesenchymal stem cells; UCMSCs: umbilical cord mesenchymal stem cells; MSC-exo: Mesenchymal stem cell-derived exosomes; GC: Gastric cancer.

Table 3. The role of MSC-exo in CRC

MSC-exo	Loaded small molecule	Cell line	Animal model	Mechanism of action	Effect	References
AMSCs	-	HCT-116	-	Inhibited the expression of aquaporin 5 and EGFR	Inhibited HCT-116 cell polarization	[41]
BMMSCs	miR-100	HCT-116	-	Downregulated the mTOR/miR-143 axis	Suppressed CRC cell proliferation and metastasis	[42]
UCMSCs	miR-1827	HCT-116; SW480; Caco-2; HT-29	HCT-116 cell xenograft in BALB/c nude mice	Downregulating SUCNR1 expression	Inhibited macrophage M2 polarization; prevented colorectal liver metastasis	[43]
BMMSCs	miR-16-5p	Caco-2; SW480; SW620; LoVo; HT29	Caco-2 BALB/c cell xenograft in BALB/c nude mice	Downregulated ITGA2 expression	Inhibited CRC cell proliferation, migration, and invasion	[44]
AMSCs	-	HCT-116	HCT-116 cell xenograft in BALB/c nude mice	Upregulated TRPC3 expression	Accelerated CRC progression by inducing the MT-CAF cell phenotype	[45]
UCMSCs	miR-431-5p	Caco-2; SW480; SW620; LoVo; HCT 116	LoVo cell xenograft in BALB/c nude mice	Downregulated PRDX1 expression	Suppressed CRC cell growth	[46]
BMMSCs	miR-4461	DLD1; HCT116; SW480	-	Downregulated COPB2 expression	Inhibited CRC cell tumorigenesis	[47]

Abbreviations: AMSCs: Adipose mesenchymal stem cells; BMMSCs: Bone marrow mesenchymal stem cells; CAF: Cancer-associated fibroblasts; MT: Mesenchymal stem cell-transformed; UCMSCs: Umbilical cord mesenchymal stem cells; MSC-exo: Mesenchymal stem cell-derived exosomes; CRC: Colorectal cancer; DLD: Deterministic lateral displacement.

PRDX1.[46] Chen *et al.*[47] demonstrated that miR-4461 level is lower in CRC cells and tissues. BMMSC-exo-induced miR-4461 overexpression reduces CRC cell migration by downregulating *COPB2*. Pishavar *et al.*[48] developed an effective method to load SN38 into exosomes modified with *MUC1* aptamers to target MUC1-overexpressing cells, demonstrating good inhibitory effects on CRC. *In vivo* studies in a BALB/c mouse C26 ectopic model demonstrated that a single intravenous injection of doxorubicin (DOX)-loaded MUC1-modified UCMSC-exo (UCMSC-exo-DOX) significantly inhibited tumor growth compared to the group with conventional DOX.[49] Additional research indicated that UCMSC-exo-DOX exhibited greater accumulation in tumors and quicker clearance by the liver compared to the group treated with conventional DOX. Han *et al.*[50] constructed an iRGD-Lysosome-associated membrane protein 2 (Lamp2b) fusion gene-modified UCMSCs and isolated and purified exosomes. They loaded anti-mir-221 into exosomes through electroporation. The findings demonstrated that exosomes modified with iRGD effectively suppressed the colony formation of CRC cells. It was further revealed that these iRGD-modified exosomes were internalized by CRC cells from their interaction with the NRP-1. *In vivo* experiments also indicated a significant accumulation of iRGD-modified exosomes at the tumor site.[50] Taken together, MSC-exo holds great promise as drug delivery vehicles, but further research is warranted to fully realize the exosomes' potential.

3.4. Pancreatic cancer

The prognosis for pancreatic cancer is extremely poor, characterized by difficulties in early diagnosis, low surgical resection rates, and a high tendency for recurrence and metastasis. Studies have indicated that the impact of MSC-exo on pancreatic cancer varies and lacks consistency. Ding *et al.*[51] discovered that miR-100-5p is highly expressed in UCMSC-exo, promoting the growth of PANC-1 and BxPC3 cells. In addition, miR-145-5p is highly expressed in UCMSC-exo, but it suppresses pancreatic ductal cell carcinoma by inhibiting the *TGF-β/Smad3* signaling pathway.[52] Other studies have reported that BMMSC-exo carrying miR-1231 can inhibit pancreatic cancer by suppressing the *EGFR/cyclin E* pathway[53] (Table 4).

