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Review:

Mesenchymal stem cells as therapeutic agents and in gene delivery for the treatment of glioma*

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Abstract: Mesenchymal stem cells (MSCs) are plastic-adherent cells with a characteristic surface phenotype and properties of self-renewal, differentiation, and high proliferative potential. The characteristics of MSCs and their tumor-tropic capability make them an ideal tool for use in cell-based therapies for cancer, including glioma. These cells can function either through a bystander effect or as a delivery system for genes and drugs. MSCs have been demonstrated to inhibit the growth of glioma and to improve survival following transplantation into the brain. We briefly review the current data regarding the use of MSCs in the treatment of glioma and discuss the potential strategies for development of a more specific and effective therapy.

Key words: Cancer; Glioma; Mesenchymal stem cells; Stem cells; Therapy
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1 Introduction

Malignant glioma, the most prevalent primary malignant brain tumor, is one of the most aggressive and lethal human cancers. Despite surgical resection and chemotherapy, glioma always recurs, resulting in poor patient prognosis (Surawicz *et al.*, 1998; Deangelis, 2001). Tumor cells that infiltrate the surrounding crucial areas of the brain and cannot be eliminated successfully are thought to be responsible for tumor regrowth (Keles and Berger, 2004; Lefranc *et al.*, 2005). New therapies that target single tumor cells residing in normal brain tissue are in serious demand.

Mesenchymal stem cells (MSCs), also called mesenchymal stromal cells, have been the focus of research aimed at developing a new clinical therapy for glioma for years. It was difficult to predict how MSCs would change the focus of research when they were first identified by McCulloch and Parker (1957). Subsequent studies were performed to delineate the properties of MSCs. Friedenstein *et al.* (1970) found that fibroblasts from bone marrow are capable of spontaneous bone formation and are able to induce osteogenesis in diffusion chambers. In 1974, the capacities of self-renewal and multipotential differentiation of human bone marrow-derived MSCs (BM-MSCs) were demonstrated (Friedenstein *et al.*, 1974). In the 1980s, the plasticity of these cells was also revealed (Owen and Friedenstein, 1988). Over several decades, MSCs were identified in many tissues, including adipose tissue, umbilical cord blood, and dental pulp, and they were used in the development of treatments of many types of diseases (Zuk *et al.*, 2001; Parolini *et al.*, 2008; Nagano *et al.*, 2010). In 2000, an annual meeting of the International Society for Cellular Therapy (ISCT) reported on the "stemness" of these cells and recommended clarification of the

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nomenclature for progenitor cells (Dominici *et al.*, 2006). The above mentioned characteristics make MSCs a potentially valuable therapeutic tool. This article reviews the recent findings of MSC on the therapy of glioma to provide a better understanding of the current situation.

2 Migration: tumor-tropic

Currently, gene therapy, in which an antitumor substance is delivered to a tumor, has been applied for treatment but has shown only limited success in clinical trials (Castro *et al.*, 2003). The main reason for this limited success may be the inefficient and unsustained spread of vectors in tumors (Pulkkanen and Yla-Herttuala, 2005). The discovery of the tumor-tropic capability of MSCs highlights the potential for overcoming these shortcomings.

The tropism of MSCs to glioma was first demonstrated by Nakamura *et al.* (2004). This group implanted human umbilical cord-derived MSCs (UC-MSCs) in the contralateral hemisphere, distant from established gliomas. After implantation, migration of MSCs along the corpus callosum was observed. Further, tumor-tropic migration was shown to be increased in immunocompromised mice injected with human BM-MSCs into the ipsilateral and contralateral carotid arteries (Nakamizo *et al.*, 2005), whereas implanted rat fibroblasts remained at the injection site and did not migrate to the rat 9L glioma (Miletic *et al.*, 2007).

