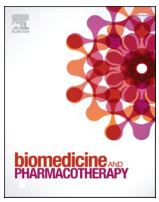
Biomedicine & Pharmacotherapy 167 (2023) 115505

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha



Review

Current progress in engineered and nano-engineered mesenchymal stem cells for cancer: From mechanisms to therapy

Forough Shams [a], Bahareh Pourjabbar [b], Nader Hashemi [c], Navid Farahmandian [d], Ali Golchin [e,f], Ghader Nuoroozi [g], Azam Rahimpour [b,*]

[a] Student Research Committee, Department of Medical Biotechnology, School of Advanced Technologies in Medicine, Shahid Beheshti University of Medical Sciences, 1968917313 Tehran, Iran
[b] Department of Tissue Engineering and Applied Cell Sciences, School of Advanced Technologies in Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[c] Department of Medical Biotechnology, School of Advanced Technologies in Medicine, Shahid Beheshti University of Medical Sciences, 1968917313 Tehran, Iran
[d] Department of Tissue Engineering & Regenerative Medicine, Faculty of Advanced Technologies in Medicine, Iran University of Medical Sciences, Tehran, Iran
[e] Cellular & Molecular Research Center, Cellular & Molecular Medicine Research Institute, Urmia University of Medical Sciences, Urmia 57157993313, Iran
[f] Department of Clinical Biochemistry & Applied Cell Sciences, School of Medicine, Urmia University of Medical Sciences, Urmia 57157993313, Islamic Republic of Iran
[g] Men's Health and Reproductive Health Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Keywords:
Mesenchymal stem cells (MSCs)
Genetic modification
Nanoparticle (NP)
Exosome
Cancer therapy

ABSTRACT

Mesenchymal stem cells (MSCs), as self-renewing multipotent stromal cells, have been considered promising agents for cancer treatment. A large number of studies have demonstrated the valuable properties of MSC-based treatment, such as low immunogenicity and intrinsic tumor-trophic migratory properties. To enhance the potency of MSCs for therapeutic purposes, equipping MSCs with targeted delivery functions using genetic engineering is highly beneficial. Genetically engineered MSCs can express tumor suppressor agents such as pro-apoptotic, anti-proliferative, anti-angiogenic factors and act as ideal delivery vehicles. MSCs can also be loaded with nanoparticle drugs for increased efficacy and externally moderated targeting. Moreover, exosomes secreted by MSCs have important physiological properties, so they can contribute to intercellular communication and transfer cargo into targeted tumor cells. The precise role of genetically modified MSCs in tumor environments is still up for debate, but the beginning of clinical trials has been confirmed by promising results from preclinical investigations of MSC-based gene therapy for a wide range of malignancies. This review highlights the advanced techniques of engineering/nano-engineering and MSC-derived exosomes in tumor-targeted therapy.

1. Introduction

Mesenchymal stem cells are multipotent progenitor cells first introduced by Friedenstein et al. in 1987 [1]. They described these cells as a population of plastic adherent cells with fibroblast-like morphology isolated from bone marrow (BM) [1,2]. MSCs maintain strong proliferation abilities due to their clonogenic potential. These cells can be extracted from different adult human tissues, such as the dental pulp [3],

Abbreviations: MSCs, Mesenchymal stem cells; NP, Nanoparticle; BM, Bone marrow; AT, Adipose tissues; AD-MSCs, Adipose-derived mesenchymal stem cells; N-MSCs, Naive MSCs; Dkk1, Dickkopf-related protein 1; CSCs, Cancer stem cells; ICAMs, Intercellular adhesion molecules; VCAMs, Vascular cell adhesion molecules; MHC-II, Major histocompatibility complex class II; HLA, Human leukocyte antigens; AAV, Adeno-associated virus; ZFN, Zinc finger nuclease; Epo, Erythropoietin gene; IFN-γ, Interferon-gamma; TALENS, Transcription activator-like effector nucleases; CRISPR, Clustered regularly interspaced short palindromic repeats; PEI, Polyethylenimine; TRAIL, Tumor necrosis factor-related apoptosis-inducing ligand; IFN-ß, Interferon ß; DOX, Doxorubicin; PTX, Paclitaxel; GEM, Gemcitabine; GCB, Gemcitabine.; PT, Photothermal treatment; PA, Photoacoustic; TNBC, Triple-negative breast cancer; PLGA, Poly L-lactide-co-glycolide; PLL, Poly (α-L-lysine); Pgp, P-glycoprotein; TAT, Transactivator of transcription; Ac4ManNAz, Azidoacetylmannosamine-tetraacylated; DBCO, Dibenzyl cyclooctyne; CNT, Carbon nanotube; GDEPT, Gene-directed enzyme prodrug therapy; HSV-TK, Herpes simplex virus thymidine kinase; GCV, Ganciclovir; CE, carboxylesterase; CPT-11, Irinotecan; CD, Cytosine deaminase; 5-FC, 5-Fluorocytosine; CYP, Cytochrome P450; CPA, Cyclophosphamide; 4-PB, 4-phenylbutyrate; VPA, Valproic acid; Cx, Connexin; HCC, Hepatocellular carcinoma; EVs, Extracellular vehicles; MSCs-Exo, Exosomes produced by mesenchymal stem cells; SEAP, Secretory embryonic alkaline phosphatase; VEGF, Vascular endothelial growth factor; ROS, Reactive oxygen species; PC3, Prostate cancer; MDR, multi-drug resistance.

* Corresponding author.
E-mail address: rahimpour@sbmu.ac.ir (A. Rahimpour).

https://doi.org/10.1016/j.biopha.2023.115505
Received 10 August 2023; Received in revised form 11 September 2023; Accepted 12 September 2023
Available online 15 September 2023

gingiva, articular cartilage, brain, dental tissue, endometrium, menstrual blood, and skin. Bone marrow and adipose tissues (AT) are rich and more established sources of MSC. BM has been the primary source of MSCs for many years; however, cell collection from this tissue is an invasive and painful process [4]. AT is also one of the richest origins of MSC identified in 2001 by Zuk et al. [5], which offers some benefits such as ease of tissue processing, high yield of initial cells, and robust in vitro proliferative ability. In recent years, adipose-derived mesenchymal stem cells (AD-MSCs) have become appealing alternatives to BM-MSCs [6]. Like other cells, MSCs have limited cell division capacity and reach senescence after 43–77 days of cultivation (7–12 passages) which is morphologically demonstrated by irregular and enlarged cell shapes and ultimately proliferation arrest [5,7]. However, some factors such as the source of tissue, donor sex, and culture conditions impact the degree and duration of MSC proliferation. Due to these unique characteristics, MSCs are a leading candidate for cell-based therapeutics used in regenerative medicine, immune modulation, and cancer therapy [8].

Early research on MSCs and tumors was related to the impact of naive (unmodified) MSCs (N-MSCs) on tumors. N-MSCs are isolated from natural tissue sources and can be homed to tumors to effectively target the tumor microenvironment and investigate their application as antitumor agents. According to published research, N-MSCs co-cultured with in vitro tumor cells might inhibit tumor cell proliferation. Ramasamy et al. [9] demonstrated that N-MSCs could prevent in vitro proliferation of leukemia cell lines and solid tumor cell lines. However, the inhibitory action of N-MSCs was dose-dependent, the inhibition rate was reduced at higher N-MSC proportions [9]. The inhibitory effect of N-MSC could include the N-MSC-mediated secretion of soluble factors such as Dickkopf-related protein 1 (Dkk1), which prevents Wnt signaling pathways in tumor cells. N-MSCs cause apoptosis in tumor cells through the upregulation of caspase 3, a protease associated with apoptosis. These cells can increase the proportion of cancer stem cells (CSCs) across populations of tumor cells and implicitly block tumor development by angiogenesis inhibitors. N-MSCs also prevent angiogenesis by either inducing apoptosis in endothelial vascular cells or directly inhibiting the development of vascular networks. N-MSCs are related to the differentiation of MSCs in advancement to vascular endothelial cells in melanoma and advance of CSCs that promote tumorigenesis and metastasis, leading to the recurrence of tumors such as breast cancer and enhancing the expansion of gastritis cells.

Additionally, N-MSCs promote the growth of tumor cells by producing chemokines such CCL5, CXCR4, intercellular adhesion molecules (ICAMs), and vascular cell adhesion molecules (VCAMs) in malignancies. Through signals and pathways largely based on many inflammatory cytokines, chemokines, growth factors, and proteases, and other effects, tumors and their microenvironments cause MSC homing [10]. However, N-MSCs have been correlated with bidirectional influences on tumor growth, and there are numerous inconsistencies between studies as to whether MSCs are implicated in the promotion or suppression of tumors. Recent studies have demonstrated that this cell population exhibits an uncommon property of homing-in to sites of tumorigenesis and directly repressing tumor growth by contacting target cells and preventing their Akt (protein kinase B) activity. Furthermore, emerging evidence suggests that MSCs can simplify targeted delivery to metastatic cancer since they tend to move to the same homing destination by following CSC migration. Therefore, the attributes of MSCs make them an appealing choice as tumor-selective cellular carriers. The therapeutic potential of MSCs originates from (1) paracrine factors involving peptides, proteins, and hormones, and (2) the transfer of microvesicles or exosomes in packaging different molecules. These potentials may be engineered to mediate these factors in vesicles [11]. Engineering strategies may prepare MSCs for the targeted delivery of various factors focused on biological approaches. MSCs can be engineered for different utilities such as carriers of suicide genes, drug delivery, induction of cytokine gene expression, carriers of anti-mitotic factors, and carriers of anti-angiogenesis factors. Furthermore, greater knowledge of modified exosomes is required to shed light on the functions of these vesicles in clinical applications. Moreover, the utility of exosomes as biological delivery vehicles for transferring miRNA, siRNA, and lncRNA is considerable. The development of MSC engineering as a tumor-targeted therapy is the main topic of this review.

2. Potency of MSCs in cancer therapy

Over the past decade, a great deal of attention has been paid to the role of MSCs in the treatment of tumors. Some studies have suggested that nonengineered MSCs may exert antitumor activities [12]. In 1999, Maestroni et al. [13] discovered that MSCs had the capability to migrate towards the tumor site. MSCs communicate with tumor cells in different ways, suppressing or supporting tumor growth. In this regard, they showed that BM-derived MSCs release some cytokines that prevent lung carcinoma and B16 melanoma growth in mice [13,14]. The tumor acts as a wound mimic to take advantage of a consecutive source of chemokines and cytokines in various responsive cells like MSCs [15]. Therefore, high concentrations of growth factors and inflammatory chemokines are the leading sources for integrating MSCs into the tumor stroma. Moreover, the microenvironment of MSCs is considered a site of chronic inflammation [15].

MSCs, like other mature stem cells, are a potentially valuable source in regenerative medicine [16]. Although the harvest of MSCs is less invasive and easy to work with, the clinical application of MSCs raises numerous ethical and safety concerns. Results obtained from completed and ongoing clinical studies indicate the huge therapeutic potential of MSCs-based therapy while ethical issues in regenerative and transplantation medicine are an important dilemma. Expression of cell surface markers like CD44, CD73, CD105, CD90, CD271, and ganglioside GD2 was observed in more than 95 % of these cells. Furthermore, the ability to differentiate into adipocytes, osteoblasts, and chondrocytes is a significant competency of MSCs [17]. AT compared to BM can be easily isolated from subcutaneous tissue without ethical concerns as well, and the extracted MSCs have about a 40-fold higher yield. In this way, adipose tissue as a valuable source of MSCs has gained significant consideration in recent years [18]. Other characteristics of MSCs include (1) their low immunogenicity (loss of expression of costimulatory molecules), (2) immune-specific status (as a result of the absence of major histocompatibility complex class II (MHC-II) and the limited expression of MHC-I), and (3) innate tropism for tumors and their metastases. MSCs, due to their attributes like integration into tumor stroma, tumor tropism, and immune-specific status, could be the perfect delivery vehicle for antitumor biological factors [19]. MSCs have no impact on host immune response induction or rejection when injected into human leukocyte antigens (HLA)-incompatible recipients. These features allow the infusion of MSCs into recipients without HLA matching. Therefore, MSCs can be used as cellular vehicles for the delivery of anticancer agents particularly to tumors [20,21].

3. Genetic modifications in MSCs

Genetically engineered cells have emerged as tremendous platforms for addressing the different challenges faced by synthetic delivery systems. In order to dominate diverse physiological barriers and control their interaction with the tumor microenvironment, engineered cells can be used to present natural biomolecules or synthetic ligands. As the clinical function of MSCs is often associated with unsatisfactory performance in vivo, genetic engineering is a suitable method to ameliorate in vivo performance. In this direction, engineered MSCs have been successfully applied to express particular proteins and peptides to treat metastatic or localized tumors. MSCs are genetically modified to secrete factors that can enable them to increase their survival in hypoxic states or situations, apoptosis, and other inherent features, such as cardiac protection, migration, and differentiation to a specific lineage [22]. As an important characteristic, modified MSCs have no difference from

naive MSCs in differentiation, proliferation, surface antigenicity, and tumor homing potentials. Generally, MSCs have been engineered to express pro-apoptotic, anti-angiogenic, and anti-proliferative agents that target tumor cancers. As mentioned, MSCs have a dual role in supporting tumor growth and having antitumor properties in cancer [23]. To solve this duality influence, engineered MSCs with exogenous delivery could convert into specific therapeutic goals. Genetic modification of MSCs is generally performed by applying viral and non-viral vectors (Fig. 1A). For instance, modified MSCs can mediate tumor cell death to ameliorate host immune response against cancer cells [22].

