Mesenchymal stem cell-derived exosomes for gastrointestinal cancer

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Abstract
Gastrointestinal (GI) malignancies, a series of malignant conditions originating from the digestive system, include gastric cancer, hepatocellular carcinoma, pancreatic cancer, and colorectal cancer. GI cancers have been regarded as the leading cancer-related cause of death in recent years. Therefore, it is essential to develop effective treatment strategies for GI malignancies. Mesenchymal stem cells (MSCs), a type of distinct non-hematopoietic stem cells and an important component of the tumor microenvironment, play important roles in regulating GI cancer development and progression through multiple mechanisms, such as secreting cytokines and direct interactions. Currently, studies are focusing on the anti-cancer effect of MSCs on GI malignancies. However, the effects and functional mechanisms of MSC-derived exosomes on GI cancer are less studied. MSC-derived exosomes can regulate GI tumor growth, drug response, metastasis, and invasion through transplanting proteins and miRNA to tumor cells to activate the specific signal pathway. Besides, the MSC-derived exosomes are also seen as an important drug delivery system and have shown potential in anti-cancer treatment. This study aims to summarize the effect and biological functions of MSC-derived exosomes on the development of GI cancers and discuss their possible clinical applications for the treatment of GI malignancies.

Key Words: Mesenchymal stem cells; Exosomes; Gastrointestinal cancer; Cancer treatment; Drug delivery system; Transplanting miRNA

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EXOSOMES: A DISTINCT POPULATION OF EXTRACELLULAR VESICLES

INTRODUCTION

Gastrointestinal (GI) cancer is one of the most common malignancies in the digestive system, such as the stomach, liver, pancreas, and colorectum[1]. Based on the latest global epidemiological data, GI cancer accounts for 26% of all kinds of cancers and 35% of cancer patients died from GI cancer with approximately 4.8 million new cases and 3.4 million deaths each year[2,3]. Current therapeutic strategies for GI malignancies mainly include surgery, endoscopy, radiotherapy, chemotherapy, targeted therapy, and immunotherapy[4-6]. Despite that treatment strategies are becoming mature and diverse, the prognosis of GI cancer is still very poor due to the fact that most patients miss the therapeutic window[7]. If detected at an early stage, GI cancers are highly curable with traditional treatment methods[8]. However, the early diagnosis of GI cancer is a significant challenge. Therefore, more promising treatment strategies are needed to cut down the mortality of GI malignancies.

Mesenchymal stem cells (MSCs), a type of distinct non-hematopoietic stem cells, possess the capacity of self-renewal and multipotential differentiation[9,10]. It has been shown that MSCs are involved in tumor development, including tumorigenesis, tumor growth and metastasis, as well as regulation of tumor microenvironment[11-13]. Therefore, MSCs have been commonly used in anti-cancer studies. However, the underlying mechanisms of how MSCs affect tumor development are still controversial[14]. A series of literature has reported that MSCs are capable of promoting tumor progression through secreting pro-tumorigenic factors[15] and differentiating into cancer-associated fibroblasts[16,17]. Nevertheless, other evidence suggests that MSCs could suppress tumor proliferation via secreting cycle inhibitor P21 and anti-tumorigenic factors such as interleukins, IFN-γ, Dkk-1, and promote tumor cell apoptosis through secreting apoptotic executor caspase 3[18,19]. Although the underlying mechanisms of how MSCs regulate tumor cells are still unclear, there is no doubt that MSC-derived exosomes play a key role in the interaction between MSCs and tumor cells[20].

Exosomes, a distinct population of extracellular vesicles, are vital for cell-to-cell communication[21]. Exosomes can be derived from mesenchymal cells, immune cells, and tumor cells and the effects of exosomes of different sources are distinct[22]. MSC-derived exosomes show many similar effects with MSCs, and have also been seen as an important component of the tumor microenvironment[13,23]. More importantly, compared to MSCs, MSC-derived exosomes are safer and show better penetrability, biocompatibility, and stability during the interaction with tumor cells[24,25]. In recent years, the functions of MSC-derived exosomes in GI treatment have been studied with in vitro experiments and animal models[21]. However, a systematic review is rare. This paper summarizes the features of exosomes and the effects of MSC-derived exosomes on GI cancers. Besides, the therapeutic potential of MSC-derived exosomes on GI malignancies is highlighted and future research opportunities related to MSC-derived exosomes are also proposed.