Near-infrared (NIR) fluorescence imaging confirmed the tumor tropism and distribution of UC-MSCs (Kim *et al.*, 2016). Pre-exposure of human adipose tissue-derived MSCs (AT-MSCs) to conditioned media of U87 glioma cells and extracellular matrix proteins could enhance their homing to brain cancer (Smith *et al.*, 2015). However, Bexell *et al.* (2012) found no evidence of long-distance rat BM-MSCs migration through the intact striatum toward syngeneic D74 (RG2), N32, and N29 gliomas in the ipsilateral hemisphere or across the corpus callosum to gliomas located in the contralateral hemisphere, while MSCs of intratumoral origin migrated extensively, specifically within N32 gliomas. In addition, Bexell *et al.* (2009) found that intratumoral implantation resulted in a more efficient distribution of rat BM-MSCs than intravenous (i.v.) injection. This decreased efficiency observed with i.v. injection may have been due to the trapping of i.v. injected MSCs in the lungs of the mice, resulting in their inability to reach the arterial system (Harting *et al.*, 2009; Prockop, 2009). These findings indicate that the route of MSC delivery and the source of MSCs may be important factors for the extent of MSC engraftment.

Above all, the tumor-tropic capacity of MSCs makes them potential vectors for the delivery of antitumor substances to gliomas without causing adverse effects on normal brain tissue.

Many previous studies have demonstrated MSC migration; however, the precise underlying mechanism remains unknown. An early report published by Hidemitsu Sato *et al.* (2005) revealed that murine BM-MSCs transduced with epidermal growth factor receptor (EGFR) had stronger migratory abilities than non-transduced MSCs and that the enhanced migration of EGFR-MSCs may be attributed to EGF-EGFR, protein kinase C, mitogen-activated protein (MAP) kinase, and actin polymerization. In addition, Nakamizo *et al.* (2005) have found that growth factors, such as platelet-derived growth factors, stromal-derived factor-1, and epidermal growth factor, but not basic fibroblast growth factor, may play important roles in human BM-MSC migration. Subsequently, other studies have shown that chemokines, such as monocyte chemoattractant protein-1 (MCP-1), growth-related oncogene (GRO)-α, interleukin (IL)-8, and IL-12, enhance the tumor-tropic ability of MSCs (Kim *et al.*, 2009; 2011; Xu *et al.*, 2010; Ryu *et al.*, 2011). This migration may occur through CXC chemokine receptor 1 (CXCR1), CXCR2, and CXCR4. Further, antagonist or antibody treatment against chemokines could reduce these migration events. In addition to chemokines, other factors may influence the tumor-tropic ability of MSCs. Fewer observed $p27^{-/-}$ MSCs in the C6 tumor area compared with $p27^{+/+}$ MSCs implied the function of p27 in the migration of murine BM-MSCs (Gao *et al.*, 2010). Matrix metalloproteinases (MMPs), which are zinc-dependent endopeptidases, participate in the migratory activities of various MSCs. Knock-out of MMP1 causes inhibition of the migratory abilities of MSCs. Conversely, its overexpression in poorly migrating MSCs enhances their migratory abilities. In addition, disruption of the interaction between MMP1 and protease-activated

receptor 1 (PAR1) seriously inhibits the migratory abilities of human BM-MSCs (Ho *et al.*, 2009).

An in vivo study has demonstrated that rat BM-MSC migration and vessel formation are decreased in the presence of inhibitors of angiogenic signaling factors (Bexell *et al.*, 2009). Another study suggests that UC-MSCs migration is dependent, at least in part, on angiogenic signaling factors and that it may share common pathways with tumor angiogenesis (Kim *et al.*, 2009). This could be a potential advantage of the use of MSCs for the treatment of glioma.

Due to the different MSC sources and isolation protocols, it is difficult to compare studies for determining the precise mechanisms of MSC migration. Though the studies above have revealed some possible ways, further research is needed to elucidate the precise molecular mechanisms before these cells can be used in the treatment of glioma.

3 Therapeutic effects of MSCs

MSC migration has been demonstrated in many studies, but the exact function of these cells in the tumor microenvironment remains unknown. In lymphoma-bearing mice, intraperitoneal injection of human BM-MSCs has been demonstrated to improve survival through induction of endothelial cell (EC) apoptosis (Secchiero *et al.*, 2010). Further, Otsu *et al.* (2009) have found that endothelial derived-MSCs (EC-MSCs) cause capillary degeneration in a co-culture system of MSCs and ECs and that they intercalate into the capillary networks of ECs to inhibit B16F10 melanoma growth in vivo. In addition, an antitumor function of human UC-MSCs exerted through upregulation of PTEN in glioma cells (SNB19, U251, 4910, and 5310) has been subsequently demonstrated (Dasari *et al.*, 2010).

