Chapter

Human Pluripotent Stem Cell-Derived Mesenchymal Stem Cells for Oncotherapy

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Abstract

Mesenchymal stem/stromal cells (MSCs) with hematopoietic-supporting and immunoregulatory properties have aroused great expectations in the field of regenerative medicine and the concomitant pathogenesis. However, many obstacles still remain before the large-scale preparation of homogeneous and standardized MSCs with high cellular vitality for clinical purposes ascribe to elusive nature and biofunction of MSCs derived from various adult and fetal sources. Current progress in human pluripotent stem cells (hPSCs), including embryonic stem cells (ESCs) and induced PSCs (iPSCs), have highlighted the feasibility of MSC development and disease remodeling, together with robust MSC generation dispense from the inherent disadvantages of the aforementioned MSCs including ethical and pathogenic risks, donor heterogeneity and invasiveness. Herein, we review the state-of-the-art updates of advances for MSC preparation from hPSCs and multiple tissues (perinatal tissue, adult tissue) as well as tumor intervention with biomaterials, and thus propose a framework for MSCs-based oncotherapy in regenerative medicine. Collectively, we describe the landscape of *in vitro* generation and functional hierarchical organization of hPSC-MSCs, which will supply overwhelming new references for further dissecting MSC-based tissue engineering and disease remodeling.

Keywords: hPSCs, MSCs, drug delivery, oncotherapy, biomaterials

1. Introduction

Human pluripotent stem cells (hPSCs), including human induced PSCs (hiPSCs) and human embryonic stem cells (hESCs), are cell population with unique self-renewal and multi-lineage differentiation potential [1–3]. Attribute to the aforementioned properties, hPSCs have been considered as splendid alternatives for tissue engineering and disease remodeling [3, 4]. For instance, we and other investigators have been devoted to verifying the feasibility of high-efficient generation of MSCs from hPSCs (hPSCS-MSCs) for diverse disease treatment, including osteoarthritis, colitis, liver fibrosis [4–6]. Therewith, hPSCs have served as advantageous alternative sources for MSC preparation for regenerative medicine [7].

MSCs with unique immunoregulatory properties and tissue-repair capacity have been considered as advantageous cytotherapy for various refractory and recurrent disorders. For instance, preclinical studies and clinical practice have suggested the safety and efficiency of MSCs against hematological diseases, articular diseases, neurological diseases, digestive diseases, immune diseases and vascular diseases [8–11]. Meanwhile, the unique characteristic of MSCs with a lower immunogenicity as recommended by the International Society for Cellular Therapy (ISCT), which is appropriate for cell-based cancer immunotherapy [4, 12].

Currently, a certain number of studies have been reported that the capability of MSCs can migrate directionally to tumor sites and contribute to tumor microenvironment formation. Moreover, MSCs exert therapeutic function through an immune evasive mechanism, which will protect MSCs from immune detection and prolong their persistence *in vivo* [13, 14]. Numerous preclinical studies have indicated MSCs as gene transfer systems and ideal drug carries for targeted tumor therapy by releasing cytokines or suppressing tumor cells [15]. For examples, MSCs can load with anti-tumor drugs (as PTX or GBA), enzyme prodrug (as 5-FC/CD, GCV/HSV-TK or CPT-11) or oncolytic viruses, which thus provide antitumor effects with improved safety profiles. In addition, MSCs genetically modified to express interleukin (e.g., IL-2, IL-10, IL-12, IL-15, IL-18, IL-21) and interferon (e.g., IFN-a, IFN-β) could elicit antitumor immunity *in vivo* and inhibit tumor growth in vitro. Although, a large number of pre-clinical studies have been conducted to investigate engineering MSCs and revealed that the effects of it on tumor progress, only a small number of registered and completed clinical trials of engineering MSCs for tumors treatments. In this review, we briefly review the pre-clinical and clinical trials of engineered MSCs as gene transfer systems or drug delivery vehicles for the treatment of solid tumors, as well as summarize the therapeutic mechanism of cancers with engineered MSCs and future prospects.

2. Cell sources for MSC preparation

2.1 Adult tissue-derived MSCs

Since the 1960s, MSCs have been isolated from various sources, including adult tissues (e.g., bone marrow, adipose, dental pulp), perinatal tissues (e.g., umbilical cord, amniotic membrane, placenta) and even derived from human pluripotent stem cells (e.g., hESCs and hiPSCs) [16, 17]. Of them, MSCs were firstly isolated from bone marrow in clinical practice, followed by relative tissues such as adipose tissue, dental pulp and apical root papilla [18]. Bone marrow-derived MSCs (BM-MSCs) have been considered with the widest range of clinical applications, whereas adipose tissue-derive MSCs (AD-MSCs) have been recognized with superiority in adipogenesis over the relative tissue-derived MSCs [4, 19, 20].

2.2 Perinatal tissue-derived MSCs

To date, diverse perinatal tissues have been applied for MSC preparation, including umbilical cord, umbilical cord blood, amniotic membrane, amniotic fluid and placenta. For instance, Zhao *et al.* reported the generation of MSCs from umbilical cord (UC-MSCs) as well as the variations in biological and molecular properties at series passages [12]. Instead, Wei *et al.* and Du *et al.* took advantage of the cytokine

cocktail-based strategies for the high-efficient generation of VCAM-1$^+$ UC-MSCs with preferable immunoregulatory and proangiogenic properties [21, 22]. Of note, we and other investigators in the field verified the superiority of UC-MSCs over relative counterpart in immunoregulatory properties [8, 23]. As to placenta tissue-derived MSCs (P-MSCs), Hou *et al.* reported the spatio-temporal metabolokinetics as well as the efficacy upon mice with refractory Crohn's-like enterocutaneous fistula as well [24].

2.3 Human PSCs-derived MSCs

State-of-the-art literatures have reported the generation of MSCs from both hESCs and hiPSCs. Generally, there are four typical procedures for high-efficient hPSC-MSC preparation, including the monolayer model, the coculture model, the embryonic body (EB) model, and the cell programming strategy. For instance, we took advantage of a transcription factor, MSX2, for the initiation of MSC differentiation within 2 weeks [4]. Furthermore, we turned to small molecular cocktail-based strategies for high-efficient hPSC-MSC generation [5]. Notably, the hPSC-MSCs revealed considerable efficacy for the management of colitis, critical limb ischemia (CLI) and osteoarthritis [4–6]. Meanwhile, Li *et al.* and Yan *et al.* reported the therapeutic effect of hESC-MSCs for the treatment of autoimmune and inflammatory diseases under serum-containing or serum-free condition, respectively [25, 26]. Additionally, Wang and the colleagues generated hESC-MSCs with immune modulatory property via a trophoblast-like intermediate stage, which would also help understand the early mesengenesis in vitro [27].

3. Current strategies for MSC engineering

3.1 Nano-engineered mesenchymal stem cells

The therapeutic index of chemotherapeutic drugs can be improved by site-designed administration by reducing the exposure of drugs in non-target tissues. Current methods of targeted drug delivery mainly rely on nano-drug carriers, which can be accumulated in solid tumors. However, this passive accumulation is very inefficient, resulting in less than 5% of the dosage is delivered to the tumor, and the distribution of nano-drug carriers within the tumor is unevenly. More interestingly, MSCs can load with anti-tumor drugs as chemotherapeutic drug paclitaxel (PTX), galbanic acid (GBA) and doxorubicin (DOX), which can uniformly infiltrate into tumor tissue, and improve the distribution of therapeutic drugs within the tumor as shown in **Table 1**. For examples, Pessina *et al.* have demonstrated that MSCs-PTX could produce dramatic antitumor effects in MOLT-4 cells *in vitro* through negatively regulated intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) expression on microvascular endothelium in 2013 [48]. Moreover, PTX-loaded BM-MSCs and AT-MSCs were respectively co-cultured with NCI-H28 cells and CG5 cells *in vitro*, it showed that both of them could intensely suppress these cancer cell line proliferation and significant improvement in these cell apoptosis [20, 49]. Dual drug loading modalities including cell surface conjugation or endocytosis have been investigated in order to overcome the limited drug loading of MSCs. MSCs have been engineered with various types of organic or inorganic nanoparticles with aimed to improve their drug loading and therapeutic efficacy [35, 50]. For examples, to investigate the efficacy of adipose tissue-derived from MSCs as drug carriers for delivery of galbanic acid