MESENCHYMAL STEM CELLS

MSCs, with anticancer, angiogenic, anti-apoptotic, and multi-differentiation capacity, have been commonly used in oncotherapy, and tissue regeneration and restoration[6,26]. Based on the sources, MSCs can be divided into bone marrow-derived MSCs,
embryo-derived MSCs, human umbilical cord-derived MSCs, adipose tissue-derived MSCs, dental MSCs, and menstrual blood-derived MSCs[27-29]. It has also been shown that MSCs are key mediators of inflammation and the tumor microenvironment [30]. Based on these discoveries, a new clinical treatment strategy called cell therapy has been developed, which works via transplanting MSCs into human bodies to treat related diseases. At present, cell therapy based on MSCs is still in the clinical trial phase. Although MSC transplantation has shown huge potential in clinical application, more and more side effects and limitations have been found. For example, it has been proposed that MSC transplantation could increase the risk of tumorigenicity and cell death[31]. Besides, MSCs are limited by the lung barrier[32]. To solve these problems, researchers have proposed to replace MSCs with MSC-derived exosomes for cell therapies, because these exosomes show many similar functions with MSCs, are safer and more stable, and can be used as a vehicle to deliver anti-tumor drugs and bioactive factors[33]. In addition, it has been discovered that the MSC-derived exosomes could regulate tumor progression via changing the microenvironment of tumors[34].

EXOSOMES

Exosomes, cell-derived membranous structures, originate from the invagination of the endosomal system or segregation of the plasma membrane[35]. Abundant biomolecules such as biomarker proteins, regulatory RNA and DNA, functional cytokines, growth factors, etc.[36,37], are included in exosomes. To date, it has been discovered that MSC-derived exosomes contain more than 300 miRNAs and at least 730 proteins[38,39]. The sizes of exosomes are from 50 nm to 200 nm, which play a central role in cell-to-cell signaling networks[36,40]. One study has reported that exosomes are capable of regulating the pathway of downstream signals of recipient cells via releasing a variety of biomolecules and transporting the genetic material to downstream cells[26]. Interestingly, exosomes can play a dual role in tumorigenesis, both anti-tumor and pro-tumor, which may be because the exosomes can be derived from different tissues[41]. For instance, one study has proposed that normal tissue MSC-derived exosomes are capable of suppressing tumor development through blocking carcinogenic reprogramming signaling pathways. In contrast, tumor cell-derived exosomes can drive recipient cells to establish malignancy, resulting in tumorigenesis[42]. The main sources of exosomes include MSCs, immune cells, tumor cells, etc. [22]. MSC-derived exosomes have been commonly used in the studies of cancer development. Yang et al[43] have proposed that MSC-derived exosomes could promote tumor growth through secreting matrix metalloproteinase-2 (MMP-2) or MMP-2 enzyme to alter the tumor microenvironment and cellular functionalities. It has also been found that MSC-derived exosomes are capable of supporting tumor growth via transporting tumor-supportive factors such as proteins, miRNA, and metabolites to recipient tumor cells[44]. Besides, MSC-derived exosomes can suppress tumor growth by carrying tumor-inhibiting factors into tumor cells and decreasing the expression of vascular endothelial growth factor (VEGF)[45].

Because of the special properties and biological functions, exosomes have been used as natural nanocarriers to transport drugs and specific factors to tumor sites[46]. For example, one study has indicated that MSC-derived exosomes could reach a higher cell-target specificity by delivering paclitaxel (PTX) to tumor sites[47]. In addition, the glioma-associated MSC-derived exosomes could deliver miR-1387 to recipient glioma stem-like cells, increasing the proliferation and aggressiveness of glioblastoma through down-regulating the expression of the tumor-suppressor NCOA1[48]. Furthermore, it has also been demonstrated that MSC-derived exosomes could improve anti-cancer therapeutic efficacy through regulating immune response and reversing the chemoresistance[49,50]. The following section describes the effect of MSC-derived exosomes on gastric cancer (GC), hepatoma, pancreatic cancer (PC), and colorectal cancer (CRC) (Table 1).

MSC-DERIVED EXOSOMES FOR GC

GC is the fourth most common malignant neoplasm and the third prominent cause of cancer death globally[51]. Despite routine gastroscopy increasing the rate of early diagnosis, the 5-year survival rate of GC patients is still less than 30%[52]. In the current treatments for GC, perioperative or adjuvant chemotherapy can significantly
Table 1 Effect of mesenchymal stem cells-derived exosomes on gastrointestinal cancer

