REVIEW

Therapeutic potential of mesenchymal stem cells in gastrointestinal cancers – current evidence

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Abstract: Mesenchymal stem (or stromal) cells (MSCs) are nonhematopoietic progenitor cells that can be obtained from bone marrow and adipose tissue. Due to the ability of MSCs to migrate to damaged and cancerous tissue, this behavior of MSCs has been exploited as a tumor-targeting strategy for cell-based cancer therapy to improve the efficacy and minimize the toxicity of current gene therapy approaches in the treatment of cancers. In this review, we focus on the current developments of MSC-based gene therapy in gastrointestinal cancer studies, in particular, the role of MSCs as tumor-targeted therapy vehicles and the prospects in their clinical application.

Keywords: mesenchymal stem cells, gastrointestinal cancers, cancer therapy

Introduction

Mesenchymal stem cells (MSCs) are a group of heterogeneous multipotent cells, which can be isolated from many tissues such as bone marrow,[1] peripheral blood,[2] and adipose tissue.[3] These do have the potential to treat a wide range of diseases.[4] MSCs have the same self-renewal characteristics as undifferentiated cells and are characterized as adherent cells that have the ability to differentiate into osteocytes, fibroblasts, adipocytes, chondrocytes, and marrow stroma.[1,5] For their regenerative potential and immune-suppressive capacity, MSCs can be used in regenerative medicine,[6,7] tissue transplantation,[8–10] and cancer therapy.[4,11]

The surface markers to identify MSCs are different among these cells because they originate from different tissues or are cultured in different conditions.[12,13] The Mesenchymal and Tissue Stem Cell Committee of the International Society proposes minimal criteria to define human MSCs for MSC therapy, which have to fulfill a standardized phenotype for cellular therapies.[14] These criteria include the expression of CD105, CD90, and CD73, but not CD79a, CD45, CD34, CD19, CD14, CD11b, and HLA-DR.[5,15,16]

The migration of MSCs to tumor

A number of studies have shown that MSCs do migrate to sites of injury, ischemia, and tumor microenvironments. The mechanisms by which MSCs migrate across the endothelium and home to the target tissues are not yet fully understood. It may be related to the MSC receptors, the target tissue, and the cell surface receptors. It is shown that homing of MSCs is dependent on chemokine receptors such as CXCR4, c-Met, VEGFR, PDGFr, and CCR2. SDF-1, and its receptor CXCR4 have been previously

characterized in MSC homing.[17–21] It has been shown that freshly isolated MSCs have the best homing ability, and their homing efficiency gets worse with rising passage numbers.[22] Some studies demonstrated that the use of cytokines (IL [interleukin]-6, IL-1β, hepatocyte growth factor [HGF], etc) to pretreat the cultured MSCs will enhance the expression of chemokines and increase the homing effect of MSCs.[23–25] Several studies also suggest that MSCs are attracted to sites of irradiation.[26–28] In a recent study, François et al[28] used total body irradiation (TBI) with or without additional local irradiation to research the potential therapeutic efficacy of MSCs for irradiation damage. They found that not only did TBI induce an increase of engraftment levels of human MSCs (hMSCs) in the brain, heart, bone marrow, and muscles, but also more MCSs migrated to the exposed area of local irradiation after TBI as compared to TBI alone.[28]

MSCs in gastrointestinal cancer therapy
The biological function of MSCs on cancer

In a number of studies, MSCs have been shown to migrate to the tumor site and demonstrate antitumor effects both in vitro and in different cancer mouse models.[29] Kidd et al[30] observed that in an in vivo model of pancreatic cancer, intraperitoneally injected hMSCs migrated to primary and metastatic tumor sites and potentially inhibited tumor growth. Maestroni et al[31] also showed that coinjection of mouse MSCs with tumor cells can decrease the tumor volume. In some studies for hepatocellular cancer (HCC), MSCs were able to inhibit the tumor growth in vivo and decrease the cell proliferation while increasing apoptosis via downregulation of NFκB- or Wnt-signaling pathways.[32,33]

However, several other studies with different types of tumors have demonstrated that MSCs can promote tumor growth or metastasis and are related to the formation of tumor-supporting stroma.[34–36] More specifically, it has been reported that nontherapeutic MSCs enhanced tumor growth on HCC cells in vivo.[37] Similarly, Zhu et al[38] showed that MSCs could enhance the invasive capacity of cancer cells via extensive angiogenesis and tumor cell protection of immune cell recognition.[39]