3.1. Viral vectors

MSCs have a great propensity for viral modification. The most common viral vectors are lentivirus, baculovirus, retrovirus, and adeno-associated virus (AAV). Most of these viral vehicles produce permanent expression, while adenoviruses create transient expression. In the viral method, more than 90 % of MSCs can be transduced without affecting the quality of the offspring or lineage differentiation by standard procedures. Some vectors, like retrovirus, lead to the integration of the transgene into the host genome which results in limitations in some activities such as activation of oncogenes, insertional mutagenesis, packaging capacity of exogenous DNA, and neutralizing antibodies against AAV. To solve this problem, Benabdallah et al. [24] designed non-integrating vectors to bypass activating oncogenes and achieve targeted integration by applying zinc finger nuclease (ZFN) to add the erythropoietin gene (*Epo*) into the chemokine (C-C motif) receptor-5 gene locus of MSC. The *Epo* gene was delivered to MSCs using integrase-defective lentiviral vectors and ZFN was delivered by using adenovirus [24]. Since a large portion of the human population can

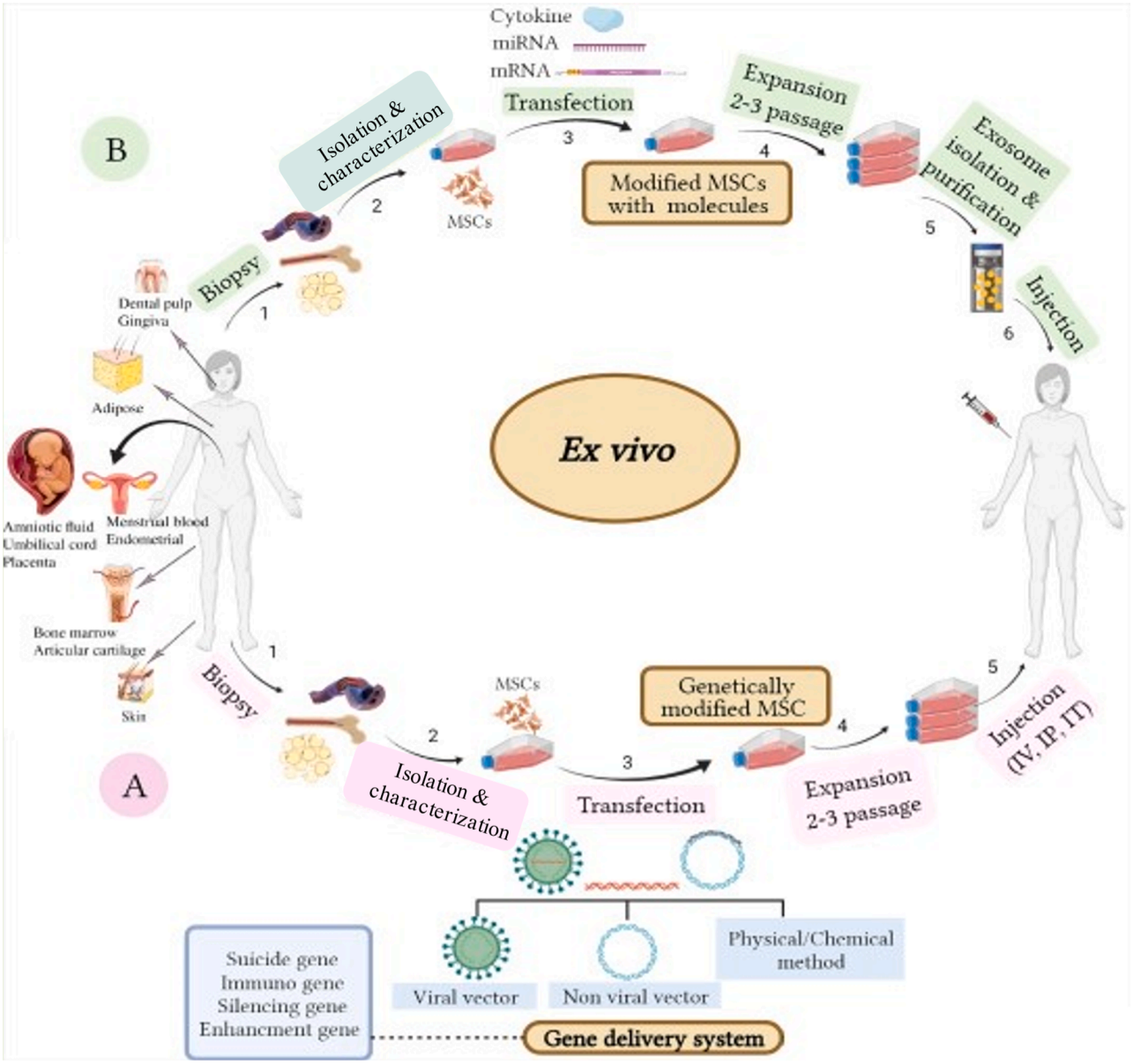


Fig. 1. Schematic representing the strategies of genetically engineered MSC and MSC-derived exosomes for cancer therapy. (A) (1–2) MSCs are isolated from adipose tissue, bone marrow, and umbilical cord. (3) Various genes are transferred into MSCs by three main techniques; viral vectors, non-viral vectors, and physical/chemical methods. (4–5) Expansion of genetically modified MSC for 2–3 passages and administration via veins for cancer treatment. (B) MSC-derived exosomes represent an attractive therapeutic approach for treating cancer tumors. (1–2) MSCs are isolated from adipose tissue, bone marrow, and umbilical cord. (3) MSCs are altered with therapeutic molecules such as mRNA, miRNAs and cytokines. (4–5) Expansion of MSC for 2–3 passages and exosomes are isolated, purified and characterized from modified MSC. (6) Administration of exosomes via veins for cancer therapy.

neutralize AAV antibodies, the in vivo effect decreases dramatically. Hence, AAV vectors may be among the most promising vectors because of their reduced pathogenicity in humans and their ability to achieve long-term gene expression. Implantation of engineered MSCs via viral vectors may induce a target-specific therapeutic impact on tumor cancer procession and metastasis [25]. For instance, Relation et al. [26] showed that MSCs expressing interferon-gamma (IFN-γ) prevented tumor growth in mouse lung carcinoma and neuroblastoma models. These modified MSCs used a lentiviral vector for expressing human IFN-γ by the same backbone vector [26]. Recently, site-directed integration by transcription activator-like effector nucleases (TALENS) and clustered regularly interspaced short palindromic repeats (CRISPR) have been used for MSC engineering. Although viral vectors have high efficiency, their high production costs and incompatible immune reactions still present significant problems. Instead, non-viral vectors cause little stimulation of the immune system, and their flexibility and compatibility have made these vectors largely superior [23].

3.2. Non-viral vectors

Non-viral vector-mediated gene transfer is another option that is amenable to increased manufacturing, adaption with a broad array of design choices, and decreased immune stimulation. Common procedures used for transfecting MSCs include chemical and physical methods. Chemical methods include polymeric carriers, lipid agents, inorganic nanoparticles, and dendrimers. Using inorganic nanoparticles (NPs) for transfecting MSCs is frequently associated with polycations. For instance, gold nanoparticles with Jet-polyethylenimine (PEI) reagent led to a 2.5-fold increase in transfection efficiency over conventional Jet-PEI polyplexes [27]. PEI (25 kD) is a synthetic, water-soluble, linear/-branched polymer, and water-soluble. Due to the ability to generate a complex with DNA and support the release of endosomal through the "proton sponge effect", it is widely used in gene delivery systems [28].

In this regard, Park et al. [29] showed that the function of silica with PEI was better than PEI, which led to a 75 % increase in efficiency for human MSC transfection [29]. Furthermore, Muroski and colleagues [30] recently created modified gold NPs using Ku70 peptide via N-cysteine to improve MSCs transfection up to 80 % [30]. Polymeric and lipid agents can achieve a transfection efficiency ranging 2–35 % in MSC. Also, dendrimers (repetitively branched molecules) typically transfect MSCs with about 10–17 % efficiency [22]. Physical methods include nucleofection, electroporation, and sonoporation. In nucleofection, the nucleic acid is directly transferred into the nucleus of target cells by an electrical pulse. In electroporation, the pores of cells are opened by an electrical pulse and then the nucleic acid directly drives into the cytoplasm. Sonoporation increases the permeability of the cell membrane and allows the transport of nucleic acid into the cells. Although Otani and colleagues [31] showed the successful transfection of siRNA into MSCs by using a combination of ultrasound and microbubbles, the acoustic severity significantly affected the viability of the cells [31]. Because transient gene expression and low efficiency of transfection are the limitations of non-viral vectors in MSCs, they have been used in limited studies and are only favorable for regenerative medicine [29].

4. Applications of modified MSCs

4.1. Engineered MSCs for drug delivery and secreting antitumor molecules

MSCs are good candidates for targeted drug delivery vehicles due to their unique properties, including (1) anti-inflammatory properties by using cytokine secretion and growth factors; (2) tissue homing ability, and (3) low immunogenicity due to the lack of MHC-II expression [22]. MSCs are applied exogenously to produce protein-based agents for treating cancers or genetic diseases. Engineered MSCs mostly lead to enhanced retention, survival, growth factor production, and migration of regenerative medicine towards cancer cells for cancer therapy [32]. Engineered MSCs are used to present natural biomolecules or synthesizing ligands to overcome different physiological barriers and control their interaction with the tumor microenvironment (Fig. 2A) [25]. They have also been engineered to produce prodrug-activating enzymes against tumors and a wide variety of proteins for cancer therapy [22,33]. These proteins include interferon-β, interleukins (IL-18, IL-12, and IL-2), and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) [34]. Moreover, MSCs are genetically engineered to express suicide genes (cytosine deaminase, thymidine kinase, and carboxylesterase). For the first time, Studeny et al. [32] showed the application of engineered MSCs for direct delivery of the interferon ß (IFN-ß) gene to melanoma xenograft mice. This study demonstrated that decreasing tumor growth prolongs the survival of tumor-bearing mice.

Another current approach for treating cancer is transporting an oncolytic virus (Fig. 2B) designed to amplify in tumor cells and the target site. Several studies have showed that MSCs can be an effective carrier of oncolytic viruses in treating human hepatocellular carcinoma [35] and ovarian tumors [36]. According to the host immune response's role in preventing the virus translation process and subsequent weak diffusion of the virus, only a few oncolytic viruses have been successfully used in clinical trials to date [22]. Although engineered MSCs have shown effectiveness in treating cancer, monotherapy has not demonstrated efficiency in treating highly heterogeneous cancer. Therefore, combination therapy is a suitable therapeutic approach due to resistance to chemotherapy during cancer evolution. For instance, TRAIL-engineered MSCs transported along with temozolomide in treating glioblastomas were more effective than monotherapy. In the following, to ensure that both drugs reach the tumor site together, the secreted CD20-specific single-chain Fv antibody of engineered MSC linked to TRAIL (scFvCD20-TRAIL) was explored [37]. Moreover, this combination (temozolomide plus TRAIL-engineered MSC) leads to simultaneous induction of apoptosis and inhibition of proliferation in cancer cells, which is more beneficial to treat non-Hodgkin's lymphoma. A concern about genetically engineered MSCs is the long-term safety of viral gene therapy; while non-viral gene transfection can reduce this concern, it has low efficiency. As genetically engineered MSCs can only deliver protein and peptide-based drugs, nanoparticle delivery strategies are used for delivering non-peptide drugs and therapeutic nucleic acids [37]. Engineered MSCs used for tumor-targeted drug delivery are summarized in Table 1.

4.2. Nanoengineered MSCs for drug delivery

MSCs can be modified to carry chemical anticancer agents like doxorubicin (DOX), paclitaxel (PTX), gemcitabine (GEM), or gemcitabine-carboplatin (GCB) (Fig. 2D). Besides tumor-targeted delivery, nanoengineered MSCs can be used as diagnostic aids for imaging tumors [38]. Xu et al. employed MSCs loaded with plasmonic-magnetic hybrid NPs (LDGI: lipids, doxorubicin, gold nanorods, and iron oxide nanocluster) for photothermal treatment (PT), chemotherapy, and photoacoustic (PA) imaging of triple-negative breast cancer (TNBC) tumors. Gold nanorods are primarily interesting from the point of view of their optical properties, which strongly depend on both the particle size and shape. Such optical attributes are related to the interaction between the metal conduction electrons and the electric field component of incident electromagnetic radiation, leading to strong and characteristic absorption bands in the visible part of the spectrum [39]. Iron oxide nanoparticle possess an important place due to its superparamagnetic nature, and its small size. Iron oxide nanoparticle is biocompatible to a certain extent with the human system as the chelator of hemoglobin contains Fe(II) atoms [40]. LDGI hybrid NPs and iron oxide nanoclusters increased MSC migration toward cancer cells and CXCR4 expression.[41,42] MSC exposure to nanoparticles with adsorbed doxorubicin controlled drug release and reduced breast cancer, lung melanoma metastases, and glioblastoma in mice. In vitro and in vivo,

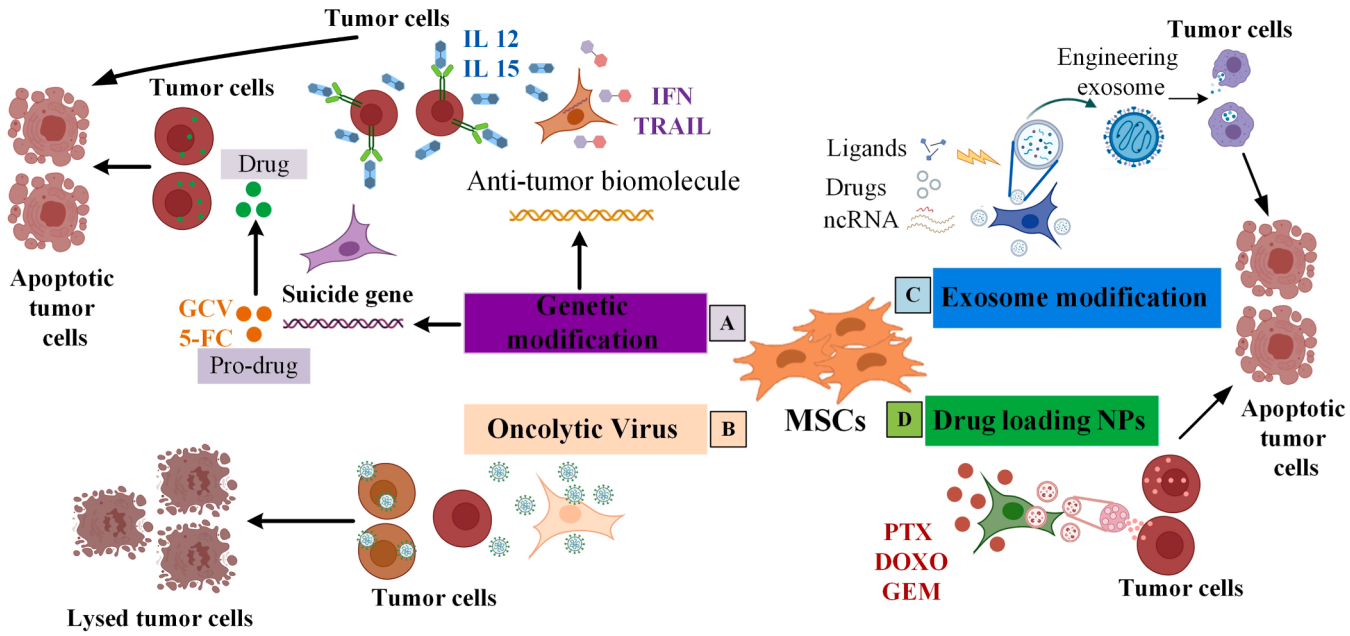


Fig. 2. Different engineering strategies enable MSCs to release antitumor agents for cancer therapy. (A) Genetic modification of MSCs with therapeutic genes can express "suicide genes" and secrete antitumor molecules that function directly on tumor cells. Suicide genes can activate an inactive prodrug to the active anticancer drug for expressing prodrug activating enzymes, including cytosine deaminase (CD) or thymidine kinase (TK), which converts a prodrug (e.g, 5-FC, GCV) into a cytotoxic molecule and induces apoptosis that can kill cancer cells. Engineered MSCs are used to induce the production of antitumor molecules such as pro-apoptotic molecules (e.g., TRAIL), interferons (e.g., IFN-α, IFN-β, IFN-γ) and interleukins (e.g., IL-2, IL-12, IL-15, IL-18). These proteins can bind to their receptors expressed to induce apoptosis and bolster the host inflammatory response via crosstalk with tumor-infiltrating leukocytes. (B) MSCs can be used as carriers and amplifiers of oncolytic viruses. These cells provide an appropriate vehicle to protect viruses from host immune responses and deliver them into tumor sites. (C) Engineered exosomes can be used as a delivery carrier for targeting cancer tumor. Extrinsic ncRNA and/or anticancer drugs after being loaded into exosomes can directly target tumors and block their further development. In addition, the surface modification of exosomes with ligands corresponding to receptors overexpressed on cancer cell surfaces can improve the cellular uptake of exosomes by tumor cells. (D) MSCs can be loaded with anticancer drugs/nanoparticles specifically for migration to the cancer site and effective release of therapeutic nanoparticles or active drugs. Drugs are dissolved in the MSC culture media and MSCs as cellular vehicles of delivery of NPs absorb doxorubicin (DOXO), paclitaxel (PTX), or gemcitabine (GEM) and release them in their active forms into the tumor microenvironment, inhibiting tumor cell growth.