| Tumor type          | Exosomes source | Cell lines | Function                                      | Mechanism                                                                 | Ref.     |
|---------------------|-----------------|------------|-----------------------------------------------|---------------------------------------------------------------------------|----------|
| Gastric cancer      | hUCMSCs         | HGC-27; MGC-803; SGC-7901 | Conferring tumor chemoresistance | (1) Upregulating the expression of multi-drug resistance-associated genes and proteins; (2) Activating calcium/calmodulin-dependent protein kinases (CaMKs) and Raf/MEK/ERK pathway; and (3) Enhancing the functionality of P-gp/MDR | [13]     |
|                     | hBMSCs          | Animal model | Promoting tumor development | (1) Activating ERK1/2 and p38 MAPK pathways; and (2) Enhancing the expression of VEGF | [55]     |
|                     | hBMSCs          | SGC-7901   | No effect |                                             | [55]     |
|                     | hUCMSCs         | HGC-27     | Promoting tumor development | (1) Activating the Akt signal pathway; (2) Inducing the epithelial-mesenchymal transition (EMT); and (3) Enhancing the tumorigenicity and stemness | [61]     |
|                     | hBMSCs          | SGC-7901   | Promoting tumor development | Secreting miR-221 to activate Hedgehog signaling pathway | [64]     |
|                     | GC-MSCs         | HGC-27     | No effect |                                             | [55]     |
|                     | hUCMSCs         | HGC-27     | Promoting tumor development | (1) Activating the Akt signal pathway; (2) Inducing the epithelial-mesenchymal transition (EMT); and (3) Enhancing the tumorigenicity and stemness | [61]     |
|                     | hBMSCs          | SGC-7901   | Promoting tumor development | Secreting miR-221 to activate Hedgehog signaling pathway | [64]     |
|                     | hBMSCs          | Animal model | Promoting tumor development | Increasing the expression of miR-214, miR-221, and miR-222 | [66]     |
|                     | GC-MSCs         | HGC-27     | No effect |                                             | [61]     |
|                     | mBMSCs          | MFC        | Promoting tumor development | Increasing the expression of miR-214, miR-221, and miR-222 | [66]     |
|                     |                  |            |                                                | Delivering UBR2 to activate Wnt/β-catenin signaling pathway | [69]     |
| Liver cancer        | hBMSCs          | HepG-2     | Inhibiting tumor development | (1) Blocking the cell cycle progression; and (2) Inducing tumor cells apoptosis | [93]     |
|                     | AMSCs           | HepG-2     | Inhibiting tumor development | Secreting miR-122 to improve chemosensitivity of HepG2 HCC cells and inhibiting tumor development | [83]     |
|                     | AMSCs           | Huh-7; SMMC-7721 | Increasing tumor chemosensitivity | Delivering miR-199a-3p to improve liver cancer cell line chemosensitivity | [87]     |
|                     | mBMSCs          | Animal model | Inhibiting tumor development | (1) Promoting tumor cells apoptosis; and (2) Inhibiting angiogenic activity, metastasis, and invasiveness | [96]     |
|                     | AMSCs           | Animal model | Inhibiting tumor development | Uregulating local and systemic NK cells | [95]     |
|                     | AMSCs           | Huh-7; SMMC-7721 | Increasing tumor chemosensitivity | Delivering miR-199a-3p to tumor sites | [87]     |
| Pancreatic cancer   | hBMSCs          | BxPC-3; PANC-1 | Inhibiting tumor development | Secreting miR-1231 to suppress tumor development | [107]    |
|                     | hBMSCs          | PANC-1     | Inhibiting tumor development and promoting tumor cells apoptosis | Upregulating the expression of a disintegrin and a metalloproteinase-9 (ADAM9) | [108]    |
|                     | mBMSCs          | AsPC-1; PANC-1 | Inhibiting tumor development and promoting tumor cells apoptosis | Delivering miR-124 to regulate the expression of EZH2 | [109]    |
|                     | mBMSCs          | CFPAC-1    | Inhibiting tumor development | Delivering anticancer agents | [47]     |
| Normal fibroblast-like MSCs | AMSCs          | PANC-1     | Inhibiting tumor development | Delivering short interfering RNA or short hairpin RNA to target oncogenic KRAS | [105]    |
|                     | BMSCs           | MiaPaca-2  | Inhibiting tumor development | Loading PTX and gemcitabine monophosphate (GEMP) to pancreatic cancer | [100]    |
|                     | BMSCs           | Tumor model | Enhancing tumor immunotherapy | Constructing a dual delivery biosystem to achieve the combined therapy | [106]    |
| Colorectal cancer   | hBMSCs          | SW-480     | Promoting tumor development | Activating ERK1/2, p38, and JNK pathways | [55]     |
|                     | BMSCs           | Caco-2; SW-480; SW-620; LoVo; HT-29 | Inhibiting tumor development and promoting tumor cells apoptosis | Uregulating the expression of miR-16-5p to downregulate integrin α2 (ITGA2) | [124]    |
|                     | BMSCs           | DLD-1; HCT- | Inhibiting tumor | Secreting miR-4461 to downregulate the expression of COPB2 | [125]    |
MSCs: Mesenchymal stem cells; hBMSCs: Human bone marrow-derived mesenchymal stem cells; AMSC: Adipose-derived mesenchymal stem cells; mBMSCs: Murine bone marrow-derived mesenchymal stem cells; hUCMSCs: Human umbilical cord mesenchymal stem cells; GC-MSCs: Gastric cancer tissue-derived mesenchymal stem cells; MFC: Murine foregastric carcinoma; CSCs: Cancer stem cells; NA: Not available.

