

Mesenchymal Stem Cells for the Treatment of Liver Disease: Present and Perspectives

Seong Hee Kang^{1,2,3}, Moon Young Kim^{1,2}, Young Woo Eom^{1,2}, and Soon Koo Baik^{1,2,3}

¹Department of Internal Medicine, ²Cell Therapy and Tissue Engineering Center, and ³Institute of Evidence Based Medicine, Yonsei University Wonju College of Medicine, Wonju, Korea

Mesenchymal stem cell transplantation is an emerging therapy for treating chronic liver diseases. The potential of this treatment has been evaluated in preclinical and clinical studies. Although the mechanisms of mesenchymal stem cell transplantation are still not completely understood, accumulating evidence has revealed that their immunomodulation, differentiation, and antifibrotic properties play a crucial role in liver regeneration. The safety and therapeutic effects of mesenchymal stem cells in patients with chronic liver disease have been observed in many clinical studies. However, only modest improvements have been seen, partly because of the limited feasibility of transplanted cells at present. Here, we discuss several strategies targeted at improving viable cell engraftment and the potential challenges in the use of extracellular vesicle-based therapies for liver disease in the future. (**Gut Liver 2020;14:306-315**)

Key Words: Mesenchymal stromal cells; Liver disease; Cell transplantation; Cell survival

INTRODUCTION

Chronic liver injury, such as that arising from viral infection, alcohol abuse, or metabolic diseases, causes liver cirrhosis and failure.^{1,2} The ultimate treatment for end-stage cirrhosis is liver transplantation.³ However, transplants are not readily available in many countries, and in countries where transplants are available, organ shortages and high costs related with transplantation make this an impractical option for many patients.

Stem cell transplantation has been proposed as a potential strategy for patients with hepatic diseases to prevent progression and treat those with advanced fibrosis. Stem cell transplantation including hematopoietic, induced pluripotent, and

mesenchymal stem cells (MSCs) can be manipulated for division into hepatocyte-like cells both *in vitro* and *in vivo*.^{4,5} Of these cell types, MSCs have been shown to have the advantages of being obtained relatively easily and possessing low immunogenicity.⁶ They have self-renewal ability and can differentiate into cells of various lineages, including osteoblasts, adipocytes, and chondrocytes.⁷ Additionally, MSCs are safe in terms of ethical concerns because they do not originate from somatic cells. Furthermore, MSC transplantation has been considered safe and widely assessed in clinical settings of various diseases with promising results.⁸

The purpose of this review is to present the therapeutic effects of MSCs in liver diseases to address questions regarding efficacy, safety, and possible risks involved, as well as to discuss recent clinical advances involving clinical MSC-based therapies, opening a new path toward further studies.

OVERVIEW OF MSC TRANSPLANTATION

1. Definition and sources of MSC transplantation

MSCs can differentiate into either mesodermal or ectodermal cells, resulting in adherent multipotent fibroblast-type stem cells.⁹ Different investigators define MSC characteristics in varying ways. To address this problem, the International Society for Cellular Therapy recommends a set of three criteria to define human MSCs;¹⁰ adherence to plastic, specific surface antigen expression, and multipotent differentiation potential (Table 1). MSCs can be isolated from most organs or tissues, including bone marrow (BM), umbilical cord blood (UCB), adipose tissue (AT), peripheral blood, trabecular bone, synovial membrane, cartilage, and muscle.^{11,12} Among these, three main sources have been demonstrated as capable of treating liver disease: BM-MSCs, UCB-MSCs, and AT-MSCs. Generally, MSCs derived

Correspondence to: Soon Koo Baik

Department of Internal Medicine, Yonsei University Wonju College of Medicine, 20 Ilsan-ro, Wonju 26426, Korea

Tel: +82-33-741-1223, Fax: +82-33-741-0951, E-mail: baiksk@yonsei.ac.kr

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Table 1. Criteria of the International Society for Cellular Therapy for Defining MSCs

