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Progress of mesenchymal stem cell-derived exosomes in targeted delivery of antitumor drugs

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Abstract

Mesenchymal stem cells (MSCs) are currently being used in clinical trials for the treatment of a wide range of diseases and have a wide range of applications in the fields of tissue engineering and regeneration. Exosomes are extracellular vesicles containing a variety of components such as proteins, nucleic acids and lipids, which are widely present in biological fluids and have the functions of participating in intercellular information transfer, immune response and tissue repair, and can also be used as carriers to target and deliver tumors to improve therapeutic effects. Mesenchymal stem cell-derived Exosomes (MSC-Exos), which have the advantages of low immunogenicity and high tumor homing ability, have attracted much attention in targeted drug delivery. Here, we review the current knowledge on the involvement of MSC-Exos in tumor progression and their potential as drug delivery systems in targeted therapies. It also discusses the advantages and prospects of MSC-Exos as a drug carrier and the challenges that still need to be overcome.

Keywords Mesenchymal stem cells, Exosomes, Tumor, Drug delivery, Targeted tumor therapy

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Introduction

Tumor as a consumptive disease is a serious threat to human health. The 5-year survival rate for most tumors is about 10–30%[1, 2]. Despite the increasing research on tumors, the underlying mechanisms of tumorigenesis are still poorly understood. Stem cells hold promise as a new treatment for tumor diseases [3]. MSCs are present in a wide variety of tissues and have the potential to differentiate into ectodermal, mesodermal, and endodermal lineages, contributing to tissue regeneration. MSCs may be involved in inhibiting or/and promoting tumor progression [4, 5]. MSCs may target multiple aspects of the tumor microenvironment (TME), including immune cells, endothelial cells, and fibroblasts, to regulate tumor development [6, 7]. MSCs release a variety of immunomodulatory factors (IL-4, IL-6, IL-10, and nitric oxide) that can affect tumor progression by influencing immune cell recruitment and altering the phenotype of cancer-associated fibroblasts (CAFs) [8]. In addition, MSCs carry substances that may affect growth by interfering with signaling or altering tumor drug resistance [9]. For example, MSCs carrying the LncRNA SNHG7 regulate drug resistance in pancreatic cancer cells by affecting the Notch1/Jagged1/Hes-1 signaling pathway, thereby promoting cancer cell death [10]. Furthermore, MSCs can be determined by tumor-associated mesenchymal stem cells (TA-MSCs) and transformed into a tumor-supporting phenotype to promote tumor growth [11].

Extracellular vesicles (EVs) can be categorized into three subtypes based on their origin, namely Exosomes (30–150 nm), microvesicles (200–1000 nm), and apoptotic vesicles (800–2000 nm) [12]. Exosomes are nanovesicles formed by the invagination of the plasma membrane of the cell membrane and subsequently released into the extracellular environment [13]. Exosomes contain a variety of contents (proteins, nucleic acids, and lipids) and are widely found in blood, saliva, urine, tears, cerebrospinal fluid, and other body fluids [14, 15, 16]. Exosomes are involved in a variety of cellular activities, including immune response signaling and antigen presentation [17, 18, 19]. A large number of signaling molecules (proteins, nucleic acids, proinflammatory factors, cytokines, and transcription factor receptors) are present on the membrane surface of Exosomes and can be involved in intercellular signaling through receptor-ligand interactions [20]. In addition, Exosomes are now known to have functions similar to those of parental cells and to influence disease progression by mediating reprogramming of the TME through intercellular communication [21, 22]. A growing number of studies suggest that mesenchymal stem cell-derived Exosomes (MSC-Exos) may act as paracrine mediators capable of regulating tumor cell proliferation, angiogenesis, and metastasis through the transfer of signaling molecules [23, 24]. Exosome biogenesis and uptake by target cells is shown in Fig. 1.

MSC-Exos as a type of extracellular vesicles with similar characteristics to their mother cells and lower immunogenicity, have great power in targeting tumors as vectors [25, 26, 27]. MSC-Exos have been used as drug-loaded therapies for a wide range of diseases, including tumors, neurodegenerative diseases, and immune disorders, and have made tremendous progress [28, 29]. MSC-Exos have the advantages of good biocompatibility, high stability and membrane permeability, and can even penetrate the blood-brain barrier, but challenges such as short circulating half-life, low targeted delivery efficiency, and difficulties in large-scale production and purification have limited their clinical applications [30, 31]. There are studies that artificially modifying MSC-Exos by engineering methods can improve these deficiencies to a certain extent, but the exact mechanism of how the engineered modification methods can improve the therapeutic efficacy of MSC-Exos is not clear [32]. Zhao et al. Phase I/II clinical trial using Exosomes carrying a small molecule STING agonist for the treatment of advanced solid tumors formally initiated [33]. Gomari et al. found that adriamycin delivered by MSC-Exos significantly reduced tumor growth in a mouse breast cancer model [34]. These results suggest that MSC-Exos may have a promising future in tumor therapy as a promising drug delivery system for tumors.