Improve the therapeutic effect on advanced GC[53]. However, chemoresistance is one of the major obstacles[54]. One recent study has reported that human umbilical cord MSC-derived exosomes could confer chemoresistance to GC cells (HGC-27, MGC-803, and SGC-7901) through upregulating the expression of multi-drug resistance genes and proteins, activating calcium/calmodulin-dependent protein kinases and the Raf/MEK/ERK pathway, and enhancing the functionality of P-gp/MDR. In this way, GC cells are protected from chemotherapy-induced apoptosis[13]. In other words, the efficacy of chemotherapy in GC treatment can be improved by targeting the interaction between MSC-derived exosomes and tumor cells. For example, chemoresistance in GC can be overcome by blocking the CaM-Ks/Raf/MEK/ERK pathway. In conclusion, the therapeutic potential and efficacy of GC treatment can be improved based on the effects of MSC-derived exosomes on drug resistance.

The effect of MSC-derived exosomes on GC development remains controversial. In a mouse model experiment, researchers have observed that human bone marrow-derived MSCs (hBMSCs)-derived exosomes could promote the growth of SGC-7901 gastric tumor cells[55]. Further studies have indicated that MSC-derived exosomes are capable of promoting the incidence and growth of tumors via activating angiogenesis and facilitating tumor cell proliferation in vivo[56]. After the co-implantation with hBMSC-derived exosomes in vivo, MSC-derived exosomes show a tumor-promoting effect in these rat models, and significant up-expression of Bcl-2, phosphorylated ERK1/2, α-smooth muscle actin (α-SMA), CXCR4, VEGF, and MDM2 mRNA, all of which are very essential for tumor growth, metastasis, and angiogenesis, has been detected in the tumor microenvironment[55]. In contrast, it has been discovered that hBMSC-exosomes do not affect SGC-7901 cell proliferation in vitro, suggesting that the effect of MSC-derived exosomes on the incidence and growth of tumor is exerted through indirect mechanisms[55]. To further illustrate the mechanism of how hBMSC-exosomes affect tumor growth, researchers have examined the expression levels of VEGF and CXCR4 in vitro. They discovered that hBMSC-exosomes could promote tumor growth via activating the ERK1/2 and p38 MAPK pathways, and therefore the expression of VEGF is upregulated, which, in turn, activates tumor angiogenesis[55-59]. Previous studies have also shown MSC-derived exosomes could increase the expression of octamer-binding transcription factor 4, exeter mining region Y-box 2, and Lin28B, and therefore promote the formation of tumor blood vessels and potentiate gastric tumor growth[55,60,61]. Further studies have discovered that hUCMSC-derived exosomes can promote HGC-27 gastric tumor cell invasion and metastasis through increasing the expression of mesenchymal indicators, activating the Akt signaling pathway, and decreasing the expression of epithelial indicators, and therefore the epithelial-mesenchymal transition (EMT) of gastric tumor cells is induced [61]. EMT, an initial stage of tumor metastasis, can stimulate tumor cells to lose epithelial cell polarity, render mesenchymal features, infiltrate into adjacent tissues, and increase self-renewal capacity[62,63]. In addition to contributing to obtaining the EMT, hUCMSC-derived exosomes also contribute to enhancing the tumorigenicity and stemness of HGC-27 cells. After the treatment with hUCMSC-derived exosomes, the expression of Oct4, Sox2, and Lin28B is increased, all of which are stemness-relevant indicators[61].

Other studies have proposed that BMSC-derived exosomes could secret miR-221 as a pro-tumor molecule to activate the Hedgehog signaling pathway, promoting the proliferation and progression of gastric tumors[64,65]. Furthermore, the miR-221 level in the peripheral blood could also be seen as a GC diagnostic marker, and the high expression level of miR-221 is reckoned as an indicator of poor clinical prognosis of
gastric tumors[34]. Another study has found that GC tissue-derived MSCs (GC-MSCs) are capable of increasing the expression of miR-214, miR-221, and miR-222, all of which are positively correlated with the development of GC[66]. For instance, the upregulation of miR-214 can be seen as a sign of venous invasion and unfavorable outcome of GC[67]. The high expression of miR-222 is mainly associated with serosal invasion and lymph node metastasis[66] and miR-221 is mainly involved in advanced stages of node metastasis, local invasion, and lymphatic metastasis of GC[68]. Therefore, it has been reported that the tumor-promoting effects of GC-MSCs could be impaired by using a miRNA inhibitor to downregulate the expression of miR-221[66].