Considering the preceding reports, Ho *et al.* (2013) explored the biological effects of human BM-MSCs using a tumor model of immunodeficient BALB/c-nu/nu mice. In this study, the researchers inoculated primary human glioma cells and carboxymethyl-DiI-labeled MSCs from human bone marrow into the mice. After 21 d, the mice were sacrificed. A peripheral rim of tumor cells bordering a zone of necrosis was observed in hematoxylin and eosin (H&E)-stained co-cultured tumor sections, but necrosis was not observed in the DGli36 or DGli36/iNHA tumor section. Subsequently, the researchers evaluated vessel morphology and microvessel density by CD31 staining and pericyte coverage (α-smooth muscle actin (α-SMA)) analyses. The results showed that CD31 cells were present in regional areas of the representative DGli36 and DGli36/MSC tumor sections and that α-SMA cells were only present in the DGli36/MSC sections. Next, the researchers found that the presence of BM-MSCs inhibited tube formation by 50% in the DGli36 co-culture by in vitro angiogenesis assay, indicating that BM-MSCs may impair tumor angiogenesis through the release of anti-angiogenic factors. A proteome array performed using harvested conditional medium (CM) and quantitative polymerase chain reaction (Q-PCR) of the co-cultured cells revealed that platelet-derived growth factor (PDGF)-BB, phosphorylated Akt, and cathepsin expression was decreased. The researchers concluded that the PDGF/PDGFR (PDGF receptor) axis, which plays a key role in glioma angiogenesis, may also have an important role in the antitumor effects of MSCs.

In another study, the researchers found that cord UC-MSCs inhibited U87 glioblastoma multiforme growth and promoted apoptosis (Akimoto *et al*., 2013). This inhibition may be mediated by tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and downregulation of cyclin D1 expression (Jiao *et al.*, 2011; Akimoto *et al.*, 2013). In addition, conditioned media from human AT-MSCs and UC-MSCs have been shown to efficiently induce apoptosis and differentiation of human U251 glioma cell lines in vitro (Yang *et al.*, 2014). Kolosa *et al.* (2015) found that the expression of cyclin D1 was downregulated when NCH421k cells were cultured in the MSC-CM. However, they thought that the cycle arrest was rather associated with the senescence and differentiation of the glioma cells than with apoptosis, though the mitochondrial membrane potential was decreased. Using PCR array and flow cytometry, Kolosa *et al.* (2015) revealed significantly deregulated expression of 13 genes associated with senescence including *ATM*, *CDKN1A*, and *CDKN2A* and expression of the differentiation markers such as neuronal marker b III tubulin, vimentin, and glial fibrillary acidic protein (GFAP). These also increased the sensitivity of the

glioma cell toward temozolomide. This was consistent with the study of Motaln *et al.* (2012) that human BM-MSCs may promote the senescence of the tumor cells by inducing cell morphology and cytokine changes.

In contrast, other studies have reported that MSCs also promote tumor growth. Djouad *et al.* (2003) have shown that murine C3H10T1/2 MSCs favor B16 tumor growth in allogeneic animals by exerting an immunosuppressive effect. Further, Karnoub *et al.* (2007) have reported that BM-MSCs promote tumor growth in breast cancer metastasis (MCF7/Ras, MDA-MB-231, MDA-MB-435, and HMLER), and Coffelt *et al.* (2009) have reported similar promotion of growth of OVCAR-3 tumors. Additionally, Pillat *et al.* (2016) suggested that BM-MSCs may promote U87 glioma invasion both in co-cultures indirectly or directly, by increasing the expression of kinin B1 receptor (B1R), kinin B2 receptor (B2R), and matrix metalloproteases in U87. In addition, several studies have reported that MSCs have no apparent effect on N32 tumor cell growth (Komarova *et al.*, 2006; Kucerova *et al.*, 2007; Bexell *et al.*, 2009). Another study using extracellular vesicles from different sources has revealed that the different effects of BM-, UC-, and AT-MSCs on U87 tumor cell growth may depend on the tissue of origin (del Fattore *et al.*, 2015). This finding demonstrates the complexity of MSCs. Further study is necessary before MSCs can be used in clinical therapy.