Roles of MSC-Exos in cancer

The tumor microenvironment consists of different cell types, such as fibroblasts, immune cells, and endothelial cells. This microenvironment-tumor crosstalk appears to be critical for tumor cell growth and progression [35, 36]. Previous studies have shown that MSC-Exos can act as paracrine mediators through transfer signaling molecules to regulate tumor cell proliferation, angiogenesis, and metastasis by controlling multiple cellular pathways [23, 24].

Tumor promotion and suppression

MSC-Exos has a dual role in tumor growth, both promoting and inhibiting tumor growth. this duality mainly stems from the complex molecular components carried by exosomes and their interactions with the tumor microenvironment. MSC-Exos can be utilized in tumor therapy by taking advantage of this dual role. Inhibition of protumorigenic effects: (i) inhibition of pro-angiogenic factors in exosomes by gene editing or drugs. (ii) Enhance anti-tumor immunity by modifying exosomes to reduce immunosuppressive factors. Enhancement of anti-tumor effects: (i) using exosomes to deliver miRNA or drugs to directly inhibit tumor growth. (ii) Modify exosomes to carry tumor antigens and activate the immune system.

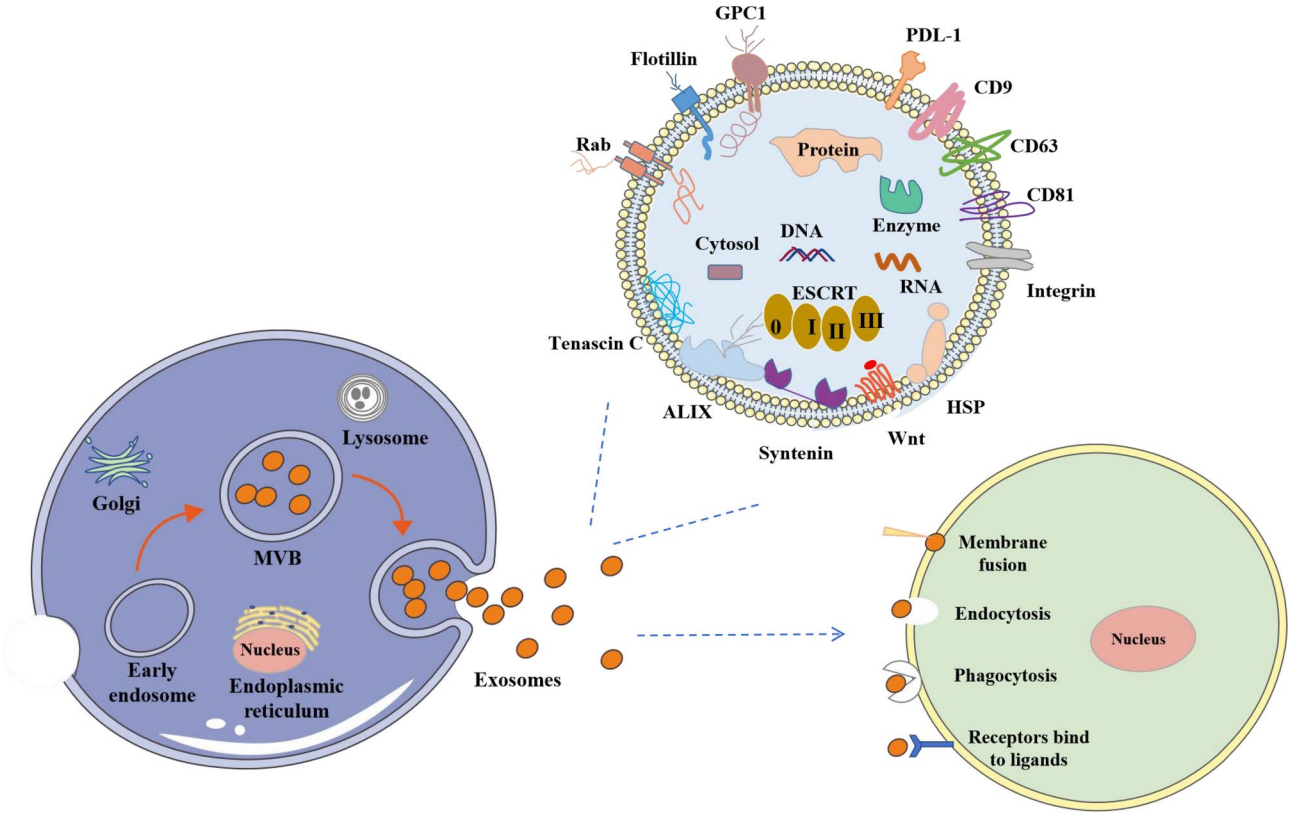

Fig. 1 Exosome biogenesis, composition and targeted uptake. Exosome formation begins with the formation of early endosomal vesicles through plasma membrane invagination, and early endosomal vesicles invaginate to form late endosomes, which then regulate the accumulation of mRNA and proteins, lipids, and other substances through a variety of complex mechanisms to form multivesicular bodies. Multivesicular bodies can be fused with lysosomes to be degraded, and can also release exosomes through fusion with the plasma membrane. Exosomes are surrounded by a phospholipid bilayer and contain different types of cell surface proteins, intracellular proteins and DNA. Several molecules are used as exosome markers (CD9, CD63, CD81 and ALIX). Exosomes can also be taken up by target cells through direct membrane fusion, membrane invagination to form an endosomal envelope that fuses with the membrane, membrane protrusion phagocytosis, and receptor-ligand binding