Based on the above discoveries, the exosomal miR-214, miR-221 and miR-222 can be used for the early diagnosis and treatment of gastric tumors in the future.

In a recent preclinical study, Mao et al[69] have used the p53 deficient mouse BM-MSC exosomes to deliver UBR2 into murine foregastric carcinoma cells. They found that UBR2 enriched by exosomes could promote the proliferation and migration of these tumor cells through activating the Wnt/β-catenin signaling pathway. Previous studies have demonstrated that the Wnt/β-catenin pathway plays a key role in regulating the growth and metastasis of GC cells, and the maintenance of cancer stem cells (CSCs)[70].

MSC-DERIVED EXOSOMES FOR LIVER CANCER

Liver cancer is the second leading cause of cancer-related death worldwide[71]. Hepatocellular carcinoma (HCC) is the most common type of liver cancer, accounting for more than 90% of cases[72]. Especially, the prognosis of patients with advanced HCC is poor due to the lack of an effective treatment strategy[73,74]. Currently, although many clinical treatments for HCC such as surgical techniques, conventional chemotherapy, transarterial chemoembolization, radiotherapy, targeted therapy, and liver transplantation have been applied, the 5-year survival rate of liver cancer patients is still not more than 20%[75,76]. In recent years, with more studies focusing on exosomes, it has been proposed that exosomes, especially MSC-derived exosomes, have shown substantial anticancer potential in the clinical application, especially in the treatment of HCC[37].

Chemotherapy has been regarded as the most common curative measure for HCC. However, HCC shows high resistance to conventional chemotherapeutic drugs and agents[77]. Therefore, new therapeutic approaches are needed to enhance HCC chemosensitivity. Previous studies have indicated that miR-122 plays a key role in diagnosing and prognosis of hepatoma[19]. For example, it has been proposed that the loss or downregulation of miR-122 could be reckoned as the sign of poor prognosis and metastasis of HCC[78], and is closely related hepatocarcinogenesis and HCC development[79]. On the other hand, it has been found that miR-122 could increase the sensitivity of liver cancer cells to chemotherapeutic drugs such as 5-fluorouracil (5-FU) and doxorubicin[37,80]. Recent studies have demonstrated that upregulated miR-122 could inhibit the formation and development of HCC, and increase the chemotherapeutic sensitivity of these tumor cells[81,82]. Moreover, another study also reported that adipose MSC (AMSC)-derived exosomes could secret miR-122 to improve chemosensitivity of HepG2 HCC cells[83]. MiR-199a-3p, a highly expressed miRNA in normal liver cells, can increase HCC chemosensitivity by downregulating the gene expression of YAP1, CD151, and mTOR[84-86]. It has been proposed that AMSC-derived exosomes could be used to deliver miR-199a-3p to improve the chemosensitivity of Huh7 and SMMC-7721 liver cancer cell lines[87]. According to the above discoveries, there is no doubt that miR-122-modified exosomes and miR-199a-modified exosomes are two effective liver cancer treatment alternatives. However, finding a safe and effective vehicle for miR-122 and miR-199a-3p delivery is a challenge and researchers have studied how to use exosomes as a biological delivery vehicle for miRNA transfer[88]. Compared to other vehicles, MSC-derived exosomes possess less immunogenicity, higher biocompatibility, and less toxicity[89]. Besides, as the most prolific producers among exosome-producing cells, MSCs are suited for the mass production of exosomes[90]. All in all, MSC-derived exosomes can be used as a new nanocarrier of miRNAs and drugs[37].

Previous studies have indicated that MSCs can both suppress and promote liver cancer progression[6]. The function of MSC-derived exosomes on HCC progression, similar to that of MSCs, is not determined[91-94]. For example, one study has reported that BM-MSC-derived exosomes can inhibit HepG2 cell growth via blocking the cell cycle progression and inducing apoptosis in vitro[95]. In another study, AMSC-derived
exosomes have been directly injected into nude mice bearing HepG2 cells, and no significant differences compared to the control group have been observed[83]. Moreover, another rat model study has reported that AMSC-derived exosomes could inhibit HCC development through upregulating local and systemic NK cells[95]. The above studies show that mechanisms of the regulation of different MSC-derived exosomes on HCC progression are distinct. Although the experimental results may be interfered by experimental models, tumor types, MSC sources, as well as exosome injection administration, there is no doubt that AMSC-derived exosomes can be effectively used to transfer miR-122 to increase HepG2 liver cancer cell chemosensitivity and inhibit HCC growth and progression, providing a new treatment strategy for HCC[83].