4 MSC delivery of therapeutic genes

Because of the complex effects of MSCs on tumors and their unsatisfactory results in the treatment of glioma, research on MSCs has focused more on pioneering their use in gene transfer. The gene most commonly used is *TRAIL*. *TRAIL*, a member of the tumor necrosis factor (TNF) superfamily, was first identified and cloned by its sequence homology to TNF and CD95L (Wiley *et al.*, 1995). It efficiently induces apoptosis of cancer cells. Additionally, it is not toxic to normal cells (Wu, 2009). These factors make *TRAIL* an attractive genetic tool for use in the treatment of tumors.

Choi *et al.* (2011) were the first to demonstrate short- and long-term therapeutic efficacies using TRAIL-producing human AT-MSCs. Their study included both in vitro and in vivo experiments. In the in vitro experiment, the researchers co-cultured TRAIL-producing AT-MSCs and F98 glioma cells in a Transwell tissue culture plate. After 3 d, the number of F98 cells cultured with TRAIL-producing AT-MSCs was decreased by 59.5% compared with that of the control F98 cells cultured alone. In the in vivo experiment, the researchers intratumorally implanted MSCs into rats at 3 d after inoculation of F98 tumor cells. The animals were sacrificed and fixed after 18 d. Histological analysis revealed that the tumor volume was reduced by 56.3% in the TRAIL-producing AT-MSCs-treated rats compared with the phosphate buffered saline (PBS)-treated and AT-MSCs-treated rats. In a survival experiment with a maximum duration of 100 d, the TRAIL-producing AT-MSC group also exhibited significantly increased survival. These results demonstrate the therapeutic efficacy of MSCs expressing TRAIL. Other studies have reported that BM-MSCs are very tolerant of the transfection of TRAIL-bearing vectors (Tang *et al.*, 2014) and that MSC-based secretable trimeric TRAIL (*stTRAIL*) gene delivery exhibits greater therapeutic efficacy than direct injection of adenovirus encoding the *stTRAIL* gene into a C6 tumor mass. *TRAIL* also can be combined with other genes, such as thrombospondin-1, in therapy to achieve enhanced effects (Choi *et al.*, 2015). Transfection of both stTRAIL and three type-1 repeats (3TSR) domain of thrombospondin-1 into AT-MSC could up-regulate DR4/DR5 expression and induce apoptosis of the HBMVEC glioma cells via caspase 3/7/8. Simultaneously, AT-MSCs-3TSR inhibits angiogenesis and sensitizes brain ECs to *TRAIL* in a CD36-dependent manner. The combination displayed a synergistic cytotoxic effect. Collectively, these studies have demonstrated the benefits and potential of *TRAIL* in stem cell-based targeted gene therapy for clinical application.

However, despite the effectiveness of *TRAIL* in many tumors, some types of tumor cells, including glioma cells, are resistant to *TRAIL*-induced apoptosis, suggesting that the use of *TRAIL* alone may not be sufficient. Thus, novel drugs are required that sensitize glioma cells to *TRAIL*-induced apoptosis, or new strategies are needed to overcome *TRAIL* resistance that can be combined with MSCs-*TRAIL*. Working toward these goals, different groups have explored

various methods, including the use of *TRAIL* along with chemotherapeutic agents (Johnson *et al.*, 2013; Kim *et al.*, 2014), radiotherapy (Kim *et al.*, 2010), lipoxygenase (Kim *et al.*, 2012), and carbenoxolone (Yulyana *et al.*, 2013). These methods have all had better therapeutic results than those using *TRAIL* alone. Combined treatment with *TRAIL* and another agent may be a novel and useful strategy for improving treatment of malignant glioma.