Furthermore, MSCs appear to have a complex biology. Li et al[40] reported that hMSCs could significantly enhance tumor growth in vivo in a HCC subcutaneous model, but decrease the number of lung metastases, while the same cell type enhanced proliferation but inhibited invasiveness in vitro. It has also been shown that the promoting role of hMSCs on esophageal cancer growth in vivo was related to an increase of tumor vessel formation, whereas MSCs were found to inhibit proliferation and invasion of esophageal cancer cells in vitro.[41] Thus, the role of MSCs seems to be controversial in carcinogenesis.

The use of MSCs as tumor-targeted therapy vehicles

In recent years, there has been considerable interest in the use of MSCs as delivery vehicles for antitumor drugs, proteins, and other therapeutic agents because of the homing abilities and the fact that MSCs can evade host immune response.[42] The systemic use of these biologic agents in cancer therapy is generally limited due to their short biologic half-life and toxicity at the required therapeutic dose (Table 1).[43]

Immunostimulatory agents

IL-12 is a pleiotropic cytokine that exerts potent antitumor activity and creates an interconnection between the innate and adaptive immunity.[44,45] Three kinds of tumor models containing melanoma, Lewis lung cancer (LLC) and HCC were established by Chen et al;[46] they injected IL-12 gene-engineered MSCs into the C57BL/6 and BALB/c mice before tumor cell inoculation. Then the mice were divided into three groups with 12 mice per group. There were only three mice in all three groups that presented a tumor (one in the HCC group and two in the LLC group), while almost all mice without IL-12-gene-engineered MSCs developed tumors.[46] IL-15 is a cytokine with structural similarity to IL-2[47] and can rapidly be released by tumor-associated and tumor-infiltrating macrophages induced by IL-12.[48,49] This could be a tool for cancer immunotherapy because of the effect of maintaining long-lasting T-cell antitumor immunity.[50–52] Jing et al[53] found out that IL-15-transduced MSCs could inhibit tumor growth and prolong the survival of mice that bear pancreatic tumors by inducing natural killer (NK) cell and T-cell accumulation. The cytokine interferon (IFN)-β is known to have potent proapoptotic effects and is capable of inhibiting both tumor growth and angiogenesis.[54,55] Kidd et al[30] showed that engineered hMSCs expressing IFN-β are able to produce the biological agents locally at the tumor site and in this way inhibit the growth of pancreatic cancer in vivo.

Prodrug

Prodrugs are inactive compounds, which convert nontoxic prodrugs into toxic antimetabolites to produce a toxic

Table 1 Selected preclinically engineered MSC-based cancer therapy studies in gastrointestinal cancers

Transfected products	MSCs	Tumor	Effects
Immunostimulatory agents			
IL-12	Mouse BM-MSCs (intraperitoneal)	Hepatocellular carcinoma[46]	Tumor prevention
IL-15	Human UC-MSCs (iv)	Pancreatic cancer[53]	Inhibit tumor growth and prolong survival
INF-β	Human BM-MSCs (iv)	Pancreatic cancer[30]	Inhibit tumor growth
Prodrug			
CD/5-FC	Human BM-MSCs (iv)	Gastric cancer[57]	Inhibit tumor growth
TK/GCV	Mouse BM-MSC (iv)	Pancreatic cancer[35,36]	Inhibit tumor growth, prolong survival, and reduce liver metastases
		Hepatocellular cancer[37]	Inhibit tumor growth
Cytotoxic agents			
TRAIL	Human BM-MSCs (coimplantation with tumor cells sc)	Colorectal cancer[63]	Inhibit tumor growth
	Human BM-MSC (iv)	Colorectal cancer[64]	Inhibit tumor growth
	Human AT-MSCs (iv)	Colorectal cancer[65]	Inhibit tumor growth
	Rat BM-MSCs (sc)	Hepatocellular cancer[67]	Inhibit tumor growth and prolong survival
	Human UC-MSCs (iv)	Hepatocellular cancer[68]	Inhibit tumor growth
Growth factor antagonists			
NK4	Human BM-MSCs (iv)	Gastric cancer[72]	Inhibit tumor growth