Alzahrani et al[96] have conducted a long-term model study and found that BMSC-derived exosomes could inhibit the development of diethylnitrosamine-induced HCC in vivo. After BM-MSC-derived exosomes being injected into established HCC, the overexpression of apoptotic genes, Bax and p53, and the downregulated antiapoptotic gene, Bcl2, were observed. In contrast, CSC-derived exosomes are capable of suppressing apoptosis, increasing angiogenic activity, promoting metastasis and invasiveness, and inducing EMT.

Liver cancer is a highly angiogenic cancer, whose growth requires sufficient blood supply as nourishment. It is acknowledged that VEGF plays an important role during angiogenesis. MSC-derived exosomes can inhibit tumor angiogenesis by downregulating VEGF[45] and suppressing liver cancer cell progression. Some studies have found that MSC-derived exosomes are beneficial for acute liver injury and liver fibrosis via activating the proliferative and regenerative responses[97,98]. Moreover, it has been reported that tumor-derived exosomes could work with BM-MSCs to inhibit HCC cell growth through arresting these cells in the G0/G1 phase[99]. All in all, MSC-derived exosomes have shown unlimited potential in liver cancer treatment, but there is still a long way to go before clinical application.

**MSC-DERIVED EXOSOMES FOR PANCREATIC CANCER**

PC, especially pancreatic ductal adenocarcinoma (PDAC), is a highly fatal malignancy with a 5-year survival rate less than 6%[100]. To date, despite an increasing number of clinical treatments, surgery remains the only curative treatment for PC. However, the surgical resection rate is only approximately 20% as most patients present transforming diseases upon diagnosis, and therefore chemotherapy remains the main strategy for clinical PC treatment[101]. However, traditional chemotherapy is not effective enough due to chemotherapy resistance, abnormally abundant extracellular matrix, and extremely deficient neovascularization in the tumor microenvironment [102,103]. To overcome the pathophysiological barrier of PC, an increasing number of nanotechnology-based drug delivery strategies have been proposed.

Previous studies have shown that MSCs could regulate the tumor microenvironment and the development of PDAC[104]. With the deepening studies, it has been discovered that MSC-derived exosomes are capable of circumventing the tumor extracellular matrix barrier, overcoming chemoresistance, and efficiently targeting and penetrating tumor cells[100,105]. Therefore, the MSC-derived exosomes can be seen as novel systems to load chemotherapeutics to target PC. For example, one study has used the MSC-derived exosomes to load PTX and gemcitabine monophosphate homing to PC, and these exosomes show more preferable penetration and superior anti-tumor efficacy than the control group both in vivo and in vitro[100]. In a recent preclinical study, Zhou et al[106] have used the BMSC-derived exosomes to construct a dual delivery biosystem, which is capable of carrying both oxaliplatin (OXA) and siRNA for enhancing PDAC immunotherapy. The siRNA-exosomes-OXA nanoparticles can elicit anti-tumor immunity and exert significant therapeutic effects while showing better stability and fewer side effects than traditional synthetic delivery systems. More specifically, the combined therapy of iEXO-OXA could activate innate and adaptive anti-PDAC immunity by inducing the immunogenic cell death of tumor cells, initiating dendritic cell maturation and antigen presentation, and reversing immunosuppression and recruiting antitumoral cytotoxic T lymphocytes. Based on the findings above, it can be concluded that MSC-derived exosomes can serve as a promising nanoscale drug delivery platform for PC over the long run.

In addition to functioning as a carrier for drug delivery, MSC-derived exosomes can also affect PC progression through secreting multiple miRNAs[107]. For example, the expression level of miR-1231 in exosomes derived from the peripheral blood is
correlated with the pathological stage of PC, suggesting that miR-1231 may benefit PC diagnosis. Further studies have proposed that miR-1231 is capable of inhibiting the growth and development of BxPC-3 and PANC-1 pancreatic tumor cells[107]. Based on the above discoveries, it can be concluded that BMSC-derived exosomes with a high expression level of miR-1231 can be efficiently used in anti-cancer medicines, especially medicines for PC. Wu et al[108] have transfected miR-126-3p into the exosomes of BMSCs and found that the exosomes could downregulate the expression of a disintegrin and a metalloproteinase-9 and promote the apoptosis while suppressing the proliferation, invasion, and metastasis of PANC-1 pancreatic tumor cells. Therefore, the miR-126-3p can be reckoned as a novel biomarker for PC treatment. In a recent study, Xu et al[109] have indicated that miR-124-carried BMSC-derived exosomes could inhibit the proliferation, metastasis, and invasion, and induce apoptosis of PC cells (AsPC-1 and PANC1) by regulating the expression of EZH2, which is a target of miR124[110]. Previous studies have also demonstrated that miR-124 serves as a tumor suppressor for many cancers, such as HR-HPV-positive cervical cancer[111], breast cancer[112], and bladder cancer[113]. The above findings suggest that MSC-derived exosomes can be considered as a potential vehicle to transport miR-124 in PC treatment.