Source of MSCs	Vector systems	Cancer type	Anti-tumor drug	Mainly results	Reference
BM-MSCs	PLGA nanoparticles	Lung cancer	PTX	Incorporating PTX induces upregulation of CXCR4 expression and improves tumor homing	[28]
WJ-MSCs	Exosomes	Cervical cancer	PTX	Incorporating PTX induces apoptosis, and suppressed epithelial-mesenchymal transition proteins in Hela cells	[29]
BM-MSCs	HA-PLGA nanoparticles	Glioma	PTX	The survival of orthotopic glioma-bearing rats was significantly extended	[30]
AD-MSCs	N/A	Ovarian Cancer	PTX	Inhibited ovarian cancer cells migration/dissemination in 2D and 3D models	[31]
AD-MSCs	N/A	Glioblastoma	PTX	Inhibited the activity of the human pancreatic carcinoma (CFPAC-1) and glioblastoma (U87-MG) by PTX loaded MSCs-TRAIL	[32]
Gingival-MSCs	Exosomes	Pancreatic cancer	PTX	Exerted a significant anticancer effect on both human pancreatic carcinoma and squamous carcinoma cells	[33]
BM-MSCs	Exosomes	Breast cancer	PTX	Decreased the viability of MDA-MB-231 cells *in vitro* and inhibited the tumor growth *in vivo*	[34]
AD-MSCs	PLGA nanoparticles	Colon cancer	GBA	Shown to be efficient in killing C26 colon cancer cells *in vitro* in a dose-dependent manner	[35]
BM-MSCs	Exosomes	Osteosarcoma	DOX	Demonstrates excellent antitumor properties both *in vivo* and *in vitro*	[36]
BM-MSCs	Exosomes	Osteosarcoma	DOX	Shown the low cytotoxicity in myocardial cells and killed the osteosarcoma cells more effectively	[37]
BM-MSCs	Exosomes	Neuroblastoma	DOX	Increased inhibitory effect against NB tumor progression *in vivo* and promote NB cell apoptosis *in vitro*	[38]

Source of MSCs	Vector systems	Cancer type	Anti-tumor drug	Mainly results	Reference
UC-MSCs	Exosomes	Hepatocellular carcinoma	DOX	Cellular uptake and cell cytotoxicity against HepG2 cells *in vitro* and *in vivo*	[39]
BM-MSCs	Exosomes	Osteosarcoma	DOX	Enhanced toxicity against osteosarcoma and less toxicity in heart tissue	[40]
UC-MSCs	Exosomes	Breast cancer	DOX/ CBD	Reduced tumor burden in MDA-MB-231 xenograft tumor model	[41]
BM-MSCs	silica nanoparticles	Hepatocellular carcinoma	DOX	Inhibited the growth of tumors and decreased the side effects in HepG2 xenograft mice	[42]
BM-MSCs	Fe_3O_4 nanoparticle	Osteosarcoma	DOX/ MLT	Improved anticancer efficacy in Saos-2 and MG-63 cells and thus reduced toxicity in normal cells.	[43]
BM-MSCs	Exosomes	Colorectal cancer	DOX	Suppressed C26-tumor growth in vivo	[44]
BM-MSCs	Superpara-magnetic iron oxide (SPIO) nanoparticles	Colon cancer	DOX	Enhanced tumor treatment efficacy of MC38 tumor-bearing C57BL/6 mice	[45]
BM-MSCs	Exosomes	Breast cancer	DOX	Reduced the tumor growth rate of murine breast cancer model	[46]
BM-MSCs	N/A	Breast/thyroid cancer	DOX	Showed enhanced anti-tumor effects in cancer xenograft models	[47]

Table 1.
Pre-clinical experiments of nano-engineered MSCs for cancer therapy within 5 years (2018–2023).

(GBA)-loaded poly (lactic-co-glycolic acid) (PLGA) nanoparticles (nano-engineered MSCs) against tumor cells, the results have performed the nano-engineered MSCs could effectively induce cell death in C26 cells, which is considered to be as a valuable platform for drug delivery in cancer therapy [35]. Remarkably, exosomes derived from MSCs can delivery chemotherapeutic agents (DOX) in the treatment of various cancer. For instance, Liu Y *et al*. have indicated doxorubicin-loaded MSCs encapsulated into superparamagnetic iron oxide (SPIO) nanoparticles could mainly enhance anti-tumor effects and reduce the immune system response in the treatment of colon cancer [45].

3.2 Genetically modified MSCs via non-viral and viral vector systems

During previous years, cytokine-mediated cancer therapy has the potential to enhance immunotherapeutic approaches through the endowing of the immune

Source of MSCs	Vector systems	Cancer type	Cytokine	Mainly results	Reference
UC-MSCs	Lentiviral	Lung cancer	IFN-β	Inhibited the growth of tumor in A549 lung cancer-bearing mice	[52]
G-MSCs	Lentiviral	Squamous cell carcinoma (SCC)	IFN-β	Inhibited the proliferation of tongue squamous cell carcinoma cells *in vitro* and *in vivo*	[53]
AF-MSCs	Non-viral	Lung cancer	IFN-β/ IFN-γ	IFN-primed AFMSCs in suppressing tumor progression *in vivo*	[54]
AD-MSCs	Non-viral	Hepatocellular Carcinoma Cells (HCCs)	IFN-β/ TRAIL	Suppressed proliferation of HCCs through activated STAT1-mediated p53/ p21 by IFN-β, but not TRAIL	[55]
BM-MSCs	Lentiviral	lymphoma	IFN-β/ TRAIL	Exhibited tumor size reduction, growth delay, or apparent tumor clearance	[56]
AD-MSCs	Non-viral	Lung cancer	IFN-β/ TRAIL	reduced tumor weight in H460-derived cancer animal models	[57]
BM-MSCs	Non-viral	Breast Cancer	IFN-γ	increased the apoptosis of MCF-7 cells	[58]
AD-MSCs	Lentiviral	Breast Cancer	IL-2	induced apoptosis in breast cancer cells and stimulated the proliferation of immune cells	[59]
AD-MSCs	Lentiviral	Neuroblastoma	IL-2	Reduced SH-SY5Y proliferation and activate PBMCs *in vitro*	[60]
BM-MSCs	Lipofectamine	Pancreatic Cancer	IL-10	impeded the pancreatic cancer cells proliferation *in vitro* and reduced the growth of tumor xenograft *in vivo*	[61]
BM-MSCs	Lentiviral	Glioblastoma	IL-12	showed a strong inhibitory effect in glioma-bearing nude mice	[62]
BM-MSCs	Lentiviral	Lymphoma	IL-12/ TRAIL	reduced tumor volume and increased survival in mice	[63]
BM-MSCs	Adenovirus	Melanomas	IL-12	inhibition of tumor growth and reduction in the number of metastases in mice	[64]

Source of MSCs	Vector systems	Cancer type	Cytokine	Mainly results	Reference
BM-MSCs	Lentiviral	peritoneal cancer	IL-12/ IL-21	reducing the risk for systemic immune-mediated toxicities	[65]
UC-MSCs	Adenovirus	Glioblastoma	IL-15	exerted stronger therapeutic effects and promoted macrophage/ microglia infiltration in a Vivo model.	[66]
GC-MSCs	Non-viral	Gastric cancer	IL-15	promote tumor cell EMT and induce Tregs ratio increase to affect GC progression	[67]
UC-MSCs	Lentiviral	Breast cancer	IL-18	inhibit the proliferation and metastasis of breast cancer cells *in vivo*	[68]

G-MSCs: gingiva-derived mesenchymal stromal cells; AF-MSCs: amniotic fluid-derived mesenchymal stem cells; and GC-MSCs: gastric cancer-derived mesenchymal stem cells.

Table 2.
Pre-clinical experiments of genetically modified MSCs for cancer therapy within 5 years (2018–2023).

system by providing improved anti-cancer immunity. Nevertheless, the influence of interleukins originated therapeutics is still restricted by short half-life, systemic dose-limiting toxicities, and side-effects. In order to overcome these defects, as gene delivery platform, MSCs have been genetically modified by using viral and non-viral vectors result in the secretion of proinflammatory cytokines to enhance the host immune response to cancer cells, as well as to directly mediate tumor cell death, which have already been reported in several preclinical and clinical trials [51]. Hererin, we have summarized several cytokines engineered MSCs as drug vehicles in the treatment of cancers as seen in **Table 2**.

IFN-β is known to exhibit the classic antitumor effect, which has been certified to inhibit the proliferation of tumor cells and induce apoptosis *in vitro*, however, IFN-β could not generate and maintain therapeutic dose in the tumor sites due to its short half-life; Meanwhile, it leads to the toxicity of organ with serious side effects [52]. To overcome this problem, mesenchymal stem cells (MSCs) have been utilized as drug carriers for IFN-β gene delivery. This IFN-β expressing MSCs as therapeutic agents via systemic administration have been demonstrated effective in attenuation of cancers as melanoma [69], breast cancer [70], pancreatic cancer [71], lung cancer [52], squamous cell carcinoma [53].