Adherence to plastic	Surface antigen expression		Multipotent differentiation
	Positive ($\geq 95\%$)	Negative ($\leq 2\%$)	
Adherence to plastic in standard culture conditions	CD73	CD14/CD11b	Differentiation potential into osteoblasts, adipocytes, chondroblasts, which is demonstrated by staining of <i>in vitro</i> cultured cells
	CD90	CD79 α /CD19	
	CD105	CD34	
		CD45	
		HLA-DR	

MSCs, mesenchymal stem cells; HLA-DR, human leukocyte antigen-DR isotype.

from these three sources are well-known to express similar surface antigens, whereas their morphology and proliferation rate vary.¹³ First, although BM is the largest source, BM-derived MSCs may have restricted clinical use because of the invasive procedure required for their isolation, insufficient cell number, and reduced differentiation ability with increasing age.¹⁴ Next, UCB-MSCs, which can be obtained using less-invasive methods, have been addressed as a substitute source.⁷ UCB-MSCs are easy to obtain for collection after delivery; further, they remain viable even after cryopreservation. Finally, AT-MSCs have several advantages. They have the highest proliferative capacity and carry the benefits of requiring a less-invasive procedure and are easily obtained through simple lipo-aspiration.¹⁵ Until now, BM has been the most common source in clinical settings. However, important concerns regarding the choice of MSC source must still be addressed to make stem cell therapies applicable for liver disease.

2. Therapeutic mechanisms of MSC transplantation in liver disease

1) Trans-differentiation into hepatocyte-like cells

Hepatocyte-like cells derived from MSCs have been considered substitute sources for liver regeneration.¹⁶ Hepatic differentiation of MSCs is influenced by several factors. First, MSCs can be differentiated into hepatocyte-like cells by processing with many cytokines and growth factors such as hepatocyte growth factor (HGF), fibroblast growth factor-2/4, epidermal growth factor, oncostatin M, leukemia inhibitory factor, dexamethasone, insulin-transferrin-selenium, or nicotinamide.¹⁷ Injured liver tissue surrounded with the extracellular matrix (ECM) has been used as the location for MSC engraftment and differentiation because it has been shown that liver ECM triggers MSC differentiation. Additionally, co-culture with liver cells¹⁸ and pellet culture¹⁹ can induce MSC differentiation into hepatocyte-like cells. However, the trans-differentiation of MSCs into hepatocytes occurs in less than 1% of the total liver mass in preclinical settings.²⁰ A more efficient hepatocyte differentiation technique should be developed to utilize hepatocyte-differentiated MSCs for treating liver disease.

2) Immunomodulation

Chronic liver injury caused by inflammation is accompanied by infiltration of T cells, B cells, and monocytes (Fig. 1).²¹ It has been reported that immunosuppressive agents can be beneficial to liver regeneration before and after liver transplantation.^{22,23} In this respect, MSCs' immunomodulatory properties can have favorable effects in liver disease. First, MSCs can downregulate T cells by releasing various soluble factors, such as nitric oxide, prostaglandin E (PGE)-2, indoleamine 2, 3-dioxygenase, interleukin (IL)-6, IL-10, and human leukocyte antigen G. These factors can control the proliferation and functions of various immune cells and upregulate T_{reg} cells.²⁴ MSCs can also inhibit the proliferation of T cells by directly interacting with T-lymphocytes. The immunosuppressive ability of MSCs is generated by a combination of cytokines such as interferon- γ , IL-1 α , and tumor necrosis factor (TNF)- α .²⁵ These cytokines help some chemokines and immune cells stay in contact with the MSCs and regulate immune reactions. Additionally, MSCs can inhibit the activation of B cells, reducing levels of immunoglobulin. Co-culture with MSCs has been associated with a significant reduction of surface expression of chemokine receptor (CXCR4, CXCR7, and CXCR5).²⁶ In addition, natural killer (NK) cells have been well-known as an important factor in immune reactions against viral infections and cancer.²⁷ MSCs induce IL-2 expression, resulting in reduced IL-15 secretion from IL-2-induced NK cells by either cell-to-cell interactions or secretion of soluble factors such as PGE2 and transforming growth factor (TGF)- β .²⁸ Finally, MSCs have been shown to induce the polarization of inflammatory macrophages toward alternative macrophages. This alteration releases the soluble factors (i.e., IL-10 and IL-1Ra) that improve liver injury.²⁹