MSC-DERIVED EXOSOMES FOR COLORECTAL CANCER

CRC ranks as the third most commonly diagnosed cancer and the most common in GI cancers[71,114]. In recent years, with the improvement of screening tests and therapeutic strategies, the 5-year survival rate of CRC in China has increased to 31% [115]. However, the incidence rates of CRC, especially those in most developing countries, increase sharply due to the lifestyle changes, growing population, and aging of the population[116]. In 2020, the new cases of CRC were more than 1.9 million in 185 countries[71]. Therefore, it is very necessary to explore more effective diagnostic and therapeutic strategies for CRC. Previous studies have pointed out different effects of MSCs on CRC. For example, it has been proposed that hBMSCs could promote the growth of the low-malignancy CRC cell line HT29, but could not affect the progression of the high-malignancy CRC cell line HCT 116[117]. With the discovery of anti-tumor and tumor homing properties, MSCs have been widely used in CRC studies. Despite that MSC therapy in CRC remains controversial due to MSCs can promote immune evasion of tumor cells in the tumor microenvironment, which might be caused by the powerful immunosuppression function of MSCs[118], the application of MSCs is still a promising strategy to ameliorate CRC. First, MSCs are capable of depressing tumor metastasis and complications[119]. For example, one study has reported that MSCs could inhibit CRC metastasis and decrease the formation of malignant ascites by suppressing VEGF expression[120]. It has also been shown that MSCs could inhibit the proliferation of colonic cancer via depressing the expression of proinflammatory factors, ERK, STAT3 phosphorylation, and Smad2, and blocking PI3K/AKT signaling pathway[121-123].

On the other hand, MSC-derived exosomes are also involved in CRC proliferation, migration, and invasion. For example, it has been reported that BMSC-derived exosomes are capable of overexpressing miR-16-5p to downregulate integrin α2 (ITGA2), and inhibiting the growth and progression but promoting the apoptosis of CRC cells (Caco-2, SW480, SW620, LoVo, and HT29)[124]. Therefore, miR-16-5p derived from MSC-derived exosomes can be developed as an effective therapy for CRC. Besides, Chen et al[125] have transfected BMSC-derived exosomes into CRC cells (DLD1, HCT116, and SW480) and found that the proliferation of these cells is inhibited and the content of miR-4461 increases significantly, indicating that exosomal miR-4461 might inhibit the growth of CRC cells. Further studies have proposed that the expression level of miR-4461 is lower in CRC cells than that in normal cells and miR-4461 is capable of downregulating the expression of coatomer protein complex subunit beta 2 (COPB2). Based on these discoveries, it can be concluded that miR-4461 derived from BMSCs exosomes can inhibit CRC tumorigenesis by downregulating the expression of COPB2, a target gene of miR-4461. In the future, miR-4461 can be applied for the diagnosis and treatment of CRC.

Li et al[126] have treated SW1116 and Caco2 colorectal tumor cells with miR-142-3p and found that miR-142-3p could inhibit the proliferation and invasion of CRC cells but increase the population of CSCs of colon cancer. Further studies have found that miR-142-3p promotes colon CSC-like traits by decreasing the expression of Numb while increasing the expression of Notch target genes, such as Hes1, P21, and Cyclin.
D3. On the other hand, the underlying mechanism of inhibited tumor proliferation could be that miR-142-3p can target CD133 and Lgr5.\textsuperscript{[127]}

Li et al.\textsuperscript{[128]}

have transfected hUCMSC-derived exosomes containing miR-3940-5p into HT-29 and DLD-1 colorectal tumor cells and found that the exosomes suppress EMT, metastasis, progression, and invasion of these CRC cells by downregulating the expression of Integrin alpha6 (ITGA6) and inhibiting the activity of transforming growth factor-beta1 (TGF-\(\beta\)) signaling pathway. Previous studies have indicated that overexpression of ITGA6 could trigger CRC progression and migration \textit{via} upregulating transforming growth factor-beta1 (TGF-\(\beta\)).\textsuperscript{[129,130]}

Significant progress has been made in the development of an efficient vehicle for the delivery of anticancer agents to tumor tissue. Similar to many kinds of natural exosomes, MSC-derived exosomes also possess many distinctive characteristics such as good stability, low toxicity and immunogenicity, good biocompatibility, and long circulation\textsuperscript{[131]}. Therefore, Bagheri et al.\textsuperscript{[132]}

have loaded doxorubicin into MSC-derived exosomes using the electroporation method and found that MSC-derived exosomes inhibit the growth of C26 and MCF7 colon tumor cells more significantly and have proposed that MSC-derived exosomes can be used to construct a novel biomanufacturing drug delivery platform for CRC therapy. One study has proposed that MSC-derived exosomes can also be used in inflammatory bowel disease (IBD) treatment\textsuperscript{[133]}

as treatment with MSC-exosomes substantially mitigates IBD through inhibiting inflammatory responses, maintaining intestinal barrier integrity, and polarizing M2b macrophages.