IFN-γ can not only enhance the antigen presentation of dendritic cells, up-regulate co-stimulatory molecules, and promote lymphocyte differentiation, and effectively stimulate the activation of effector cells in immune system. Although IFN-γ has many advantages, the ability to induce apoptosis and inhibit angiogenesis will also influence on the normal tissues of body, resulting in side effects. In clinical trials, large doses of IFN-γ have been found to cause the side effects of nervous, blood and liver system. However, using MSCs as a drug carrier with chemotropism and precisely delivery characters, which can not only improve the concentration of IFN-γ in tumor tissues and achieve better therapeutic effectiveness, but also significantly reduce the side effects of IFN-γ on normal tissues.

IL-2 as an immunomodulatory agent was firstly approved by the U.S. Food and Drug Administration (FDA) for the treatment of melanoma and carcinoma, which is required by both effector T lymphocyte and regulatory T cell. However, the short half-life and high-dose toxicity caused by IL-2 limit the clinical application [72, 73]. For instance, Joonbeom Bae and the colleagues reported that exogenous IL-2 gene modified mesenchymal stem cells elicited antitumor immunity and rejuvenate $CD8^+$ tumor-infiltrating lymphocytes (TILs) [74].

IL-10 is produced by innate and adaptive immune cells, and mainly functions as an immune suppressor that inhibits the cancer immunity cycle. However, the half-life of IL-10 in the body is very short. For example, Zhao *et al.* verified that IL-10 modified MSCs could inhibit the growth of the transplanted tumor *in vivo* and prolong survival of bearing animals [61].

IL-12 is mainly produced by antigen-presenting cells (APCs) that regulate the immune response and serves as an effective inducer for T lymphocytes and NK cells to produce interferon-γ (IFN-γ), which is a promising therapeutic agent for the treatment of cancers. However, a short half-life and dose-limited toxicity of IL-12 limits its clinical application [75]. Numerous studies have reported that IL-12 gene modified MSCs could exhibit strengthen the anti-tumor effect in various cancer. For examples, Wu *et al.* have demonstrated that IL-12 derived from lentivirus-mediated IL-12-modified BM-MSCs combined with Fuzheng Yiliu decoction shows a strong inhibitory effect against tumor growth of glioma-nude mice, which have shown promise as an excellent drug delivery vehicle for antitumor-targeted therapy [62]. In another research, Ryu *et al.* took advantage of a delivery system based on IL-12-expressing human umbilical cord blood-derived MSCs (UC-MSCs) significantly inhibited tumor growth and prolonged the survival of glioma-bearing mice, which thus induced long-term antitumor immunity against intracranial gliomas [76].

IL-15 is mainly secreted by activated myeloid cells that are structurally and functionally similar to IL-2. IL-15 supports the persistence of $CD8^+$ memory T cells, while inhibits IL-2-induced T cell death that better maintains long-term anti-tumor immunity [77]. For instance, Wei *et al.* have demonstrated that umbilical cord blood derived MSCs (UCB-MSCs)-transduced with lentivirus vector coding IL-15 could significantly inhibit tumor growth and prolong the survival of Pan02 pancreatic tumor mice, which were associated with tumor cell apoptosis, natural killer (NK) cell—and T-cell accumulation [78].

IL-18 as an interferon (IFN)-γ-inducing factor, which has been reported to be involved in Th1- and Th2- mediated immune responses, as well as in the activation of NK cells and macrophages. IL-18 plays a pivotal role in linking inflammatory immune responses, tumor progression and macrophage activation [79, 80]. For instance, Liu *et al.* indicated that UC-MSCs genetically modified with IL-18 could inhibit the proliferation and metastasis of breast cancer cells *in vivo* by activating immunocytes and immune cytokines, and inhibiting tumor angiogenesis [68].

IL-21 has been reported to induce a cell mediated immune responses, including NK cells and T cells. Moreover, IL-21 as an immunotherapeutic agent has been extensively applied for tumor administration. For examples, Kim *et al.* found that IL-21-expressing MSCs could inhibit the development of disseminated B-cell lymphoma and prolonged survival, which were associated with the infusion of IL-21/MSCs led to induction of effector T and NK cells [81].

4. Programmed MSCs for cytotherapy

4.1 Gene-directed enzyme prodrug therapy

Gene-directed enzyme prodrug therapy (GDEPT) is a novel approach to cancer treatment. Genetically engineered MSCs expressing suicide genes (cytosine deaminase, thymidine kinase, and carboxylesterase) have been indicated to have significant anti-tumor responses as shown in **Table 3**. To date, there are three common pro-drug activating enzymes to modify MSCs (including herpes simplex virus-hymidine kinase (HSV-TK), cytosine deaminase (CD), and rCE) to combine with ganciclovir (GCV), 5-fluorocytosine (5-FC), or Irinotecan hydrochloride (CPT-11), which can effectively inhibit DNA synthesis of tumor, as well as decrease systemic toxicity [86]. As to CD/5-FC, a certain number of researchers have reported MSCs with CD suicide gene expression have been conformed to suppress the development of breast cancer, glioma, melanoma, osteosarcoma and lung carcinoma via converting non-toxic prodrug 5-FC into cytotoxic chemotherapeutic drug 5-FU [92–96]. For instance, Daniela Klimova *et al.* have demonstrated that intravenous injection of adipose-tissue and BM-MSCs-CD/5FC inhibited the progression of tumor in the transgenic adenocarcinoma of the mouse prostate (TRAMP) model [97]. The authors have proposed that MSC/CD combined with 5-FC and TMZ could increase cell cycle arrest and DNA breakage, which could be used in patients with glioblastoma multiforme (GBM) during the immediate postoperative period to sensitize tumors to subsequent adjuvant chemo- and radiotherapy [98]. Moreover, it has been suggested that extracellular vesicles derived from MSCs with CD gene delivery as cargo have an inhibitory effect on the growth of tumor cell lines *in vitro*, as Daniela Klimova engineered the MSCs-EV were cultivated with gemcitabine (GCB), which significantly inhibited the cell growth of pancreatic carcinoma cell lines *in vitro* via converting non-toxic prodrug 5-fluorocytosine (5-FC) to highly cytotoxic prodrug 5-fluorouracil (5-FU), and thereby provide a therapeutic option for tumors [82]. In addition, the transduced iPSC-MSCs both limited growth of preformed tumors and decreased lung metastases after administration of the prodrug (5-FC) [99]. As HSV-TK/GCV, the thymidine kinase (TK)/ganciclovir (GCV) system is a gene-directed enzyme prodrug therapy. Therefore, the herpes simplex virus 1 thymidine kinase (HSV-TK) gene as a suicide gene is introduced into cells phosphorylates a prodrug GCV, which inhibits DNA synthesis and causes cell apoptosis. Although the group of HSV-TK/GCV as suicide gene therapy method is safe and effective in pre-clinical experiments, yet it is not effective in clinical trials due to the lower transfection rate of target cells [100]. In this regard, using engineered MSCs as drug carriers to induce tumor regression in human tumors mainly based on the strong migration ability to especially invasive tumors. For examples, Wei *et al.* have reported that HSV-TK-expressing UC-MSCs combined with prodrug GCV exerted a better effect in the treatment of subcutaneous tumor models and brain intracranial tumor models [88]. Azra Kenarkoohi *et al.* further investigated the anti-tumor activity of MSCs transduced with the HSV/TK in a mouse cervical cancer model via intratumoral injection, which performed significant reduction in tumor size and improvement of NK and CTL activity [85]. As rCE/CPT-11, carboxylesterases (CEs) are enzymes that can convert the prodrug CPT-11 (irinotecan) to its active metabolite SN-38, which has significant cytotoxicity to tumor cells [101]. For example, Seung Ah Choi *et al.* reported that adipose tissue-derived from MSCs

Source of MSCs	Vector systems	Cancer type	Pro-drug	Mainly results	Reference
DP-MSCs	Exosomes	Pancreatic carcinoma	5-FC	Significantly inhibited the cell growth of pancreatic carcinoma cell lines *in vitro*	[82]
AD/UC/ DP-MSCs	Exosomes	Glioblastomas	GCV	inhibited the growth of cerebral C6 glioblastomas *in vivo*.	[83]
AD-MSCs	Microparticles/ ECM	Prostate cancer	GCV	inhibited tumor growth of human prostate cancer *in vivo*	[84]
AD-MSCs	Lentiviral	Cervical cancer	GCV	Significant reduction in tumor size *in vivo*	[85]
AD/BM/ DP/UC/ BP-MSCs	Exosomes	Glioblastoma	GCV	Induce tumor cell death	[86]
BM-MSCs	N/A	Glioblastoma	GCV	Provide a significant growth inhibition and increase survival in a glioblastoma model	[87]
UC-MSCs	N/A	Glioblastoma	GCV	exerts a strong bystander effect on tumor cells	[88]
P-MSCs	Lentiviral	colon cancer	GCV	inhibiting tumor proliferation and inducing tumor apoptosis	[89]
BM-MSCs	PEI-PLL	Glioblastoma	GCV	reduced cell proliferation and angiogenesis in rat C6 glioma	[90]
AD-MSCs	Plasmid	Ovarian Cancer	CPT-11	overcoming drug resistance in ovarian cancer	[91]

DP-MSCs: dental pulp MSCs; AD: Adipose tissue; BM: bone marrow; DP: dental pulp; UC: umbilical cord; BP: blood platelets; P-MSCs: placenta MSCs; and PEI-PLL: polylysine-modified polyethylenimine copolymer.

