

Role of BMSCs in liver regeneration and metastasis after hepatectomy

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Abstract

Hepatocellular carcinoma (HCC), which develops from liver cirrhosis, is highly prevalent worldwide and is a malignancy that leads to liver failure and systemic metastasis. While surgery is the preferred treatment for HCC, intervention and liver transplantation are also treatment options for end-stage liver disease. However, the success of partial hepatectomy and intervention is hindered by the decompensation of liver function. Conversely, liver transplantation is difficult to carry out due to its high cost and the lack of donor organs. Fortunately, research into bone-marrow stromal cells (BMSCs) has opened a new door in this field. BMSCs are a type of stem cell with powerful proliferative and differential potential that represent an attractive tool for the establishment of successful stem cell-based therapy for liver diseases. A number of different stromal cells contribute to the therapeutic effects exerted by BMSCs because BMSCs can differentiate into functional hepatic cells and can produce a series of growth factors and cytokines capable of suppressing inflammatory responses,

reducing hepatocyte apoptosis, reversing liver fibrosis and enhancing hepatocyte functionality. Additionally, it has been shown that BMSCs can increase the apoptosis rate of cancer cells and inhibit tumor metastasis in some microenvironments. This review focuses on BMSCs and their possible applications in liver regeneration and metastasis after hepatectomy.

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Key words: Bone marrow stromal cells; Liver cancer; Liver regeneration; Liver metastasis

Core tip: Recent research has demonstrated that bone-marrow stromal cells (BMSCs) are a type of stem cell with powerful proliferative and differential potential that play an important role in the repair and regeneration of multiple organs and tissues, and these cells have become the focus of recent research. This review discusses the involvement of BMSCs in liver regeneration and metastasis after hepatectomy.

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BONE-MARROW STROMAL CELLS AND LIVER REGENERATION

Multipotent bone-marrow stromal cells (BMSCs) are a group of cells that are originally found in adult bone marrow. Continued analysis of their characteristics, niches and functions has become the interest of many investigators in the past decade. Notably, numerous researchers have focused on the role of BMSCs in the liver regeneration pro-

cess by utilizing animal models of hepatectomy. Multiple cell populations within the liver, including hepatocytes, bile duct epithelial cells, Kupffer cells and endothelial cells, quickly respond to injury to promote liver regeneration after a partial hepatectomy^[1]. After severe liver injury, liver progenitors, known as “oval cells”, are also activated to participate in the regeneration process^[2]. As the storage pool of progenitor cells, the bone marrow plays an important role in cellular mobilization during liver regeneration. Within 24–48 h after liver injury, nearly 90% of hepatocytes enter into the S phase of the cell cycle. At this time, DNA replication begins, and various cell factors and growth factors are released through autocrine or paracrine modes of action; these factors include epithelial growth factors, hepatocyte growth factors, insulin-like growth factors, vascular endothelial growth factors, tumor necrosis factors and urokinase^[3]. Other cells within the liver promote the mitosis of hepatocytes by secreting small molecules. For example, interleukin (IL)-6, secreted by Kupffer cells, is one of the vital factors among such small molecules. Survivin and transforming growth factor (TGF)- β 1 are highly expressed in the liver regeneration process^[4].

BMSCs are bone-marrow derived non-hematopoietic stromal cells^[5] that are capable of differentiating into multiple types of cells and contribute to the regeneration of both mesenchymal and non-mesenchymal tissues^[5–12]. These cells are characterized by their easy access, proliferative potential *in vitro* and features that are not easily lost^[13]. BMSCs are absent of immunogenicity and can express numerous surface markers, excluding hematopoietic cell markers such as CD45, CD34, CD14, and CD11. It has been reported that surface markers of BMSCs include HLA class I⁺, HLA class II⁺, CD40⁺, CD80⁺ and CD86^[14–16]. Because BMSCs lack co-stimulatory molecules, they are unable to generate T-cell mediated immuno-responses.