These Exosomes can influence TME by carrying metastasis-associated signaling molecules that promote tumor progression. Since MSCs-Exo is not a substance but a genus containing multiple species, the function of MSCs-Exo is mainly determined by the substances it carries [37]. MSC-Exos carry proteins and miRNAs to a wide range of recipient cells to regulate TME function, including cancer cells, endothelial cells, cancer-associated fibroblasts, tumor-associated macrophages, and Myeloid-derived suppressor cells [4]. MSC-Exos from different tissue sources have different (promotional or inhibitory) effects on tumors. Exosomes secreted by bone marrow mesenchymal stem cells promote proliferation of lung cancer and osteosarcoma cells by carrying different microRNAs [38, 39]. It was shown that MSC-Exos contains waveform protein and N-calmodulin molecules that promote proliferation and EMT in nasopharyngeal carcinoma by initiating the FGF19/FGFR4-dependent ERK signaling pathway [40]. Gu et al. found that MSC-Exos could induce EMT in gastric cancer cells by activating the AKT signaling pathway [41]. In vitro, miR-221 carried by bone marrow MSC-Exos (BM-MSCs-Exo) was found to have metastasized into human gastric cancer (HGC-27) cells, thereby accelerating their growth and increasing their invasive capacity [42]. MSCs-Exo induces Wnt signaling activation to create a microenvironment that supports breast cancer growth and metastasis [43]. In another study, the authors concluded that crosstalk between BM-MSCs-Exo and human multiple myeloma (MM) facilitated MM proliferation and migration through the activation of pathways such as p53, AKT, and c-Jun N-terminal kinase (JNK), which was likely attributable to regulatory factors carried in the Exosomes [44]. In addition, MSC-Exos could maintain metastasis and invasion of renal cell carcinoma cells by delivering functional mRNAs and microRNAs to activate AKT and ERK1/2 signaling pathways, which induced the cell cycle from G0/1 phase to S phase [45]. Combined, these findings suggest that MSCs-Exo play a vital role in tumor promotion. (Table 1).

In addition to mediating the tumor-promoting effects of TME, there is also evidence that MSC-Exos

Table 1 The tumor-promoting effects of MSC-Exos

Source of exosomes	Tumor type	Mechanism affecting tumors	Effect on tumor progression	Reference
Human Bone marrow	lung cancer	Activates STAT3 signaling pathway	Promoting lung cancer cell invasion	[38]
Human Bone marrow	osteosarcoma cell	Downregulation of PDCD4 and activation of ERK1/2 pathway	Promoting osteosarcoma cell proliferation, migration and invasion	[39]
Human Bone Marrow	Nasopharyngeal carcinoma	Activating FGF19/FGFR4-dependent ERK signaling	MSC-Exos stimulate nasopharyngeal carcinoma progression	[40]
Human umbilical cord	Gastric cancer	Activating the protein kinase B (AKT) signaling pathway	MSC-Exos increase the invasive ability of gastric cancer cells by inducing epithelial-mesenchymal transition	[41]
Gastric cancer tissue	Gastric cancer	Exosomal delivery of miR-221 to gastric cancer cells	Accelerates the growth and invasiveness of stomach cancer	[42]
Human adipose	Breast cancer	Activation of the Wnt signaling pathway	Promotes migration of breast cancer cells	[43]
Bone marrow stromal cells	Multiple myeloma	BM-MSC-Exos regulates the activation of multiple survival-related pathways, including c-Jun N-terminal kinase and AKT pathways	BMSC-Exos facilitate the proliferation and migration of multiple myeloma cells	[44]
Human Wharton's Jelly	Renal Cancer	Activation of AKT and ERK1/2 signaling pathways	Inducible hepatocyte growth factor promotes growth and invasion of carcinoid renal cancer cells	[45]