**DISCUSSION**

It can be concluded from the above findings that MSC-derived exosomes have shown unlimited therapeutic potential for GI cancer treatment. The main methods for developing new treatment strategies are summarized as: (1) To use the nature contents of MSC-derived exosomes to inhibit tumor proliferation and invasion. To date, it has been shown that the main inhibitory factors are some miRNAs and proteins, but the specific mechanisms have not been found out\textsuperscript{[44,134]}. Therefore, in future studies, more efforts are needed to illustrate the possible mechanism; (2) to target the interaction between MSC-derived exosomes and tumor cells. It has been shown that MSC-derived exosomes could promote the growth of some GI cell lines and increase the chemoresistance of these cell lines through upregulating the expression of the factors and proteins or activating some special signal pathways\textsuperscript{[13]}. Therefore, relative receptors can be targeted and the relative pathway can be blocked to improve therapeutic effectiveness; and (3) to modify MSC-derived exosomes as a drug delivery carrier. After being modified with special anti-cancer drugs, these exosomes are capable of homing to tumor sites with less immunogenicity.

Increasing studies have demonstrated that MSC-derived exosomes could exert both anti-tumor and pro-tumor effects on GI malignancies\textsuperscript{[42-44]}. The reasons why MSC-derived exosomes can play different functions in the development of GI cancers are concluded as: (1) The tumor cell lines chosen for the experimental research are different. For example, different types of CRC cells lines, such as Caco-2, SW-480, SW-620, HT-29, HCT-116, and DLD-1, are used in CRCs studies and the experimental results are different, which may be due to that different types of tumor cell lines show different invasion, metastasis, and proliferation capability\textsuperscript{[135]}; (2) the sources of exosomes are different, and the contents, such as factors, signaling lipids, proteins, and miRNAs, of different types of MSC-derived exosomes are distinct. Therefore MSC-derived exosomes can cross-talk with tumor cells through different mechanisms and exert different effects on tumor development; and (3) the experimental methods and models are different. The \textit{in vitro} and \textit{in vivo} studies can show different and even opposite results. Besides, the tumor microenvironment and cell cultivation conditions can both influence the experimental results.

Despite that both MSCs and MSC-derived exosomes can be used in anti-cancer research, MSC-derived exosomes show many potential advantages. First, MSC transplantation may result in the transfer of mutated or damaged DNA into normal cells, and an increasing risk of a new disease\textsuperscript{[136]}. Fortunately, if MSC-derived exosomes are directly transferred into the body, these problems can be effectively avoided. Second, with smaller sizes, MSC-derived exosomes can circulate and pass through various barriers, such as capillary bed and lung barriers easily. Third, with the same infusion dose, the effect of MSCs-derived exosomes can be kept for a longer time than MSCs post-transplant, which can achieve a greater circulation extent\textsuperscript{[137]}. 
To date, despite that MSC-derived exosomes have showing substantial therapeutic potential in GI treatment, many challenges and obstacles need to be overcome. The most common obstacle is to achieve large-scale production of MSC-derived exosomes. In addition, isolating these exosomes from MSCs without modification of the cargos of these MSCs is also a big challenge. Furthermore, because the sources or donors of MSCs are different, MSC-derived exosomes show heterogeneity and even the exosomes derived from the same type of MSCs can exert opposite effects on tumor development, which might be due to the fact that these exosomes carry different molecules. Therefore, before applying MSC-derived exosomes in clinical trials, researchers need to improve the methods for mass-production, isolation, and homogeneity maintenance of MSC-derived exosomes[138]. The internal living conditions of MSCs can be simulated to achieve a function-specific and large-scale production of MSC-derived exosomes. Besides, more methods for storing and recovering these MSC-derived exosomes and a potency assay for therapeutic efficacy evaluation of exosomes are needed. Based on MSC-based clinical trials, MSC-derived exosome therapies can be developed more rapidly.

CONCLUSION

This review analyzes the effects of MSCs-derived, hBMSC-derived exosomes, mBMSC-derived exosomes, hUCMSC-derived exosomes, and GC-MSC-derived exosomes on GI malignancy development. However, the reasons why different MSC-derived exosomes exert distinct effects on GI malignancies are not determined. In the future, a better understanding of the mechanisms of how MSC-derived exosomes regulate GI malignancy development is needed, which will help to develop more promising treatment methods for GI cancer.

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