doxorubicin-loaded liposomes on MSC outer membranes had a specific cytotoxic effect on colon cancer without affecting MSC as carrier cells. Paclitaxel-loaded MSC was effective against pancreatic, brain, squamous cell, mesothelioma, metastatic lung, and leukemia. In a recent study, drug pharmacokinetics and pharmacodynamics after MSC containing paclitaxel-loaded nanoparticles were analyzed. The authors found that 2×10^6 MSC (equivalent to 50 μg or 2.5 mg/kg of paclitaxel) completely eradicated mouse orthotopic human lung tumors. A transcription-activating peptide on MSC membranes increased nanoparticle formation and paclitaxel-mediated cytotoxicity against target lung cancer cells. Gemcitabine-releasing MSC inhibited human pancreatic cancer and squamous cell carcinoma development without changing MSC multi-lineage differentiation capacity or surface marker expression. Coupling nanoparticles with MSCs can be accomplished through cell surface anchorage and cellular internalization. In this way, drugs can be released in a sustained and local manner via the migration of MSCs to the tumor [22]. Hence, this nanohybrid-loaded MSC delivery system could be advanced as a synergistic strategy combining chemotherapy, PA imaging, and PT therapy to treat cancers effectively [43]. Nano-engineered MSCs used for drug delivery in cancer therapy are summarized in Table 1.

4.2.1. Nanoengineering via cellular internalization

Cellular internalization represents one of the techniques used for drug loading. In this approach, drug-encapsulated NPs are encompassed through endocytosis. Subsequently, an evasion process occurs to navigate away from the endolysosomal compartment, facilitating the delivery of MSCs with drug delivery capabilities. Some small therapeutic cargos can be directly loaded onto MSC without any vehicle encapsulation. Panyam et al. [44], for the first time, indicated that NPs formulated from specific polymers like poly L-lactide-co-glycolide (PLGA) can leave the endosomal portion and lead to greater intracellular preservation of the encapsulated drug [44]. PLGA is generated from the polymerization of lactic acid (LA) and glycolic acid (GA) and is widely used in medical engineering materials and pharmaceuticals due to its biodegradability, non-toxicity, good plasticity, and biocompatibility [45]. Based on organic phase solvents the mean particle sizes of PLGA are different between 70 and 290 nm [46].

Applying NPs with cationic surfaces such as poly (α-L-lysine) (PLL) and PEI results in improving the cellular uptake of MSCs for the non-viral gene. PLL with a molecular weight between 30 and 70 kDa is a water-soluble cationic biopolymer generated by the polymerization of L-lysine monomer. PLLs, have naturally inherent properties such as non-antigenicity, biocompatibility, antibacterial property, and biodegradability, are used in different pharmaceutical fields and biomedical domains [47]. Kostura et al. [48] demonstrated that the use of PLL in coating superparamagnetic iron oxide (SPIO) NPs leads to enhanced cell uptake by MSCs. SPIO nanoparticles have been utilized as probes for cell and subcellular structure identification, and gene delivery due to their interesting size-dependent characteristics and relative biocompatibility [49]. PEI-SPIO NPs are another series of molecules designed and optimized for MSCs loading. These NPs have no remarkable toxicity effect on MSCs and in conclusion, they demonstrated high loading efficiency [50]. Recently, liposomal NPs have been used to deliver therapeutic cargos to MSCs through endocytosis and release their cargos by integrating them into the endosomal membrane intracellularly. In contrast to polymeric NPs, high doses of liposomal NPs are essential for cellular loading and have significant cytotoxicity [51]. An essential property of

Table 1
Engineered and nano-engineered MSCs used for tumor-targeting drug delivery.

Type of engineering	Engineering methods	Delivery technique	Target cancer	Target gene or drugs	Study method	Outcome	Ref.
Genetically Modified MSC	Direct Gene manipulating	Viral vector	Non-Hodgkin's lymphoma	scFvCD20-TRAIL	In vivo In vitro	Selectively migrated to the tumor site Inhibited tumor growth	[127]
			HCC	E1A	In vivo In vitro	Specific antitumor activity High tumor-migrating tropism	[128]
			Breast cancer	IFN-β	In vivo In vitro	Reduced tumor growth, metastases and prolonged survival	[129,130]
			Lung carcinoma	PEDF	In vivo In vitro	Reduced tumor growth and prolonged survival	[110]
			Mesothelioma	TRAIL	In vivo In vitro	Reduced tumor growth	[111]
			Ovarian Cancer	Endostatin	In vivo In vitro	Preferential homing to the tumor site Significantly decreased tumor volume without apparent systemic toxic effects	[131]
			HCC	Apoptin	In vivo In vitro	Reduced tumor volume	[132]
				HNF4α	In vivo In vitro	Reduced tumor growth	[133]
			Liver cancer	NK4	In vivo In vitro	Apoptosis induction, angiogenesis and lymphangiogenesis suppression	[122]
			Glioma	BMP4	In vivo In vitro	Prolonged survival in a murine model of GBM[a]	[134]
			Melanoma	IFN-a	In vivo In vitro	Apoptosis induction, angiogenesis suppression and significantly prolonged survival	[135]
			Leukemia	IFN-g	In vitro	Immunostimulation, and apoptosis induction	[136]
			Breast tumor	TNF-α/CD40L	In vivo In vitro	Led to a valuable antitumor immune response and longest mouse survival	[137]
			Glioma	3TSR/S-TRAIL	In vivo In vitro	Significantly targeted both tumor cells and vascular component of GBMs, inhibited tumor progression, and extended survival of mice bearing highly vascularized GBM	[138]
			Glioma	IL-2	In vivo In vitro	Antitumor effect and further prolonged the survival of tumor-bearing rats	[139]
			Ovarian carcinoma	IL-12	In vivo In vitro	Immune system cell activation and induced cellular apoptosis	[140]
			Ascites	IL-12	In vivo In vitro	Reduced ascites volume and prolonged survival	[141]
			Lymphoma	IL-21	In vivo In vitro	Delayed tumor development and prolonged survival	[142]
			Colorectal Cancer	IL7, IL12	In vivo In vitro	Established a pro-inflammatory response that prolonged T cell antitumor attack Successfully counteracted repression through the tumor environment	[143]
			HCC	IFN-γ, IL-10	In vivo In vitro	Significantly reduced tumor growth Increased expression of cell cycle inhibitors p21 and p27 Inhibited HCC in vitro and in vivo by modulating cell cycle regulators and MAPK pathway	[144]
			Glioma	IL-18, IFN-β	In vivo In vitro	Promoted cell apoptosis, antitumor cytokine production Significantly prolonged survival and inhibited tumor growth in a rat intracranial glioma model CD4+ and CD8+ T-cell infiltration in intracranial glioma tissues	[145]
			Lung tumor	CX3CL1	In vivo In vitro	Cytotoxic T cells and NK cells activation	[146]
			Pancreatic cancer	miR-126–3p	In vivo In vitro	Overexpressed miR-126-3p derived from BMSCs[b] exosomes inhibited the proliferation, invasion, and metastasis of pancreatic cancer cells, and promoted their apoptosis both in vitro and in vivo.	[147]
			Lung carcinoma	PEDF	In vivo In vitro	Inhibited tumor angiogenesis and induced apoptosis	[110]
			Glioma	microRNA-584	In vivo In vitro	Suppressed tumor progress Decreased tumor mass weights	[148]
			Glioma	miR-124	In vitro	Enhanced the chemosensitivity of GBM cells to temozolomide and decreased the migration of GBM cells	[149]
			Glioma	miR-145, miR-124	In vitro	Decreased the migration of glioma cells and the self-renewal of glioma stem cells	[150]
			Glioma	PE cytotoxin	In vivo In vitro	Blocked protein synthesis, antitumor agent Long-term survival of mice	[151]

(*continued on next page*)

Table 1 (*continued*)

Type of engineering	Engineering methods	Delivery technique	Target cancer	Target gene or drugs	Study method	Outcome	Ref.
			Glioblastoma, Breast and Lung tumors	Oncolytic viruses	In vivo In vitro	Induced caspase-mediated apoptosis and tumor destruction by virus replication	[152,153]
			Angiogenesis	kringle1–5	In vivo In vitro	Decreased microvessel density and blood flow	[154]41
			Glioma	PTEN	In vitro	Cytotoxic effects on glioma cells and induction of G (1)-phase cell cycle arrest	[146]
		Non-viral	Pancreas	HSV-TK, CCL5	In vivo In vitro	Reduced tumor growth and metastases	[155]
			Glioma	TRAIL	In vivo In vitro	Induced tumor-specific apoptosis Inhibited GBM growth, extended survival, and reduced the occurrence of microsatellites	[156]
			Pancreatic cancer	IL-25	In vivo In vitro	Hypothesized induction of apoptosis in cancer cells	[144]
			Glioblastoma	NIS	In vivo	Noticeably slower rate of tumor development and a longer median survival.	[157]
			Glioblastoma	NIS	In vivo	Delayed tumor growth and improve median survival up to 60 %.	[158]
			Glioblastoma	NIS	In vitro	Decrease in tumor growth and a significant extension of survival.	[159]
			Glioblastoma	NIS	In vitro In vivo	NIS is a sensitive reporter gene and can be monitored by high-resolution PET imaging using the radiotracers sodium iodide.**	[160]
			Glioblastoma	NIS	In vitro In vivo	Significant delay in tumor growth and prolong survival.	[161]
			Thyroid cancer	NIS	In vivo	saRNA-mediated NIS expression increasing iodide uptake via AMPK/mTOR pathway.	[162]
			Thyroid cancer	NIS	In vitro In vivo	MSCs, when combined with the hNIS gene, can effectively combat tumors using 131I therapy.	[163]
			Thyroid cancer	NIS	In vitro	NIS expression in genetically modified MSCs enables therapeutic 131I application and non-invasive imaging	[164]
			HCC	NIS	In vivo In vitro	Significantly delayed tumor growth and prolonged survival	[165]
	Gene-directed enzyme prodrug therapy	Viral vector	Glioma	HSVtk GCV	In vivo In vitro	Significant in vitro and in vivo bystander effect	[166–168]
				TK-GCV VPA	In vivo In vitro	Significantly inhibited tumor growth and prolonged the survival of glioma-bearing mice	[169]
				CDb (5-FC)	In vivo In vitro	Significantly prolonged survival compared with control animals Tumor regression was possible using nontoxic levels of 5-FC Bystander effect of 5-FC/CD gene therapy did not require direct cell-to-cell contact	[170]
				CDy::UPRT (5-FC)	In vivo In vitro	Tumor regression and increased survival time	[171]
				CYP2B6 (CPA)	In vivo In vitro	Tumor-selective migration and antitumor effects in glioma	[172]
			Melanoma	CDy::UPRT (5-FC)	In vivo In vitro	Therapeutic cell homing into subcutaneous melanoma and mediated tumor growth inhibition	[173]
			Prostate cancer	CDy::UPRT (5-FC)	In vivo In vitro	Significantly inhibited PC tumor growth after intravenous administration	[174]
		Non-viral	Pancreatic carcinoma	HSVtk GCV	In vivo In vitro	Reduced primary pancreatic tumor growth and reduced liver metastases	[155]
			HCC		In vivo In vitro	Reduced tumor growth Microvessel density remained unchanged by suicide gene treatment	[175]
			Pancreatic breast cancer		In vivo In vitro	Toxic tumor-specific environment Significantly reduced primary tumor growth and prolonged life in both tumor models	[176]
			Pulmonary melanoma		In vivo In vitro	Engineered BMSCs had significant suicide effects Tendency to target tumor nodules after systemic delivery	[21]
			Gastric cancer	CDb (5-FC)	In vivo In vitro	Tumor volumes and weights of mice injected with CD-hMSC decreased significantly after treatment with 5–FC	[177]
Non Genetically Modified MSC	Nano Engineering	Cellular internalization (Endocytosis)	Lung Adenocarcinoma	Paclitaxel	In vivo In vitro	Improved biodistribution in lung tumors Improved antitumor efficacy Reduced dose dependent toxicity	[54]
			Glioma	Doxorubicin	In vivo In vitro	Enhanced penetration and sustained release of doxorubicin in tumor Improved survival	[178]

(*continued on next page*)

Table 1 (*continued*)

Type of engineering	Engineering methods	Delivery technique	Target cancer	Target gene or drugs	Study method	Outcome	Ref.
			Glioma	None	In vivo In vitro	NP-loaded cells migrated toward an experimental human glioma model	[38]
			Tumor cells	Paclitaxel	In vitro	Size, surface charge, starving time of MSCs, incubating time and concentration of NPs could influence the efficiency of NPs uptake	[52]
			Glioma	None	In vivo In vitro	Improved cell homing efficiency, and tracked the fate of the cells in vivo	[52]
			Osteosarcoma	Porphyrin (TPPS)	In vitro	Efficient targeted delivery strategy in killing human OS cells Novel tri-component system able to induce controlled and massive cells death in a short time frame when stimulated with laser light	[179]
			Lung and ovarian cancer	Paclitaxel	In vivo In vitro	Selective accumulation and retention in tumors	[53]
			Breast Cancer	Doxorubicin	In vivo In vitro	Improved payload capacity Improved survival and tumor inhibition	[58]
			Lung tumor	TNF- TRAIL	In vivo In vitro	Effective tumor target delivery vehicle in cancer gene therapy	[180]
				Doxorubicin	In vivo In vitro	Enhanced targeting and permeation into tumor nest Significant reduction of lung metastases	[181]
				None	In vivo In vitro	MSCs could be tracked in vivo to multiple lung metastases using MRI	[182]
			Breast Cancer	Doxorubicin	In vivo In vitro	Enhanced migration and penetration Improved antitumor efficacy	[41]
		Cell penetrating peptide	Lung adenocarcinoma	Paclitaxel	In vivo In vitro	Improved payload capacity Improved survival and tumor inhibition	[56]
		Cell surface anchoring	Lung adenocarcinoma	Doxorubicin	In vivo In vitro	Improved survival and tumor inhibition	[61]
			Ovarian adenocarcinoma MA148 cell line	Paclitaxel	In vivo In vitro	Improved payload capacity of MSCs Improved delivery and anticancer efficacy Inhibited tumor growth ($p < 0.05$) and improved survival	[60]
			Glioma	Doxorubicin	In vivo In vitro	Improved penetration and tumor kill	[183]

[a] Glioblastoma multiforme.
[b] Bone marrow stromal cells.