3) Anti-fibrotic activities

Chronic liver injury causes the trans-differentiation of quiescent hepatic stellate cells (HSCs) into fibrogenic myofibroblasts, producing excess ECM proteins and resulting in fibrosis. This proliferation of activated HSCs and collagen deposition can be attenuated with MSC treatment by indirect or direct cell-cell contact. In the indirect contact mechanism, several soluble factors (i.e., TGF- β 3, TNF- α , IL-10, and HGF) secreted by MSCs

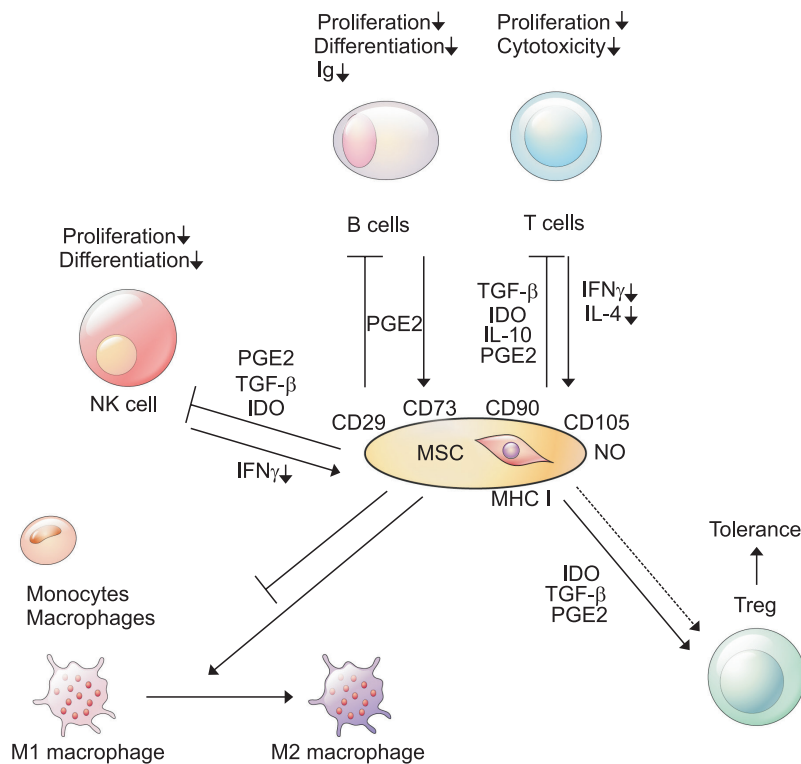


Fig. 1. Immunomodulation by mesenchymal stem cell (MSC) transplantation in liver disease occurs at multiple levels.

Ig, immunoglobulin; NK, natural killer; PGE, prostaglandin E; TGF, transforming growth factor; IDO, indoleamine 2,3-dioxygenase; IFN, interferon; IL, interleukin; MHC, major histocompatibility complex, NO, nitric oxide.

attenuate collagen synthesis,^{30,31} whereas HGF and nerve growth factor induce the apoptosis of HSCs.³² Next, MSCs co-cultured with HSCs inhibit the proliferation of HSCs and expression of α -smooth muscle actin (SMA) through cell-to-cell contact.³³ It is well-known that matrix metalloproteinases (MMPs) and tissue inhibitors of MMPs (TIMPs) contribute to both the progression and regression of liver fibrosis. In several fibrosis models, MSCs regulate the expression of MMPs (i.e., MMP-2, -9, -13, and -14) and TIMP-1; increasing the expression of MMPs and decreasing the expression of TIMPs.^{32,34}

ARE WE READY FOR MSC TRANSPLANTATION IN ROUTINE CLINICAL PRACTICE?