Kuo *et al.*^[17] demonstrated that the transplantation of BMSCs can significantly improve mortality in a murine model of lethal fulminant hepatic failure induced with carbon tetrachloride (CCl₄) by oral gavage. In addition, a number of cells expressing albumin have been detected by Western blot, as well as cytokeratin 18, hepatocyte nuclear factor 4, cytochrome P450 and glutamine synthetase. Using the same model, Banas *et al.*^[18] observed a much higher concentration of hepatocyte-stimulating factors, including IL-8, granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, monocyte chemoattractant protein-1, nerve growth factor and hepatocyte growth factor, after BMSC transplantation. Qihao *et al.*^[19] co-cultured BMSCs with mature hepatocytes to induce BMSCs to differentiate into hepato-like cells. Their results demonstrated that co-cultured cells display typical hepatocyte morphology and have a high proliferative potential, expressing albumin, AFP and CK18 at both the mRNA and protein levels. After 70% of the liver was removed from congenital albumin-deficient mice and BMSCs were transplanted through portal vein immediately following the tissue removal^[20], albumin mRNA and protein were both detected in hepatocytes

4 wk later, and the serum was albumin positive as well. The above-mentioned studies suggest that (1) BMSCs have the potential to differentiate into hepato-like cells after liver injury; and (2) BMSCs can secrete a number of hepatocyte growth stimulating factors to promote the proliferation of stem cells. Both features improve liver regeneration.

BMSCS AND HEPATOCELLULAR CARCINOMA

The early diagnosis and treatment of hepatocellular carcinoma

Because early detection is difficult in hepatocellular carcinoma (HCC), the disease is usually diagnosed in the end stages when patients are symptomatic. Early-stage HCC, which is usually found during a physical examination, has a good prognosis after hepatectomy. Hepatectomy is also the primary treatment for advanced liver cancer^[21]. To remove the cancerous tissue completely, the resection of a large amount of liver tissue is necessary, as the tumor presents a large mass. The surgery will have a major influence on the patients' liver function, ultimately leading to liver failure and, in some cases, leaving the patient with no other option but liver transplantation^[22]. However, shortages in donor organs limit the development of clinical liver transplantation^[23]. Molecular targeted drugs have shown potential in the treatment of HCC^[24,25] but are very costly. Currently, no satisfactory treatment for HCC is available. It has been reported that only 30% of HCC patients can afford a hepatectomy or liver transplantation. In comparison, BMSCs will present a prospective clinical application if they demonstrate a therapeutic effect on HCC.

BMSCs in the treatment of HCC

Little is known regarding the usage of BMSCs in the treatment of HCC. SCID mice injected with HepG2 human liver cancer cells developed detectable tumors^[26]. When injected with both HepG2 and hBMSCs, 20% of the mice did not form tumors, while others showed delayed tumor formation compared to those injected with HepG2 only. Additionally, immunoblot analysis showed that treatment of HepG2 liver cancer cell lines with hBMSCs-conditioned media resulted in a down-regulation of β -catenin, Bcl-2, c-Myc, PCNA and survivin, as well as an inhibition of the proliferative rate of the cells. Abdel aziz *et al.*^[27] co-cultured liver cancer cells HepG2 with hBMSCs to detect apoptosis of liver cancer cells using flow cytometry. They observed that BMSCs can increase the apoptosis rate of liver cancer cells.

Effect of BMSCs in liver fibrosis

HCC, which typically develops from liver fibrosis, can be delayed or even inhibited if effective interventions are performed during the period of liver cirrhosis, which is initiated by Ito cells located in the Disse space^[28]. These cells are able to promote liver fibrosis by expressing fibrogenetic factors such as TGF- β 1^[29]. Previous stud-

ies demonstrated that TGF- β 1 is up-regulated in HCC tissues and peri-neoplastic stroma and plays key roles in liver fibrogenesis and hepatocarcinogenesis. Its expression level is markedly increased in cirrhotic liver and is a potent inducer of cell proliferation and collagen production^[30]. van Zijl *et al.*^[31] found that TGF- β 1 facilitates the epithelial-to-mesenchymal transition process through the activation of the platelet-derived growth factor (PDGF) signaling pathway, promoting the process of liver cirrhosis. BMSCs have been reported to reduce the expression of TGF- β 1 in animal studies, thus inhibiting liver fibrosis^[32]. Abdel Aziz *et al.*^[33] demonstrated that BMSC transplantation in a mouse model of liver fibrosis can significantly improve liver function and delay the process of fibrosis. Zhao *et al.*^[34] observed that the survival rate in mice is increased after BMSC transplantation in a CCl₄-induced liver cirrhosis model. Transplanting BMSCs into mice before CCl₄ injection has been shown to reduce the rate of liver cirrhosis^[35].