NPs is keeping the encapsulated drug from efflux vehicles existing on the MSCs that increase absorption and payload capacity. Several groups have demonstrated that using MSCs as delivery vehicles for cytotoxic drugs is limited by their overexpression of drug efflux transporters like P-glycoprotein (Pgp), which leads to poor intracellular drug accumulation. Hence, the uptake of NPs inside MSCs is dependent on size, concentration, and time [52,53]. Moreover, Dai et al. [52] demonstrated that the migration of MSCs was weakened by loading of NPs [52]. Nonetheless, this problem was solved by an effective tumor-targeting strategy based on engineering MSCs with paclitaxel-loaded PLGA NPs [53]. In the study, the nanoengineering strategy did not affect the differentiation or migration of MSCs in vivo and in vitro. Nanoengineered MSCs demonstrated very little effect on cell viability through concentration and time-dependent uptake of NPs. Furthermore, MSCs with the property of dose-dependent cytotoxicity were used against MA148 human epithelial ovarian carcinoma cells and A549 human lung adenocarcinoma cells in vitro [53,54].

Although intravenous injection of nano-engineered MSCs led to selective tumor maintenance and accumulation in an orthotopic lung tumor model, free NPs were mainly circulated in the spleen and liver [53]. Layek et al. [54], in their study using the A549 orthotopic lung tumor model, demonstrated that nano-engineered MSCs could home to tumor sites and store cellular drugs that released a drug payload over a long period. It was determined that nano-engineered MSCs had more effective tumor growth inhibition and superior survival than NP-encapsulated forms of paclitaxel. Based on pharmacokinetic studies, the drug exposure of paclitaxel led to ameliorating the antitumor efficacy of nano-engineered MSCs in the tumor tissue. Moreover, the usual side effects of paclitaxel, such as leukopenia, were decreased via this strategy compared to paclitaxel solution and paclitaxel-loaded PLGA NPs; meanwhile, nano-engineered MSCs require a much lower dose to improve anticancer efficacy [54]. In a similar study, Wang et al. [55] compared nano-engineered MSCs with paclitaxel-loaded PLGA NPs; they found that free paclitaxel-primed MSCs can increase and sustain the release of paclitaxel. Thus, the nanoengineering process has little effect on the cell cycle, migration, and differentiation of MSCs [55]. One of the problems with internalizing NPs is that the rate of exocytosis results in low drug loading and maintenance. In this regard, Moku et al. [56] assessed PLGA NPs surface-functionalized with transactivator of transcription (TAT) peptides for increasing drug loading in MSCs. They reported that applying TAT can increase the intracellular drug accumulation of NPs and enhance their maintenance. As well, nano-engineered MSCs resulted in significant inhibition of tumor growth ($p < 0.05$) and ameliorated survival of orthotopic mouse models with lung cancer compared to paclitaxel-encapsulated NPs or free NPs [56]. All the studies mentioned above demonstrate that MSCs can directly internalize the therapeutic agent-loaded NPs or drugs. Nano-engineered MSCs usually display more efficient potency for drug loading than polymeric NPs and liposomal NPs. However, a positive NP charge increases the cell loading efficiency. Receptor-mediated endocytosis is also a possible strategy to elevate the cell loading yield. Furthermore, decorating NPs with antibodies against MSCs surface antigen CD90 could ameliorate the kinetics of NP internalization [51,57].

4.2.2. Nanoengineering via surface anchoring

The drug loading capacity of nano-engineered MSCs limits their use in small-molecule drug delivery. To overcome this restriction, cell-surface conjugation or dual drug-loading strategies containing membrane conjugation and endocytosis have been evaluated. Covalent conjugation or physical association by electrostatic and hydrophobic

interactions are used to attach NPs to the surface of MSCs. When NPs interact with the MSC membrane surface, the cargos are carried and anchored on the cell. Therefore, a synthetic "receptor" could be developed on the cell surface. For instance, a novel nano-engineering process was provided by promoting endocytosis of doxorubicin conjugates associated with cell surface anchoring of the drug conjugates through avidin-biotin complex formation. Modified MSCs mainly migrated into foci of metastatic tumors in the lung. These drug-carrying MSCs could prolong the survival of tumor-bearing mice and inhibit tumor growth compared to free doxorubicin and doxorubicin conjugates. Hence, this approach leads to higher drug loading than each of the other modes [58]. Another interesting strategy that can anchor drug-loaded NPs on the MSCs membrane is glycol-engineering of MSCs to express synthetic functional groups like azides. Layek et al. [59] showed that culturing MSCs in N-azidoacetylmannosamine-tetraacylated (Ac4ManNAz) supplemented media significantly expressed azide-bearing sialic acid on the cell surface without modifying their differentiation potential, viability, and migration [59]. In another study, Layek et al. [60] used azide groups on the surface to conjugate dibenzyl cyclooctyne (DBCO)-functionalized, paclitaxel-loaded NPs to MSCs, which provided for remarkably enhanced NP loading in MSCs [60]. This study used a novel two-step tumor-targeting strategy via glycol-engineered MSCs for tumor-localized anchors. A highly dense artificial receptor (azide groups) pool in tumor tissues is developed by systemic administration of azide-expressing MSCs that can enhance the tumor-targeting ability of DBCO-functionalized NPs through copper-free click chemistry. Layek et al. [60] demonstrated the incorporation of DBCO-functionalized NPs on azide-labeled MSCs along with paclitaxel compared with paclitaxel-loaded NPs in an orthotopic metastatic ovarian tumor model led to enhanced survival, migration, and tumor growth inhibition [60]. Kim et al. [61] also showed the co-destruction of lung tumor cells by MSCs loaded with nano-drug conjugations. They reported that secreting CXCL12 and IL-8 by lung cancer cells leads to attracting BM-derived MSCs with high affinity. MSCs were nano-engineered by combination with carbon nanotube (CNT)-doxorubicin either via surface engineering with CD90, CD73, or through intracellular uptake. The membrane of engineered MSCs demonstrated 9-fold more drug uptake and higher cytotoxicity in H1975 lung cancer cells in vitro. Also, it emphasized a remarkable diminution in tumor growth in A549 lung tumors in vivo. Moreover, it was reported that the destruction of engineered MSCs membranes via secreted chemokines from the dead tumor cells led to improved tumor growth inhibition compared to common chemotherapeutic approaches [61].

4.3. MSCs as a vehicle for targeting suicide genes

One of the promising alternatives to conventional chemotherapy is gene-directed enzyme prodrug therapy (GDEPT), also known as suicide gene therapy. In 1986, for the first time, using suicide genes against cancer was reported by Moolten et al. [62]. This strategy refers to the expression of a suicide gene in tumor cells for the in situ transformation of a prodrug into cytotoxic metabolites and thus promises decreased systemic toxicities compared to conventional chemotherapy drugs [62]. There are two steps in the GDEPT concept: (1) delivery of an encoding gene of a prodrug-activating enzyme, (2) applying an inactive prodrug that is topically activated by this enzyme into cytotoxic metabolites. Common combinations used for suicide genes with anticancer properties include herpes simplex virus thymidine kinase (HSV-TK) along with ganciclovir (GCV), carboxylesterase (CE) with irinotecan (CPT-11), *E. coli* cytosine deaminase (CD) with 5-fluorocytosine (5-FC), and cytochrome P450 (CYP) with cyclophosphamide (CPA). These compounds have been examined successfully in preclinical animal models with malignant tumors such as brain tumors, ovarian carcinomas, hepatocellular carcinomas, and prostate cancers [33]. Utilization of the GDEPT process by MSCs in the treatment of solid tumors has significantly increased. It has been shown that integrating viruses, such as retroviruses or lentiviruses, permanently express the suicide gene in MSCs. However, the application of viral vectors for targeting suicide genes is associated with several limitations, such as high immunogenicity.

Furthermore, GDEPT has limitations due to its systemic toxicity and low specificity for tumor cells. Hence, using genetically-modified MSCs in the GDEPT strategy may overcome restrictions related to viral vectors, systemic administration of some cytokines, and anti-neoplastic agents with a short half-life and high toxicity [63]. According to the GDEPT theory, MSC-targeted gene therapy involves a two-step approach. First, the gene of a foreign enzyme (bacterial, viral, or yeast) can be transduced by MSCs into the tumor site and second, transcription of the gene encoding the prodrug-drug transforming enzyme develops a fatal substance at the tumor site [64]. For example, HSV-TK/ GCV is the combination that has been most studied in MSC-based tumor therapy. GCV is phosphorylated by thymidine kinase from HSV-1 to a monophosphate (GCV-MP).

Human MSCs express both the mitochondrial and the cytosolic TK enzymes, while these endogenous enzymes have a lower ability to modify GCV compared to HSV-1. These kinases augment the alteration to the active triphosphate GCV-TP, which inhibits DNA synthesis, leading to cell death through apoptosis. Zhang et al. [21] reported that the delivery of MSC-TK/GCV to tumor cells led to more efficient induction of cytotoxic effect. It was determined that the cytotoxic metabolite of GCV (GCV-TP) needs gap junctions to penetrate the membranes of tumor cells [21]. In order to increase the antitumor effects of MSC-TK/GCV, some preclinical studies suggested the combination of HSV-TK/GCV with other drugs, such as histone deacetylase inhibitor 4-phenylbutyrate (4-PB) and valproic acid (VPA), enhanced the bystander effect of suicide gene therapy. VPA upregulates gap junction proteins, like connexin (Cx) 43 and 26, in glioma cells, thereby increasing the bystander effect and the number of gap-junctional connections between glioma cells and therapeutic BM-MSCs. This kind of MSC modification is an attractive solution for cancer treatment because there were no adverse side effects for tumor neighboring normal cells and HSV-TK-engineered BM-MSCs [65]. Therefore, improving the antitumor effects of MSC-TK/GCV and HSV-TK modified MSC is the most suitable approach that could be effectively transferred to the cancer area. Generally, HSV-TK-engineered MSCs function via the "bystander effect", which is not only toxic in the cells where it is produced but also maintains this attribute after transfer to the neighboring target cells [66]. HSV-TK-engineered MSCs have been utilized in different types of tumors such as hepatocellular carcinoma (HCC), pulmonary melanoma metastasis, pancreatic carcinoma, prostate tumor, and gliomas [67].

For instance, HSV-TK engineering of BM-MSCs improved the tumoricidal effect by cotransfection of the *TRAIL* gene despite some drawbacks such as antagonistic antitumor activity [68]. In order to increase the therapeutic effects of modified cells, HSV-TK engineering might be applied with additional modifications. In this regard, the overexpression of HSV-TK accompanied by cytosine deaminase expression was used in lung metastases treated with engineered ATMSCs [69]. CD has been claimed to be the most effective prodrug system and thus may be a good candidate for prodrug anticancer strategies. Moreover, CD is considered safe for the essential biologic properties of ATMSCs and BM-MSCs. Therefore, CD-overexpressing MSCs were successfully applied in glioblastoma, glioma, osteosarcoma, gastric cancer, melanoma, and medullary thyroid carcinoma [67]. Significant tumor growth inhibition was noticed in the prostate cancer and colon cancer mice models after the administration of CD-engineered AT-MSC [67,70].

4.4. MSC-derived exosomes for cancer therapy

MSCs release several extracellular vehicles (EVs), including microvesicles (MVs; between 0.1 and 2 mm in diameter) and exosomes (between 30 and 150 nm in diameter), which participate in intercellular communication between MSCs and target cells [71,72]. Exosomes made

by MSCs have important physiological properties and are released by MVs, which are the inner buds of the late endosome membrane. Exosomes are released into the extracellular environment when MVs fuse with the cell membrane. Target cells nearby or biological fluids can transport them far away [73]. These nanoscale particles carry complex cargo, including lipids, proteins, and nucleic acids (Fig. 2C). They exhibit a strong compatibility with biologically active molecules, such as RNAs and proteins. Therefore, these particles protect homeostasis within the tissue and respond to external stimulation [74]. These exosomes show the common surface markers of exosomes, like CD81 and CD9, and some adhesion molecules, like CD73, CD44, and CD29, that are found on the membrane of MSCs [75]. Other studies have demonstrated that MSC-derived exosomes are able to recapitulate the biological function of MSCs, and can serve as a substitute agent for whole-cell therapy [73,76]. Moreover, exosomes can spontaneously attach to the tumor microenvironment [77]. Exosomes produced by MSCs (MSCs-Exo) start dynamic interactions that can significantly change the phenotypes of receiving tumor or stromal cells (Fig. 3). Additionally, via transporting chemicals, MSCs-Exo can perform pro-tumor [78] and anti-tumor[79] actions in recipient cells (Fig. 1). It is noteworthy that MSCs-Exo generated from various tissue sources have distinct (promoting or inhibitory) impacts on malignancies. It is possible for exosomes to carry messenger RNAs (mRNAs), and microRNAs (miRNAs). Short, non-coding RNAs known as miRNAs are linked to antitumor activity and frequently show altered gene expression in a range of cancers. By releasing a variety of therapeutic compounds—most notably, miRNAs—exosomes produced from MSCs can assist in tissue repair [80]. Bio fluids can carry them long distances, or target cells close by. When exosomal miRNA is absorbed by a neighboring or distant cell, it takes a role in post-transcriptional regulation of genes. Through partial sequence complementarity, exosomal miRNAs bind to the mRNA of the target gene once they reach the target cells. For mRNA identification, the seed region at the 5′ end is essential, and MiRISC regulates translation by guiding the attachment of miRNA [81]. Exosomes produced from MSCs have the potential to stimulate tumor development in many ways. When Valadi et al. discovered that exosomes include microRNA and mRNA, they suggested naming this type of RNA “exosomal RNA” [82,83]. MicroRNA-containing exosomes are hypothesized to control cancer stem cell and cell communication [84]. Exosomal miRNAs released by stem cells have been demonstrated in a number of recent studies to impact the biological activity of cancer cells [85]. Figueroa et al. examined the exosomal composition in order to assess the impact of MSC-derived exosomal microRNAs on cancer cells. They found that miR-1587 functions as a mediator of the exosomal-promoted effects of glioma-associated human MSCs (hMSCs) on glioma cells [86]. By transmitting miRNA-21 and miR-34a, exosomes produced by serum-derived hMSCs have been shown by Vallabhaneni et al. to stimulate breast cell proliferation [87]. MiR-221 was shown to be a highly specific microRNA in exosomes from MSCs produced from gastric cancer tissue in research by Wang et al. [88]. The exosomes facilitated the transfer of functional miR-221 to gastric cancer cells and encouraged their migration and proliferation. Roccaro et al. discovered that normal and multiple myeloma (MM) bone marrow-derived MSCs (BM-MSCs) had different exosomal microRNA contents. MM BM-MSC exosomes promoted the growth of MM tumors due to their comparatively high content of the tumor suppressor miR-15a, whereas normal BM-MSC exosomes inhibited the growth of MM cells. Long noncoding RNAs (lncRNAs) defined as non-coding transcripts of more than 200 nucleotides have been implicated in the control of MM development in recent years [89]. In research by Deng et al. LINC00461 was delivered to multiple myeloma cells via MSC-derived exosomes, which increased cell proliferation and inhibited apoptosis by modifying the expression of microRNA/BCL-2 [90,91]. Due to their activities as oncogenes (onco--miRs) or tumor suppressors (TS-miRNAs), dysregulation of miRNAs occurs in the majority of malignancies not only as a result of cancer progression but also directly during tumor initiation and development. The typical methods for achieving miRNA restoration involve either downregulating oncomiRs via the use of anti-miRNAs or overexpressing TS-miRNAs through generation of synthetic miRNA mimics and viral vectors [92]. For example, by transporting various microRNAs, exosomes released by bone marrow MSCs encourage the growth of osteosarcoma and lung cancer cells [93,94]. In contrast, human umbilical cord MSC-derived exosomes that carried microRNA-375 inhibited ENAH to halt the progression of esophageal squamous cell carcinoma [94], and adipose-derived MSC-derived exosomes encouraged the differentiation of Th17 and Treg from naive CD4+ T cells to exert anti-tumor ability by carrying miR-10a [95]. However, practically all research on exosomes produced by TA-MSCs indicates that they can aid in the growth of tumors [96]. Only 26 % and 46 % of research, respectively, demonstrated an oncosuppressive impact for BM-MSCs and AT-MSCs, according to a meta-analysis, whereas 88 % of studies verified a tumor-suppressive function for hUC-MSCs [97]. A crucial step in the development of