Other cytokines have also been engineered into MSCs for the treatment of glioma. Inhibition of tumor growth by cytokine transfer using MSCs has been demonstrated in many tumor models. These cytokines include IL-2, IL-12, IL-18, interferon (IFN)-α, IFN-β, CXC3CL1, EGFR, and vascular endothelial growth factor A (VEGF-A) (Studeny *et al.*, 2002; Nakamura *et al.*, 2004; Sato *et al.*, 2005; Schichor *et al.*, 2006; Hong *et al.*, 2009; Xu *et al.*, 2009; Park *et al.*, 2015). $CD4^+$ and $CD8^+$ T cells, infiltration by natural killer cells, and long-term antitumor immunity probably enhanced these results. Peripheral immunotherapy using IFN-γ-transduced autologous tumor cells with intratumoral delivery of IL-7 was also demonstrated in regressed rat gliomas and was shown to improve the survival of glioma-bearing rats (Gunnarsson *et al.*, 2010). Further analysis revealed that this improvement was mediated through the secretion of low levels of the immunosuppressive molecules IL-10 and prostaglandin E2 and enhancement of the responses of major histocompatibility complex (MHC) classes I and II to IFN-γ treatment (Strojby *et al.*, 2014).

The prodrug-converting enzyme cytosine deaminase (CD) is a suicide gene that converts the prodrug 5-fluorocytosine (5-FC) to a toxic metabolite 5-fluorouracil (5-FU). 5-FU, an inhibitor of RNA synthesis, can cross the blood-brain barrier easily and is nontoxic to normal neuronal cells. It makes 5-FU an effective drug for the treatment of brain tumors. Gene therapy with 5-FC/CD also induces a strong bystander effect that does not require direct cell-to-cell contact (Ichikawa *et al.*, 2000). However, due to the inefficient, unsustained spread of vectors in tumors, there is a need for a more efficient and specific vector system, such as MSCs, to achieve substantial therapeutic effects. A regimen involving transduction of CD into human BM-MSCs and subsequent injection of the MSCs intracranially has been demonstrated to have anti-cancer effects in early-stage brain tumors and to repress C6 tumor cell growth during the later stage (Chang *et al.*, 2010). Accordingly, this therapeutic regimen has been reported to be efficacious in some cancers, such as glioma (Lee *et al.*, 2009; Kosaka *et al.*, 2012; Song *et al.*, 2012), colon carcinoma (Kucerova *et al.*, 2007), prostate tumor (Cavarretta *et al.*, 2010), and melanoma (Kucerova *et al.*, 2008). Further, genetically engineered MSCs have been shown to exhibit therapeutic efficacy against brainstem glioma.

Carboxylesterase enzyme (CE) efficiently converts the prodrug CPT-11 (irinotecan-7-ethyl-10-(4-(1-piperidino)-1-piperidino)carbonyloxycamptothecin) into the active drug SN-38 (7-ethyl-10-hydroxycamptothecin), a potent topoisomerase I inhibitor. As activation of CPT-11 by human esterase is poor, exogenous CE would be very useful for converting CPT-11 to SN-38 (Wierdl *et al.*, 2001; Danks *et al.*, 2007). Choi *et al.* (2012) have demonstrated that human AT-MSCs engineered with CE exhibit more effective growth inhibition of F98 cells and significantly increased survival than MSCs alone

5 MSC delivery of viruses

Oncolytic virus preferentially infects and kills cancer cells by lysis. As the infected cancer cells are destroyed, they release new infectious virus particles to help destroy the remaining tumor (Ferguson *et al.*, 2012). The results of the Phase I and Phase II clinical trials in glioblastoma multiforme (GBM) patients had showed the anti-tumor activity and safety of oncolytic adenoviruses (Parker *et al.*, 2009). However, oncolytic viruses are often neutralized by immune reactions following injection due to the high immunogenicities of the viral particles (Lichty *et al.*, 2014). Thus, cellular vectors that protect oncolytic viruses from host immune systems are very much needed. Using human BM-MSCs as delivery vectors, oncolytic viruses have been applied in the treatment of mice bearing human U87 gliomas and ovarian tumors (Komarova *et al.*, 2006; Yong *et al.*, 2009). Further, human AT-MSCs with a hyaluronidase-expressing oncolytic virus have been demonstrated to have even better effects in the treatment of glioma (U87-MG, LN308, U138, and LN229) (Martinez-Quintanilla *et al.*, 2015).