Abbreviations: BM-MSCs, bone marrow-derived mesenchymal stem cells; UC-MSCs, umbilical cord-derived MSCs; AT-MSCs, adipose tissue-derived MSCs; iv, intravenous; sc, subcutaneous; MSCs, mesenchymal stem cells.

antitumor effect. It has been shown that prodrugs possess some advantages over conventional drugs, such as increased solubility, improved permeability and bioavailability, reduced adverse effects, and prolonged half-lives.[56] You et al engineered human adipose tissue-derived MSCs to express the suicide gene cytosine deaminase::uracil phosphoribosyltransferase (CD::UPRT) which can convert the relatively nontoxic 5-fluorocytosine (5-FC) into the highly toxic antitumor 5-fluorouracil (5-FU).[57] It has been demonstrated that hMSCs express the prodrug-activating enzyme CD that is able to convert the prodrug 5-FC into 5-FU, which shows anticancer therapeutic potential in vitro and in vivo.[57] The combined use of the prodrug ganciclovir (GCV) and thymidine kinase of the herpes simplex virus (HSV-Tk) is commonly used in antitumor therapy. GCV is an analog nucleotide that can be phosphorylated into a monophosphate GCV by HSV-Tk. So when cells are transfected with the *HSV-Tk* gene, endogenous kinases will then change the monophosphate GCV into the active bi- and triphosphate GCV, which will block the cell cycle and induce apoptosis through inhibiting DNA synthesis.[58–60] Furthermore, transfected MSCs exposed to GCV can kill adjacent tumor cells via bystander effect; this effect is reliant on the transfer of monophosphate GCV between cells via gap junctions.[61,62] Recently, our group found that engineered MSCs expressing HSV-Tk under the control of the CCL5 or Tie2/Tek promoter could significantly inhibit the growth of pancreatic,[35,36] breast,[35] and hepatocel-lular carcinoma[37] as well as incidence of metastases in vivo. CCL5 act as chemoattractant and is associated to increased tumor neovascularization. The *Tie2/Tek* gene encodes an angiopoietin receptor tyrosine kinase, essential for blood vessel formation.[35–37]

Cytotoxic agents and growth factor antagonists

Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), a member of the TNF family, is considered as a potential agent for cancer therapy due to its ability to induce apoptosis in a variety of cancer cells without affecting the majority of normal human cells.[43] In recent studies, engineered MSCs were used as a vehicle to deliver TRAIL that lead to colorectal,[63–65] pancreatic,[65,66] and HCC[67–69] cell apoptosis and death in vitro and were able to significantly reduce tumor growth in vivo. HGF is a heterodimeric molecule, which promotes tumor growth, and is also a mesenchymal or stromal-derived mediator with angiogenic activity. As an antagonist of HGF receptors, NK4 inhibits cell proliferation and induces apoptosis through antagonizing the HGF[70] and promotes antiangiogenic activities through the competitive inhibition of angiogenic growth factors to endothelial cells.[71] In a gastric cancer study, Zhu et al[72] found that MSCs transduced with NK4 could obviously inhibit the growth of gastric cancer in vivo by decreasing the microvessel density of tumor xenografts and by inducing apoptosis of tumor cells.

Synergistic approaches utilizing MSCs combined with radiation therapy

The irradiation technique has resulted in a wide application of radiation therapy in gastrointestinal cancer. It is known that radiation therapy is associated with radiation exposure of surrounding healthy tissues and the development of acute injury, followed by late structural and/or functional damage.[73] Recent studies showed that local irradiation not only induced homing of MSCs at exposed sites but also promoted their widespread engraftment to multiple organs.[28] Chapel et al[74] further found a potential role of the MSCs contribution to the repair process in various tissues after irradiation. Zielske et al[75] demonstrated that the radiation-induced injury could be used to target MSCs to tumors, which might increase the effectiveness of MSC cancer gene therapy. These findings suggested that radiation therapy combined with the MSCs was able to increase the therapeutic efficacy. A novel application was shown by Knoop et al[76] in an HCC xenograft mouse model by using sodium–iodide symporter (NIS) MSCs as an ideal gene delivery vehicle. Three cycles of systemic MSC-mediated *NIS* gene delivery followed by ^{131}I application resulted in a significant delay in tumor growth.[76] Therefore, the combined application of irradiation and MSCs should promote the therapeutic potential of engineered MSC cancer therapy without a damage of irradiation on MSCs,[77] and the continued irradiation after the treatment of MSCs might improve the effective duration and extend the treatment cycle as well.