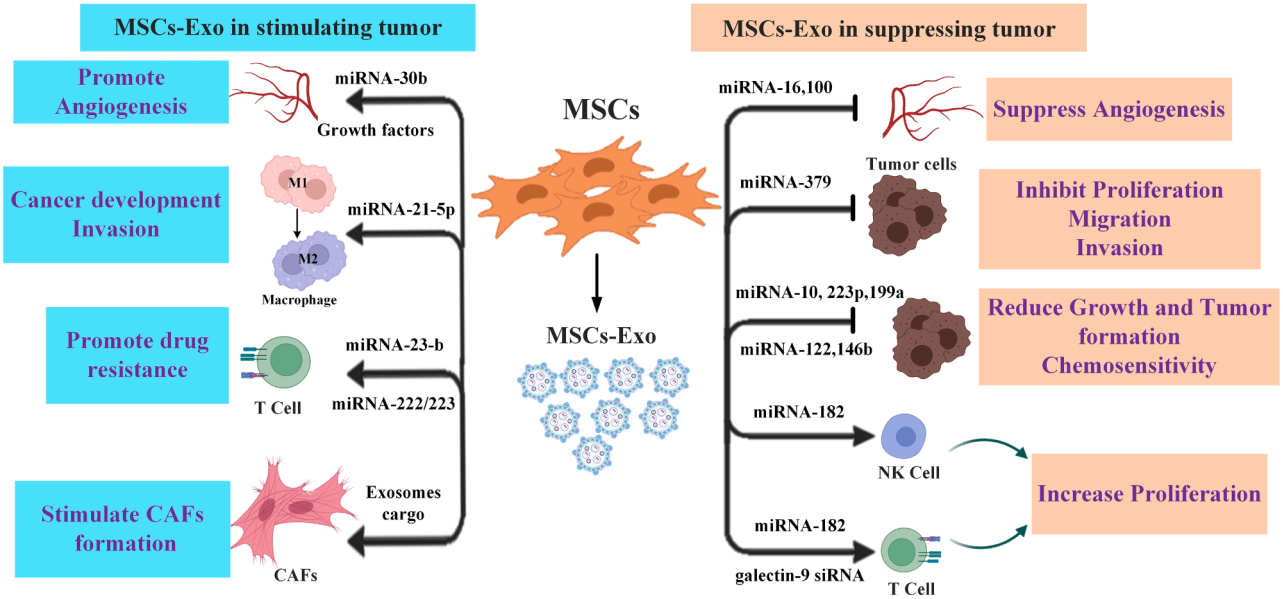


Fig. 3. Role of exosomes secreted by MSCs (MSCs-Exo) in stimulating and suppressing inhibiting tumors.

tumors is immune escape. Immune cells, which are significant TME constituents, cooperate to keep the TME in balance. The activation status of regulatory T cells (Tregs) and anti-inflammatory cytokines can both be affected by MSCs-Exo-carried cargo, according to studies, which also demonstrate that neutrophil mobilization and macrophage polarization can be affected [98–100]. For instance, MSCs-Exo influence immune effector cell function, such as T and B lymphocytes and NK cells, to increase immunosuppression and tumor spread. MSCs-Exo increase the mRNA expression levels of anti-inflammatory factors IL-10 and TGFB1 and decrease the levels of pro-inflammatory molecules IL-1B, IL-6, TNFA, and IL-12P40. They do this by encouraging the expression of polymyxin-resistant, MYD88-dependent secretory embryonic alkaline phosphatase (SEAP). In a similar way, exosomes that are made when IFNG is stimulated increase the production of immunosuppressive molecules while decreasing the production of pro-inflammatory molecules [101]. By releasing paracrine factors, MSCs-Exo can also stop T-cell activation. When CD4+ T cells are exposed to MSCs-Exo, the growth of Th2 cells is favored over the growth of Th1 and Th17 cells [102]. It is possible that MSCs-Exo can restrict immune function by downregulating T-cell activation in order to prevent an excessive inflammatory response and protect tissue cells from immune-damaged cells activating them. Macrophages are crucial immune system elements that inhibit inflammation and promote the growth of tumors. MSCs-Exo-carried miR-21-5p cause M2 macrophage polarization under the impact of a hypoxic environment in vivo via mediating PTEN downregulation, consequently promoting lung cancer development and invasion [103]. These immunosuppressive effects, therefore, could actually create an environment that is conducive to tumor development and metastasis when the microenvironmental balance is upset. There was a theory in this direction that exosomes may reprogram tumor behavior by transmitting molecular contents [104]. Angiogenesis can hasten the evolution of tumors, but MSCs can slow it down by controlling the production of vascular endothelial growth factor (VEGF) in an exosome-dependent way. In order to test this theory, exosomes were characterized and breast tumor cells internalized microvesicles because they had different protein and RNA profiles from their parents [105]. Angiogenesis in breast cancer cells was suppressed by murine MSCs-Exo, whose impact was partly mediated by miRNA-16 produced from MSCs-Exo, according to recent research [106]. This effect was considerable and dose-dependent. According to Rosenberger et al. [107], paracrine mediators produced by MSCs-Exo may mediate the downregulation of VEGF and inhibit the formation of oral squamous cell cancer. By reducing VEGF release, NF-κB activity, and increasing the production of reactive oxygen species (ROS), exosomes from menstrual blood-derived MSCs also prevented angiogenesis in prostate cancer (PC3) cells [108]. AKT phosphorylation may be decreased and the production of cleaved caspase-3 may be increased by hUC-MSCs-Exo, which has also been found to slow the proliferation of bladder cancer cells [109]. The results revealed that exosomes considerably down-regulated VEGF expression in cancer cells, which led to in vitro and in vivo inhibition of tumor angiogenesis. In addition, MSCs-Exo could facilitate VEGF suppression and inhibit the growth of oral squamous cell carcinoma [110] and prostate cancer cells by preventing VEGF production and NF-κB signaling [111]. Pakravan et al. demonstrated that miRNA-100 transferred by MSCs-Exo could inhibit angiogenesis and breast cancer development, through the mTOR/HIF1A/VEGF signaling pathway [112]. The roles of MSCs-Exo in angiogenesis look to be conflicting, maybe due to the type of MSCs-Exo cargo that results in different tumor regulatory properties. In this way, MSC-derived exosomes may act as an important cell-to-cell communication mediator inside the tumor microenvironment and, through the transfer of anti-angiogenic molecules, suppress angiogenesis. One of the intrinsic properties of the MSC-derived exosomes is that they serve as ideal vehicles to transport and deliver molecules such as therapeutic genes, enzymes, drugs, or RNA to targeted cells. These exosomes can protect their contents against enzymatic degradation and promote their intracellular uptake through endocytosis. These biocompatible particles can be used to carry different types of therapeutic drugs for the treatment of cancer cells [113].

Poor tumor treatment results are mostly due to the resistance of tumor cells to chemotherapy agents. Tumor heterogeneity may be brought on by MSCs-Exo-induced drug resistance. MSCs-Exo may include proteins and RNAs that contribute to tumor treatment resistance. For instance, Xu et al. proposed that activation of the PSMA3-AS1/PSMA3 pathway by BM-MSCs-Exo is specifically responsible for MM cells' resistance to proteasome inhibitors [114]. Similar to this, miR-23b generated from BM-MSCs-Exo was demonstrated to cause resistance to the frequently used chemotherapeutic drug docetaxel, a proteasome inhibitor, in breast cancer [105]. BM-MSCs-Exo proteins were found to lessen the chemosensitivity of breast cancer cells in the latter investigation by preventing the cleavage of cystathionin-9, cystathionin-3, and PARP. Through their impact on signal transduction pathways, MSCs-Exo may potentially aid in the promotion of chemoresistance. In a rat model of pheochromocytoma, BM-MSCs-Exo may reduce glutamate toxicity by activating the PI3K/AKT pathway, indicating that glutamate excitotoxicity may be connected to this system [115]. According to a study on gastric cancer, MSCs-Exo increased the expression of proteins linked to multidrug resistance, such as MDR, MRP, and LRP, by activating calcium/calmodulin-dependent protein kinases (CaM-Ks) and the Raf/MEK/ERK cascade, increasing cancer cells' resistance to fluorouracil [116]. Crosstalk between MSCs-Exo and TME cells also creates an environment that is resistant to chemotherapeutic drugs. The resistance of tumor cells to chemotherapy-induced apoptosis is influenced by interactions between MSCs-Exo-secreted CXCR4 and cells in the TME [104]. MSCs-Exo-carried miRNAs, such as mir-222 and mir-223, can confer drug resistance in breast cancer cells [117]. Chemotherapeutic agents such as paclitaxel, hydrophobic phytopolylphenolcurcumin, and doxorubicin can be effectively encapsulated into exosomes [118]. Encapsulation of exosomes can improve the solubility, efficacy, and uptake of loaded cargo [119,120]. For instance, Kim et al.[121] showed that to overcome multi-drug resistance (MDR) in breast cancer tumors, PTX was encapsulated into RAW 264.7 macrophages and their cytotoxic effects were investigated [121]. Furthermore, in order to treat malignant glioma, Katakowski et al. transfected miR-146b into MSCs, demonstrating the transport of microRNA in exosomes. In a rat model, intra-tumoral injection of collected exosomes from MSCs reduced the formation of glioma xenograft tumors. Also, MiR-199a overexpression suppressed glioma development and higher sensitivity to temozolomide by inhibiting AGAP2 expression in vitro and in vivo [122].

miRNA-182 can be delivered by umbilical cord-MSCs-Exo in tumor cells which results in the enhancement of cancer cell death by increasing the proliferation of T and NK cells and by managing the sensitivity of cancer cells to immune cells [123]. Zhou et al. [124] presented an engineered bone marrow that secreted MSCs-Exo with galectin-9 siRNA and oxaliplatin. Results demonstrated that these exosomes induced antitumor immunity by repressing cytotoxic T lymphocyte enrollment, Treg down-regulation, and macrophage polarization. MiR-379 was transfected into MSC-derived exosomes by O'Brien et al. [112] which showed increased miR-379 expression. Additionally, no negative consequences were noticed after transfer to tumor-bearing animals. MiR-379 reportedly prevents tumor cells from proliferating, migrating, and invading healthy tissue. It was hypothesized that by boosting miR-379, malignancies would be suppressed since their expression declines in malignant cells [112]. The mTOR pathway is used by AT-MSCs-Exo to transfer miRNA-199a and increase the chemosensitivity of hepatocellular carcinoma cells, according to recent research [4]. According to the authors, miRNA-199a, which is carried by AT-MSCs-Exo, may provide new opportunities for enhancing hepatocellular carcinoma cell chemosensitivity. By altering the expression of genes that are susceptible to chemotherapeutic drug interactions in hepatocellular carcinoma cells, Lou et al. demonstrated in a related

investigation that miRNA-122 from AT-MSCs-Exo expressly increased the antitumor efficacy of sorafenib in vivo [125]. These findings show that hepatocellular carcinoma can become more chemosensitive when treated with AT-MSCs-Exo. Therefore, they showed that treatment with the engineered exosomes considerably reduced the growth rate of tumors in the breast cancer-bearing mice [77,112].

In another study on melanoma, MSC-derived exosomes were used with radiotherapy, and it was found that the radiation was more effective at stopping melanoma cells from spreading to other parts of the body. Thus, exosomes may have a systemic influence in combination with radiotherapy in the treatment of tumor growth and metastasis [126]. The size, complexity, and immunogenicity of exosomes in comparison to MSCs are lower [73,125]. Therefore, exosome-based cancer therapy might be a fantastic substitute due to its advantages over using MSCs (Fig. 1B). Moreover, exosome production and storage are available and can be a favorable therapeutic selection for cancer treatment. In Table 2, a comprehensive list of MSC-derived exosomes for cancer therapy is summarized. Collectively, the results of these studies suggest that successful treatment strategies will likely need to concomitantly overcome TEM-dependent and immunomodulatory factor-driven resistance mechanisms and signaling pathway-mediated tumor drug resistance.

5. Conclusions

Due to the remarkable immunosuppressive, self-renewal, and multipotent potency of MSCs, they are promising candidates for the design of novel cancer therapy. Expressing exogenous genes, combining therapeutic cargos, or presenting targeting moieties for improved homing, survival, and therapeutic efficacy are characteristic of engineered MSCs. Genetically modified MSCs can carry and deliver anticancer agents into tumor cells and mediate cell death. However, recent studies have reported that the effects of MSCs engineered to express different genes or serve as therapeutic cargos for cancer tumors may depend on the condition of tumors and interactions with other cell types in the tumor microenvironment. Furthermore, MSC-derived exosomes can act as an alternative for MSCs-based therapy. These outcomes are sometimes inconsistent, and MSC-derived exosomes and factors released from modified MSCs have a role in metastases and the growth of cancerous cells. Ultimately, these findings show great hope for engineering MSCs and MSC-derived exosomes to treat cancers.