1. Present efficacy and safety of MSC transplantation

Several clinical trials have elucidated the advantages of MSC treatment in chronic liver disease (Table 2).³⁵⁻⁵²

A pilot study conducted by Mohamadnejad *et al.*³⁵ in 2007 showed that infusion of autologous MSCs was safe and feasible for treatment in four patients with decompensated liver cirrhosis. Model for End-Stage Liver Disease (MELD) scores improved in three out of four patients at 6 months and two of them remained stable up to 12 months. In a phase 2 study conducted by Amer *et al.*³⁷ published in 2011, 40 patients with hepatitis C-related liver cirrhosis were randomized into two groups of 20 patients: the first group received autologous BM-derived MSCs, while the second group received the best supportive treatment.

Compared to the second group, the first group showed significant improvement in Child-Pugh and MELD scores, which was maintained for 6 months. Shi *et al.*⁴⁰ reported that 24 patients with hepatitis B-related acute-on-chronic liver failure were treated with intravenous UCB-MSC transfusions, and 19 patients were treated with saline as controls. The UCB-MSC transfusions significantly increased the survival rates for 72 weeks and no significant side effects were observed until the end of the follow-up. Similar results were obtained by Amin *et al.*⁴² who showed that intrasplenic autologous transplantation improved liver function in 20 patients with hepatitis C-related liver cirrhosis, as determined by significant decreases in the total bilirubin, aspartate transaminase, and alanine aminotransferase levels, and prothrombin time as well as a significant increase in the albumin at 6-month follow-up. An open-label trial published by Jang *et al.*⁴⁵ in 2014 showed beneficial effects of autologous BM-MSC transplantation via the hepatic artery for treating alcohol abuse-related liver cirrhosis. Histological improvements were observed in 54.5% of patients; the Child-Pugh score was improved from 7.1 to 5.4, and the levels of fibrosis-related markers including TGF- β 1, type 1 collagen, and α -SMA were significantly decreased 12 weeks after the second injection. Recently, a randomized phase 2 trial reported that hepatic arterial injections of autologous BM-MSCs for 72 patients with alcohol-related liver cirrhosis could alleviate liver fibrosis and improve Child-Pugh scores.⁴⁹ A recent clinical study also reported the feasibility, safety, and tolerability of MSC therapy

Table 2. Main Characteristics and Outcomes of MSC-Based Therapy for Liver Disease

