ISSN 1948-5204 (online)

World Journal of *Gastrointestinal Oncology*

World J Gastrointest Oncol 2021 December 15; 13(12): 1850-2222

Published by Baishideng Publishing Group Inc

World Journal of Gastrointestinal Oncology

Contents

Monthly Volume 13 Number 12 December 15, 2021

FRONTIER

REVIEW

MINIREVIEWS

World Journal of Gastrointestinal Oncology

Monthly Volume 13 Number 12 December 15, 2021

Contents

World Journal of Gastrointestinal Oncology

Monthly Volume 13 Number 12 December 15, 2021

Contents

World Journal of Gastrointestinal Oncology

Monthly Volume 13 Number 12 December 15, 2021

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Oncology*, Ladan Teimoori-Toolabi, MD, PhD, Associate Professor, Department of Molecular Medicine, Pasteur Institute of Iran, Tehran 1316943551, Iran. iteimoori@pasteur.ac.ir

AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Oncology* (*WJGO*, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc*.

INDEXING/ABSTRACTING

The *WJGO* is now indexed in Science Citation Index Expanded (also known as SciSearch®), PubMed, PubMed Central, and Scopus. The 2021 edition of Journal Citation Reports® cites the 2020 impact factor (IF) for *WJGO* as 3.393; IF without journal self cites: 3.333; 5-year IF: 3.519; Journal Citation Indicator: 0.5; Ranking: 163 among 242 journals in oncology; Quartile category: Q3; Ranking: 60 among 92 journals in gastroenterology and hepatology; and Quartile category: Q3. The *WJGO*'s CiteScore for 2020 is 3.3 and Scopus CiteScore rank 2020: Gastroenterology is 70/136.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Ying-Yi Yuan*; **Production Department Director:** *Xiang Li*; **Editorial Office Director:** *Ya-Juan Ma*.

NAME OF JOURNAL
World Journal of Gastrointestinal Oncology

ISSN
ISSN 1948-5204 (online)

LAUNCH DATE
February 15, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Rosa M Jimenez Rodriguez, Pashtoon M Kasi, Monjur Ahmed, Florin Burada

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1948-5204/editorialboard.htm

PUBLICATION DATE
December 15, 2021

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Gastrointestinal Oncology

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Oncol 2021 December 15; 13(12): 1981-1996

DOI: 10.4251/wjgo.v13.i12.1981

ISSN 1948-5204 (online)

REVIEW

Mesenchymal stem cell-derived exosomes for gastrointestinal cancer

Lin-Xian Zhao, Kai Zhang, Bing-Bing Shen, Jian-Nan Li

ORCID number: Lin-Xian Zhao 0000-0003-2436-6966; Kai Zhang 0000-0002-4499-7186; Bing-Bing Shen 0000-0002-9358-3844; Jian-Nan Li 0000-0001-9744-7666.

Author contributions: Zhao LX wrote the paper; Zhang K and Shen BB collected the data; Li JN designed the review and revised the paper; Zhao LX, Zhang K, Shen BB, and Li JN performed the approval of final revision; Zhao LX and Zhang K contributed equally to this work.

Conflict-of-interest statement: The authors declare that there is no conflict of interest for this manuscript.

Supported by Science and Technology Development Project of Jilin Province, No. 3D5197434429; and Youth Program of the National Natural Science Foundation of China, No. 3A4205367429.

Country/Territory of origin: China

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review report's scientific quality classification

Lin-Xian Zhao, Kai Zhang, Jian-Nan Li, Department of General Surgery, The Second Hospital of Jilin University, Changchun 130041, Jilin Province, China

Bing-Bing Shen, Department of Hepatobiliary Surgery, Renmin Hospital of Wuhan University, Wuhan 430060, Hubei Province, China

Corresponding author: Jian-Nan Li, MD, PhD, Assistant Professor, Department of General Surgery, The Second Hospital of Jilin University, No. 218 Ziqiang Street, Changchun 130041, Jilin Province, China. jnli@ciac.ac.cn

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

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

Received: April 29, 2021
Peer-review started: April 29, 2021
First decision: June 5, 2021
Revised: August 15, 2021
Accepted: September 8, 2021
Article in press: September 8, 2021
Published online: December 15, 2021

P-Reviewer: Kida YS, Saleh F
S-Editor: Yan JP
L-Editor: Wang TQ
P-Editor: Guo X

Core Tip: Mesenchymal stem cells (MSCs) have shown potential for anti-cancer therapy. As an important content of MSCs, MSC-derived exosomes are attracting more and more researchers for anti-cancer studies. We herein summarize the effect of MSC-derived exosomes on gastrointestinal malignancies and discuss their therapeutic potential.

Citation: Zhao LX, Zhang K, Shen BB, Li JN. Mesenchymal stem cell-derived exosomes for gastrointestinal cancer. *World J Gastrointest Oncol* 2021; 13(12): 1981-1996
URL: https://www.wjgnet.com/1948-5204/full/v13/i12/1981.htm
DOI: https://dx.doi.org/10.4251/wjgo.v13.i12.1981

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 multipotentiality 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[28]. 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-1587 to recipient glioma stem-like cells, increasing the proliferation and aggressiveness of glioblastoma through down-regulating the expression of the tumor-suppressor NCOR1[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	NA	[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	Promoting tumor development	Increasing the expression of miR-214, miR-221, and miR-222	[66]
	mBMSCs	MFC	Promoting tumor development	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 and increasing tumor chemosensitivity	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 angiogenetic activity, metastasis, and invasiveness	[96]
	AMSCs	Animal model	Inhibiting tumor development	Upregulating 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	Downregulating 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	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	Upregulating 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]

	116; SW-480	development		
BMSCs	SW-1116; Caco-2	Inhibiting tumor development and promoting CSCs phenotype	Secreting miR-142-3p to decrease the expression of Numb. (1) Increasing the expression of Notch target genes; and (2) Secreting miR-142-3p to target CD133 and Lgr5	[126] [127]
hUCMSCs	HT-29; DLD-1	Inhibiting tumor development	(1) Downregulating the expression of Integrin alpha6 (ITGA6); and (2) Inhibiting the activity of transforming growth factor-beta1 (TGF-β1) signaling pathway	[128]
mBMSCs	C-26; MCF-7	Inhibiting tumor development	Loading doxorubicin (DOX) to tumor cells	[132]

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 barrow-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 (a-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 vivo*. 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, ex deter 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*[93]. 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 angiogenetic 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 tumorous 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 exosomic 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*[127].

Li *et al*[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-β1) signaling pathway. Previous studies have indicated that overexpression of ITGA6 could trigger CRC progression and migration *via* upregulating transforming growth factor-beta1 (TGF-β1)[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[131]. Therefore, Bagheri *et al*[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[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[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[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[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[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 crosstalk with tumor cells through different mechanisms and exert different effects on tumor development; and (3) the experimental methods and models are different. The *in vitro* and *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[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[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 di□erent 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 cancer development is needed, which will help to develop more promising treatment methods for GI cancer.