Table 3.
Pre-clinical experiments of MSCs-based enzyme prodrug for cancer therapy within 5 years (2018–2023).

expressing rCE as cellular vehicles could convert CPT-11 to SN-38, which revealed cytotoxic effect on F98 cell *in vitro* and effectively inhibited the progression of tumor in a rat brainstem glioma model. Therewith, the genetically modified MSCs-rCE as drug delivery have showed therapeutic potential against brainstem gliomas [102].

4.2 Trail prodrug therapy

The death ligand tumor necrosis factor (TNF)-related apoptosis inducing ligand (TRAIL), a member of the TNF cytokine superfamily, has long been recognized for its

potential as a cancer therapeutic due to its capacity to induce apoptosis in many types of cancer cells via the receptors DR4 (TRAIL-R1) and DR5 (TRAIL-R2/KILLER), and Fas ligand (FasL) binding to the Fas receptor [103, 104]. Based on the previous research, TRAIL-MSCs as delivery vehicles could induce strength cytotoxicity against cancer cells, which furtherly inhibited tumor growth and prolonged survival in cancer

Source of MSCs	Vector systems	Cancer type	Pro-drug	Mainly results	Reference
AD-MSCs	Lentiviral	Breast cancer	TRAIL	induce TRAIL-mediated apoptosis *in vitro* and *in vivo* in breast cancer mouse models	[105]
UC-MSCs	Lentiviral	B-ALL	TRAIL	inhibit B-ALL cells proliferation *in vitro* and *in vivo*	[106]
UC-MSCs	Lentiviral	AML	TRAIL/IFN-γ	induce apoptosis in both primary AML patient-derived leukemic cells and AML cell lines	[107]
AD-MSCs	Plasmid	Lung cancer	TRAIL	inhibitory effects on H460 tumor growth both *in vitro* and *in vivo*	[108]
BM-MSCs	Adenoviral	Glioblastoma	TRAIL/VPA	increases the therapeutic effects of MSCs-TRAIL against glioma *in vitro* and *in vivo*	[109]
AD-MSCs	AAV	Hepatocellular carcinoma	TRAIL	inhibit tumor growth and the metastasis of implanted HCC tumors	[110]
BM-MSCs	Exosomes	Hepatocellular carcinoma	TRAIL	enhanced the apoptotic effect of HCC cells *in vitro* and *in vivo*	[111]
BM-MSCs	Plasmid	Melanoma	TRAIL/PEI	induce cell death in B16F0 cells *in vitro* and efficiently reduce tumor weights	[112]
AD-MSCs	N/A	Lung cancer	TRAIL	Protect A549 cancer cells from undergoing apoptosis and increase the survival of cancer cells.	[113]
UC-MSCs	Plasmid	Glioblastoma	TRAIL	significantly higher inhibitory effect and tumor killing effect of gliomas cells *in vitro and in vivo*	[114]
AD-MSCs	Plasmid	Glioblastoma	TRAIL/ Panobinostat	induced decreases in tumor volume and prolonged survival	[115]
BM-MSCs	Adenoviral	Intracranial glioma	TRAIL/VPA	increased migratory capacity toward tumor sites	[109]

B-All: B-cell acute lymphocytic leukemia; AML: acute myeloid leukemia; VPA: valproic acid; AAV: adeno-associated virus; PEI: polyethylenimine; and VPA: valproic acid.

Table 4.
Pre-clinical experiments of TRAIL-MSCs for cancer therapy within 5 years (2018–2023).

models as shown in **Tables 2** and **4**. For instance, Young Un Choi *et al.* constructed the genetically engineered AD-MSCs with TRAIL expression and verified the suppressive effects upon tumor growth in an H460 xenograft model [108]. Chen *et al.* found that TRAIL-MSCs could significantly inhibit the proliferation and promote the apoptosis of B-cell acute lymphocytic leukemia (B-ALL) cells *in vitro* and *in vivo* [106]. Moreover, iPSC-MSCs overexpressing TRAIL are also considered an effective option for the treatment of cancer. For example, Wang and the colleagues have reported that genetically modified iPSCs-MSCs with TRAIL could significantly induce apoptosis in various tumor cell lines *in vitro*, as well as inhibit tumor growth in tumor-bearing mice models via the activation of apoptosis-associated signaling pathways [116].

5. Clinical application of engineering MSCs in tumor

Although numerous preclinical trials have been published, only a small number of clinical trials were registered and completed for the treatment of solid tumors with engineering MSCs. For example, Hanno Niess *et al.* conducted a single-arm phase I/II study for the treatment of gastrointestinal tumors by genetically modified autologous BM-MSCs. According to another clinical trial in the stage of phase I, the safety of the investigational medicinal product (IMP) is evaluated in six patients by 3 times injection of MSCs at diverse concentrations followed by administration of the prodrug Ganciclovir. In the stage of phase II, 16 patients will be enrolled receiving IMP treatment [117]. One completed clinical trial is an investigational study for INF-β modified MSCs in the treatment of ovarian cancer with the aim to evaluated the safety of MSCs/INF-β in the stage of Phase I (without published results). For the treatment of lung cancer, TRAIL engineered allogeneic MSCs as therapeutic agent to treat the metastatic non-small cell lung cancer (NSCLC) patients in a Phase I/II clinical trial. Furthermore, an exploratory trial reported four children with metastatic neuroblastoma to received autologous MSCs infected with ICOVIR-5, and the results exhibited a well-tolerance and safety of MSCs delivered with oncolytic adenoviruses in the treatment of metastatic neuroblastoma [118].

In summary, according to preclinical investigations and clinical trials, we suppose that engineered MSCs as drug delivery is a multifaceted player in oncotherapy development and the clinical transformation of MSCs is urgently needed to accelerate tumor therapy.

6. Prospective and challenges

Longitudinal studies have indicated hPSCs as advantageous cell sources for functional cell generation and the concomitant therapeutic strategy for regenerative medicine and oncotherapy. As mentioned above, the unique property, including self-renewal and multipotent differentiation, have endowed hPSCs with first-rate potential for disease remodeling and alternative cell source preparation. Even though, the significant disadvantages such as teratoma formation and the low differentiation efficiency should not be neglected [3]. Distinguish from the other counterparts, hPSC-MSCs revealed more robust cellular viability and considerable therapeutic effect upon diverse diseases, which thus hold promising prospects for serving as alternative sources of adult tissue- or perinatal tissue-derived MSCs [4].

Notably, considering the rapid progress in gene-editing and MSC-based cytotherapy, it would be of great interesting to further explore the feasibility of generating hESC-MSCs or hiPSC-MSCs with specific targets for the next-generation of oncotherapy in preclinical and clinical practice.

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Conflict of interest

The authors declare no conflict of interest.

Notes/thanks/other declarations

Not applicable.