Ethics approval and consent to participate

Not applicable.

Funding

The authors did not receive support from any organization for the submitted work.

CRediT authorship contribution statement

FSH is a major contributor to writing the manuscript. BP, AGH, NH, NF, and GHN assisted with the format of the manuscript. FSH and AR revised the manuscript and supervised the work. AR and FSH have given final approval for the version to be published. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

Table 2
MSCs-derived exosomes (MSCs-Exo) for cancer therapy.

Source of exosome	Cargo type	Target cancer	Exosomal cargo/pathway	Study model	Outcome	Ref.
BM-MSC	miR	Breast cancer	miR-100	In vitro	Suppressed angiogenesis	[184]
MSCs			antagomiR-222/223	In vivo	Stimulated cycling quiescence and early cancer dormancy	[117]
BM-MSC			miR-23b	In vivo	Promoted dormancy	[105]
BM-MSC			miR-16	In vivo	Suppressed angiogenesis Suppressed angiogenesis by transferring anti-angiogenic molecules	[106]
BM-MSC		Glioma	miR-124 and miR-145	In vitro	Decreased glioma stem cells migration and self-renewal	[185]
BM-MSC			miR-146b	In vivo	Inhibited tumor growth	[186]
BM-MSC			miR-124a	In vivo	Reduced the viability of cancer stem cells Prolonged survival of mice with glioblastoma	[187]
BM-MSC			miR-133b	In vivo	Inhibited proliferation, invasion, and migration	[188]
BM-MSC		Osteosarcoma	miR-143	In vitro	Suppressed tumor cell migration	[189]
ADSCs		HCC	miR-122	In vivo	Increased the antitumor efficacy of sorafenib in mouse model Enhanced growth inhibition	[190]
ADSCs		Prostate cancer	miR-145	In vivo	Suppressed cancer progression Induced apoptosis	[191]
BM-MSC			miR-143	In vivo	Inhibited cell migration and invasion Promoted apoptosis	[192]
BM-MSCs		Multiple myeloma (MM)	miR-15a	In vivo	Inhibited the growth of cancer stem cells	[78]
BM-MSC		GBM[a]	anti-miR-9	In vitro	Reversed chemoresistance	[193]
BM-MSC		Pancreatic cancer	miRNA-1231	In vivo	Inhibited cancer activity	[194]
BM-MSC	siRNA	Pancreatic cancer	siKrasG12D-1	In vivo	Induced apoptosis Increased survival Reduced metastasis	[71]
BM-MSC		HCC	siGRP78	In vivo	Inhibited the growth and metastasis of tumor cells in mouse model	[195]
MSC		Bladder cancer cell lines	PLK-1 siRNA	In vitro	Inhibited proliferation Induced apoptosis and necrosis	[196]
hUC-MSC	Pathway	Human leukemia cells	Activated caspase pathway	In vitro	Enhanced apoptosis	[197]
BM-MSC	Drug	Breast cancer cells	PTX	In vivo	Reduced viability Inhibited tumor growth	[198]
MSC		HeLa cells	Iron oxide	In vitro	Ablated cancer cells	[199]

[a] Glioblastoma multiforme.

Availability of Data and Material

Not applicable.

Acknowledgements

This study is related to Project no. 1398/9776 from the Student Research Committee, Shahid Beheshti University of Medical Sciences, Tehran, Iran. We appreciate the "Student Research Committee" and "Research & Technology Chancellor" at Shahid Beheshti University of Medical Sciences.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

References

[1] A.J. Friedenstein, R.K. Chailakhyan, U.V. Gerasimov, Bone marrow osteogenic stem cells: in vitro cultivation and transplantation in diffusion chambers, Cell Tissue Kinet. 20 (3) (1987) 263–272.
[2] A.G. Via, A. Frizziero, F. Oliva, Biological properties of mesenchymal stem cells from different sources, Muscles Ligaments Tendons J. 2 (3) (2012) 154.
[3] L.d.S. Meirelles, P.C. Chagastelles, N.B. Nardi, Mesenchymal stem cells reside in virtually all post-natal organs and tissues, J. Cell Sci. 119 (11) (2006) 2204–2213.
[4] C. Yan, et al., Human umbilical cord mesenchymal stem cells as vehicles of CD20-specific TRAIL fusion protein delivery: a double-target therapy against non-Hodgkin's lymphoma, Mol. Pharmaceut. 10 (1) (2013) 142–151.
[5] P.A. Zuk, et al., Multilineage cells from human adipose tissue: implications for cell-based therapies, Tissue Eng. 7 (2) (2001) 211–228.
[6] K. Bieback, et al., Critical parameters for the isolation of mesenchymal stem cells from umbilical cord blood, Stem Cells 22 (4) (2004) 625–634.
[7] W. Wagner, et al., Replicative senescence of mesenchymal stem cells: a continuous and organized process, PLoS One 3 (5) (2008) e2213.
[8] A. Golchin, et al., Combination therapy of stem cell-derived exosomes and biomaterials in the wound healing, Stem Cell Rev. Rep. 18 (6) (2022) 1892–1911.
[9] R. Ramasamy, et al., Mesenchymal stem cells inhibit dendritic cell differentiation and function by preventing entry into the cell cycle, Transplantation 83 (1) (2007) 71–76.
[10] R. Uchibori, et al., Cancer gene therapy using mesenchymal stem cells, Int. J. Hematol. 99 (4) (2014) 377–382.
[11] J.L. Spees, R.H. Lee, C.A. Gregory, Mechanisms of mesenchymal stem/stromal cell function, Stem Cell Res. Ther. 7 (1) (2016) 125.
[12] D. Chanda, et al., Therapeutic potential of adult bone marrow-derived mesenchymal stem cells in prostate cancer bone metastasis, Clin. Cancer Res. 15 (23) (2009) 7175–7185.
[13] G.J. Maestroni, E. Hertens, P. Galli, Factor(s) from nonmacrophage bone marrow stromal cells inhibit Lewis lung carcinoma and B16 melanoma growth in mice, Cell. Mol. Life Sci. 55 (4) (1999) 663–667.
[14] X.Y. Sun, et al., Mesenchymal stem cell-mediated cancer therapy: a dual-targeted strategy of personalized medicine, World J. Stem Cells 3 (11) (2011) 96–103.
[15] H.F. Dvorak, Tumors: wounds that do not heal. Similarities between tumor stroma generation and wound healing, N. Engl. J. Med. 315 (26) (1986) 1650–1659.
[16] Y. Han, et al., Mesenchymal stem cells for regenerative medicine, Cells 8 (8) (2019).
[17] M. Compte, et al., Tumor immunotherapy using gene-modified human mesenchymal stem cells loaded into synthetic extracellular matrix scaffolds, Stem Cells 27 (3) (2009) 753–760.
[18] S. Kern, et al., Comparative analysis of mesenchymal stem cells from bone marrow, umbilical cord blood, or adipose tissue, Stem Cells 24 (5) (2006) 1294–1301.
[19] K. O'Donoghue, et al., Microchimerism in female bone marrow and bone decades after fetal mesenchymal stem-cell trafficking in pregnancy, Lancet 364 (9429) (2004) 179–182.
[20] S. Kidd, et al., The (in) auspicious role of mesenchymal stromal cells in cancer: be it friend or foe, Cytotherapy 10 (7) (2008) 657–667.
[21] T.Y. Zhang, et al., Gene recombinant bone marrow mesenchymal stem cells as a tumor-targeted suicide gene delivery vehicle in pulmonary metastasis therapy using non-viral transfection, Nanomedicine 10 (1) (2014) 257–267.
[22] J.S. Park, et al., Engineering mesenchymal stem cells for regenerative medicine and drug delivery, Methods 84 (2015) 3–16.
[23] A. Golchin, F. Shams, F. Karami, Advancing mesenchymal stem cell therapy with CRISPR/Cas9 for clinical trial studies, Adv. Exp. Med. Biol. 1247 (2020) 89–100.
[24] B.F. Benabdallah, et al., Targeted gene addition to human mesenchymal stromal cells as a cell-based plasma-soluble protein delivery platform, Cytotherapy 12 (3) (2010) 394–399.
[25] S. Cheng, et al., Engineered mesenchymal stem cells for targeting solid tumors: therapeutic potential beyond regenerative therapy, J. Pharm. Exp. Ther. 370 (2) (2019) 231–241.
[26] T. Relation, et al., Intratumoral delivery of interferongamma-secreting mesenchymal stromal cells repolarizes tumor-associated macrophages and suppresses neuroblastoma proliferation in vivo, Stem Cells 36 (6) (2018) 915–924.
[27] E. Uchimura, et al., Method for reverse transfection using gold colloid as a nano-scaffold, J. Biosci. Bioeng. 103 (1) (2007) 101–103.
[28] X. Zhu, et al., Mastocarcinoma therapy synergistically promoted by lysosome dependent apoptosis specifically evoked by 5-Fu@ nanogel system with passive targeting and pH activatable dual function, J. Control. Release 254 (2017) 107–118.
[29] J.S. Park, et al., Non-viral gene delivery of DNA polyplexed with nanoparticles transfected into human mesenchymal stem cells, Biomaterials 31 (1) (2010) 124–132.
[30] M.E. Muroski, et al., A gold nanoparticle pentapeptide: gene fusion to induce therapeutic gene expression in mesenchymal stem cells, J. Am. Chem. Soc. 136 (42) (2014) 14763–14771.
[31] K. Otani, et al., Nonviral delivery of siRNA into mesenchymal stem cells by a combination of ultrasound and microbubbles, J. Control Release 133 (2) (2009) 146–153.
[32] M. Studeny, et al., Bone marrow-derived mesenchymal stem cells as vehicles for interferon-β delivery into tumors, Cancer Res. 62 (13) (2002) 3603–3608.
[33] I. Amara, et al., Mesenchymal stem cells as cellular vehicles for prodrug gene therapy against tumors, Biochimie 105 (2014) 4–11.
[34] L.P. Mueller, et al., TRAIL-transduced multipotent mesenchymal stromal cells (TRAIL-MSC) overcome TRAIL resistance in selected CRC cell lines in vitro and in vivo, Cancer Gene Ther. 18 (4) (2011) 229–239.
[35] O.G. Donnelly, et al., Recent clinical experience with oncolytic viruses, Curr. Pharm. Biotechnol. 13 (9) (2012) 1834–1841.
[36] E.K. Mader, et al., Optimizing patient derived mesenchymal stem cells as virus carriers for a phase I clinical trial in ovarian cancer, J. Transl. Med. 11 (2013) 20.
[37] S.M. Kim, et al., Potential application of temozolomide in mesenchymal stem cell-based TRAIL gene therapy against malignant glioma, Stem Cells Transl. Med. 3 (2) (2014) 172–182.
[38] M. Roger, et al., Mesenchymal stem cells as cellular vehicles for delivery of nanoparticles to brain tumors, Biomaterials 31 (32) (2010) 8393–8401.
[39] J. Pérez-Juste, et al., Gold nanorods: synthesis, characterization and applications, Coord. Chem. Rev. 249 (17) (2005) 1870–1901.
[40] A.V. Samrot, et al., A review on synthesis, characterization and potential biological applications of superparamagnetic iron oxide nanoparticles, Curr. Res. Green Sustain. Chem. 4 (2021) 100042.
[41] C. Xu, et al., A light-triggered mesenchymal stem cell delivery system for photoacoustic imaging and chemo-photothermal therapy of triple negative breast cancer, Adv. Sci. 5 (10) (2018) 1800382.
[42] F. Shams, et al., Nanotechnology-based products for cancer immunotherapy, Mol. Biol. Rep. 49 (2) (2022) 1389–1412.
[43] C. Vicinanza, et al., Modified mesenchymal stem cells in cancer therapy: a smart weapon requiring upgrades for wider clinical applications, World J. Stem Cells 14 (1) (2022) 54–75.
[44] J. Panyam, et al., Rapid endo-lysosomal escape of poly(DL-lactide-co-glycolide) nanoparticles: implications for drug and gene delivery, FASEB J. 16 (10) (2002) 1217–1226.
[45] Y. Lu, et al., Properties of poly (lactic-co-glycolic acid) and progress of poly (lactic-co-glycolic acid)-based biodegradable materials in biomedical research, Pharmaceuticals 16 (2023), https://doi.org/10.3390/ph16030454.
[46] K.C. Song, et al., The effect of type of organic phase solvents on the particle size of poly(D,L-lactide-co-glycolide) nanoparticles, Colloids Surf. A: Physicochem. Eng. Asp. 276 (1) (2006) 162–167.
[47] M. Zheng, et al., Poly(α-L-lysine)-based nanomaterials for versatile biomedical applications: current advances and perspectives, Bioact. Mater. 6 (7) (2021) 1878–1909.
[48] L. Kostura, et al., Feridex labeling of mesenchymal stem cells inhibits chondrogenesis but not adipogenesis or osteogenesis, NMR Biomed. 17 (7) (2004) 513–517.
[49] A. Aleid, et al., Estimation of SPIO nanoparticles uptakes by macrophages using transmission electron microscopy, Int. J. Mol. Sci. 23 (2022), https://doi.org/10.3390/ijms232213801.
[50] G. Liu, et al., Low molecular weight alkyl-polycation wrapped magnetite nanoparticle clusters as MRI probes for stem cell labeling and in vivo imaging, Biomaterials 32 (2) (2011) 528–537.
[51] L. Pascucci, et al., 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 192 (2014) 262–270.
[52] T. Dai, et al., Preparation and drug release mechanism of CTS-TAX-NP-MSCs drug delivery system, Int. J. Pharm. 456 (1) (2013) 186–194.
[53] T. Sadhukha, T.D. O'Brien, S. Prabha, Nano-engineered mesenchymal stem cells as targeted therapeutic carriers, J. Control Release 196 (2014) 243–251.
[54] B. Layek, et al., Nano-engineered mesenchymal stem cells increase therapeutic efficacy of anticancer drug through true active tumor targeting, Mol. Cancer Ther. 17 (6) (2018) 1196–1206.