REFERENCES

1 **Arnold M**, Abnet CC, Neale RE, Vignat J, Giovannucci EL, McGlynn KA, Bray F. Global Burden of 5 Major Types of Gastrointestinal Cancer. *Gastroenterology* 2020; **159**: 335-349.e15 [PMID: 32247694 DOI: 10.1053/j.gastro.2020.02.068]

2 **Ferlay J**, Colombet M, Soerjomataram I, Parkin DM, Piñeros M, Znaor A, Bray F. Cancer statistics for the year 2020: An overview. *Int J Cancer* 2021 [PMID: 33818764 DOI: 10.1002/ijc.33588]

3 **Ramai D**, Heaton J, Ghidini M, Chandan S, Barakat M, Dhindsa B, Dhaliwal A, Facciorusso A. Population-Based Long-term Cardiac-Specific Mortality Among Patients With Major Gastrointestinal Cancers. *JAMA Netw Open* 2021; **4**: e2112049 [PMID: 34137831 DOI: 10.1001/jamanetworkopen.2021.12049]

4 **Rao D**, Parakrama R, Augustine T, Liu Q, Goel S, Maitra R. Immunotherapeutic advances in gastrointestinal malignancies. *NPJ Precis Oncol* 2019; **3**: 4 [PMID: 30729176 DOI: 10.1038/s41698-018-0076-8]

5 **Gottumukkala S**, Tumati V, Hrycushko B, Folkert M. Endoluminal and Interstitial Brachytherapy for the Treatment of Gastrointestinal Malignancies: a Systematic Review. *Curr Oncol Rep* 2017; **19**: 2 [PMID: 28110462 DOI: 10.1007/s11912-017-0561-1]

6 **Li JN**, Li W, Cao LQ, Liu N, Zhang K. Efficacy of mesenchymal stem cells in the treatment of gastrointestinal malignancies. *World J Gastrointest Oncol* 2020; **12**: 365-382 [PMID: 32368316 DOI: 10.4251/wjgo.v12.i4.365]

7 **Siegel RL**, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin* 2019; **69**: 7-34 [PMID: 30620402 DOI: 10.3322/caac.21551]

8 **Harmsen S**, Rogalla S, Huang R, Spaliviero M, Neuschmelting V, Hayakawa Y, Lee Y, Tailor Y, Toledo-Crow R, Kang JW, Samii JM, Karabeber H, Davis RM, White JR, van de Rijn M, Gambhir SS, Contag CH, Wang TC, Kircher MF. Detection of Premalignant Gastrointestinal Lesions Using Surface-Enhanced Resonance Raman Scattering-Nanoparticle Endoscopy. *ACS Nano* 2019; **13**: 1354-1364 [PMID: 30624916 DOI: 10.1021/acsnano.8b06808]

9 **Baksh D**, Song L, Tuan RS. Adult mesenchymal stem cells: characterization, differentiation, and application in cell and gene therapy. *J Cell Mol Med* 2004; **8**: 301-316 [PMID: 15491506 DOI: 10.1111/j.1582-4934.2004.tb00320.x]

10 **Kolf CM**, Cho E, Tuan RS. Mesenchymal stromal cells. Biology of adult mesenchymal stem cells: regulation of niche, self-renewal and differentiation. *Arthritis Res Ther* 2007; **9**: 204 [PMID: 17316462 DOI: 10.1186/ar2116]

11 **Ho IA**, Toh HC, Ng WH, Teo YL, Guo CM, Hui KM, Lam PY. Human bone marrow-derived mesenchymal stem cells suppress human glioma growth through inhibition of angiogenesis. *Stem Cells* 2013; **31**: 146-155 [PMID: 23034897 DOI: 10.1002/stem.1247]

12 **Kidd S**, Spaeth E, Dembinski JL, Dietrich M, Watson K, Klopp A, Battula VL, Weil M, Andreeff

M, Marini FC. Direct evidence of mesenchymal stem cell tropism for tumor and wounding microenvironments using in vivo bioluminescent imaging. *Stem Cells* 2009; **27**: 2614-2623 [PMID: 19650040 DOI: 10.1002/stem.187]

13 **Ji R**, Zhang B, Zhang X, Xue J, Yuan X, Yan Y, Wang M, Zhu W, Qian H, Xu W. Exosomes derived from human mesenchymal stem cells confer drug resistance in gastric cancer. *Cell Cycle* 2015; **14**: 2473-2483 [PMID: 26091251 DOI: 10.1080/15384101.2015.1005530]

14 **Ridge SM**, Sullivan FJ, Glynn SA. Mesenchymal stem cells: key players in cancer progression. *Mol Cancer* 2017; **16**: 31 [PMID: 28148268 DOI: 10.1186/s12943-017-0597-8]

15 **Mognetti B**, La Montagna G, Perrelli MG, Pagliaro P, Penna C. Bone marrow mesenchymal stem cells increase motility of prostate cancer cells *via* production of stromal cell-derived factor-1α. *J Cell Mol Med* 2013; **17**: 287-292 [PMID: 23301946 DOI: 10.1111/jcmm.12010]

16 **Quante M**, Tu SP, Tomita H, Gonda T, Wang SS, Takashi S, Baik GH, Shibata W, Diprete B, Betz KS, Friedman R, Varro A, Tycko B, Wang TC. Bone marrow-derived myofibroblasts contribute to the mesenchymal stem cell niche and promote tumor growth. *Cancer Cell* 2011; **19**: 257-272 [PMID: 21316604 DOI: 10.1016/j.ccr.2011.01.020]

17 **Djouad F**, Plence P, Bony C, Tropel P, Apparailly F, Sany J, Noël D, Jorgensen C. Immunosuppressive effect of mesenchymal stem cells favors tumor growth in allogeneic animals. *Blood* 2003; **102**: 3837-3844 [PMID: 12881305 DOI: 10.1182/blood-2003-04-1193]

18 **Zhu Y**, Sun Z, Han Q, Liao L, Wang J, Bian C, Li J, Yan X, Liu Y, Shao C, Zhao RC. Human mesenchymal stem cells inhibit cancer cell proliferation by secreting DKK-1. *Leukemia* 2009; **23**: 925-933 [PMID: 19148141 DOI: 10.1038/leu.2008.384]

19 **Lu YR**, Yuan Y, Wang XJ, Wei LL, Chen YN, Cong C, Li SF, Long D, Tan WD, Mao YQ, Zhang J, Li YP, Cheng JQ. The growth inhibitory effect of mesenchymal stem cells on tumor cells in vitro and in vivo. *Cancer Biol Ther* 2008; **7**: 245-251 [PMID: 18059192 DOI: 10.4161/cbt.7.2.5296]

20 **Keshtkar S**, Azarpira N, Ghahremani MH. Mesenchymal stem cell-derived extracellular vesicles: novel frontiers in regenerative medicine. *Stem Cell Res Ther* 2018; **9**: 63 [PMID: 29523213 DOI: 10.1186/s13287-018-0791-7]

21 **Zhou J**, Tan X, Tan Y, Li Q, Ma J, Wang G. Mesenchymal Stem Cell Derived Exosomes in Cancer Progression, Metastasis and Drug Delivery: A Comprehensive Review. *J Cancer* 2018; **9**: 3129-3137 [PMID: 30210636 DOI: 10.7150/jca.25376]