These above mentioned studies indicate that BMSCs present a promising anti-fibrosis effect^[21,36]. Considering its extensive sources, high proliferative rate *in vitro*, simple transplantation approach and tendency to migrate to injured areas to take part in the regenerative process, BMSCs present high a potential for clinical use. Patients are more likely to accept this new approach because it is less costly than liver transplantation.

EFFECT OF BMSCS ON TUMOR CELL METASTASIS

Metastasis is a multistep process that requires acquisition of malignant cell phenotypes, which allow tumor cells to escape from the primary tumor site. Although the German pathologist Cohnheim reported, for the first time, that stem cells can migrate to sites of injury^[37], the exact effects of BMSCs on tumor cell metastasis remains unknown. A number of studies have shown that BMSCs have the potential to exacerbate the pathogenesis of tumors and cancer metastasis *in situ* via cell-cell interaction, secretion of cytokines and growth factors, and the organization of an extracellular matrix^[38,39]. Karnoub *et al.*^[40] observed that BMSCs, when combined with otherwise weakly metastatic human breast carcinoma cells, caused a dramatic increase in the metastatic potency of cancer cells when these cell mixtures were introduced into a subcutaneous site and allowed to form a tumor xenograft. BMSCs secrete CCL5, which then acts in a paracrine manner on the cancer cells to enhance their motility, invasion and metastasis. Furthermore, it has been detected that long-term exposure of BMSCs to tumor-conditioned medium from a human breast cancer cell line, MDA-MB231, induces a phenotype reminiscent of carcinoma-associated fibroblasts. Co-injection of these treated BMSCs with MDA-MB231 cells resulted in robust tumor growth in nude mice^[41]. Moreover, BMSCs accelerate tumor growth in new sites by secreting large amounts of CXCL12 and CXCL13 to attract circulatory cancer cells

in vivo, including breast cancer cells, leukemia cells and myeloma cells, and to produce soluble factors such as PGE2 and galactin-binding proteins^[42]. Gao *et al.*^[43] found that BMSCs secrete SDF-1 when exposed to either the highly invasive MDA-MB231 human breast cancer cell line or to conditioned medium from these cell cultures. Autocrine signaling of SDF-1 results in the activation of Jak2/STAT3 and ERK1/2 signaling, thereby promoting FAK activation and cell migration. However, contradictory findings have been reported. Li *et al.*^[44] observed that BMSCs down-regulate the expression of TGF- β 1 and MMP and inhibit the invasiveness and metastasis of HCC when co-cultured with MHCC97-H cells *in vitro*. BMSC-treated mice exhibit significantly larger tumors but had decreased cellular numbers of lung metastases, possibly because of the blocking of the TGF- β pathways in metastasis of HCC. It is known that TGF- β 1 is activated by MMP-2 or MMP-9, which are both richly expressed in the tumor microenvironment. Once activated, TGF- β 1 binds to TGF receptor II, phosphorylates TGF- β receptor I and activates down-stream signaling through Smad-2 and Smad-3. TGF- β pathways have been proven to play an important role in tumor development^[45-47]. TGF- β 1 regulates oncogenic mRNA expression to promote cell growth, migration and invasion of HCC cells, thus promoting HCC progression^[48]. A previous study showed that TGF- β 1 plays the role of chemo-attractant for CD105-expressing endothelial cells and thus promotes tumor angiogenesis^[49]. The role of TGF- β 1 may shift from tumor suppressor to oncogenic growth factor *via* the activation of c-Jun N-terminal kinase (JNK)^[50-53]. In normal epithelial cells during the early stages of tumor development, TGF- β acts as a tumor suppressor by inhibiting proliferation and inducing apoptosis of tumor cells. As a tumor progresses, TGF- β becomes an oncogenic factor, promoting proliferation, angiogenesis, invasion and metastasis, as well as suppressing the anti-tumoral immune response.

Above all, BMSCs change the microenvironment of the tumor in a paracrine or autocrine manner to influence the growth and metastasis of tumors, as well as the homing capability of BMSCs to sites of tumor formation, which makes them attractive candidates as shuttles for anti-cancer therapy. However, whether BMSCs promote or inhibit the metastasis of tumor cells requires further study. Nevertheless, it is certain that TGF- β plays a vital role in tumor metastasis and will be one of the decisive factors in evaluating the potential of tumor metastasis.