[55] X. Wang, et al., Mesenchymal stem cells loaded with paclitaxel-poly(lactic-co-glycolic acid) nanoparticles for glioma-targeting therapy, Int. J. Nanomed. 13 (2018) 5231–5248.
[56] G. Moku, et al., Improving payload capacity and anti-tumor efficacy of mesenchymal stem cells using TAT peptide functionalized polymeric nanoparticles, Cancers 11 (4) (2019).
[57] D. Sarkar, et al., Cellular and extracellular programming of cell fate through engineered intracrine-, paracrine-, and endocrine-like mechanisms, Biomaterials 32 (11) (2011) 3053–3061.
[58] S. Yao, et al., Maximized nanodrug-loaded mesenchymal stem cells by a dual drug-loaded mode for the systemic treatment of metastatic lung cancer, Drug Deliv. 24 (1) (2017) 1372–1383.
[59] B. Layek, T. Sadhukha, S. Prabha, Glycoengineered mesenchymal stem cells as an enabling platform for two-step targeting of solid tumors, Biomaterials 88 (2016) 97–109.
[60] B. Layek, et al., Nanoengineering of mesenchymal stem cells via surface modification for efficient cancer therapy, Adv. Ther. 2 (9) (2019) 1900043.
[61] S.W. Kim, et al., Mutual destruction of deep lung tumor tissues by nanodrug-conjugated stealth mesenchymal stem cells, Adv. Sci. 5 (5) (2018) 1700860.
[62] F.L. Moolten, Tumor chemosensitivity conferred by inserted herpes thymidine kinase genes: paradigm for a prospective cancer control strategy, Cancer Res. 46 (10) (1986) 5276–5281.
[63] M. Mohammadi, et al., Mesenchymal stem cell: a new horizon in cancer gene therapy, Cancer Gene Ther. 23 (9) (2016) 285–286.
[64] I. Amara, et al., Engineered mesenchymal stem cells as vectors in a suicide gene therapy against preclinical murine models for solid tumors, J. Control Release 239 (2016) 82–91.
[65] W.Y. Lee, et al., Immortalized human fetal bone marrow-derived mesenchymal stromal cell expressing suicide gene for anti-tumor therapy in vitro and in vivo, Cytotherapy 15 (12) (2013) 1484–1497.
[66] M. Matuskova, et al., Intrinsic properties of tumour cells have a key impact on the bystander effect mediated by genetically engineered mesenchymal stromal cells, J. Gene Med. 14 (12) (2012) 776–787.
[67] A. Nowakowski, et al., Engineered mesenchymal stem cells as an anti-cancer trojan horse, Stem Cells Dev. 25 (20) (2016) 1513–1531.
[68] S.W. Kim, et al., Complete regression of metastatic renal cell carcinoma by multiple injections of engineered mesenchymal stem cells expressing dodecameric TRAIL and HSV-TK, Clin. Cancer Res. 19 (2) (2013) 415–427.
[69] M. Matuskova, et al., Combined enzyme/prodrug treatment by genetically engineered AT-MSC exerts synergy and inhibits growth of MDA-MB-231 induced lung metastases, J. Exp. Clin. Cancer Res. 34 (2015) 33.
[70] A. Abrate, et al., Mesenchymal stem cells expressing therapeutic genes induce autochthonous prostate tumour regression, Eur. J. Cancer 50 (14) (2014) 2478–2488.
[71] M. Mendt, et al., Generation and testing of clinical-grade exosomes for pancreatic cancer, JCI Insight 3 (8) (2018).
[72] N. Heldring, et al., Therapeutic potential of multipotent mesenchymal stromal cells and their extracellular vesicles, Hum. Gene Ther. 26 (8) (2015) 506–517.
[73] G. Lou, et al., Mesenchymal stem cell-derived exosomes as a new therapeutic strategy for liver diseases, Exp. Mol. Med. 49 (6) (2017) (p. e346-e346).
[74] E.J. Bunggulawa, et al., Recent advancements in the use of exosomes as drug delivery systems, J. Nanobiotechnol. 16 (1) (2018) 1–13.
[75] B. Yu, X. Zhang, X. Li, Exosomes derived from mesenchymal stem cells, Int. J. Mol. Sci. 15 (3) (2014) 4142–4157.
[76] L. Bagno, et al., Mesenchymal stem cell-based therapy for cardiovascular disease: progress and challenges, Mol. Ther. 26 (7) (2018) 1610–1623.
[77] X. Xie, et al., Progress in the application of exosomes as therapeutic vectors in tumor-targeted therapy, Cytotherapy 21 (5) (2019) 509–524.
[78] A.M. Roccaro, et al., BM mesenchymal stromal cell-derived exosomes facilitate multiple myeloma progression, J. Clin. Invest. 123 (4) (2013) 1542–1555.
[79] V. Fonsato, et al., Human liver stem cell-derived microvesicles inhibit hepatoma growth in SCID mice by delivering antitumor microRNAs, Stem Cells 30 (9) (2012) 1985–1998.
[80] Y. Han, et al., Exosomes from hypoxia-treated human adipose-derived mesenchymal stem cells enhance angiogenesis through VEGF/VEGF-R, Int. J. Biochem. Cell Biol. 109 (2019) 59–68.
[81] A.M.B. Al-Dhalimy, et al., The pathological and therapeutically role of mesenchymal stem cell (MSC)-derived exosome in degenerative diseases; particular focus on LncRNA and microRNA, Pathol.-Res. Pract. (2023) 154778.
[82] R.e.M. Qazi, et al., Lyophilization based isolation of exosomes, Int. J. Mol. Sci. 24 (13) (2023) 10477.
[83] M. Ragusa, D. Barbagallo, M. Purrello, Exosomes: nanoshuttles to the future of BioMedicine, Cell Cycle 14 (3) (2015) 289–290.
[84] A.S. Azmi, B. Bao, F.H. Sarkar, Exosomes in cancer development, metastasis, and drug resistance: a comprehensive review, Cancer Metastasis Rev. 32 (2013) 623–642.
[85] C. Kahlert, R. Kalluri, Exosomes in tumor microenvironment influence cancer progression and metastasis, J. Mol. Med. 91 (2013) 431–437.
[86] J. Figueroa, et al., Exosomes from glioma-associated mesenchymal stem cells increase the tumorigenicity of glioma stem-like cells via transfer of miR-1587, Cancer Res. 77 (21) (2017) 5808–5819.
[87] K.C. Vallabhaneni, et al., Extracellular vesicles from bone marrow mesenchymal stem/stromal cells transport tumor regulatory microRNA, proteins, and metabolites, Oncotarget 6 (7) (2015) 4953.
[88] M. Wang, et al., Deregulated microRNAs in gastric cancer tissue-derived mesenchymal stem cells: novel biomarkers and a mechanism for gastric cancer, Br. J. Cancer 110 (5) (2014) 1199–1210.
[89] A.M. Roccaro, et al., BM mesenchymal stromal cell–derived exosomes facilitate multiple myeloma progression, J. Clin. Investig. 123 (4) (2013) 1542–1555.
[90] M. Deng, et al., Exosome-transmitted LINC00461 promotes multiple myeloma cell proliferation and suppresses apoptosis by modulating microRNA/BCL-2 expression, Cytotherapy 21 (1) (2019) 96–106.
[91] R. Zhao, et al., Dual role of MSC-derived exosomes in tumor development, Stem Cells Int. 2020 (2020).
[92] B. Sohrabi, et al., Mesenchymal stem cell (MSC)-derived exosomes as novel vehicles for delivery of miRNAs in cancer therapy, Cancer Gene Ther. 29 (8–9) (2022) 1105–1116.
[93] X. Zhang, et al., Hypoxic BMSC-derived exosomal miRNAs promote metastasis of lung cancer cells via STAT3-induced EMT, Mol. Cancer 18 (2019) 1–15.
[94] Z. He, et al., Human umbilical cord mesenchymal stem cells-derived exosomes deliver microRNA-375 to downregulate ENAH and thus retard esophageal squamous cell carcinoma progression, J. Exp. Clin. Cancer Res. 39 (1) (2020) 1–18.
[95] Z. Bolandi, et al., Adipose derived mesenchymal stem cell exosomes loaded with miR-10a promote the differentiation of Th17 and Treg from naive CD4+ T cell, Life Sci. 259 (2020) 118218.
[96] Y. Shi, et al., Tumour-associated mesenchymal stem/stromal cells: emerging therapeutic targets, Nat. Rev. Drug Discov. 16 (1) (2017) 35–52.
[97] I. Christodoulou, et al., Mesenchymal stem cells in preclinical cancer cytotherapy: a systematic review, Stem Cell Res. Ther. 9 (1) (2018) 1–38.
[98] A. Del Fattore, et al., Immunoregulatory effects of mesenchymal stem cell-derived extracellular vesicles on T lymphocytes, Cell Transpl. 24 (12) (2015) 2615–2627.
[99] D. Ti, et al., LPS-preconditioned mesenchymal stromal cells modify macrophage polarization for resolution of chronic inflammation via exosome-shuttled let-7b, J. Transl. Med. 13 (2015) 1–14.
[100] Y.G. Zhu, et al., Human mesenchymal stem cell microvesicles for treatment of Escherichia coli endotoxin-induced acute lung injury in mice, Stem Cells 32 (1) (2014) 116–125.
[101] T. Deuse, et al., Immunogenicity and immunomodulatory properties of umbilical cord lining mesenchymal stem cells, Cell Transpl. 20 (5) (2011) 655–667.
[102] W. Chen, et al., Immunomodulatory effects of mesenchymal stromal cells-derived exosome, Immunol. Res. 64 (4) (2016) 831–840.
[103] W. Ren, et al., Extracellular vesicles secreted by hypoxia pre-challenged mesenchymal stem cells promote non-small cell lung cancer cell growth and mobility as well as macrophage M2 polarization via miR-21-5p delivery, J. Exp. Clin. Cancer Res. 38 (1) (2019) 62.
[104] F. Zhang, et al., Mesenchymal stem cell-derived exosome: a tumor regulator and carrier for targeted tumor therapy, Cancer Lett. 526 (2022) 29–40.
[105] M. Ono, et al., Exosomes from bone marrow mesenchymal stem cells contain a microRNA that promotes dormancy in metastatic breast cancer cells, Sci. Signal. 7 (332) (2014) (p. ra63-ra63).
[106] J.K. Lee, et al., Exosomes derived from mesenchymal stem cells suppress angiogenesis by down-regulating VEGF expression in breast cancer cells, PLoS One 8 (12) (2013) e84256.
[107] L. Rosenberger, et al., Stem cell exosomes inhibit angiogenesis and tumor growth of oral squamous cell carcinoma, Sci. Rep. 9 (1) (2019) 663.
[108] F. Alcayaga-Miranda, et al., Prostate tumor-induced angiogenesis is blocked by exosomes derived from menstrual stem cells through the inhibition of reactive oxygen species, Oncotarget 7 (28) (2016) 44462.
[109] S. Wu, et al., Microvesicles derived from human umbilical cord Wharton's jelly mesenchymal stem cells attenuate bladder tumor cell growth in vitro and in vivo, PLoS One 8 (4) (2013) e61366.
[110] Q. Chen, et al., Therapeutic potential of bone marrow-derived mesenchymal stem cells producing pigment epithelium-derived factor in lung carcinoma, Int. J. Mol. Med. 30 (3) (2012) 527–534.
[111] E.K. Sage, et al., Systemic but not topical TRAIL-expressing mesenchymal stem cells reduce tumour growth in malignant mesothelioma, Thorax 69 (7) (2014) 638–647.
[112] K.P. O'Brien, et al., Employing mesenchymal stem cells to support tumor-targeted delivery of extracellular vesicle (EV)-encapsulated microRNA-379, Oncogene 37 (16) (2018) 2137–2149.
[113] G. Turturici, et al., Extracellular membrane vesicles as a mechanism of cell-to-cell communication: advantages and disadvantages, Am. J. Physiol.-Cell Physiol. 306 (7) (2014) C621–C633.
[114] H. Xu, et al., Exosome-transmitted PSMA3 and PSMA3-AS1 promote proteasome inhibitor resistance in multiple myeloma, Clin. Cancer Res. 25 (6) (2019) 1923–1935.
[115] S.-S. Lin, et al., Bone marrow mesenchymal stem cell-derived microvesicles protect rat pheochromocytoma PC12 cells from glutamate-induced injury via a PI3K/Akt dependent pathway, Neurochem. Res. 39 (2014) 922–931.
[116] R. Ji, et al., Exosomes derived from human mesenchymal stem cells confer drug resistance in gastric cancer, Cell Cycle 14 (15) (2015) 2473–2483.
[117] S.A. Bliss, et al., Mesenchymal stem cell-derived exosomes stimulate cycling quiescence and early breast cancer dormancy in bone marrow, Cancer Res. 76 (19) (2016) 5832–5844.
[118] J. Ding, et al., Exosome-mediated miR-222 transferring: an insight into NF-κB-mediated breast cancer metastasis, Exp. Cell Res. 369 (1) (2018) 129–138.
[119] F. Aqil, et al., Exosomal formulation enhances therapeutic response of celastrol against lung cancer, Exp. Mol. Pathol. 101 (1) (2016) 12–21.