22 **Sun F**, Wang JZ, Luo JJ, Wang YQ, Pan Q. Exosomes in the Oncobiology, Diagnosis, and Therapy of Hepatic Carcinoma: A New Player of an Old Game. *Biomed Res Int* 2018; **2018**: 2747461 [PMID: 30148162 DOI: 10.1155/2018/2747461]

23 **Zhang X**, Yang Y, Chen H, Tu H, Li J. Exosomes from Bone Marrow Microenvironment-Derived Mesenchymal Stem Cells Affect CML Cells Growth and Promote Drug Resistance to Tyrosine Kinase Inhibitors. *Stem Cells Int* 2020; **2020**: 8890201 [PMID: 33414831 DOI: 10.1155/2020/8890201]

24 **Lee JR**, Park BW, Kim J, Choo YW, Kim HY, Yoon JK, Kim H, Hwang JW, Kang M, Kwon SP, Song SY, Ko IO, Park JA, Ban K, Hyeon T, Park HJ, Kim BS. Nanovesicles derived from iron oxide nanoparticles-incorporated mesenchymal stem cells for cardiac repair. *Sci Adv* 2020; **6**: eaaz0952 [PMID: 32494669 DOI: 10.1126/sciadv.aaz0952]

25 **Zagrean AM**, Hermann DM, Opris I, Zagrean L, Popa-Wagner A. Multicellular Crosstalk Between Exosomes and the Neurovascular Unit After Cerebral Ischemia. Therapeutic Implications. *Front Neurosci* 2018; **12**: 811 [PMID: 30459547 DOI: 10.3389/fnins.2018.00811]

26 **Wang M**, Xu X, Lei X, Tan J, Xie H. Mesenchymal stem cell-based therapy for burn wound healing. *Burns Trauma* 2021; **9**: tkab002 [PMID: 34212055 DOI: 10.1093/burnst/tkab002]

27 **Kim S**, Kim TM. Generation of mesenchymal stem-like cells for producing extracellular vesicles. *World J Stem Cells* 2019; **11**: 270-280 [PMID: 31171955 DOI: 10.4252/wjsc.v11.i5.270]

28 **Dalirfardouei R**, Jamialahmadi K, Jafarian AH, Mahdipour E. Promising effects of exosomes isolated from menstrual blood-derived mesenchymal stem cell on wound-healing process in diabetic mouse model. *J Tissue Eng Regen Med* 2019; **13**: 555-568 [PMID: 30656863 DOI: 10.1002/term.2799]

29 **Stanko P**, Altanerova U, Jakubechova J, Repiska V, Altaner C. Dental Mesenchymal Stem/Stromal Cells and Their Exosomes. *Stem Cells Int* 2018; **2018**: 8973613 [PMID: 29760738 DOI: 10.1155/2018/8973613]

30 **Fitzsimmons REB**, Mazurek MS, Soos A, Simmons CA. Mesenchymal Stromal/Stem Cells in Regenerative Medicine and Tissue Engineering. *Stem Cells Int* 2018; **2018**: 8031718 [PMID: 30210552 DOI: 10.1155/2018/8031718]

31 **Trounson A**, McDonald C. Stem Cell Therapies in Clinical Trials: Progress and Challenges. *Cell Stem Cell* 2015; **17**: 11-22 [PMID: 26140604 DOI: 10.1016/j.stem.2015.06.007]

32 **Fischer UM**, Harting MT, Jimenez F, Monzon-Posadas WO, Xue H, Savitz SI, Laine GA, Cox CS Jr. Pulmonary passage is a major obstacle for intravenous stem cell delivery: the pulmonary first-pass effect. *Stem Cells Dev* 2009; **18**: 683-692 [PMID: 19099374 DOI: 10.1089/scd.2008.0253]

33 **Cai J**, Wu J, Wang J, Li Y, Hu X, Luo S, Xiang D. Extracellular vesicles derived from different sources of mesenchymal stem cells: therapeutic effects and translational potential. *Cell Biosci* 2020; **10**: 69 [PMID: 32483483 DOI: 10.1186/s13578-020-00427-x]

34 **Huang Y**, Liu K, Li Q, Yao Y, Wang Y. Exosomes Function in Tumor Immune Microenvironment. *Adv Exp Med Biol* 2018; **1056**: 109-122 [PMID: 29754177 DOI: 10.1007/978-3-319-74470-4_7]

35 **van Niel G**, D'Angelo G, Raposo G. Shedding light on the cell biology of extracellular vesicles. *Nat*