The TME of pancreatic cancer differs from that of other tumors. Beyond the typical cellular elements, pancreatic cancer features an abundant extracellular matrix (ECM) composed of collagen, matrix proteins, and a variety of soluble factors, including cytokines, chemokines, and growth factors. Essentially, the TME in pancreatic cancer is characterized by a dense stromal structure resulting from excessive fibrosis driven by active connective tissue proliferation and accumulation. This extensive fibrosis, along with a lack of vasculature, immune infiltration, and a hypoxic stromal environment, not only promotes tumor growth and invasion but also induces resistance to anti-tumor drugs. Therefore, studying the roles of different components within the TME of pancreatic cancer and

Table 4. The role of MSC-exo in pancreatic cancer

MSC-exo	Loaded small molecule	Cell line	Animal model	Mechanism of action	Effect	References
UCMSCs	miR-100-5p	BxPC-3; PANC-1	PANC-1 cell xenograft in BALB/c nude mice	-	Promoted pancreatic ductal adenocarcinoma growth	[51]
UCMSCs	miR-145-5p	PANC-1; BxPC; Capan-1; CFPAC-1	BALB/c PANC-1 cell xenograft in BALB/c nude mice	Downregulated the TGF-β/Smad3 pathway	Inhibited pancreatic cancer progression	[52]
BMMSCs	miR-1231	BxPC-3; MIA PaCa-2; PANC-1; SW1990	BxPC-3 cell xenograft in BALB/c nude mice	Downregulated the EGFR/cyclin E pathway	Inhibited pancreatic cancer cell proliferation	[53]

Abbreviations: BMMSCs: Bone marrow mesenchymal stem cells; UCMSCs: Umbilical cord mesenchymal stem cells; MSC-exo: Mesenchymal stem cell-derived exosomes.

targeting therapies is crucial for the future management of pancreatic cancer. The good tumor-targeting ability and deep tissue penetration capability of MSC-exo make them ideal carriers for drugs targeting pancreatic cancer.[54-56]

In an effort to address the chemoresistance of pancreatic cancer, Zhou *et al.*[57] encapsulated PTX, gemcitabine monophosphate, and an intermediate metabolite of gemcitabine into purified BMMSC-exo. Their findings revealed that the BMMSC-exo-based drug delivery system demonstrated excellent targeting and tissue penetration capabilities. This approach resulted in a promising anti-tumor effect while minimizing systemic toxicity.[57] Zhou *et al.*[58] employed BMMSC-exo to simultaneously deliver galectin-9 siRNA and OXA, effectively reversing the immunosuppressive TME. This was achieved by suppressing M2 macrophage polarization and promoting the recruitment of cytotoxic T cells, thereby improving the efficacy of immunotherapy in treating pancreatic cancer.

OXA is a critical component of the standardized FOLFIRINOX regimen for pancreatic cancer, capable of triggering immunogenic cell death (ICD) at the tumor site and killing tumor cells by inhibiting DNA synthesis and repair. To further enhance the anti-tumor effect, a research group used galectin-9 siRNA to block the *galectin-9/dectin-1* interaction, synergizing with OXA to reverse M2 tumor-associated macrophage-induced immunosuppression.[58] This delivery platform was developed by encapsulating galectin-9 siRNA via electroporation and functionalizing the surface with an OXA prodrug to act as an ICD inducer. In addition, the research group engineered siRNA-exosome-OXA (iEXO-OXA) nanoparticles and reported that siRNA EXO-OXA enhanced the drug concentration at the tumor site. EXO-OXA promoted anti-tumor immunity by driving the polarization of tumor-suppressive macrophages, recruiting cytotoxic T lymphocytes, and reducing regulatory T cells (Tregs), resulting in notable therapeutic outcomes in cancer treatment. The findings suggest that MSC-exo can be used as drug delivery vehicles to enhance immunogenicity and regulate the TME, providing a theoretical foundation for the advancement of novel pancreatic cancer treatments.[58]

3.5. Other malignant tumors of the digestive system

MSC-exo has also demonstrated certain potential for the treatment of esophageal cancer. For example, miR-375 in UCMSC-exo can inhibit the proliferation, invasion, and migration of esophageal squamous cell carcinoma cells while promoting apoptosis by suppressing *ENAH* expression and regulating the protein levels of *Bax* and *E-cadherin*.[59] Several studies have focused on using MSC-exo for treating biliary tract cancer. For example, miR-15a-5p in UCMSC-Exo can hinder the progression of cholangiocarcinoma by inhibiting *CHEK1* expression.[60] However, the role of MSC-exo in tumor cells remains controversial, likely due to the exosomes' inherent complexity and diversity, as well as variations in culture conditions.