[120] M. Hadla, et al., Exosomes increase the therapeutic index of doxorubicin in breast and ovarian cancer mouse models, Nanomedicine 11 (18) (2016) 2431–2441.
[121] M.S. Kim, et al., Development of exosome-encapsulated paclitaxel to overcome MDR in cancer cells, Nanomedicine 12 (3) (2016) 655–664.
[122] C. Cai, et al., The inhibitory effect of mesenchymal stem cells with rAd-NK4 on liver cancer, Appl. Biochem. Biotechnol. 183 (1) (2017) 444–459.
[123] D. Li, et al., Exosomes derived from mesenchymal stem cells curbs the progression of clear cell renal cell carcinoma through T-cell immune response, Cytotechnology 73 (4) (2021) 593–604.
[124] W. Zhou, et al., Pancreatic cancer-targeting exosomes for enhancing immunotherapy and reprogramming tumor microenvironment, Biomaterials 268 (2021) 120546.
[125] F. Vakhshiteh, F. Atyabi, S.N. Ostad, Mesenchymal stem cell exosomes: a two-edged sword in cancer therapy, Int. J. Nanomed. 14 (2019) 2847–2859.
[126] V. de Araujo Farias, et al., Exosomes derived from mesenchymal stem cells enhance radiotherapy-induced cell death in tumor and metastatic tumor foci, Mol. Cancer 17 (1) (2018) 122.
[127] C. Yan, et al., Human umbilical cord mesenchymal stem cells as vehicles of CD20-specific TRAIL fusion protein delivery: a double-target therapy against non-Hodgkin's lymphoma, Mol. Pharm. 10 (1) (2013) 142–151.
[128] Z. Li, et al., E1A-engineered human umbilical cord mesenchymal stem cells as carriers and amplifiers for adenovirus suppress hepatocarcinoma in mice, Oncotarget 7 (32) (2016) 51815–51828.
[129] M. Studeny, et al., Mesenchymal stem cells: potential precursors for tumor stroma and targeted-delivery vehicles for anticancer agents, J. Natl. Cancer Inst. 96 (21) (2004) 1593–1603.
[130] X. Ling, et al., Mesenchymal stem cells overexpressing IFN-beta inhibit breast cancer growth and metastases through Stat3 signaling in a syngeneic tumor model, Cancer Microenviron. 3 (1) (2010) 83–95.
[131] L. Zheng, et al., Antitumor activities of human placenta-derived mesenchymal stem cells expressing endostatin on ovarian cancer, PLoS One 7 (7) (2012) e39119.
[132] J. Zhang, et al., Inhibitory effect of genetically engineered mesenchymal stem cells with apoptin on hepatoma cells in vitro and in vivo, Mol. Cell. Biochem. 416 (1–2) (2016) 193–203.
[133] N. Wu, et al., Overexpression of hepatocyte nuclear factor 4alpha in human mesenchymal stem cells suppresses hepatocellular carcinoma development through Wnt/beta-catenin signaling pathway downregulation, Cancer Biol. Ther. 17 (5) (2016) 558–565.
[134] Q. Li, et al., Mesenchymal stem cells from human fat engineered to secrete BMP4 are nononcogenic, suppress brain cancer, and prolong survival, Clin. Cancer Res. 20 (9) (2014) 2375–2387.
[135] C. Ren, et al., Therapeutic potential of mesenchymal stem cells producing interferon-alpha in a mouse melanoma lung metastasis model, Stem Cells 26 (9) (2008) 2332–2338.
[136] X. Li, et al., In vitro effect of adenovirus-mediated human gamma interferon gene transfer into human mesenchymal stem cells for chronic myelogenous leukemia, Hematol. Oncol. 24 (3) (2006) 151–158.
[137] S. Shahrokhi, S. Daneshmandi, F. Menaa, Tumor necrosis factor-alpha/CD40 ligand-engineered mesenchymal stem cells greatly enhanced the antitumor immune response and lifespan in mice, Hum. Gene Ther. 25 (3) (2014) 240–253.
[138] S.H. Choi, et al., Antiangiogenic variant of TSP-1 targets tumor cells in glioblastomas, Mol. Ther. 23 (2) (2015) 235–243.
[139] K. Nakamura, et al., Antitumor effect of genetically engineered mesenchymal stem cells in a rat glioma model, Gene Ther. 11 (14) (2004) 1155–1164.
[140] W.H. Zhao, et al., Human umbilical cord mesenchymal stem cells with adenovirus-mediated interleukin 12 gene transduction inhibits the growth of ovarian carcinoma cells both in vitro and in vivo, Nan Fang Yi Ke Da Xue Xue Bao 31 (5) (2011) 903–907.
[141] J. Han, et al., Mesenchymal stem cells genetically modified by lentivirus-mediated interleukin-12 inhibit malignant ascites in mice, Exp. Ther. Med. 8 (4) (2014) 1330–1334.
[142] N. Kim, et al., IL-21-expressing mesenchymal stem cells prevent lethal B-cell lymphoma through efficient delivery of IL-21, which redirects the immune system to target the tumor, Stem Cells Dev. 24 (23) (2015) 2808–2821.
[143] A.A. Hombach, et al., IL7-IL12 engineered mesenchymal stem cells (MSCs) improve A CAR T cell attack against colorectal cancer cells, Cells 9 (4) (2020) 873.
[144] Z. Piri, A. Esmaeilzadeh, M. Hajikhanmirzaei, Interleukin-25 as a candidate gene in immunogene therapy of pancreatic cancer, J. Med. Hypotheses Ideas 6 (2) (2012) 75–79.
[145] G. Xu, et al., Bone marrow-derived mesenchymal stem cells co-expressing interleukin-18 and interferon-beta exhibit potent antitumor effect against intracranial glioma in rats, Oncol. Rep. 34 (4) (2015) 1915–1922.
[146] H. Xin, et al., Targeted delivery of CX3CL1 to multiple lung tumors by mesenchymal stem cells, Stem Cells 25 (7) (2007) 1618–1626.
[147] D.M. Wu, et al., Bone marrow mesenchymal stem cell-derived exosomal MicroRNA-126-3p inhibits pancreatic cancer development by targeting ADAM9, Mol. Ther. Nucleic Acids 16 (2019) 229–245.
[148] R. Kim, et al., Exosomes derived from microRNA-584 transfected mesenchymal stem cells: novel alternative therapeutic vehicles for cancer therapy, BMB Rep. 51 (8) (2018) 406–411.
[149] S. Sharif, M.H. Ghahremani, M. Soleimani, Delivery of exogenous miR-124 to glioblastoma multiform cells by Wharton's jelly mesenchymal stem cells decreases cell proliferation and migration, and confers chemosensitivity, Stem Cell Rev. Rep. 14 (2) (2018) 236–246.
[150] H.K. Lee, et al., Mesenchymal stem cells deliver synthetic microRNA mimics to glioma cells and glioma stem cells and inhibit their cell migration and self-renewal, Oncotarget 4 (2) (2013) 346–361.
[151] D.W. Stuckey, et al., Engineering toxin-resistant therapeutic stem cells to treat brain tumors, Stem Cells 33 (2) (2015) 589–600.
[152] T. Hakkarainen, et al., Human mesenchymal stem cells lack tumor tropism but enhance the antitumor activity of oncolytic adenoviruses in orthotopic lung and breast tumors, Hum. Gene Ther. 18 (7) (2007) 627–641.
[153] M. Duebgen, et al., Stem cells loaded with multimechanistic oncolytic herpes simplex virus variants for brain tumor therapy, J. Natl. Cancer Inst. 106 (6) (2014) dju090.
[154] Y. Chu, et al., Human placenta mesenchymal stem cells expressing exogenous kringle1-5 protein by fiber-modified adenovirus suppress angiogenesis, Cancer Gene Ther. 21 (5) (2014) 200–208.
[155] C. Zischek, et al., Targeting tumor stroma using engineered mesenchymal stem cells reduces the growth of pancreatic carcinoma, Ann. Surg. 250 (5) (2009) 747–753.
[156] X. Jiang, et al., Nanoparticle engineered TRAIL-overexpressing adipose-derived stem cells target and eradicate glioblastoma via intracranial delivery, Proc. Natl. Acad. Sci. USA 113 (48) (2016) 13857–13862.
[157] C. Kitzberger, et al., Mesenchymal stem cell–mediated image-guided sodium iodide symporter (NIS) gene therapy improves survival of glioblastoma-bearing mice, Clin. Cancer Res. 29 (5) (2023) 930–942.
[158] C. Kitzberger, et al., Interleukin-6-controlled, mesenchymal stem cell-based sodium/iodide symporter gene therapy improves survival of glioblastoma-bearing mice, Mol. Ther.-Oncolytics (2023).
[159] R. Spellerberg, et al., Selective sodium iodide symporter (NIS) gene therapy of glioblastoma mediated by EGFR-targeted lipopolyplexes, Mol. Ther.-Oncolytics 23 (2021) 432–446.
[160] C. Kitzberger, et al., The sodium iodide symporter (NIS) as theranostic gene: its emerging role in new imaging modalities and non-viral gene therapy, EJNMMI Res. 12 (1) (2022) 1–14.
[161] R. Spellerberg, et al., Dual EGFR-and TfR-targeted gene transfer for sodium iodide symporter gene therapy of glioblastoma, Mol. Ther.-Oncolytics 27 (2022) 272–287.
[162] L. Jia, et al., Small activating RNA-activated NIS gene promotes 131I uptake and inhibits thyroid cancer via AMPK/mTOR pathway, Pathol.-Res. Pract. 229 (2022) 153735.
[163] C. Belmar-López, et al., Mesenchymal stem cells delivery in individuals with different pathologies: multimodal tracking, safety and future applications, Int. J. Mol. Sci. 23 (3) (2022) 1682.
[164] Y. Han, et al., Taking advantage of the TGFB1 biology in differentiated thyroid cancer to stimulate sodium iodide symporter (NIS)-mediated iodide uptake in engineered mesenchymal stem cells, J. Endocr. Soc. 5 (Suppl._1) (2021) (p. A1033-A1033).
[165] C. Schug, et al., TGFB1-driven mesenchymal stem cell-mediated NIS gene transfer, Endocr. Relat. Cancer 26 (1) (2019) 89–101.
[166] S. Li, et al., Bystander effect in glioma suicide gene therapy using bone marrow stromal cells, Stem Cell Res. 9 (3) (2012) 270–276.
[167] X.Y. Bak, J. Yang, S. Wang, Baculovirus-transduced bone marrow mesenchymal stem cells for systemic cancer therapy, Cancer Gene Ther. 17 (10) (2010) 721–729.
[168] M. Matuskova, et al., HSV-tk expressing mesenchymal stem cells exert bystander effect on human glioblastoma cells, Cancer Lett. 290 (1) (2010) 58–67.
[169] C.H. Ryu, et al., Valproic acid enhances anti-tumor effect of mesenchymal stem cell mediated HSV-TK gene therapy in intracranial glioma, Biochem. Biophys. Res. Commun. 421 (3) (2012) 585–590.
[170] H. Kosaka, et al., Therapeutic effect of suicide gene-transferred mesenchymal stem cells in a rat model of glioma, Cancer Gene Ther. 19 (8) (2012) 572–578.
[171] V. Altanerova, et al., Human adipose tissue-derived mesenchymal stem cells expressing yeast cytosinedeaminase::uracil phosphoribosyltransferase inhibit intracerebral rat glioblastoma, Int. J. Cancer 130 (10) (2012) 2455–2463.
[172] J. Mercapide, et al., Primary gene-engineered neural stem/progenitor cells demonstrate tumor-selective migration and antitumor effects in glioma, Int. J. Cancer 126 (5) (2010) 1206–1215.
[173] L. Kucerova, et al., Cytosine deaminase expressing human mesenchymal stem cells mediated tumour regression in melanoma bearing mice, J. Gene Med. 10 (10) (2008) 1071–1082.
[174] I.T. Cavarretta, et al., Adipose tissue-derived mesenchymal stem cells expressing prodrug-converting enzyme inhibit human prostate tumor growth, Mol. Ther. 18 (1) (2010) 223–231.
[175] H. Niess, et al., Selective targeting of genetically engineered mesenchymal stem cells to tumor stroma microenvironments using tissue-specific suicide gene expression suppresses growth of hepatocellular carcinoma, Ann. Surg. 254 (5) (2011) 767–774 (discussion 774–5).
[176] C. Conrad, et al., Linking transgene expression of engineered mesenchymal stem cells and angiopoietin-1-induced differentiation to target cancer angiogenesis, Ann. Surg. 253 (3) (2011) 566–571.
[177] M.H. You, et al., Cytosine deaminase-producing human mesenchymal stem cells mediate an antitumor effect in a mouse xenograft model, J. Gastroenterol. Hepatol. 24 (8) (2009) 1393–1400.
[178] X. Zhang, et al., Tumor tropic delivery of doxorubicin-polymer conjugates using mesenchymal stem cells for glioma therapy, Biomaterials 39 (2015) 269–281.
[179] S. Duchi, et al., Mesenchymal stem cells as delivery vehicle of porphyrin loaded nanoparticles: effective photoinduced in vitro killing of osteosarcoma, J. Control Release 168 (2) (2013) 225–237.

[180] Y.L. Hu, et al., Mesenchymal stem cells as a novel carrier for targeted delivery of gene in cancer therapy based on nonviral transfection, Mol. Pharm. 9 (9) (2012) 2698–2709.
[181] Y. Zhao, et al., Targeted delivery of doxorubicin by nano-loaded mesenchymal stem cells for lung melanoma metastases therapy, Sci. Rep. 7 (2017) 44758.
[182] M.R. Loebinger, et al., Magnetic resonance imaging of mesenchymal stem cells homing to pulmonary metastases using biocompatible magnetic nanoparticles, Cancer Res. 69 (23) (2009) 8862–8867.
[183] L. Li, et al., Silica nanorattle-doxorubicin-anchored mesenchymal stem cells for tumor-tropic therapy, ACS Nano 5 (9) (2011) 7462–7470.
[184] K. Pakravan, et al., MicroRNA-100 shuttled by mesenchymal stem cell-derived exosomes suppresses in vitro angiogenesis through modulating the mTOR/HIF-1α/VEGF signaling axis in breast cancer cells, Cell. Oncol. 40 (5) (2017) 457–470.
[185] H.K. Lee, et al., Mesenchymal stem cells deliver synthetic microRNA mimics to glioma cells and glioma stem cells and inhibit their cell migration and self-renewal, Oncotarget 4 (2) (2013) 346.
[186] M. Katakowski, et al., Exosomes from marrow stromal cells expressing miR-146b inhibit glioma growth, Cancer Lett. 335 (1) (2013) 201–204.
[187] F.M. Lang, et al., Mesenchymal stem cells as natural biofactories for exosomes carrying miR-124a in the treatment of gliomas, Neuro-Oncology 20 (3) (2018) 380–390.
[188] H. Xu, et al., Mesenchymal stem cell-derived exosomal microRNA-133b suppresses glioma progression via Wnt/beta-catenin signaling pathway by targeting EZH2, Stem Cell Res. Ther. 10 (1) (2019) 381.
[189] K. Shimbo, et al., Exosome-formed synthetic microRNA-143 is transferred to osteosarcoma cells and inhibits their migration, Biochem. Biophys. Res. Commun. 445 (2) (2014) 381–387.
[190] G. Lou, et al., Exosomes derived from miR-122-modified adipose tissue-derived MSCs increase chemosensitivity of hepatocellular carcinoma, J. Hematol. Oncol. 8 (1) (2015) 122.
[191] K. Takahara, et al., 245 MicroRNA-145 mediates the inhibitory effect of adipose-derived stem cells on androgen-independent prostate cancer, Eur. Urol. Suppl. 15 (3) (2016), e245.
[192] Y. Che, et al., Exosomes derived from miR-143-overexpressing MSCs inhibit cell migration and invasion in human prostate cancer by downregulating TFF3, Mol. Ther. Nucleic Acids 18 (2019) 232–244.
[193] J.L. Munoz, et al., Delivery of functional anti-miR-9 by mesenchymal stem cell-derived exosomes to glioblastoma multiforme cells conferred chemosensitivity, Mol. Ther. Nucleic Acids 2 (2013) e126.
[194] S. Shang, et al., Exosomal miRNA-1231 derived from bone marrow mesenchymal stem cells inhibits the activity of pancreatic cancer, Cancer Med. 8 (18) (2019) 7728–7740.
[195] H. Li, et al., Exosomes derived from siRNA against GRP78 modified bone-marrow-derived mesenchymal stem cells suppress Sorafenib resistance in hepatocellular carcinoma, J. Nanobiotechnol. 16 (1) (2018) 103.
[196] K.A. Greco, et al., PLK-1 silencing in bladder cancer by sirna delivered with exosomes, Urology 91 (2016) (p. 241 e1-7).
[197] Y. Liu, et al., Exosomes from mesenchymal stromal cells enhance imatinib-induced apoptosis in human leukemia cells via activation of caspase signaling pathway, Cytotherapy 20 (2) (2018) 181–188.
[198] S. Kalimuthu, et al., A new approach for loading anticancer drugs into mesenchymal stem cell-derived exosome mimetics for cancer therapy, Front. Pharm. 9 (2018) 1116.
[199] U. Altanerova, et al., Human mesenchymal stem cell-derived iron oxide exosomes allow targeted ablation of tumor cells via magnetic hyperthermia, Int. J. Nanomed. 12 (2017) 7923–7936.