Rev Mol Cell Biol 2018; **19**: 213-228 [PMID: 29339798 DOI: 10.1038/nrm.2017.125]
36 **Phinney DG**, Pittenger MF. Concise Review: MSC-Derived Exosomes for Cell-Free Therapy. *Stem Cells* 2017; **35**: 851-858 [PMID: 28294454 DOI: 10.1002/stem.2575]
37 **Li X**, Li C, Zhang L, Wu M, Cao K, Jiang F, Chen D, Li N, Li W. The significance of exosomes in the development and treatment of hepatocellular carcinoma. *Mol Cancer* 2020; **19**: 1 [PMID: 31901224 DOI: 10.1186/s12943-019-1085-0]
38 **Record M**, Carayon K, Poirot M, Silvente-Poirot S. Exosomes as new vesicular lipid transporters involved in cell-cell communication and various pathophysiologies. *Biochim Biophys Acta* 2014; **1841**: 108-120 [PMID: 24140720 DOI: 10.1016/j.bbalip.2013.10.004]
39 **Collino F**, Deregibus MC, Bruno S, Sterpone L, Aghemo G, Viltono L, Tetta C, Camussi G. Microvesicles derived from adult human bone marrow and tissue specific mesenchymal stem cells shuttle selected pattern of miRNAs. *PLoS One* 2010; **5**: e11803 [PMID: 20668554 DOI: 10.1371/journal.pone.0011803]
40 **Simons M**, Raposo G. Exosomes--vesicular carriers for intercellular communication. *Curr Opin Cell Biol* 2009; **21**: 575-581 [PMID: 19442504 DOI: 10.1016/j.ceb.2009.03.007]
41 **Sharma A**. Role of stem cell derived exosomes in tumor biology. *Int J Cancer* 2018; **142**: 1086-1092 [PMID: 28983919 DOI: 10.1002/ijc.31089]
42 **Brinton LT**, Sloane HS, Kester M, Kelly KA. Formation and role of exosomes in cancer. *Cell Mol Life Sci* 2015; **72**: 659-671 [PMID: 25336151 DOI: 10.1007/s00018-014-1764-3]
43 **Yang Y**, Bucan V, Baehre H, von der Ohe J, Otte A, Hass R. Acquisition of new tumor cell properties by MSC-derived exosomes. *Int J Oncol* 2015; **47**: 244-252 [PMID: 25963929 DOI: 10.3892/ijo.2015.3001]
44 **Vallabhaneni KC**, Penfornis P, Dhule S, Guillonneau F, Adams KV, Mo YY, Xu R, Liu Y, Watabe K, Vemuri MC, Pochampally R. Extracellular vesicles from bone marrow mesenchymal stem/stromal cells transport tumor regulatory microRNA, proteins, and metabolites. *Oncotarget* 2015; **6**: 4953-4967 [PMID: 25669974 DOI: 10.18632/oncotarget.3211]
45 **Lee JK**, Park SR, Jung BK, Jeon YK, Lee YS, Kim MK, Kim YG, Jang JY, Kim CW. Exosomes derived from mesenchymal stem cells suppress angiogenesis by down-regulating VEGF expression in breast cancer cells. *PLoS One* 2013; **8**: e84256 [PMID: 24391924 DOI: 10.1371/journal.pone.0084256]
46 **Luan X**, Sansanaphongpricha K, Myers I, Chen H, Yuan H, Sun D. Engineering exosomes as refined biological nanoplatforms for drug delivery. *Acta Pharmacol Sin* 2017; **38**: 754-763 [PMID: 28392567 DOI: 10.1038/aps.2017.12]
47 **Pascucci L**, Coccè V, Bonomi A, Ami D, Ceccarelli P, Ciusani E, Viganò L, Locatelli A, Sisto F, Doglia SM, Parati E, Bernardo ME, Muraca M, Alessandri G, Bondiolotti G, Pessina A. Paclitaxel is incorporated by mesenchymal stromal cells and released in exosomes that inhibit in vitro tumor growth: a new approach for drug delivery. *J Control Release* 2014; **192**: 262-270 [PMID: 25084218 DOI: 10.1016/j.jconrel.2014.07.042]
48 **Figueroa J**, Phillips LM, Shahar T, Hossain A, Gumin J, Kim H, Bean AJ, Calin GA, Fueyo J, Walters ET, Kalluri R, Verhaak RG, Lang FF. Exosomes from Glioma-Associated Mesenchymal Stem Cells Increase the Tumorigenicity of Glioma Stem-like Cells *via* Transfer of miR-1587. *Cancer Res* 2017; **77**: 5808-5819 [PMID: 28855213 DOI: 10.1158/0008-5472.CAN-16-2524]
49 **Munoz JL**, Bliss SA, Greco SJ, Ramkissoon SH, Ligon KL, Rameshwar P. Delivery of Functional Anti-miR-9 by Mesenchymal Stem Cell-derived Exosomes to Glioblastoma Multiforme Cells Conferred Chemosensitivity. *Mol Ther Nucleic Acids* 2013; **2**: e126 [PMID: 24084846 DOI: 10.1038/mtna.2013.60]
50 **Taylor DD**, Gercel-Taylor C. Exosomes/microvesicles: mediators of cancer-associated immunosuppressive microenvironments. *Semin Immunopathol* 2011; **33**: 441-454 [PMID: 21688197 DOI: 10.1007/s00281-010-0234-8]
51 **Smyth EC**, Nilsson M, Grabsch HI, van Grieken NC, Lordick F. Gastric cancer. *Lancet* 2020; **396**: 635-648 [PMID: 32861308 DOI: 10.1016/S0140-6736(20)31288-5]
52 **Machlowska J**, Baj J, Sitarz M, Maciejewski R, Sitarz R. Gastric Cancer: Epidemiology, Risk Factors, Classification, Genomic Characteristics and Treatment Strategies. *Int J Mol Sci* 2020; **21** [PMID: 32512697 DOI: 10.3390/ijms21114012]
53 **Lee JH**, Chang KK, Yoon C, Tang LH, Strong VE, Yoon SS. Lauren Histologic Type Is the Most Important Factor Associated With Pattern of Recurrence Following Resection of Gastric Adenocarcinoma. *Ann Surg* 2018; **267**: 105-113 [PMID: 27759618 DOI: 10.1097/SLA.0000000000002040]
54 **Guan J**, Chen J. Mesenchymal stem cells in the tumor microenvironment. *Biomed Rep* 2013; **1**: 517-521 [PMID: 24648978 DOI: 10.3892/br.2013.103]
55 **Zhu W**, Huang L, Li Y, Zhang X, Gu J, Yan Y, Xu X, Wang M, Qian H, Xu W. Exosomes derived from human bone marrow mesenchymal stem cells promote tumor growth in vivo. *Cancer Lett* 2012; **315**: 28-37 [PMID: 22055459 DOI: 10.1016/j.canlet.2011.10.002]
56 **Hood JL**, Pan H, Lanza GM, Wickline SA; Consortium for Translational Research in Advanced Imaging and Nanomedicine (C-TRAIN). Paracrine induction of endothelium by tumor exosomes. *Lab Invest* 2009; **89**: 1317-1328 [PMID: 19786948 DOI: 10.1038/labinvest.2009.94]
57 **Yoshino Y**, Aoyagi M, Tamaki M, Duan L, Morimoto T, Ohno K. Activation of p38 MAPK and/or JNK contributes to increased levels of VEGF secretion in human malignant glioma cells. *Int J Oncol* 2006; **29**: 981-987 [PMID: 16964394 DOI: 10.3892/ijo.29.4.981]

58 **Walczak C**, Gaignier F, Gilet A, Zou F, Thornton SN, Ropars A. Aldosterone increases VEGF-A production in human neutrophils through PI3K, ERK1/2 and p38 pathways. *Biochim Biophys Acta* 2011; **1813**: 2125-2132 [PMID: 21803079 DOI: 10.1016/j.bbamcr.2011.07.010]

59 **Essafi-Benkhadir K**, Pouysségur J, Pagès G. Implication of the ERK pathway on the post-transcriptional regulation of VEGF mRNA stability. *Methods Mol Biol* 2010; **661**: 451-469 [PMID: 20812001 DOI: 10.1007/978-1-60761-795-2_28]

60 **Zhu W**, Huang L, Li Y, Qian H, Shan X, Yan Y, Mao F, Wu X, Xu WR. Mesenchymal stem cell-secreted soluble signaling molecules potentiate tumor growth. *Cell Cycle* 2011; **10**: 3198-3207 [PMID: 21900753 DOI: 10.4161/cc.10.18.17638]

61 **Gu H**, Ji R, Zhang X, Wang M, Zhu W, Qian H, Chen Y, Jiang P, Xu W. Exosomes derived from human mesenchymal stem cells promote gastric cancer cell growth and migration *via* the activation of the Akt pathway. *Mol Med Rep* 2016; **14**: 3452-3458 [PMID: 27513187 DOI: 10.3892/mmr.2016.5625]

62 **Tsai JH**, Yang J. Epithelial-mesenchymal plasticity in carcinoma metastasis. *Genes Dev* 2013; **27**: 2192-2206 [PMID: 24142872 DOI: 10.1101/gad.225334.113]

63 **Savagner P**. The epithelial-mesenchymal transition (EMT) phenomenon. *Ann Oncol* 2010; **21** Suppl 7: vii89-vii92 [PMID: 20943648 DOI: 10.1093/annonc/mdq292]