4. MSC-exo as a vehicle for drug delivery

Drugs can be loaded into exosomes through pre-loading (before exosome isolation) and post-loading (after exosome isolation).[61] Common exogenous drug-loading methods include electroporation, co-incubation, sonication, freeze-thaw cycles, and extrusion.[62] The primary advantage of post-loading is its simple process. However, post-loading has certain drawbacks, such as the potential to damage the integrity of exosomes during the loading process. Moreover, some exosomes may fail to load the drugs successfully, necessitating additional purification steps to remove them. Pre-loading involves introducing or expressing target molecules (*e.g.*, nucleic acids, proteins, or drugs) into MSCs before exosome isolation. The target molecules are then incorporated into exosomes, which

are subsequently collected. The advantage of pre-loading is that it preserves the integrity of the exosomes, but the process is complex, time-consuming, and costly.[63] Despite substantial progress in the anti-tumor research of MSC-exo, several key unresolved issues and limitations hinder the exosomes' clinical application:

(i) Heterogeneity of MSC-exo: The heterogeneity of MSC-exo can be managed by standardizing the isolation, purification, storage, and characterization methods. Standardized procedures can maximize uniformity in exosome size, composition, and contents. In addition, different extracellular vesicle subpopulations derived from MSCs should be identified for their anti-tumor activity, as different isolation and purification methods can result in MSC-exo with varying contents, characteristics, and biological functions.[64,65]

(ii) Large-scale production and storage: The large-scale production and storage of MSC-exo present significant challenges to its translation into clinical practice, largely due to the limited availability of MSCs. Induced iPSCs, generated by reprogramming fully differentiated somatic cells through the introduction of specific transcription factors, offer a potential solution. IPSCs possess the ability to self-renew indefinitely and can differentiate into any cell type, including MSCs.[66] Therefore, iPSC-MSCs (iMSCs) could provide an unlimited source of iMSCs to overcome the limitations of primary MSCs, making them a primary source for large-scale applications. Studies have compared the efficacy of iPSC-derived MSCs with that of primary MSCs. The findings indicated that iPSC-derived MSCs and bone marrow-derived MSCs displayed no significant difference in their ability to promote collagen synthesis and angiogenesis, both effectively promoting skin wound healing.[67,68] In addition, JNKi- and DAC-programmed MSCs from human embryonic stem cells (hESC-MSCs) exhibit similar adipogenic, osteogenic, and chondrogenic differentiation abilities as tissue-derived MSCs. They also facilitate hematopoiesis and alleviate hind limb ischemia.[69] These findings suggest that iMSCs and hESC-MSCs are emerging as attractive alternatives to traditional MSCs.

(iii) Exosome isolation technology: The isolation technology of exosomes warrants further optimization. At present, the commonly used exosome isolation techniques, such as ultracentrifugation and commercial kit-based methods, do not meet the needs of commercial production. Studies combining polyethylene glycol precipitation, dielectrophoresis, and deterministic lateral displacement (DLD) isolation methods indicate that integrating multiple isolation methods provides a viable approach for achieving efficient and high-purity exosome production, though further improvements in isolation efficiency are still required.[70]

(iv) Target specificity and reducing off-target toxicity: Although MSC-exo displays tumor-targeting properties, the exosomes can still bind to normal tissue cells, necessitating the optimization of exosome targeting to reduce off-target toxicity. The most commonly used method to enhance exosome targeting is genetically engineering tumor-specific ligands on the exosome membrane. Lamp2b, the transmembrane protein platelet-derived growth factor receptor, members of the tetraspanin superfamily, and lactoferrin can all serve as exosome membrane targeting ligands to improve exosome tumor targeting. RGD (Arg-Gly-Asp) peptides, present in various ECMs, are capable of precisely identifying and attaching to integrins present on the surfaces of tumor cells, acting as competitive inhibitors of RGD peptide-like substances *in vivo*. This can inhibit tumor cell adhesion and migration to the ECM, suppress tumor angiogenesis, and induce tumor cell apoptosis. Research has demonstrated that intravenous injection of DOX-containing iRGD-exosomes can effectively penetrate the blood-spinal cord barrier and deliver DOX to the spinal cord injury site, enhancing neurological function recovery.[71]

Although generating exosomes from modified MSCs offers new possibilities for cancer treatment, it also carries the risk of altering the biological properties of MSCs. Such alterations may affect the composition, function, and stability of exosomes, thereby impacting their therapeutic efficacy and safety.[72] Therefore, when developing MSC-exo-based therapeutic strategies, it is essential to fully consider the potential risks associated with modifications and to optimize the quality and function of exosomes through precise modifications and functional validation. Future research should further explore the mechanisms through which modifications affect MSCs and exosomes to advance their clinical applications.

5. Conclusion

MSC-exo is rich in various bioactive substances, including nucleic acids, proteins, and lipids. As carriers of intercellular communication, MSC-exo exhibits both tumor-promoting and tumor-inhibiting effects. This further highlights the potential of MSC-exo as novel anti-tumor drugs in clinical applications, providing new clinical options for anti-tumor therapy. However, since MSC-exo plays a critical role in tumors, further research is warranted to mitigate the tumor-promoting effects of MSC-exo and expand its application as anti-tumor therapeutics.

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Conflict of interest

Ying Liu is an employee of the Sinocelltech Ltd. company. This has not influenced the content of the manuscript. No reference to the author's company is made, but it is declared for full transparency. Other authors declare no conflict of interest.

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