Table 2 The tumor-suppressive effects of MSC-Exos

Source of exosomes	Tumor type	Mechanism affecting tumors	Effect on tumor progression	Reference
Human Bone marrow	Breast cancer	Induces dormancy by repressing the target gene MARCKS.	Promoting breast cancer cell dormancy in metastatic ecological niches	[47]
Human Bone marrow	Leukemia	MSC-Exos-carried miR-222-3p regulates the IRF2/INPP4B pathway	miR-222-3p inhibits leukemia cell proliferation and promotes apoptosis	[49]
Human Bone marrow	Pancreatic cancer	Inhibition of the Wnt8/β-catenin signaling pathway	Inhibition of invasion, migration, proliferation and stemness of pancreatic cancer cells	[49]
Human umbilical cord	Endometrial cancer	Inhibited the AKT signaling pathway	Inhibition of cell cycle protein D1 expression in endometrial cancer cells	[46]
Human Umbilical Cord Wharton's Jelly	Bladder cancer	down-regulated phosphorylation of Akt protein kinase and up-regulated cleaved Caspase 3	Induction of apoptosis in bladder tumor cells in vitro and in vivo	[47]
MenSC and umbilical cord	Oral squamous cell carcinoma	not quite clear	Inhibition of angiogenesis and tumor growth	[51]

exerts antitumor effects through multiple mechanisms (Table 2). MSC-Exos can inhibit tumor proliferation and metastasis. For example, Exosomes from human umbilical cord mesenchymal stem cells inhibit endometrial cancer cell proliferation and migration by transferring miRNA-302a and downregulating cell cycle protein D1 and AKT signaling pathways [46]. Ono et al. found that MSC-Exos from MSC-Exos could induce dormancy in breast cancer cells by transferring miRNA-23b and inhibiting MARCKS in the cells, thereby suppressing cell proliferation and metastasis [47]. Human umbilical cord-MSC-Exos reduces bladder cancer cell growth by inhibiting AKT phosphorylation and increasing cleaved cysteinyl asparagin-3 [48]. In hematologic cancers, it has been shown that bone marrow-derived MSC-Exos delivers miRNA-222-3p to THP-1 cells (leukemia cells) targeting the IRF2 gene, thereby down-regulating IRF2/INPP4B signaling and thus inhibiting cell proliferation and leukemia progression [49]. Furthermore, MSC-Exos can indirectly regulate tumor progression through its effects on signaling pathways. Yao et al. showed that bone marrow-derived MSC-Exos contains the circ_0030167 molecule, which reduces proliferation, migration, and invasion of pancreatic tumor cells by removing miRNA-338-5p, thereby targeting Wif1/Wnt8/β-catenin signaling [50]. In a rat model of glioma xenografts, miRNA-146b from MSC-Exos reduced tumor growth; however, the exact mechanism is unknown [51].

Tumor angiogenesis

A growing number of studies have shown that MSC-Exos can promote angiogenesis, which is an important component of tumor progression. In tumor, blood vessels provide oxygen and nutrients for tumor growth and metastasis [52]. MSC-Exos contains several angiogenic factors that control tumor angiogenesis. MSC-Exos stimulates angiogenesis by increasing vascular endothelial growth factor (VEGF) production in tumor cells and by stimulating ERK1/2 and p38 mitogen-activated protein kinase pathways [40]. Placental mesenchymal stem cell-derived exosomes have been shown to promote placental microvascular endothelial cell migration

and angiogenesis [53]. Platelet-derived growth factors enhance angiogenesis by causing adipose mesenchymal stem cells to secrete exosomes and microvesicles rich in proangiogenic factors [54]. In a similar study, MSC-Exos was injected into stroke rats to reduce severe symptoms by stimulating angiogenesis, neuronal remodeling and neurogenesis [55]. Zhu et al. concluded that MSC-Exos enhances VEGF expression in tumor cells by activating the ERK1/2 pathway, thereby stimulating tumor progression [56]. Similarly, Yu et al. found that MSC-Exos may enhance angiogenesis by upregulating miR-221-3p expression through the AKT/eNOS pathway [57].

Angiogenesis can accelerate tumor progression, and MSCs can inhibit angiogenesis by regulating VEGF expression in an exosome-dependent manner. For example, Lee et al. showed that mouse MSC-Exos could inhibit angiogenesis by miRNA-16 dose-dependently reducing VEGF expression in breast cancer cells [58]. In addition, MSCs-Exo could inhibit VEGF production by blocking VEGF production and NF-κB signaling thereby inhibiting the growth of oral squamous cell carcinoma and prostate cancer cells [59, 60]. In addition, it was reported that hUC-MSCs-Exo may attenuate the growth of bladder cancer cells by down-regulating AKT phosphorylation and up-regulating the production of cleaved cysteine asparaginase-3 [48]. MSC-Exos can both promote and inhibit angiogenesis, which may be due to the type of MSC-Exos cargo leading to different tumor regulatory properties.

Tumor immune responses

Previous studies have shown that MSC-Exos interacts with immune cells such as neutrophils, T-cells, B-cells and macrophages to inhibit the immune response to tumor cells [61, 62]. MSC-Exos can inhibit T cell activation by releasing paracrine factors [63]. In another study, the authors reported that CD30 transported by MSC-Exos enhanced immunosuppression by promoting adenosine accumulation [64]. Umbilical-Cord-MSC-Exos can deliver miRNA-182, which increases cancer cell mortality by increasing NK and T cell proliferation and modulating cancer cell sensitivity to immune cells [65]. In addition, MSC-Exos reduces the activation of the immune system by inducing the expression of anti-inflammatory cytokines and regulatory immune cells. MSC-Exos upregulated the mRNA expression levels of the anti-inflammatory factors IL-10 and TGFB1 and attenuated the expression levels of the pro-inflammatory factors IL-1B, IL-6, TNFA, and IL-12P40 by inducing the expression of embryonic alkaline phosphatase [66]. Macrophages are known to be a central component of the immune system. M2-type macrophages promote tumor development through the use of anti-inflammatory storms. Under the influence of hypoxic environment in vivo, miR-21-5p carried by MSC-Exos induces M2 macrophage polarization by mediating PTEN down-regulation, which supports lung cancer growth and invasion [67].