64 **Qi J**, Zhou Y, Jiao Z, Wang X, Zhao Y, Li Y, Chen H, Yang L, Zhu H. Exosomes Derived from Human Bone Marrow Mesenchymal Stem Cells Promote Tumor Growth Through Hedgehog Signaling Pathway. *Cell Physiol Biochem* 2017; **42**: 2242-2254 [PMID: 28817816 DOI: 10.1159/000479998]

65 **Ma M**, Chen S, Liu Z, Xie H, Deng H, Shang S, Wang X, Xia M, Zuo C. miRNA-221 of exosomes originating from bone marrow mesenchymal stem cells promotes oncogenic activity in gastric cancer. *Onco Targets Ther* 2017; **10**: 4161-4171 [PMID: 28860826 DOI: 10.2147/OTT.S143315]

66 **Wang M**, Zhao C, Shi H, Zhang B, Zhang L, Zhang X, Wang S, Wu X, Yang T, Huang F, Cai J, Zhu Q, Zhu W, Qian H, Xu W. Deregulated microRNAs in gastric cancer tissue-derived mesenchymal stem cells: novel biomarkers and a mechanism for gastric cancer. *Br J Cancer* 2014; **110**: 1199-1210 [PMID: 24473397 DOI: 10.1038/bjc.2014.14]

67 **Ueda T**, Volinia S, Okumura H, Shimizu M, Taccioli C, Rossi S, Alder H, Liu CG, Oue N, Yasui W, Yoshida K, Sasaki H, Nomura S, Seto Y, Kaminishi M, Calin GA, Croce CM. Relation between microRNA expression and progression and prognosis of gastric cancer: a microRNA expression analysis. *Lancet Oncol* 2010; **11**: 136-146 [PMID: 20022810 DOI: 10.1016/S1470-2045(09)70343-2]

68 **Liu K**, Li G, Fan C, Diao Y, Wu B, Li J. Increased Expression of MicroRNA-221 in gastric cancer and its clinical significance. *J Int Med Res* 2012; **40**: 467-474 [PMID: 22613407 DOI: 10.1177/147323001204000208]

69 **Mao J**, Liang Z, Zhang B, Yang H, Li X, Fu H, Zhang X, Yan Y, Xu W, Qian H. UBR2 Enriched in p53 Deficient Mouse Bone Marrow Mesenchymal Stem Cell-Exosome Promoted Gastric Cancer Progression *via* Wnt/β-Catenin Pathway. *Stem Cells* 2017; **35**: 2267-2279 [PMID: 28895255 DOI: 10.1002/stem.2702]

70 **Mao J**, Fan S, Ma W, Fan P, Wang B, Zhang J, Wang H, Tang B, Zhang Q, Yu X, Wang L, Song B, Li L. Roles of Wnt/β-catenin signaling in the gastric cancer stem cells proliferation and salinomycin treatment. *Cell Death Dis* 2014; **5**: e1039 [PMID: 24481453 DOI: 10.1038/cddis.2013.515]

71 **Sung H**, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021; **71**: 209-249 [PMID: 33538338 DOI: 10.3322/caac.21660]

72 **Llovet JM**, Kelley RK, Villanueva A, Singal AG, Pikarsky E, Roayaie S, Lencioni R, Koike K, Zucman-Rossi J, Finn RS. Hepatocellular carcinoma. *Nat Rev Dis Primers* 2021; **7**: 6 [PMID: 33479224 DOI: 10.1038/s41572-020-00240-3]

73 **Jemal A**, Ward EM, Johnson CJ, Cronin KA, Ma J, Ryerson B, Mariotto A, Lake AJ, Wilson R, Sherman RL, Anderson RN, Henley SJ, Kohler BA, Penberthy L, Feuer EJ, Weir HK. Annual Report to the Nation on the Status of Cancer, 1975-2014, Featuring Survival. *J Natl Cancer Inst* 2017; **109** [PMID: 28376154 DOI: 10.1093/jnci/djx030]

74 **Villanueva A**. Hepatocellular Carcinoma. *N Engl J Med* 2019; **380**: 1450-1462 [PMID: 30970190 DOI: 10.1056/NEJMra1713263]

75 **Kim SY**, An J, Lim YS, Han S, Lee JY, Byun JH, Won HJ, Lee SJ, Lee HC, Lee YS. MRI With Liver-Specific Contrast for Surveillance of Patients With Cirrhosis at High Risk of Hepatocellular Carcinoma. *JAMA Oncol* 2017; **3**: 456-463 [PMID: 27657493 DOI: 10.1001/jamaoncol.2016.3147]

76 **Katona BW**, Weiss JM. Chemoprevention of Colorectal Cancer. *Gastroenterology* 2020; **158**: 368-388 [PMID: 31563626 DOI: 10.1053/j.gastro.2019.06.047]

77 **Lohitesh K**, Chowdhury R, Mukherjee S. Resistance a major hindrance to chemotherapy in hepatocellular carcinoma: an insight. *Cancer Cell Int* 2018; **18**: 44 [PMID: 29568237 DOI: 10.1186/s12935-018-0538-7]

78 **Coulouarn C**, Factor VM, Andersen JB, Durkin ME, Thorgeirsson SS. Loss of miR-122 expression in liver cancer correlates with suppression of the hepatic phenotype and gain of metastatic properties. *Oncogene* 2009; **28**: 3526-3536 [PMID: 19617899 DOI: 10.1038/onc.2009.211]

79 **Tsai WC**, Hsu SD, Hsu CS, Lai TC, Chen SJ, Shen R, Huang Y, Chen HC, Lee CH, Tsai TF, Hsu MT, Wu JC, Huang HD, Shiao MS, Hsiao M, Tsou AP. MicroRNA-122 plays a critical role in liver homeostasis and hepatocarcinogenesis. *J Clin Invest* 2012; **122**: 2884-2897 [PMID: 22820290 DOI:

10.1172/JCI63455]
80 **Zhang H**, Chen Z, Wang X, Huang Z, He Z, Chen Y. Long non-coding RNA: a new player in cancer. *J Hematol Oncol* 2013; **6**: 37 [PMID: 23725405 DOI: 10.1186/1756-8722-6-37]
81 **Fornari F**, Gramantieri L, Giovannini C, Veronese A, Ferracin M, Sabbioni S, Calin GA, Grazi GL, Croce CM, Tavolari S, Chieco P, Negrini M, Bolondi L. MiR-122/cyclin G1 interaction modulates p53 activity and affects doxorubicin sensitivity of human hepatocarcinoma cells. *Cancer Res* 2009; **69**: 5761-5767 [PMID: 19584283 DOI: 10.1158/0008-5472.CAN-08-4797]
82 **Bai S**, Nasser MW, Wang B, Hsu SH, Datta J, Kutay H, Yadav A, Nuovo G, Kumar P, Ghoshal K. MicroRNA-122 inhibits tumorigenic properties of hepatocellular carcinoma cells and sensitizes these cells to sorafenib. *J Biol Chem* 2009; **284**: 32015-32027 [PMID: 19726678 DOI: 10.1074/jbc.M109.016774]
83 **Lou G**, Song X, Yang F, Wu S, Wang J, Chen Z, Liu Y. Exosomes derived from miR-122-modified adipose tissue-derived MSCs increase chemosensitivity of hepatocellular carcinoma. *J Hematol Oncol* 2015; **8**: 122 [PMID: 26514126 DOI: 10.1186/s13045-015-0220-7]
84 **Ren K**, Li T, Zhang W, Ren J, Li Z, Wu G. miR-199a-3p inhibits cell proliferation and induces apoptosis by targeting YAP1, suppressing Jagged1-Notch signaling in human hepatocellular carcinoma. *J Biomed Sci* 2016; **23**: 79 [PMID: 27832779 DOI: 10.1186/s12929-016-0295-7]
85 **Kim JH**, Badawi M, Park JK, Jiang J, Mo X, Roberts LR, Schmittgen TD. Anti-invasion and anti-migration effects of miR-199a-3p in hepatocellular carcinoma are due in part to targeting CD151. *Int J Oncol* 2016; **49**: 2037-2045 [PMID: 27599545 DOI: 10.3892/ijo.2016.3677]
86 **Fornari F**, Milazzo M, Chieco P, Negrini M, Calin GA, Grazi GL, Pollutri D, Croce CM, Bolondi L, Gramantieri L. MiR-199a-3p regulates mTOR and c-Met to influence the doxorubicin sensitivity of human hepatocarcinoma cells. *Cancer Res* 2010; **70**: 5184-5193 [PMID: 20501828 DOI: 10.1158/0008-5472.CAN-10-0145]
87 **Lou G**, Chen L, Xia C, Wang W, Qi J, Li A, Zhao L, Chen Z, Zheng M, Liu Y. MiR-199a-modified exosomes from adipose tissue-derived mesenchymal stem cells improve hepatocellular carcinoma chemosensitivity through mTOR pathway. *J Exp Clin Cancer Res* 2020; **39**: 4 [PMID: 31898515 DOI: 10.1186/s13046-019-1512-5]
88 **Hu G**, Drescher KM, Chen XM. Exosomal miRNAs: Biological Properties and Therapeutic Potential. *Front Genet* 2012; **3**: 56 [PMID: 22529849 DOI: 10.3389/fgene.2012.00056]
89 **Ha D**, Yang N, Nadithe V. Exosomes as therapeutic drug carriers and delivery vehicles across biological membranes: current perspectives and future challenges. *Acta Pharm Sin B* 2016; **6**: 287-296 [PMID: 27471669 DOI: 10.1016/j.apsb.2016.02.001]
90 **Yeo RW**, Lai RC, Zhang B, Tan SS, Yin Y, Teh BJ, Lim SK. Mesenchymal stem cell: an efficient mass producer of exosomes for drug delivery. *Adv Drug Deliv Rev* 2013; **65**: 336-341 [PMID: 22780955 DOI: 10.1016/j.addr.2012.07.001]
91 **Akyurekli C**, Le Y, Richardson RB, Fergusson D, Tay J, Allan DS. A systematic review of preclinical studies on the therapeutic potential of mesenchymal stromal cell-derived microvesicles. *Stem Cell Rev Rep* 2015; **11**: 150-160 [PMID: 25091427 DOI: 10.1007/s12015-014-9545-9]
92 **Roccaro AM**, Sacco A, Maiso P, Azab AK, Tai YT, Reagan M, Azab F, Flores LM, Campigotto F, Weller E, Anderson KC, Scadden DT, Ghobrial IM. BM mesenchymal stromal cell-derived exosomes facilitate multiple myeloma progression. *J Clin Invest* 2013; **123**: 1542-1555 [PMID: 23454749 DOI: 10.1172/JCI66517]
93 **Bruno S**, Collino F, Deregibus MC, Grange C, Tetta C, Camussi G. Microvesicles derived from human bone marrow mesenchymal stem cells inhibit tumor growth. *Stem Cells Dev* 2013; **22**: 758-771 [PMID: 23034046 DOI: 10.1089/scd.2012.0304]
94 **Wu S**, Ju GQ, Du T, Zhu YJ, Liu GH. Microvesicles derived from human umbilical cord Wharton's jelly mesenchymal stem cells attenuate bladder tumor cell growth in vitro and in vivo. *PLoS One* 2013; **8**: e61366 [PMID: 23593475 DOI: 10.1371/journal.pone.0061366]
95 **Ko SF**, Yip HK, Zhen YY, Lee CC, Huang CC, Ng SH, Lin JW. Adipose-Derived Mesenchymal Stem Cell Exosomes Suppress Hepatocellular Carcinoma Growth in a Rat Model: Apparent Diffusion Coefficient, Natural Killer T-Cell Responses, and Histopathological Features. *Stem Cells Int* 2015; **2015**: 853506 [PMID: 26345219 DOI: 10.1155/2015/853506]
96 **Alzahrani FA**, El-Magd MA, Abdelfattah-Hassan A, Saleh AA, Saadeldin IM, El-Shetry ES, Badawy AA, Alkarim S. Potential Effect of Exosomes Derived from Cancer Stem Cells and MSCs on Progression of DEN-Induced HCC in Rats. *Stem Cells Int* 2018; **2018**: 8058979 [PMID: 30224923 DOI: 10.1155/2018/8058979]
97 **Tan CY**, Lai RC, Wong W, Dan YY, Lim SK, Ho HK. Mesenchymal stem cell-derived exosomes promote hepatic regeneration in drug-induced liver injury models. *Stem Cell Res Ther* 2014; **5**: 76 [PMID: 24915963 DOI: 10.1186/scrt465]
98 **Li T**, Yan Y, Wang B, Qian H, Zhang X, Shen L, Wang M, Zhou Y, Zhu W, Li W, Xu W. Exosomes derived from human umbilical cord mesenchymal stem cells alleviate liver fibrosis. *Stem Cells Dev* 2013; **22**: 845-854 [PMID: 23002959 DOI: 10.1089/scd.2012.0395]
99 **Korashy HM**, El Gendy MA, Alhaider AA, El-Kadi AO. Camel milk modulates the expression of aryl hydrocarbon receptor-regulated genes, Cyp1a1, Nqo1, and Gsta1, in murine hepatoma Hepa 1c1c7 cells. *J Biomed Biotechnol* 2012; **2012**: 782642 [PMID: 22570534 DOI: 10.1155/2012/782642]
100 **Zhou Y**, Zhou W, Chen X, Wang Q, Li C, Chen Q, Zhang Y, Lu Y, Ding X, Jiang C. Bone marrow mesenchymal stem cells-derived exosomes for penetrating and targeted chemotherapy of pancreatic

cancer. *Acta Pharm Sin B* 2020; **10**: 1563-1575 [PMID: 32963950 DOI: 10.1016/j.apsb.2019.11.013]

101 **Guler GD**, Ning Y, Ku CJ, Phillips T, McCarthy E, Ellison CK, Bergamaschi A, Collin F, Lloyd P, Scott A, Antoine M, Wang W, Chau K, Ashworth A, Quake SR, Levy S. Detection of early stage pancreatic cancer using 5-hydroxymethylcytosine signatures in circulating cell free DNA. *Nat Commun* 2020; **11**: 5270 [PMID: 33077732 DOI: 10.1038/s41467-020-18965-w]