Appendices and nomenclature

MSCs	mesenchymal stem/stromal cells
hPSCs	human pluripotent stem cells
hESCs	human embryonic stem cells
hiPSCs	human induced pluripotent stem cells
UCB-MSCs	umbilical cord blood-derived MSCs
UC-MSCs	umbilical cord-derived MSCs
ISCT	International Society for Cellular Therapy

APCs	antigen-presenting cells
TILs	tumor-infiltrating lymphocytes
IFN-γ	interferon-γ
GDEPT	gene-directed enzyme prodrug therapy
TRAMP	transgenic adenocarcinoma of the mouse prostate
CLI	critical limb ischemia
ICAM-1	intercellular adhesion molecule-1
VCAM-1	vascular cell adhesion molecule-1
SPIO	superparamagnetic iron oxide
HSV-TK	herpes simplex virus-hymidine kinase
TRAIL	TNF-related apoptosis inducing ligand
NSCLC	non-small cell lung cancer

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References

[1] Li Y, Hermanson DL, Moriarity BS, Kaufman DS. Human iPSC-derived natural killer cells engineered with chimeric antigen receptors enhance anti-tumor activity. Cell Stem Cell. 2018;**23**(2):181-192 e185

[2] Wu H, Uchimura K, Donnelly EL, Kirita Y, Morris SA, Humphreys BD. Comparative analysis and refinement of human PSC-derived kidney organoid differentiation with single-cell Transcriptomics. Cell Stem Cell. 2018;**23**(6):869-881 e868

[3] Wu Q, Zhang L, Su P, Lei X, Liu X, Wang H, et al. MSX2 mediates entry of human pluripotent stem cells into mesendoderm by simultaneously suppressing SOX2 and activating NODAL signaling. Cell Research. 2015;**25**(12):1314-1332

[4] Zhang L, Wang H, Liu C, Wu Q, Su P, Wu D, et al. MSX2 initiates and accelerates mesenchymal stem/stromal cell specification of hPSCs by regulating TWIST1 and PRAME. Stem Cell Reports. 2018;**11**(2):497-513

[5] Wei Y, Hou H, Zhang L, Zhao N, Li C, Huo J, et al. JNKi- and DAC-programmed mesenchymal stem/stromal cells from hESCs facilitate hematopoiesis and alleviate hind limb ischemia. Stem Cell Research & Therapy. 2019;**10**(1):186

[6] Zhang L, Wei Y, Chi Y, Liu D, Yang S, Han Z, et al. Two-step generation of mesenchymal stem/stromal cells from human pluripotent stem cells with reinforced efficacy upon osteoarthritis rabbits by HA hydrogel. Cell & Bioscience. 2021;**11**(1):6

[7] Jiang B, Yan L, Wang X, Li E, Murphy K, Vaccaro K, et al. Concise review: Mesenchymal stem cells derived from human pluripotent cells, an unlimited and quality-controllable source for therapeutic applications. Stem Cells. 2019;**37**(5):572-581

[8] Yu H, Feng Y, Du W, Zhao M, Jia H, Wei Z, et al. Off-the-shelf GMP-grade UC-MSCs as therapeutic drugs for the amelioration of CCl4-induced acute-on-chronic liver failure in NOD-SCID mice. International Immunopharmacology. 2022;**113**(Pt A):109408

[9] Zhang Y, Li Y, Li W, Cai J, Yue M, Jiang L, et al. Therapeutic effect of human umbilical cord mesenchymal stem cells at various passages on acute liver failure in rats. Stem Cells International. 2018;**2018**:7159465

[10] Zhao Q, Han Z, Wang J, Han Z. Development and investigational new drug application of mesenchymal stem/stromal cells products in China. Stem Cells Translational Medicine. 2021;**10**(Suppl 2):S18-S30

[11] Zhao K, Liu Q. The clinical application of mesenchymal stromal cells in hematopoietic stem cell transplantation. Journal of Hematology & Oncology. 2016;**9**(1):46

[12] Zhao Q, Zhang L, Wei Y, Yu H, Zou L, Huo J, et al. Systematic comparison of hUC-MSCs at various passages reveals the variations of signatures and therapeutic effect on acute graft-versus-host disease. Stem Cell Research & Therapy. 2019;**10**(1):354

[13] Ankrum JA, Ong JF, Karp JM. Mesenchymal stem cells: immune evasive, not immune privileged. Nature Biotechnology. 2014;**32**(3):252-260

[14] Wu HH, Zhou Y, Tabata Y, Gao JQ. Mesenchymal stem cell-based

drug delivery strategy: From cells to biomimetic. Journal of Controlled Release. 2019;**294**:102-113

[15] Zhang X, Yang Y, Zhang L, Lu Y, Zhang Q, Fan D, et al. Mesenchymal stromal cells as vehicles of tetravalent bispecific Tandab (CD3/CD19) for the treatment of B cell lymphoma combined with IDO pathway inhibitor D-1-methyl-tryptophan. Journal of Hematology & Oncology. 2017;**10**(1):56

[16] Wang A, Zhang L, Zhao M, Yu H. Quality control and therapeutic investigations of mesenchymal stem/stromal cells during investigational new drug application for GvHD administration in China. Current Stem Cell Research & Therapy. 2023;**18**(8):1032-1040

[17] Wang M, Yuan Q, Xie L. Mesenchymal stem cell-based immunomodulation: Properties and clinical application. Stem Cells International. 2018;**2018**:3057624

[18] Yao J, Chen N, Wang X, Zhang L, Huo J, Chi Y, et al. Human supernumerary teeth-derived apical papillary stem cells possess preferable characteristics and efficacy on hepatic fibrosis in mice. Stem Cells International. 2020;**2020**:6489396

[19] Wang L, Zhang L, Liang X, Zou J, Liu N, Liu T, et al. Adipose tissue-derived stem cells from type 2 diabetics reveal conservative alterations in multidimensional characteristics. International Journal of Stem Cells. 2020;**13**(2):268-278

[20] Scioli MG, Artuso S, D'Angelo C, Porru M, D'Amico F, Bielli A, et al. Adipose-derived stem cell-mediated paclitaxel delivery inhibits breast cancer growth. PLoS One. 2018;**13**(9):e0203426

[21] Du W, Li X, Chi Y, Ma F, Li Z, Yang S, et al. VCAM-1+ placenta chorionic villi-derived mesenchymal stem cells display potent pro-angiogenic activity. Stem Cell Research & Therapy. 2016;**7**:49

[22] Wei Y, Zhang L, Chi Y, Ren X, Gao Y, Song B, et al. High-efficient generation of VCAM-1(+) mesenchymal stem cells with multidimensional superiorities in signatures and efficacy on aplastic anaemia mice. Cell Proliferation. 2020;**53**(8):e12862

[23] He Y, Guo X, Lan T, Xia J, Wang J, Li B, et al. Human umbilical cord-derived mesenchymal stem cells improve the function of liver in rats with acute-on-chronic liver failure via downregulating notch and Stat1/Stat3 signaling. Stem Cell Research & Therapy. 2021;**12**(1):396

[24] Hou H, Zhang L, Duan L, Liu Y, Han Z, Li Z, et al. Spatio-temporal Metabolokinetics and efficacy of human placenta-derived mesenchymal stem/stromal cells on mice with refractory Crohn's-like Enterocutaneous fistula. Stem Cell Reviews and Reports. 2020;**16**(6):1292-1304

[25] Yan L, Zheng D, Xu RH. Critical role of tumor necrosis factor signaling in mesenchymal stem cell-based therapy for autoimmune and inflammatory diseases. Frontiers in Immunology. 2018;**9**:1658

[26] Li E, Zhang Z, Jiang B, Yan L, Park JW, Xu RH. Generation of mesenchymal stem cells from human embryonic stem cells in a complete serum-free condition. International Journal of Biological Sciences. 2018;**14**(13):1901-1909

[27] Wang X, Lazorchak AS, Song L, Li E, Zhang Z, Jiang B, et al. Immune modulatory mesenchymal stem cells derived from human embryonic stem cells through a trophoblast-like stage. Stem Cells. 2016;**34**(2):380-391

[28] Prabha S, Merali C, Sehgal D, Nicolas E, Bhaskar N, Flores M, et al. Incorporation of paclitaxel in mesenchymal stem cells using nanoengineering upregulates antioxidant response, CXCR4 expression and enhances tumor homing. Materials Today Bio. 2023;**19**:100567

[29] Abas BI, Demirbolat GM, Cevik O. Wharton jelly-derived mesenchymal stem cell exosomes induce apoptosis and suppress EMT signaling in cervical cancer cells as an effective drug carrier system of paclitaxel. PLoS One. 2022;**17**(9):e0274607

[30] Wang XL, Zhao WZ, Fan JZ, Jia LC, Lu YN, Zeng LH, et al. Tumor tropic delivery of hyaluronic acid-poly (D,L-lactide-co-glycolide) polymeric micelles using mesenchymal stem cells for glioma therapy. Molecules. 8 Apr 2022;**27**(8):2419

[31] Borghese C, Casagrande N, Corona G, Aldinucci D. Adipose-derived stem cells primed with paclitaxel inhibit ovarian cancer spheroid growth and overcome paclitaxel resistance. Pharmaceutics. 27 Apr 2020;**12**(5):401