The targeting of tumors

Targeting tumors with MSC-Exo using the tumor-homing properties of MSCs. Induced by chemokines, MSCs can home in on diseased tissue through the circulatory system [68]. In addition, MSCs-Exo may accumulate in tumor tissue through vascular leakage, which further explains the homing effect of MSC-Exo. Similarly, MSCs-Exo can also migrate to tumor tissues via the mechanism, and the homing properties of MSC-Exo have been applied to tumor therapy [69]. For instance, hUC-MSC-Exo loaded with paclitaxel can target breast cancer tissues and significantly inhibit tumor growth [70]. In addition, engineering can improve the targeting of exosomes to tumors. The more widely studied engineering approaches are physical and chemical modifications, including surface and content modifications. For instance, the insertion of PEGylated liposomes into the surface of exosomes using hydrophobic interactions significantly prolonged the circulation time of the exosomes and improved their targeting to murine neuroblastoma cells [71]. In addition, enhancing exosomal targeting capabilities using factors that are highly expressed in tumors. The folate receptor (FR) is a glycoprotein anchored to the cell membrane via Glycosylphosphatidylinositol. Folate (FA) is overexpressed in several types of cancer, such as pancreatic cancer, while its expression in normal cells and tissues is low. Consequently, FA can be used as a targeting ligand for targeted antitumor drug delivery. Additionally, FA can be selected as a target for the preparation of FR-mediated tumor cell-targeted exosomes (Co-Exo-FA) to increase the delivery of tumor-targeted drugs [72].

MSC-Exos as drug carriers

Advantages of MSC-Exos as drug carriers

MSCs, as the most promising living cell carriers for drug delivery, have made great progress in many delivery drug-targeted therapies. However, MSC therapy still has many safety concerns, such as potential tumorigenicity, immune rejection, cell aggregation promoting embolization and infection transmission [73], and the viability, potency, and transformation of MSCs in patients are difficult to monitor and maintain [74]. In contrast, exosomes, as a paracrine transmitter, not only have similar effects to MSCs, but also have a more stable membrane structure, lower immunogenicity, smaller size and better tolerance than MSCs [75, 76]. In addition, exosomes contain transmembrane and membrane-anchored proteins that enhance endocytosis, thereby facilitating drug delivery [77]. This “cell-free therapy” overcomes the

shortcomings of MSCs and brings new hope for targeted drug delivery. These properties make them suitable as carriers of drugs for delivery to specific tissues. Therefore, the application of exosomes as drug delivery carriers, including anti-inflammatory drugs and antitumor drugs, is currently the focus of intensive research [70], [78]. Clinical trials related to MSC-Exos in tumor therapy can be accessed at ClinicalTrials.gov (Table 3).

Exosomal drug loading mode

To achieve efficient drug-targeted delivery, it is crucial to develop effective exosome loading strategies. Loading works mainly through direct and indirect methods for modification of exosomes [30]. Direct modification is the physical or chemical alteration of the composition or structure of an exosome to enhance the exosome's ability to bind drugs [79]. Physical methods (ultrasonication, electroporation, extrusion, freeze-thaw, pH gradient, etc.) usually utilize the transient disruption of the membrane by an external force to load the drug into the exosome [80]. The electroporation technique, which utilizes an electric field to form temporary hydrophilic pores in the exosome membrane to allow the drug to enter the exosome, is the more commonly used method. Gomari et al. successfully loaded adriamycin into MSC-Exos using electroporation technique with high loading efficiency measured by spectrophotometer [81]. Compared to freeze-thaw methods, extrusion methods have higher loading rates and allow the drug to be loaded uniformly into exosomes after repeated extrusion under certain parameters [82]. Although physical methods can increase the loading rate to some extent, they can compromise the integrity of the exosome and affect the function of the exosome. In contrast, chemical methods utilize a chemical reaction between transfection reagents or permeabilizing agents (e.g., saponins) to facilitate the entry of drugs into exosomes without disrupting the membrane structure [83]. Parada et al. successfully loaded drugs and plasmids into exosomes using click chemistry [84]. In addition, hydrophobic drugs can be attached to the membrane surface by co-incubation with exosomes, which is the simplest way of loading. This approach retains the maximum activity of the exosome, but the loading efficiency is affected by a number of factors and drug toxicity can also affect exosome function [85].