102 **Lunardi S**, Muschel RJ, Brunner TB. The stromal compartments in pancreatic cancer: are there any therapeutic targets? *Cancer Lett* 2014; **343**: 147-155 [PMID: 24141189 DOI: 10.1016/j.canlet.2013.09.039]

103 **Samulitis BK**, Pond KW, Pond E, Cress AE, Patel H, Wisner L, Patel C, Dorr RT, Landowski TH. Gemcitabine resistant pancreatic cancer cell lines acquire an invasive phenotype with collateral hypersensitivity to histone deacetylase inhibitors. *Cancer Biol Ther* 2015; **16**: 43-51 [PMID: 25485960 DOI: 10.4161/15384047.2014.986967]

104 **Kabashima-Niibe A**, Higuchi H, Takaishi H, Masugi Y, Matsuzaki Y, Mabuchi Y, Funakoshi S, Adachi M, Hamamoto Y, Kawachi S, Aiura K, Kitagawa Y, Sakamoto M, Hibi T. Mesenchymal stem cells regulate epithelial-mesenchymal transition and tumor progression of pancreatic cancer cells. *Cancer Sci* 2013; **104**: 157-164 [PMID: 23121112 DOI: 10.1111/cas.12059]

105 **Kamerkar S**, LeBleu VS, Sugimoto H, Yang S, Ruivo CF, Melo SA, Lee JJ, Kalluri R. Exosomes facilitate therapeutic targeting of oncogenic KRAS in pancreatic cancer. *Nature* 2017; **546**: 498-503 [PMID: 28607485 DOI: 10.1038/nature22341]

106 **Zhou W**, Zhou Y, Chen X, Ning T, Chen H, Guo Q, Zhang Y, Liu P, Li C, Chu Y, Sun T, Jiang C. Pancreatic cancer-targeting exosomes for enhancing immunotherapy and reprogramming tumor microenvironment. *Biomaterials* 2021; **268**: 120546 [PMID: 33253966 DOI: 10.1016/j.biomaterials.2020.120546]

107 **Shang S**, Wang J, Chen S, Tian R, Zeng H, Wang L, Xia M, Zhu H, Zuo C. Exosomal miRNA-1231 derived from bone marrow mesenchymal stem cells inhibits the activity of pancreatic cancer. *Cancer Med* 2019; **8**: 7728-7740 [PMID: 31642612 DOI: 10.1002/cam4.2633]

108 **Wu DM**, Wen X, Han XR, Wang S, Wang YJ, Shen M, Fan SH, Zhang ZF, Shan Q, Li MQ, Hu B, Lu J, Chen GQ, Zheng YL. Bone Marrow Mesenchymal Stem Cell-Derived Exosomal MicroRNA-126-3p Inhibits Pancreatic Cancer Development by Targeting ADAM9. *Mol Ther Nucleic Acids* 2019; **16**: 229-245 [PMID: 30925451 DOI: 10.1016/j.omtn.2019.02.022]

109 **Xu Y**, Liu N, Wei Y, Zhou D, Lin R, Wang X, Shi B. Anticancer effects of miR-124 delivered by BM-MSC derived exosomes on cell proliferation, epithelial mesenchymal transition, and chemotherapy sensitivity of pancreatic cancer cells. *Aging (Albany NY)* 2020; **12**: 19660-19676 [PMID: 33040049 DOI: 10.18632/aging.103997]

110 **Neo WH**, Yap K, Lee SH, Looi LS, Khandelia P, Neo SX, Makeyev EV, Su IH. MicroRNA miR-124 controls the choice between neuronal and astrocyte differentiation by fine-tuning Ezh2 expression. *J Biol Chem* 2014; **289**: 20788-20801 [PMID: 24878960 DOI: 10.1074/jbc.M113.525493]

111 **Liu S**, Song L, Zeng S, Zhang L. MALAT1-miR-124-RBG2 axis is involved in growth and invasion of HR-HPV-positive cervical cancer cells. *Tumour Biol* 2016; **37**: 633-640 [PMID: 26242259 DOI: 10.1007/s13277-015-3732-4]

112 **Wang Y**, Chen L, Wu Z, Wang M, Jin F, Wang N, Hu X, Liu Z, Zhang CY, Zen K, Chen J, Liang H, Zhang Y, Chen X. miR-124-3p functions as a tumor suppressor in breast cancer by targeting CBL. *BMC Cancer* 2016; **16**: 826 [PMID: 27842510 DOI: 10.1186/s12885-016-2862-4]

113 **Xiong Y**, Wang L, Li Y, Chen M, He W, Qi L. The Long Non-Coding RNA XIST Interacted with MiR-124 to Modulate Bladder Cancer Growth, Invasion and Migration by Targeting Androgen Receptor (AR). *Cell Physiol Biochem* 2017; **43**: 405-418 [PMID: 28869948 DOI: 10.1159/000480419]

114 **Wang F**, Lau JKC, Yu J. The role of natural killer cell in gastrointestinal cancer: killer or helper. *Oncogene* 2021; **40**: 717-730 [PMID: 33262461 DOI: 10.1038/s41388-020-01561-z]

115 **Edwards BK**, Ward E, Kohler BA, Eheman C, Zauber AG, Anderson RN, Jemal A, Schymura MJ, Lansdorp-Vogelaar I, Seeff LC, van Ballegooijen M, Goede SL, Ries LA. Annual report to the nation on the status of cancer, 1975-2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates. *Cancer* 2010; **116**: 544-573 [PMID: 19998273 DOI: 10.1002/cncr.24760]

116 **Tsoi KKF**, Hirai HW, Chan FCH, Griffiths S, Sung JJY. Predicted Increases in Incidence of Colorectal Cancer in Developed and Developing Regions, in Association With Ageing Populations. *Clin Gastroenterol Hepatol* 2017; **15**: 892-900.e4 [PMID: 27720911 DOI: 10.1016/j.cgh.2016.09.155]

117 **Fu X**, Xie F, Gong F, Yang Z, Lv X, Li X, Jiao H, Wang Q, Liu X, Yan L, Xiao R. Suppression of PTBP1 signaling is responsible for mesenchymal stem cell induced invasion of low malignancy cancer cells. *Biochim Biophys Acta Mol Cell Res* 2018; **1865**: 1552-1565 [PMID: 30327198 DOI: 10.1016/j.bbamcr.2018.08.002]

118 **Torre LA**, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin* 2015; **65**: 87-108 [PMID: 25651787 DOI: 10.3322/caac.21262]

119 **Kang J**, Zhang L, Luo X, Ma X, Wang G, Yang Y, Yan Y, Qian H, Zhang X, Xu W, Mao F. Systematic Exposition of Mesenchymal Stem Cell for Inflammatory Bowel Disease and Its Associated Colorectal Cancer. *Biomed Res Int* 2018; **2018**: 9652817 [PMID: 30687760 DOI:

10.1155/2018/9652817]