[32] Coccè V, Bonomi A, Cavicchini L, Sisto F, Giannì A, Farronato G, et al. Paclitaxel priming of TRAIL expressing mesenchymal stromal cells (MSCs-TRAIL) increases antitumor efficacy of their Secretome. Current Cancer Drug Targets. 15 Nov 2020. DOI: 10.2174/1568009620666201116112153 [Epub ahead of print]

[33] Coccè V, Franzè S, Brini AT, Giannì AB, Pascucci L, Ciusani E, et al. In vitro anticancer activity of extracellular vesicles (EVs) secreted by gingival mesenchymal stromal cells primed with paclitaxel. Pharmaceutics. 1 Feb 2019;**11**(2):61

[34] Kalimuthu S, Gangadaran P, Rajendran RL, Zhu L, Oh JM, Lee HW, et al. A new approach for loading anticancer drugs into mesenchymal stem cell-derived exosome Mimetics for cancer therapy. Frontiers in Pharmacology. 2018;**9**:1116

[35] Ebrahimian M, Shahgordi S, Yazdian-Robati R, Etemad L, Hashemi M, Salmasi Z. Targeted delivery of galbanic acid to colon cancer cells by PLGA nanoparticles incorporated into human mesenchymal stem cells. Avicenna Journal of Phytomedicine. 2022;**12**(3):295-308

[36] Wang J, Li M, Jin L, Guo P, Zhang Z, Zhanghuang C, et al. Exosome mimetics derived from bone marrow mesenchymal stem cells deliver doxorubicin to osteosarcoma in vitro and in vivo. Drug Delivery. 2022;**29**(1):3291-3303

[37] Wei H, Chen J, Wang S, Fu F, Zhu X, Wu C, et al. A Nanodrug consisting of doxorubicin and exosome derived from mesenchymal stem cells for osteosarcoma treatment In vitro. International Journal of Nanomedicine. 2019;**14**:8603-8610

[38] Li M, Wang J, Guo P, Jin L, Tan X, Zhang Z, et al. Exosome mimetics derived from bone marrow mesenchymal stem cells ablate neuroblastoma tumor in vitro and in vivo. Biomaterials Advances. 2022;**142**:213161

[39] Yang C, Guan Z, Pang X, Tan Z, Yang X, Li X, et al. Desialylated mesenchymal stem cells-derived extracellular vesicles loaded with doxorubicin for targeted inhibition of hepatocellular carcinoma. Cells. 25 Aug 2022;**11**(17):2642

[40] Wei H, Chen F, Chen J, Lin H, Wang S, Wang Y, et al. Mesenchymal stem cell derived exosomes as Nanodrug carrier of doxorubicin for targeted osteosarcoma therapy via SDF1-CXCR4 Axis. International Journal of Nanomedicine. 2022;**17**:3483-3495

[41] Patel N, Kommineni N, Surapaneni SK, Kalvala A, Yaun X,

Gebeyehu A, et al. Cannabidiol loaded extracellular vesicles sensitize triple-negative breast cancer to doxorubicin in both in-vitro and in vivo models. International Journal of Pharmaceutics. 2021;**607**:120943

[42] Li YS, Wu HH, Jiang XC, Zhang TY, Zhou Y, Huang LL, et al. Active stealth and self-positioning biomimetic vehicles achieved effective antitumor therapy. Journal of Controlled Release. 2021;**335**:515-526

[43] Niu G, Yousefi B, Qujeq D, Marjani A, Asadi J, Wang Z, et al. Melatonin and doxorubicin co-delivered via a functionalized graphene-dendrimeric system enhances apoptosis of osteosarcoma cells. Materials Science & Engineering. C, Materials for Biological Applications. 2021;**119**:111554

[44] Bagheri E, Abnous K, Farzad SA, Taghdisi SM, Ramezani M, Alibolandi M. Targeted doxorubicin-loaded mesenchymal stem cells-derived exosomes as a versatile platform for fighting against colorectal cancer. Life Sciences. 2020;**261**:118369

[45] Liu Y, Zhao J, Jiang J, Chen F, Fang X. Doxorubicin delivered using nanoparticles camouflaged with mesenchymal stem cell membranes to treat colon cancer. International Journal of Nanomedicine. 2020;**15**:2873-2884

[46] Gomari H, Forouzandeh Moghadam M, Soleimani M, Ghavami M, Khodashenas S. Targeted delivery of doxorubicin to HER2 positive tumor models. International Journal of Nanomedicine. 2019;**14**:5679-5690

[47] Kalimuthu S, Zhu L, Oh JM, Gangadaran P, Lee HW, Baek SH, et al. Migration of mesenchymal stem cells to tumor xenograft models and in vitro drug delivery by doxorubicin. International Journal of Medical Sciences. 2018;**15**(10):1051-1061

[48] Pessina A, Cocce V, Pascucci L, Bonomi A, Cavicchini L, Sisto F, et al. Mesenchymal stromal cells primed with paclitaxel attract and kill leukaemia cells, inhibit angiogenesis and improve survival of leukaemia-bearing mice. British Journal of Haematology. 2013;**160**(6):766-778

[49] Petrella F, Cocce V, Masia C, Milani M, Sale EO, Alessandri G, et al. Paclitaxel-releasing mesenchymal stromal cells inhibit in vitro proliferation of human mesothelioma cells. Biomedicine & Pharmacotherapy. 2017;**87**:755-758

[50] Paris JL, de la Torre P, Victoria Cabanas M, Manzano M, Grau M, Flores AI, et al. Vectorization of ultrasound-responsive nanoparticles in placental mesenchymal stem cells for cancer therapy. Nanoscale. 2017;**9**(17):5528-5537

[51] Azimifar MA, Hashemi M, Babaei N, Salmasi Z, Doosti A. Interleukin gene delivery for cancer gene therapy: In vitro and in vivo studies. Iranian Journal of Basic Medical Sciences. 2023;**26**(2):128-136

[52] Chen X, Wang K, Chen S, Chen Y. Effects of mesenchymal stem cells harboring the interferon-beta gene on A549 lung cancer in nude mice. Pathology, Research and Practice. 2019;**215**(3):586-593

[53] Du L, Liang Q, Ge S, Yang C, Yang P. The growth inhibitory effect of human gingiva-derived mesenchymal stromal cells expressing interferon-beta on tongue squamous cell carcinoma cells and xenograft model. Stem Cell Research & Therapy. 2019;**10**(1):224

[54] Du J, Liu A, Zhu R, Zhou C, Su H, Xie G, et al. The different effects of

IFN-beta and IFN-gamma on the tumor-suppressive activity of human amniotic fluid-derived mesenchymal stem cells. Stem Cells International. 2019;**2019**:4592701

[55] Byun CS, Hwang S, Woo SH, Kim MY, Lee JS, Lee JI, et al. Adipose tissue-derived mesenchymal stem cells suppress growth of Huh7 hepatocellular carcinoma cells via interferon (IFN)-beta-mediated JAK/STAT1 pathway in vitro. International Journal of Medical Sciences. 2020;**17**(5):609-619

[56] Quiroz-Reyes AG, González-Villarreal CA, Martínez-Rodriguez H, Said-Fernández S, Salinas-Carmona MC, Limón-Flores AY, et al. A combined antitumor strategy of separately transduced mesenchymal stem cells with soluble TRAIL and IFNβ produces a synergistic activity in the reduction of lymphoma and mice survival enlargement. Molecular Medicine Reports. Jun 2022;**25**(6):206

[57] Jung PY, Ryu H, Rhee KJ, Hwang S, Lee CG, Gwon SY, et al. Adipose tissue-derived mesenchymal stem cells cultured at high density express IFN-beta and TRAIL and suppress the growth of H460 human lung cancer cells. Cancer Letters. 2019;**440-441**:202-210

[58] Yenilmez EN, Genc D, Farooqi AA, Tunoglu S, Zeybek U, Akkoc T, et al. Mesenchymal stem cells combined with IFNgamma induce apoptosis of breast cancer cells partially through TRAIL. Anticancer Research. 2020;**40**(10):5641-5647

[59] Chulpanova DS, Gilazieva ZE, Kletukhina SK, Aimaletdinov AM, Garanina EE, James V, et al. Cytochalasin B-induced membrane vesicles from human mesenchymal stem cells overexpressing IL2 are able to stimulate CD8(+) T-killers to kill human triple negative breast cancer cells. Biology (Basel). 10 Feb 2021;**10**(2):141