Indirect modification, on the other hand, involves genetically engineering exosomes before they are secreted. Modification of parental cells produces exosomes that contain specific structures for better binding to the drug. Cell transfection is utilized to overexpress therapeutic agents in parental cells, which are subsequently encapsulated into exosomes. Lou et al. successfully transfected miR-122 into adipose tissue-derived MSCs and detected the elevated expression level of miR-122 in exosomes by PCR [86]. Li et al. constructed a CD9-HuR fusion protein and selectively loaded miR-155 into exosomes, which does not destroy the RNA structure and improves the loading efficiency significantly, and is expected to be a new strategy for in vivo gene delivery clinical trials [87]. Alternatively, the drug can be directly incubated with the parental cells to produce drug-containing exosomes. Exosomes containing melatonin can be generated if melatonin is incubated with MSCs [88]. This method is relatively simple, but the procedure is time-consuming and loading is inefficient.

Application of MSC-Exos as a drug carrier

Targeted delivery improves drug efficacy against tumor tissue and reduces adverse drug reactions. A variety of antitumor drugs have been studied for delivery through exosomes with remarkable therapeutic effects. Exosomal delivery of drugs to tumor cells is shown in Fig. 2.

Delivery of oncolytic virus

Oncolytic virus, a virus that induces lysis and death of tumor cells and activates anti-tumor immune response without killing normal cells, is a promising immunotherapy for cancer; however, due to the immunogenicity of the virus, systemic administration of the virus can be neutralized by antibodies, which reduces the amount that reaches the target cells to be accumulated, resulting in poor therapeutic efficacy. MSCs, due to their advantages, can release drugs directly to tumor cells via exosomes [89], which is regarded as an ideal carrier for lysosomal viruses, not only to enhance the stability of viruses in organisms, but also to promote the diffusion and release of the viruses [90]. Garofalo et al. [91] found that compared with direct use of lysosomal adenoviruses, exosome loading significantly enhanced the tumor tropism of lysosomal adenoviruses and significantly improved therapeutic efficacy. There have been few studies on the delivery of lysoviruses by MSC-Exos, and most of the studies have been on the delivery of lysoviruses by their mother cells. Most of the studies are on the delivery of

Table 3 MSC-Exos in clinical trials related to tumor therapy

Disease	Study Design	Clinical Trial ID Number	Year and Location	Status
Pancreatic cancer	Phase I, open-label	NCT03608631	2018, United States	Completed
Colorectal cancer	Phase I, open-label	NCT01294072	2011, United States	Completed
Hepatocellular carcinoma	Phase I, open-label, dose escalation	NCT05375604	2022, United States	Unknown
Lung cancer	Phase II, open-label	NCT01159288	2015, France	Completed

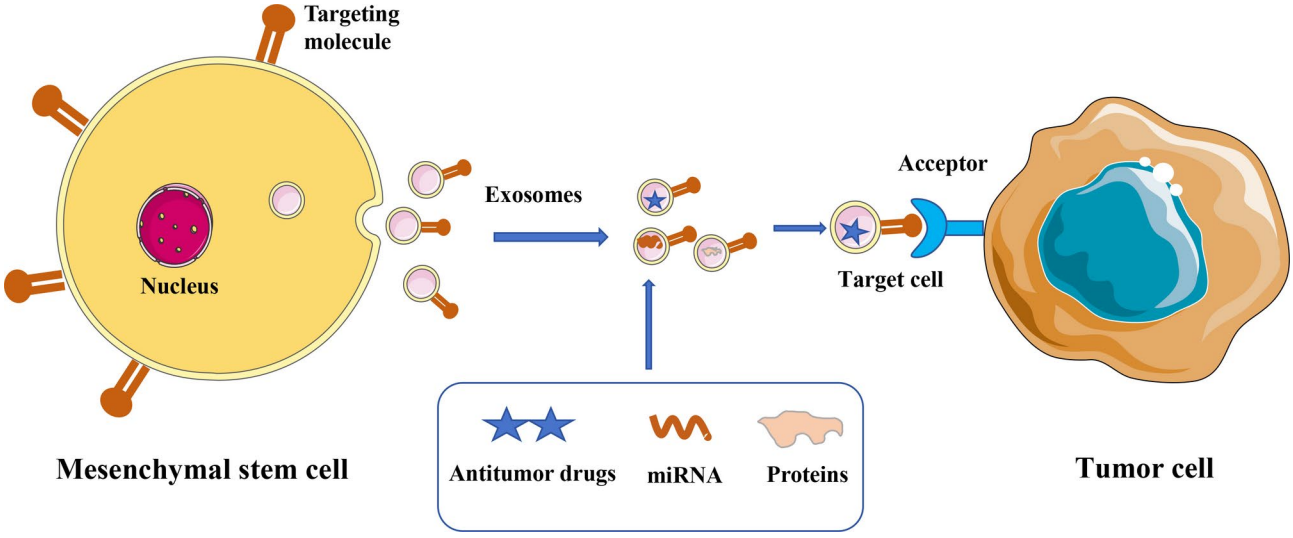

Fig. 2 MSC-Exos loaded with drug-targeted tumor cells. Co-incubation of MSCs with molecules containing the targeting peptide produces exosomes containing the targeting peptide, and then loading drugs into the exosomes using electroporation, transfection, etc., which can improve the targeting ability of the exosomes to tumor cells