120 **Yang L**, Zhang Y, Cheng L, Yue D, Ma J, Zhao D, Hou X, Xiang R, Cheng P. Mesenchymal Stem Cells Engineered to Secrete Pigment Epithelium-Derived Factor Inhibit Tumor Metastasis and the Formation of Malignant Ascites in a Murine Colorectal Peritoneal Carcinomatosis Model. *Hum Gene Ther* 2016; **27**: 267-277 [PMID: 26756933 DOI: 10.1089/hum.2015.135]

121 **Tang RJ**, Shen SN, Zhao XY, Nie YZ, Xu YJ, Ren J, Lv MM, Hou YY, Wang TT. Mesenchymal stem cells-regulated Treg cells suppress colitis-associated colorectal cancer. *Stem Cell Res Ther* 2015; **6**: 71 [PMID: 25889203 DOI: 10.1186/s13287-015-0055-8]

122 **Chen Z**, He X, Chen X, Lin X, Zou Y, Wu X, Lan P. Bone marrow mesenchymal stem cells ameliorate colitis-associated tumorigenesis in mice. *Biochem Biophys Res Commun* 2014; **450**: 1402-1408 [PMID: 25010644 DOI: 10.1016/j.bbrc.2014.07.002]

123 **Feng H**, Zhao JK, Schiergens TS, Wang PX, Ou BC, Al-Sayegh R, Li ML, Lu AG, Yin S, Thasler WE. Bone marrow-derived mesenchymal stromal cells promote colorectal cancer cell death under low-dose irradiation. *Br J Cancer* 2018; **118**: 353-365 [PMID: 29384527 DOI: 10.1038/bjc.2017.415]

124 **Xu Y**, Shen L, Li F, Yang J, Wan X, Ouyang M. microRNA-16-5p-containing exosomes derived from bone marrow-derived mesenchymal stem cells inhibit proliferation, migration, and invasion, while promoting apoptosis of colorectal cancer cells by downregulating ITGA2. *J Cell Physiol* 2019; **234**: 21380-21394 [PMID: 31102273 DOI: 10.1002/jcp.28747]

125 **Chen HL**, Li JJ, Jiang F, Shi WJ, Chang GY. MicroRNA-4461 derived from bone marrow mesenchymal stem cell exosomes inhibits tumorigenesis by downregulating COPB2 expression in colorectal cancer. *Biosci Biotechnol Biochem* 2020; **84**: 338-346 [PMID: 31631786 DOI: 10.1080/09168451.2019.1677452]

126 **Li H**, Li F. Exosomes from BM-MSCs increase the population of CSCs *via* transfer of miR-142-3p. *Br J Cancer* 2018; **119**: 744-755 [PMID: 30220706 DOI: 10.1038/s41416-018-0254-z]

127 **Shen WW**, Zeng Z, Zhu WX, Fu GH. MiR-142-3p functions as a tumor suppressor by targeting CD133, ABCG2, and Lgr5 in colon cancer cells. *J Mol Med (Berl)* 2013; **91**: 989-1000 [PMID: 23619912 DOI: 10.1007/s00109-013-1037-x]

128 **Li T**, Wan Y, Su Z, Li J, Han M, Zhou C. Mesenchymal Stem Cell-Derived Exosomal microRNA-3940-5p Inhibits Colorectal Cancer Metastasis by Targeting Integrin α6. *Dig Dis Sci* 2021; **66**: 1916-1927 [PMID: 32671583 DOI: 10.1007/s10620-020-06458-1]

129 **Guo L**, Fu J, Sun S, Zhu M, Zhang L, Niu H, Chen Z, Zhang Y, Guo L, Wang S. MicroRNA-143-3p inhibits colorectal cancer metastases by targeting ITGA6 and ASAP3. *Cancer Sci* 2019; **110**: 805-816 [PMID: 30536996 DOI: 10.1111/cas.13910]

130 **Cui M**, Chang Y, Du W, Liu S, Qi J, Luo R, Luo S. Upregulation of lncRNA-ATB by Transforming Growth Factor β1 (TGF-β1) Promotes Migration and Invasion of Papillary Thyroid Carcinoma Cells. *Med Sci Monit* 2018; **24**: 5152-5158 [PMID: 30042377 DOI: 10.12659/MSM.909420]

131 **Zhang Y**, Chen Y, Lo C, Zhuang J, Angsantikul P, Zhang Q, Wei X, Zhou Z, Obonyo M, Fang RH, Gao W, Zhang L. Inhibition of Pathogen Adhesion by Bacterial Outer Membrane-Coated Nanoparticles. *Angew Chem Int Ed Engl* 2019; **58**: 11404-11408 [PMID: 31206942 DOI: 10.1002/anie.201906280]

132 **Bagheri E**, Abnous K, Farzad SA, Taghdisi SM, Ramezani M, Alibolandi M. Targeted doxorubicin-loaded mesenchymal stem cells-derived exosomes as a versatile platform for fighting against colorectal cancer. *Life Sci* 2020; **261**: 118369 [PMID: 32882265 DOI: 10.1016/j.lfs.2020.118369]

133 **Liu H**, Liang Z, Wang F, Zhou C, Zheng X, Hu T, He X, Wu X, Lan P. Exosomes from mesenchymal stromal cells reduce murine colonic inflammation *via* a macrophage-dependent mechanism. *JCI Insight* 2019; **4** [PMID: 31689240 DOI: 10.1172/jci.insight.131273]

134 **Penfornis P**, Vallabhaneni KC, Whitt J, Pochampally R. Extracellular vesicles as carriers of microRNA, proteins and lipids in tumor microenvironment. *Int J Cancer* 2016; **138**: 14-21 [PMID: 25559768 DOI: 10.1002/ijc.29417]

135 **Reiter JG**, Baretti M, Gerold JM, Makohon-Moore AP, Daud A, Iacobuzio-Donahue CA, Azad NS, Kinzler KW, Nowak MA, Vogelstein B. An analysis of genetic heterogeneity in untreated cancers. *Nat Rev Cancer* 2019; **19**: 639-650 [PMID: 31455892 DOI: 10.1038/s41568-019-0185-x]

136 **Wang L**, Zhang F, Peng W, Zhang J, Dong W, Yuan D, Wang Z, Zheng Y. Preincubation with a low-dose hydrogen peroxide enhances anti-oxidative stress ability of BMSCs. *J Orthop Surg Res* 2020; **15**: 392 [PMID: 32907609 DOI: 10.1186/s13018-020-01916-y]

137 **Kourembanas S**. Exosomes: vehicles of intercellular signaling, biomarkers, and vectors of cell therapy. *Annu Rev Physiol* 2015; **77**: 13-27 [PMID: 25293529 DOI: 10.1146/annurev-physiol-021014-071641]

138 **Kalimuthu S**, Gangadaran P, Rajendran RL, Zhu L, Oh JM, Lee HW, Gopal A, Baek SH, Jeong SY, Lee SW, Lee J, Ahn BC. A New Approach for Loading Anticancer Drugs Into Mesenchymal Stem Cell-Derived Exosome Mimetics for Cancer Therapy. *Front Pharmacol* 2018; **9**: 1116 [PMID: 30319428 DOI: 10.3389/fphar.2018.01116]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com