Conclusion

Stem cell transplantation has gained considerable interest during the past decade, as an alternative therapeutic tool in regenerative medicine and anticancer treatment. Several issues related to MSC therapy still remain unknown and are urgently needed to be defined: cellular mechanisms, precise operating method, and timing of MSC application. MSCs can easily be obtained and maintained. They do migrate to the sites of injury, ischemia, and tumor and have immunoprivileged properties that rely on the surrounding microenvironment. These functions are not only related to different cytokines and receptors, but also to cell–cell interaction. Therefore, MSCs can be used as vehicles for tumor-targeting therapies that might overcome the limitations of existing cell therapy approaches, which cannot inhibit the tumor precisely and specifically. There are a number of clinical trials utilizing MSCs for cancer therapy (Tables 2 and 3). Some of them start to use engineered MSCs, though most of these trials still use normal MSCs. In a recent clinical trial, genetically modified autologous MSCs from eligible patients will be used to treat advanced gastrointestinal or hepatopancreatobiliary adenocarcinoma.[71]

The safety of MSC utilization must be considered and will be the major hurdle for their practical use in clinical settings due to the dual effects of MSCs concerning tumors. There is still the necessity to proceed with more studies to demonstrate the specific mechanisms concerning the relation between MSCs and tumors.

Table 2 Clinical cancer trials utilizing therapeutic MSCs registered in the US National Institute of Health

Identifier	Title	Condition	Enrollment	Phase
NCT01983709	Allogeneic human bone marrow-derived mesenchymal stem cells in localized prostate cancer (MSC)	Prostate cancer	Currently recruiting participants	Phase I
NCT01275612	Mesenchymal stem cells in cisplatin-induced acute renal failure in patients with solid organ cancers (CIS/MSC08)	Solid tumors Acute kidney injury	Currently recruiting participants	Phase I
NCT01854567	P3 study of umbilical cord blood cells expanded with MPCs for transplantation in patients with hematologic malignancies	Acute myelogenous leukemia Acute lymphoblastic leukemia Non-Hodgkin's lymphoma Hodgkin's disease	Currently recruiting participants	Phase III
NCT00790413	Haploidentical stem cell transplantation in neuroblastoma	Neuroblastoma	Currently recruiting participants	Phase 0
NCT02068794	MV-NIS-infected mesenchymal stem cells in treating patients with recurrent ovarian cancer	Ovarian cancer	Ongoing, but not recruiting participants	Phase I/II
NCT00408590	Recombinant measles virus vaccine therapy and oncolytic virus therapy in treating patients with progressive, recurrent, or refractory ovarian epithelial cancer or primary peritoneal cancer	Ovarian cancer Primary peritoneal cavity cancer	Ongoing, but not recruiting participants	Phase I
NCT02079324	Genetically modified mesenchymal stem cell therapeutic against head and neck cancer (GX-051)	Head and neck cancer	Ongoing, but not recruiting participants	Phase I

Abbreviations: MPC, mesenchymal progenitor cells; MSC, mesenchymal stem cell; MV-NIS, measles virus encoding the thyroidal sodium–iodide symporter.

Table 3 Clinical cancer trials utilizing therapeutic MSCs conducted in the European Union

EudraCT number	Title	Condition	Enrollment	Phase
2011-001822-81	Infusion of third-party mesenchymal stem cells after renal or liver transplantation: a Phase I–II, open-label, clinical study	Liver failure: end-stage liver diseases Kidney failure: end-stage renal diseases	Ongoing	Phase I/II
2012-003741-15	Treatment of advanced gastrointestinal cancer in a Phase I/II trial with modified autologous MSC_apceth_101. Open-label, multicenter, Phase I/II	Patients suffering from advanced, recurrent or metastatic gastrointestinal adenocarcinoma	Ongoing	Phase I/II
2014-004349-29	Mesenchymal stem cells for radiation-induced xerostomia (MESRIX) in previous HPV-positive oropharyngeal head and neck cancer patients	Participants with xerostomia (International Classification of Diseases-10: DQ 838A) and oropharyngeal cancer (DC 10)	Ongoing	

Abbreviations: HPV, human papillomavirus; MSCs, mesenchymal stem cells.

Disclosure

The authors report no conflicts of interest in this work.

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