Study (year)	Liver disease	Patients, sample size (MSC/control)	Cell source	Graft type	Injection route	Cell doses	Duration of follow-up (mo)	Primary outcomes
Mohamadnejad et al. (2007) ³⁵	Decompensated LC	4/0	BM	Auto	PV	31.7×10 ⁶	12	MELD score, liver function test, and liver volumes
Kharaziha et al. (2009) ³⁶	LC (MELD ≥10)	8/0	BM	Auto	Portal vein (n=6) or PV (n=2)	3.0–5.0×10 ⁷	6	MELD score, liver function test, and serum creatinine
Amer et al. (2011) ³⁷	Chronic HCV-associated LC	20/20	BM	Auto	1) IS (n=10) 2) IH (n=10)	2.0×10 ⁷	6	MELD score, Child-Pugh score, ascites, edema, liver function test, and fatigue
Peng et al. (2011) ³⁸	Chronic HBV-associated liver failure	158/0	BM	Auto	HA	1.0×10 ⁶	12	MELD score, liver function test, and self-reported symptoms
El-Ansary et al. (2012) ³⁹	Chronic HCV-associated LC	15/10	BM	Auto	PV	1.0×10 ⁶	12	MELD score and serum albumin level
Shi et al. (2012) ⁴⁰	Chronic HBV-associated liver failure	24/19	UCB	Allo	PV	0.5×10 ⁶	12	MELD score, liver function test, and survival rates
Zhang et al. (2012) ⁴¹	Chronic HBV-associated decompensated LC	30/15	UCB	Allo	PV	0.5×10 ⁶	12	MELD score, ascites, and liver function test
Amin et al. (2013) ⁴²	Chronic HCV-associated LC	20/0	BM	Auto	IS	1.0×10 ⁷	6	MELD score and liver function test
Mohamadnejad et al. (2013) ⁴³	Decompensated LC	15/12	BM	Auto	PV	1.0×10 ⁶	12	No improvement
Wang et al. (2013) ⁴⁴	UDCA-resistant PBC	7/0	UCB	Allo	PV	0.5×10 ⁶	12	Serum alkaline phosphatase and γ -GT levels
Jang et al. (2014) ⁴⁵	Alcohol-related LC	11/0	BM	Auto	HA	5.0×10 ⁷	4	MELD score and liver histology
Salama et al. (2014) ⁴⁶	Chronic HCV-associated LC	20/20	BM	Auto	PV	1.0×10 ⁶	6	MELD score and Child-Pugh score
Wang et al. (2014) ⁴⁷	UDCA-resistant PBC	10/0	BM	Allo	PV	3.0–5.0×10 ⁵	12	Serum levels of ALT, AST, γ -GT, and IgM
Xu et al. (2014) ⁴⁸	Chronic HBV-associated LC	27/29	BM	Auto	HA	8.45×10 ⁵	6	MELD score improvement and reduction in IL-6, IL-17, TNF- α levels
Suk et al. (2016) ⁴⁹	Alcohol-associated LC	37/18	BM	Auto	HA	5.0×10 ⁷	12	Child-Pugh score and Histologic fibrosis
Lanthier et al. (2017) ⁵⁰	Decompensated alcoholic hepatitis	28/30	BM	Auto	HA	4.7×10 ⁷	1	No improvement
Lin et al. (2017) ⁵¹	Chronic HBV-associated liver failure	56/54	BM	Allo	PV	1.0×10 ⁶	6	MELD score and survival rates
Detry et al. (2017) ⁵²	Liver transplant recipients	10/9	BM	Allo	PV	1.5–3.0×10 ⁶	12	No difference of rate of infection or <i>de novo</i> cancer

MSC, mesenchymal stem cell; LC, liver cirrhosis; BM, bone marrow; Auto, autogenic transplantation; PV, peripheral vein; MELD, Model for End-Stage Liver Disease; HCV, hepatitis C virus; IS, intrasplenic; IH, intrahepatic; HBV, hepatitis B virus; HA, hepatic artery; UCB, umbilical cord blood; Allo, allogenic transplantation; UDCA, ursodeoxycholic acid; PBC, primary biliary cholangitis; γ -GT, γ -glutamyl transferase; ALT, alanine aminotransferase; AST, aspartate transaminase; IgM, immunoglobulin M; IL, interleukin; TNF, tumor necrosis factor.

in liver transplant recipients (n=10). Treatment with MSCs has been proposed to have a potential beneficial effect on ischemia/reperfusion injury. This study opened a path for utilizing MSCs as a potential future therapy for liver transplant recipients who require life-long immunosuppression.⁵²

However, negative results were obtained in two clinical studies. Mohamadnejad *et al.*⁴³ reported that autologous BM-MSC transplantation (n=15) injected through the peripheral vein likely has no beneficial effect compared to controls (n=12). The absolute changes in Child-Pugh score, MELD scores, serum transaminase levels, and liver volumes did not differ between the MSC-treated and control groups at 12 months of follow-up. Another study reported that 28 patients with alcoholic hepatitis were treated with autologous BM-derived CD34⁺ stem cells and MSCs and 30 patients were treated with supportive therapy only. No significant difference between the two groups was observed in terms of the proliferative hepatocyte number in liver biopsy at the 4-week follow-up. However, patients who received stem cell treatment showed more active liver macrophagic expansion as compared to those who received standard treatment.⁵⁰

Most studies have suggested that stem cell therapy is safe and effective in patients with liver disease. However, the size and nature of the trial design of many of these clinical studies meant that meaningful conclusions could not be drawn, and thus, their efficacy has yet to be confirmed.