ONCOGENICITY OF BMSCS

Although stem cells show great promise in gene therapy, the possible oncogenicity of BMSCs requires further consideration. Murata *et al.*^[52] reported that BMSCs are a type of progenitor cell of malignant fibroma. Moreover, Ewing tumor gene expression analysis indicated that BMSCs may be the origin of those tumor cells^[54]. Houghton *et al.*^[55] investigated that gastric carcinoma, developed from

Helicobacter pylori infection, mainly originated from bone-marrow derived cells. There is also some association between stem cells and fibroblast in breast cancer^[41]. Above all, BMSCs do have tumorigenic potential, although this feature has yet to be confirmed. Dawson *et al*^[56] showed that myelomonocytic BMSCs (CD45⁺CD11b⁺Sca1⁺) significantly accelerate tumor growth and metastasis, while mesenchymal BMSCs (Sca1⁺Gr-1⁺F4/80⁺CD11b⁺CD31⁺CD45⁺) did not accelerate growth. Collectively, these findings offer direct evidence for the differential role of BMSC subsets in tumor progression. Furthermore, global gene expression profiling of human HCC showed that TGF- β gene signatures can cluster into two homogeneous groups of HCC with early or late TGF- β signatures. The late TGF- β signature is associated with an invasive HCC phenotype and an increased risk of tumor recurrence^[57].

There are two hypotheses of the oncogenicity of BMSCs. First, stem cells contribute to tumor angiogenesis by secreting pro-angiogenic factors and differentiating into endothelial-like or pericyto-like cells. It has been previously demonstrated that BMSCs secrete specific angiogenic factors, including vascular endothelial growth factor, PDGF, fibroblast growth factor and CXCL12, promoting tumor angiogenesis when co-transplanted into mice with tumor cells^[58]. Second, BMSCs are absent of immunogenicity, and can induce immunosuppression. In normal conditions, BMSCs do not take part in the immuno-regulation of T cells, B cells, Dendritic cells and Natural killer cells. However, in the tumor microenvironment, BMSCs produce immunosuppressive factors, such as PGE2, nitric oxide, Indoleamine 2,3-dioxygenase and soluble HLA-G5, to inhibit the proliferation of immunocytes and block the antigen-presenting process, thus allowing tumor cells to escape from immuno-surveillance^[59].

PROSPECT OF BMSCS IN TRANSPLANTATION THERAPY

BMSCs play a specific role in liver regeneration. It is widely accepted that BMSCs differentiate into hepatic cells or hepatic-like cells to compensate liver function according to the size of injured liver^[60-68]. In the process of chronic liver disease, BMSCs delay the process of liver cirrhosis, and prevent the occurrence of HCC in HBV infected patients. However, little is reported about the relationship between BMSCs and HBV. As a result, BMSCs provide a new approach to early intervention of HBV, if BMSCs can delay the replication of HBV. Treatment with BMSCs is also meaningful to patients with advanced liver cancer who have extrahepatic metastasis. BMSCs can not only improve the health of liver failure patients during the dangerous waiting period before liver transplantation but also aid in the repair of the injured liver and improve liver function, which can significantly improve the quality of life for HCC patients. Furthermore, using the lentiviral vector approach, BMSCs transduced with the potent chemotherapeutic drug TRAIL (TRAIL-BMSC) were shown to substantially inhibit growth of colorectal carcinoma in

subcutaneous mixed xenografts in mice^[69]. It is likely that recipients will not reject BMSCs because of their capacity for immunomodulation, making these cells even more attractive for therapeutic applications.

PROBLEMS AND SUMMARY

Due to their differentiation capabilities, BMSCs have a vast potential for tissue engineering, regenerative medicine applications and the treatment of end-stage liver disease. The fact that BMSCs may home to sites of cancer makes them attractive as shuttles for anti-cancer drug delivery. However, the exact role that BMSCs play in cancer development and progression requires further discussion and evaluation before this type of cell-based therapy becomes a reality. In addition, whether *in vitro* amplification is necessary after the cells are collected and the proper extent of proliferation both require further evaluation. Additionally, there is a lack of specific monitoring markers when BMSCs are transplanted into the human body. Finally, although BMSCs can differentiate into specific tissue cells when transplanted into humans, whether these cells can function properly remains unknown. With deeper research into BMSCs, many more patients with liver cancer will benefit.

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