[60] Chulpanova DS, Solovyeva VV, James V, Arkhipova SS, Gomzikova MO, Garanina EE, et al. Human mesenchymal stem cells overexpressing interleukin 2 can suppress proliferation of neuroblastoma cells in co-culture and activate mononuclear cells in vitro. Bioengineering (Basel). 17 Jun 2020;**7**(2):59

[61] Zhao C, Pu Y, Zhang H, Hu X, Zhang R, He S, et al. IL10-modified human mesenchymal stem cells inhibit pancreatic cancer growth through angiogenesis inhibition. Journal of Cancer. 2020;**11**(18):5345-5352

[62] Wu J, Xie S, Li H, Zhang Y, Yue J, Yan C, et al. Antitumor effect of IL-12 gene-modified bone marrow mesenchymal stem cells combined with Fuzheng Yiliu decoction in an in vivo glioma nude mouse model. Journal of Translational Medicine. 2021;**19**(1):143

[63] Quiroz-Reyes AG, Gonzalez-Villarreal CA, Limon-Flores AY, Delgado-Gonzalez P, Martinez-Rodriguez HG, Said-Fernandez SL, et al. Mesenchymal stem cells genetically modified by lentivirus-express soluble TRAIL and Interleukin-12 inhibit growth and reduced metastasis-relate changes in lymphoma mice model. Biomedicines. 17 Feb 2023;**11**(2):595

[64] Kulach N, Pilny E, Cichon T, Czapla J, Jarosz-Biej M, Rusin M, et al. Mesenchymal stromal cells as carriers of IL-12 reduce primary and metastatic tumors of murine melanoma. Scientific Reports. 2021;**11**(1):18335

[65] Gonzalez-Junca A, Liu FD, Nagaraja AS, Mullenix A, Lee CT, Gordley RM, et al. SENTI-101, a preparation of mesenchymal stromal

cells engineered to express IL12 and IL21, induces localized and durable antitumor immunity in preclinical models of peritoneal solid tumors. Molecular Cancer Therapeutics. 2021;**20**(9):1508-1520

[66] Wang P, Zhang J, Zhang Q, Liu F. Mesenchymal stem cells loaded with Ad5-Ki67/IL-15 enhance oncolytic adenovirotherapy in experimental glioblastoma. Biomedicine & Pharmacotherapy. 2023;**157**:114035

[67] Sun L, Wang Q, Chen B, Zhao Y, Shen B, Wang X, et al. Human gastric cancer mesenchymal stem cell-derived IL15 contributes to tumor cell epithelial-mesenchymal transition via upregulation Tregs ratio and PD-1 expression in CD4(+)T cell. Stem Cells and Development. 2018;**27**(17):1203-1214

[68] Liu X, Hu J, Li Y, Cao W, Wang Y, Ma Z, et al. Mesenchymal stem cells expressing interleukin-18 inhibit breast cancer in a mouse model. Oncology Letters. 2018;**15**(5):6265-6274

[69] Ahn J, Lee H, Seo K, Kang S, Ra J, Youn H. Anti-tumor effect of adipose tissue derived-mesenchymal stem cells expressing interferon-beta and treatment with cisplatin in a xenograft mouse model for canine melanoma. PLoS One. 2013;**8**(9):e74897

[70] Ling X, Marini F, Konopleva M, Schober W, Shi Y, Burks J, et al. Mesenchymal stem cells overexpressing IFN-beta inhibit breast cancer growth and metastases through Stat3 signaling in a syngeneic tumor model. Cancer Microenvironment. 2010;**3**(1):83-95

[71] Kidd S, Caldwell L, Dietrich M, Samudio I, Spaeth EL, Watson K, et al. Mesenchymal stromal cells alone or expressing interferon-beta suppress pancreatic tumors in vivo, an effect countered by anti-inflammatory treatment. Cytotherapy. 2010;**12**(5):615-625

[72] Jin D, Jiang Y, Chang L, Wei J, Sun J. New therapeutic strategies based on biasing IL-2 mutants for cancers and autoimmune diseases. International Immunopharmacology. 2022;**110**:108935

[73] Mizui M. Natural and modified IL-2 for the treatment of cancer and autoimmune diseases. Clinical Immunology. 2019;**206**:63-70

[74] Bae J, Liu L, Moore C, Hsu E, Zhang A, Ren Z, et al. IL-2 delivery by engineered mesenchymal stem cells re-invigorates CD8(+) T cells to overcome immunotherapy resistance in cancer. Nature Cell Biology. 2022;**24**(12):1754-1765

[75] Gao W, Pan J, Pan J. Antitumor activities of Interleukin-12 in melanoma. Cancers (Basel). 14 Nov 2022;**14**(22):5592

[76] Ryu CH, Park SH, Park SA, Kim SM, Lim JY, Jeong CH, et al. Gene therapy of intracranial glioma using interleukin 12-secreting human umbilical cord blood-derived mesenchymal stem cells. Human Gene Therapy. 2011;**22**(6):733-743

[77] Zhou Y, Husman T, Cen X, Tsao T, Brown J, Bajpai A, et al. Interleukin 15 in cell-based cancer immunotherapy. International Journal of Molecular Sciences. 30 Jun 2022;**23**(13):7311

[78] Jing W, Chen Y, Lu L, Hu X, Shao C, Zhang Y, et al. Human umbilical cord blood-derived mesenchymal stem cells producing IL15 eradicate established pancreatic tumor in syngeneic mice. Molecular Cancer Therapeutics. 2014;**13**(8):2127-2137

[79] Li Z, Yu X, Werner J, Bazhin AV, D'Haese JG. The role of interleukin-18

in pancreatitis and pancreatic cancer. Cytokine & Growth Factor Reviews. 2019;**50**:1-12

[80] Kuppala MB, Syed SB, Bandaru S, Varre S, Akka J, Mundulru HP. Immunotherapeutic approach for better management of cancer—Role of IL-18. Asian Pacific Journal of Cancer Prevention. 2012;**13**(11):5353-5361

[81] Kim N, Nam YS, Im KI, Lim JY, Lee ES, Jeon YW, 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 and Development. 2015;**24**(23):2808-2821

[82] Klimova D, Jakubechova J, Altanerova U, Nicodemou A, Styk J, Szemes T, et al. Extracellular vesicles derived from dental mesenchymal stem/stromal cells with gemcitabine as a cargo have an inhibitory effect on the growth of pancreatic carcinoma cell lines in vitro. Molecular and Cellular Probes. 2023;**67**:101894

[83] Tibensky M, Jakubechova J, Altanerova U, Pastorakova A, Rychly B, Baciak L, et al. Gene-directed enzyme/prodrug therapy of rat brain tumor mediated by human mesenchymal stem cell suicide gene extracellular vesicles in vitro and in vivo. Cancers (Basel). 31 Jan 2022;**14**(3):735

[84] Blanco-Fernandez B, Cano-Torres I, Garrido C, Rubi-Sans G, Sanchez-Cid L, Guerra-Rebollo M, et al. Engineered microtissues for the bystander therapy against cancer. Materials Science & Engineering. C, Materials for Biological Applications. 2021;**121**:111854

[85] Kenarkoohi A, Bamdad T, Soleimani M, Soleimanjahi H, Fallah A, Falahi S. HSV-TK expressing mesenchymal stem cells exert inhibitory effect on cervical cancer model. International Journal of Molecular and Cellular Medicine. 2020;**9**(2):146-154

[86] Pastorakova A, Jakubechova J, Altanerova U, Altaner C. Suicide gene therapy mediated with exosomes produced by mesenchymal stem/stromal cells stably transduced with HSV thymidine kinase. Cancers (Basel). 28 Apr 2020;**12**(5):1096

[87] Duhrsen L, Hartfuss S, Hirsch D, Geiger S, Maire CL, Sedlacik J, et al. Preclinical analysis of human mesenchymal stem cells: Tumor tropism and therapeutic efficiency of local HSV-TK suicide gene therapy in glioblastoma. Oncotarget. 2019;**10**(58):6049-6061

[88] Wei D, Hou J, Zheng K, Jin X, Xie Q, Cheng L, et al. Suicide gene therapy against malignant gliomas by the local delivery of genetically engineered umbilical cord mesenchymal stem cells as cellular vehicles. Current Gene Therapy. 2019;**19**(5):330-341

[89] Yang J, Lv K, Sun J, Guan J. Anti-tumor effects of engineered mesenchymal stem cells in colon cancer model. Cancer Management and Research. 2019;**11**:8443-8450