Table 4 MSC-Exos delivers traditional antitumor drugs

Drug	Source of exosomes	In vivo model	Tumor type	Loading method	Therapeutic effect	Reference
Paclitaxel	Human Umbilical cord	NODscid mice	Breast cancer	Co-incubation	With specific and more effective tumor targeting	[96]
Adriamycin	Bone marrow	BALB/c nude mice	Osteosarcoma	Dialysis	Better cellular uptake and anti-tumor effects with reduced toxicity low	[97]
Norcantharidin	Bone marrow	BALB/c nude mice	Liver cancer	Electroporation	Effectively reduce tumor cell proliferation, increase cell apoptosis and obvious in vivo anti-tumor effects	[98]
Gemcitabine phosphate	Bone marrow	BALB/c nude mice	Pancreatic	Electroporation	Effective anti-tumor effect, and has a certain overcome chemotherapy resistance effect	[99]
Cisplatinum	Human Umbilical cord	ICR mice	Ovarian cancer	Co-incubation	Reduction of drug dosage, enhancement of ovarian function and improvement of the inflammatory environment within the ovary	[100]

lysovirus by its mother cells. MSC-Exos are able to specifically deliver lysosomal adenovirus to hepatocellular carcinoma cells leading to effective tumor growth inhibition [92]. Du et al. found that MSC-Exos carrying oncolytic herpes simplex virus increased the tumor-killing effect of immune cells and significantly improved the survival time of tumor-bearing mice [93].

Delivery of conventional antitumor drugs

Traditional antitumor drugs (e.g., paclitaxel, adriamycin, Gemcitabine phosphate etc.) have poor therapeutic efficacy due to poor drug solubility, short half-life and in vivo circulating time, and low targeting, etc., and are also associated with drug resistance and various toxic side effects. MSC-Exos, as a natural delivery vehicle with perfect nano-size and stable membrane structure, can stably carry and protect drugs from degradation and inactivation [94]. Several studies have shown that loading drugs into exosomes in different ways can show better anti-tumor effects, e.g., paclitaxel delivered to target cells by co-incubation with MSCs can mediate a strong anti-tumor response, laying the foundation for exosomal delivery of anti-tumor drugs for in vivo therapy [95]. Gomari et al. found that adriamycin delivered by MSC-Exos significantly reduced tumor growth in a mouse breast cancer model [34]. Most importantly, exosomes are biocompatible and can effectively reduce the toxicity and adverse effects of chemotherapeutic drugs. In a study by Tian et al. exosomes loaded with adriamycin significantly inhibited the growth of mammary tumor cells without toxic effects in mice [25]. Some of the studies using mice to model and treatment effects are shown in Table 4 [70, 96– 100].

Table 5 MSC-Exos delivers novel anti-tumor drugs

Drug	Source of exosomes	In vivo model	Tumor type	Loading method	Therapeutic effect	Reference
miR-145-5p	Human Umbilical cord	PDAC mice	Pancreatic	Transfection	Increased tumor cell apoptosis and significantly inhibited tumor growth	[110]
miR-381	Bone marrow	None	Breast cancer	Electroporation	migratory and invasive capacity and promotes apoptosis	[111]
miR-499	Bone marrow	BALB/c nude mice	Endometrial cancer	Electroporation	Significantly inhibited endometrial cancer cell proliferation, endothelial cell tube formation, and inhibited tumor growth and angiogenesis	[112]
LNA anti-miR-142-3p	Bone marrow	SCID mice	Breast cancer	Electroporation	Reduced tumorigenicity of breast cancer stem cells in vivo	[113]
miR-124	Bone marrow	BALB/c nude mice	Pancreatic	Transfection	Inhibited cell proliferation, metastasis and epithelial mesenchymal transition and enhanced chemosensitivity to 5-fluorouracil in vitro and in vivo	[114]
Tumor Necrosis Factor α	Bone marrow	BALB/c nude mice	Melanoma	Electroporation	Good targeting properties, better anti-tumor activity and lower toxicity	[115]