The herpes simplex virus-thymidine kinase (*HSV-tk*) gene is another commonly used prodrug-converting enzyme with a strong bystander anti-cancer

effect. It converts the prodrug ganciclovir into its toxic form and inhibits DNA synthesis, resulting in cell death. Engineering of the *HSV-tk* gene into BM-MSCs results in its more efficient distribution within tumors compared with injection of this gene with viral vectors. Recently, *HSV-tk*-engineered MSCs in combination with systemic administration of ganciclovir have been used in the treatment of C6 glioma (Amano *et al.*, 2009; Uchibori *et al.*, 2009; Chang *et al.*, 2010) and Panc02 pancreatic cancer (Zischek *et al.*, 2009). When coupled with the *HSV-tk*-ganciclovir prodrug cancer gene therapy system, with delivery by either implantation into the opposite hemisphere or injection into xenografts, EC-MSCs have been demonstrated to inhibit U87 and HTB14 tumor growth and to prolong the survival of mice (Kinoshita *et al.*, 2010; Bak *et al.*, 2011; de Melo *et al.*, 2015). Additionally, Matuskova *et al.* (2010) have demonstrated the formation of gap junctions between AT-MSCs and human glioblastoma cells (8-MG-BA, 42-MG-BA, and U-118). The gap junctions rendered the tumor cells refractory to TK-MSC-mediated cytotoxicity. This result supports the mechanism of bystander cytotoxicity and the further use of MSCs in the treatment of glioma.

6 MSC delivery of miRNA

MicroRNAs (miRNAs) are important tools used to target numerous mRNAs, and some miRNAs are potent tumor suppressors (Croce, 2009). However, they cannot be injected directly because they are easily degraded. Fortunately, miRNAs are abundant in extracellular exosomes, which are 30–150 nm vesicles secreted by a wide range of mammalian cells that can be transferred between cells through their uptake and release (Hu *et al.*, 2012). Katakowski *et al.* (2013) transfected BM-MSCs with a miR-140b expression plasmid and harvested exosomes released by the MSCs, obtaining exosomes containing functional miR-140b. Following intratumoral injection of the exosomes into a rat primary brain tumor model, they found that the growth of the glioma xenograft was inhibited. This finding suggests that the inclusion of specific therapeutic miRNAs into MSC exosomes may represent a new treatment strategy for malignant glioma.

7 Prospects for clinical MSC-based glioma therapy

Malignant glioma is a primary malignant brain tumor that cannot yet be successfully eliminated. Because of their robust tropism for intracranial glioma, MSCs are highly attractive vehicles for the direct delivery of a wide variety of therapeutic gene products to tumor cells, and they can also be used to target tumor cells directly. In addition, MSCs can be easily harvested and amplified, which makes them a reliable tool for the treatment of tumors. Further, following implantation of MSCs transduced with an anti-tumor substance into tumors, the cells migrate and deliver the substance to tumors that are inaccessible by surgery, and they function synergistically.

However, extensive research must be performed before MSC-based therapy can be used in the clinic. There are no standards for the isolation and culturing of MSCs. The precise mechanism underlying the effects of MSCs on tumors is still unknown. In addition, large animal models have not yet been established. Thus, further studies are needed.

This new field of research is likely to rapidly expand in the coming years as these cells and their mechanism of action are further characterized. MSCs may be applied not only for tumor therapy but also for other types of therapies, such as those targeting reproductive problems and infertility. A new age is on the way!

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Compliance with ethics guidelines

Bing-yu XIANG, Lu CHEN, Xiao-jun WANG, and Charlie XIANG declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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中文概要

题　目：间充质干细胞在胶质瘤治疗中的作用研究

概　要：胶质瘤是颅内发病率最高的恶性肿瘤，虽然临床上可以用“手术+化疗”的方法进行治疗，但由于其浸润性，对化疗药物的低敏感性等原因，常在治疗后复发，严重威胁人类生命健康。间充质干细胞（MSC）是干细胞中的一员，具有增殖能力强、分化潜能大、免疫原性低及采集方便等优点，其趋化性更使 MSC 成为肿瘤治疗的一个理想工具。本文对干细胞治疗胶质瘤的研究现状进行了归纳总结，着重阐述了 MSC 的旁分泌途径作用及作为基因载体导入肿瘤坏死因子相关凋亡诱导配体（TRAIL）、溶瘤病毒等其他治疗基因的生物功能，以期对进一步的治疗研究提供帮助。

关键词：癌症；间充质干细胞；胶质瘤；细胞治疗