[90] Malik YS, Sheikh MA, Xing Z, Guo Z, Zhu X, Tian H, et al. Polylysine-modified polyethylenimine polymer can generate genetically engineered mesenchymal stem cells for combinational suicidal gene therapy in glioblastoma. Acta Biomaterialia. 2018;**80**:144-153

[91] Malekshah OM, Sarkar S, Nomani A, Patel N, Javidian P, Goedken M, et al. Bioengineered adipose-derived stem cells for targeted enzyme-prodrug therapy of ovarian cancer intraperitoneal metastasis. Journal of Controlled Release. 2019;**311-312**:273-287

[92] Krasikova LS, Karshieva SS, Cheglakov IB, Belyavsky AV. Mesenchymal stem cells expressing cytosine deaminase inhibit growth of murine melanoma B16F10 in vivo. Molekuliarnaia Biologiia (Mosk). 2015;**49**(6):1007-1015

[93] NguyenThai QA, Sharma N, Luong do H, Sodhi SS, Kim JH, Kim N, et al. Targeted inhibition of osteosarcoma tumor growth by bone marrow-derived mesenchymal stem cells expressing cytosine deaminase/5-fluorocytosine in tumor-bearing mice. The Journal of Gene Medicine. 2015;**17**(3-5):87-99

[94] Krassikova LS, Karshieva SS, Cheglakov IB, Belyavsky AV. Combined treatment, based on lysomustine administration with mesenchymal stem cells expressing cytosine deaminase therapy, leads to pronounced murine Lewis lung carcinoma growth inhibition. The Journal of Gene Medicine. 2016;**18**(9):220-233

[95] Nouri FS, Wang X, Hatefi A. Genetically engineered theranostic mesenchymal stem cells for the evaluation of the anticancer efficacy of enzyme/prodrug systems. Journal of Controlled Release. 2015;**200**:179-187

[96] Chung T, Na J, Kim YI, Chang DY, Kim YI, Kim H, et al. Dihydropyrimidine dehydrogenase is a prognostic marker for mesenchymal stem cell-mediated cytosine deaminase gene and 5-Fluorocytosine prodrug therapy for the treatment of recurrent gliomas. Theranostics. 2016;**6**(10):1477-1490

[97] Abrate A, Buono R, Canu T, Esposito A, Del Maschio A, Luciano R, et al. Mesenchymal stem cells expressing therapeutic genes induce autochthonous prostate tumour regression. European Journal of Cancer. 2014;**50**(14):2478-2488

[98] Chang DY, Jung JH, Kim AA, Marasini S, Lee YJ, Paek SH, et al. Combined effects of mesenchymal stem cells carrying cytosine deaminase gene with 5-fluorocytosine and temozolomide in orthotopic glioma model. American Journal of Cancer Research. 2020;**10**(5):1429-1441

[99] Ullah M, Kuroda Y, Bartosh TJ, Liu F, Zhao Q, Gregory C, et al. Erratum: iPS-derived MSCs from an expandable bank to deliver a prodrug-converting enzyme that limits growth and metastases of human breast cancers. Cell Death Discovery. 2017;**3**:17029

[100] Oishi T, Ito M, Koizumi S, Horikawa M, Yamamoto T, Yamagishi S, et al. Efficacy of HSV-TK/GCV system suicide gene therapy using SHED expressing modified HSV-TK against lung cancer brain metastases. Molecular Therapy—Methods & Clinical Development. 2022;**26**:253-265

[101] Metz MZ, Gutova M, Lacey SF, Abramyants Y, Vo T, Gilchrist M, et al. Neural stem cell-mediated delivery of irinotecan-activating carboxylesterases to glioma: Implications for clinical use. Stem Cells Translational Medicine. 2013;**2**(12):983-992

[102] Choi SA, Lee JY, Wang KC, Phi JH, Song SH, Song J, et al. Human adipose tissue-derived mesenchymal stem cells: Characteristics and therapeutic potential as cellular vehicles for prodrug gene therapy against brainstem gliomas. European Journal of Cancer. 2012;**48**(1):129-137

[103] Alizadeh Zeinabad H, Szegezdi E. TRAIL in the treatment of cancer: From soluble cytokine to nanosystems. Cancers (Basel). 19 Oct 2022;**14**(20):5125

[104] Voss OH, Arango D, Tossey JC, Villalona Calero MA, Doseff AI. Splicing reprogramming of TRAIL/DISC-components sensitizes lung cancer cells

to TRAIL-mediated apoptosis. Cell Death & Disease. 2021;**12**(4):287

[105] Chulpanova DS, Pukhalskaia TV, Gilazieva ZE, Filina YV, Mansurova MN, Rizvanov AA, et al. Cytochalasin B-induced membrane vesicles from TRAIL-overexpressing mesenchymal stem cells induce extrinsic pathway of apoptosis in breast cancer mouse model. Current Issues in Molecular Biology. 2023;**45**(1):571-592

[106] Chen F, Zhong X, Dai Q, Li K, Zhang W, Wang J, et al. Human umbilical cord MSC delivered-soluble TRAIL inhibits the proliferation and promotes apoptosis of B-ALL cell in vitro and in vivo. Pharmaceuticals (Basel). 11 Nov 2022;**15**(11):1391

[107] Sun L, Wang J, Wang Q, He Z, Sun T, Yao Y, et al. Pretreatment of umbilical cord derived MSCs with IFN-gamma and TNF-alpha enhances the tumor-suppressive effect on acute myeloid leukemia. Biochemical Pharmacology. 2022;**199**:115007

[108] Un Choi Y, Yoon Y, Jung PY, Hwang S, Hong JE, Kim WS, et al. TRAIL-overexpressing adipose tissue-derived mesenchymal stem cells efficiently inhibit tumor growth in an H460 xenograft model. Cancer Genomics Proteomics. 2021;**18**(4):569-578

[109] Park SA, Han HR, Ahn S, Ryu CH, Jeun SS. Combination treatment with VPA and MSCs-TRAIL could increase anti-tumor effects against intracranial glioma. Oncology Reports. 2021;**45**(3):869-878

[110] Liu Z, Li S, Ma T, Zeng J, Zhou X, Li H, et al. Secreted TRAIL gene-modified adipose-derived stem cells exhibited potent tumor-suppressive effect in hepatocellular carcinoma cells. Immunity, Inflammation and Disease. 2021;**9**(1):144-156

[111] Deng L, Wang C, He C, Chen L. Bone mesenchymal stem cells derived extracellular vesicles promote TRAIL-related apoptosis of hepatocellular carcinoma cells via the delivery of microRNA-20a-3p. Cancer Biomarkers. 2021;**30**(2):223-235

[112] Salmasi Z, Hashemi M, Mahdipour E, Nourani H, Abnous K, Ramezani M. Mesenchymal stem cells engineered by modified polyethylenimine polymer for targeted cancer gene therapy, in vitro and in vivo. Biotechnology Progress. 2020;**36**(6):e3025

[113] Zakaria N, Yahaya BH. Adipose-derived mesenchymal stem cells promote growth and migration of lung adenocarcinoma cancer cells. Advances in Experimental Medicine and Biology. 2020;**1292**:83-95

[114] Xue T, Wang X, Ru J, Zhang L, Yin H. The inhibitory effect of human umbilical cord mesenchymal stem cells expressing anti-HAAH scFv-sTRAIL fusion protein on glioma. Frontiers in Bioengineering and Biotechnology. 2022;**10**:997799

[115] Choi SA, Lee C, Kwak PA, Park CK, Wang KC, Phi JH, et al. Histone deacetylase inhibitor panobinostat potentiates the anti-cancer effects of mesenchymal stem cell-based sTRAIL gene therapy against malignant glioma. Cancer Letters. 2019;**442**:161-169

[116] Wang Z, Chen H, Wang P, Zhou M, Li G, Hu Z, et al. Site-specific integration of TRAIL in iPSC-derived mesenchymal stem cells for targeted cancer therapy. Stem Cells Translational Medicine. 2022;**11**(3):297-309

[117] Niess H, von Einem JC, Thomas MN, Michl M, Angele MK, Huss R, et al. Treatment of advanced gastrointestinal

tumors with genetically modified autologous mesenchymal stromal cells (TREAT-ME1): Study protocol of a phase I/II clinical trial. BMC Cancer. 2015;**15**:237

[118] Garcia-Castro J, Alemany R, Cascallo M, Martinez-Quintanilla J, Arriero Mdel M, Lassaletta A, et al. Treatment of metastatic neuroblastoma with systemic oncolytic virotherapy delivered by autologous mesenchymal stem cells: An exploratory study. Cancer Gene Therapy. 2010;**17**(7):476-483