Delivery of novel anti-tumor drugs

Currently, many new technologies are emerging to treat tumors, and among them, gene therapy, which can change the genes in diseased cells by editing the genetic material to treat the disease fundamentally, holds great promise. However, vectors are needed to overcome these drawbacks due to the susceptibility of genes to degradation, instability, and difficulty in uptake by target cells. In recent years, exosomes have been gradually used in the field of gene delivery due to their relative safety, easily regulated physicochemical properties, mass production, low cost and high loading capacity [101]. As a kind of non-coding RNA, miRNA can be abnormally expressed and cause the occurrence of diseases, and delivered to target cells through exosomal packaging can restore the abnormal gene expression and thus inhibit tumor growth [102]. siRNA could treat cancer by destroying abnormal genes. Faruqu et al. found that loading siRNA into exosomes increased the loading and delivery efficiency, and the effect of cancer treatment was remarkable [103]. Loading of galactose lectin 9 siRNA into bone marrow mesenchymal stem cell-derived exosomes via electroporation, in combination with oxaliplatin, significantly inhibited tumor growth in pancreatic cancer [104]. In addition, it has been demonstrated that macromolecular nucleic acids, such as mRNA and DNA, can also be loaded into exosomes by transfection or electroporation [105, 106], delivered to tumor cells to inhibit their activity and promote apoptosis, which improved the survival rate of mice. Macromolecular drugs such as proteins and peptides are susceptible to degradation and inactivation in the in vivo environment and are unable to perform their intended functions due to the lack of natural conformation [107]. Exosomes protect proteins from various enzymes and the immune system. It was found that catalase significantly reduced neuroinflammation and provided effective neuroprotection by different loading modalities (saponin incubation, freeze-thaw cycling, sonication and extrusion) into exosomes [108]. Currently, there are fewer studies on the application of MSC-Exos-loaded proteins to anticancer therapy, but it has been found that tumor necrosis factor-associated apoptosis-inducing ligand, as an anticancer protein, can be loaded into MSC-Exos to induce apoptosis in cancers such as lung, kidney, and breast cancers [109]. Specific studies and treatment effects are shown in Table 5 [110– 115].

Advantages and challenges

Previous studies have shown that MSCs show great potential in the field of tumor therapy, but with potential safety concerns. However, MSC-Exos has lower immunogenicity and therefore can be used as a more suitable carrier to deliver antitumor drugs to target cells to treat tumors in a safer manner [116, 117]. The exosomes are engineered and modified in a variety of ways to make the exosomes more target specific and enhance the delivery efficiency [118, 119]. It is noteworthy that MSCs produce more exosomes than other cells and that their exosomes have strong tumor-targeting ability and low immunogenicity [120, 121]. However, to apply engineered MSC-Exos in tumor clinical treatment, there are still some problems to be solved. (1) Mass production, isolation and purification of exosomes: Although mesenchymal stem cells are currently the most efficient cells for producing exosomes, the preparation of exosomes with higher purity is still challenging, in addition, the quality and purity of exosomes and their storage conditions may affect the modification efficiency. Standardized, convenient and tightly controlled production and purification methods need to be developed. (2) Exosomes are heterogeneous: The function of exosomes is related to the origin of mesenchymal stem cells, the way they are modified, and the type of cancer. Different types of MSC-Exos have different effects on the same tumor, and exosomes treated in different ways have different effects on tumor cells, and the therapeutic effects of exosomes on different

tumors are also different. Therefore, selecting the appropriate source and treatment of mesenchymal stem cells is the key to improve the therapeutic effect. (3) The fate and targeting mechanisms of exosomes in vivo are not well understood: the transport and distribution of exosomes in vivo is influenced by a variety of factors, including other components in circulation, receptor expression levels, and different drug delivery routes. Therefore, more in-depth study of the relationship between the biological characteristics, distribution and transport mode of exosomes is needed to better predict and control their behavior. (4) Long-term stability and safety assessments of exosomes are still inadequate: While some studies have demonstrated the therapeutic potential of engineered exosomes, more clinical trials are needed to verify their safety and efficacy. (5) MSC-Exos, as a novel therapeutic vehicle, may not be fully covered by the existing regulatory framework for pharmaceuticals in terms of its specificities. (6) Ethical challenges, MSC is usually derived from bone marrow, adipose tissue or umbilical cord, etc., which involves donor informed consent and privacy protection. (7) Exosomes may carry pathogens or harmful molecules and present biosafety risks. Strict quality testing of exosomes should be conducted to ensure that they are free of pathogen contamination. Although there are certain challenges in MSC-Exos research at present, the existing knowledge about MSC-Exos highlights their bright prospects for biomedical applications. Therefore, we should invest more effort in MSC-Exos to expand our understanding of this field.

Conclusions

MSC-Exos are intercellular communication mediators that play a role in tumorigenesis. Increasing evidence suggests that MSC-Exos can promote and inhibit tumor proliferation, metastasis, angiogenesis, and immune response through different signaling pathways. Importantly, MSCs-Exos have a vast potential as carriers for therapeutic agent delivery. MSCs-Exos can be modified on their surface and contents to enhance their tumor targeting ability. However, research on MSC-Exos is still in its infancy and many questions remain to be addressed. Clinical translation of MSC-Exos requires more research on its large-scale production, isolation, loading and modification.

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Author contributions
DFH, WLH and MJL searched for literature and wrote the first draft of this article. JC, DWX, ZLP, HQH, HBS, QJ and LLC edited the manuscript. DYR, MHZ and JYH reviewed the manuscript and polished the grammar. All authors contributed to the article and approved the submitted version.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
All authors are aware and have agreed to publish.

Competing interests
The authors declare that they have no conflict of interest.

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