2. Routes of MSC transplantation

There are conflicting data about engraftment of transplanted MSCs and some concerns regarding their fibrogenic potential have been raised. It seems that these unwanted effects depend on the route and dose of MSCs infusion.^{53,54} Though the effectiveness is reported to vary slightly depending on the injection route, MSCs can be transplanted into the liver through intravenous, intrahepatic, intraperitoneal, intrasplenic, or portal vein injection. The peripheral vein has been known as the most common transplantation route, followed by the hepatic artery, intrasplenic injection, intrahepatic injection, and portal vein. BM-MSCs administered through the peripheral vein have been shown to migrate well into liver parenchyma in the context of chronic injury *in vivo*. In contrast, limited MSC engraftment has been observed in an acute injury environment.⁵⁴ In addition, MSCs endured in liver tissues when injected through the intrahepatic artery, demonstrating that MSCs were present and did not differentiate into hepatocytes. Additionally, intraportal infusion was more efficient than the peripheral route in clinical trials.³⁷ However, direct approaches, such as via the portal vein or hepatic artery, may carry the risk of portal hypertensive bleeding following cell injection.⁵⁵ Overall, evidence provided by most of these clinical studies has been quite lacking until now.

3. Potential risks of MSC transplantation

So far, clinical and preclinical studies about MSC treatment for chronic liver disease have been conducted, and several problems must be cautiously considered, including the possibility of carcinogenesis and viral transmission. MSCs can secrete various growth factors that encourage tumor cell growth and angiogenesis.⁵⁶ Previous experimental studies showed that the tendency for malignant formation depended on the number of passages. For example, in mouse MSCs, chromosomal abnormalities and transformation into malignant cells, such as sarcoma, have been observed after more than three passages.^{57,58} Furthermore, MSCs may demonstrate telomeric deletions upon numerous passages.⁵⁹ Although the malignant transformation of human MSCs has not yet been observed in clinical trials, the follow-up period was too short for the occurrence of a tumor to be evident in most of them. Therefore, chromosomal integrity must be analyzed before MSCs transplantation to ensure the safety of the procedure.

In contrast to autotransplantation, allotransplantation may involve the risk of viral transmission to the patients.⁴¹ Although viral transmission of parvovirus B19 into BM cells was demonstrated *in vitro*, B19-positive MSC-related viremia has not yet been reported in humans. However, no information is yet available on the transmission of herpes simplex virus (HSV) and cytomegalovirus (CMV) via MSCs *in vivo*. Therefore, both MSC recipients and donors may need to be screened for parvovirus B19, HSV, and CMV because of the possibility of infection in immunosuppressed patients.

FUTURE DIRECTIONS OF MSC TRANSPLANTATION IN LIVER DISEASE

Clinical studies have demonstrated only a moderate benefit, at least in part because of the limited viability of the transplanted cells, irrespective of the cell source. Even some reports reported that less than 1% of transplanted cells may survive because of the inflexibilities of the microenvironment they encounter upon transplantation.⁶⁰ In this section, we will review the strategies that have been utilized to improve the effects of cell therapy in MSC transplantation (Fig. 2).

1. Tissue engineering

The tissue engineering approach aims to allow cell homing and adaptation in the transplanted organ before starting their regeneration, resulting in improved cell survival. The ECM plays a crucial role in cellular organization and function.⁶¹ Several approaches have been investigated, including co-culture and the development of 3-dimensional (3D) systems.^{62,63} It is possible that cells grown in 3D systems would behave more like cells *in vivo* and be implanted directly. These 3D systems can be classified into scaffold-based and scaffold-free systems.

Several synthetic polymers, including poly lactic co-glycolic

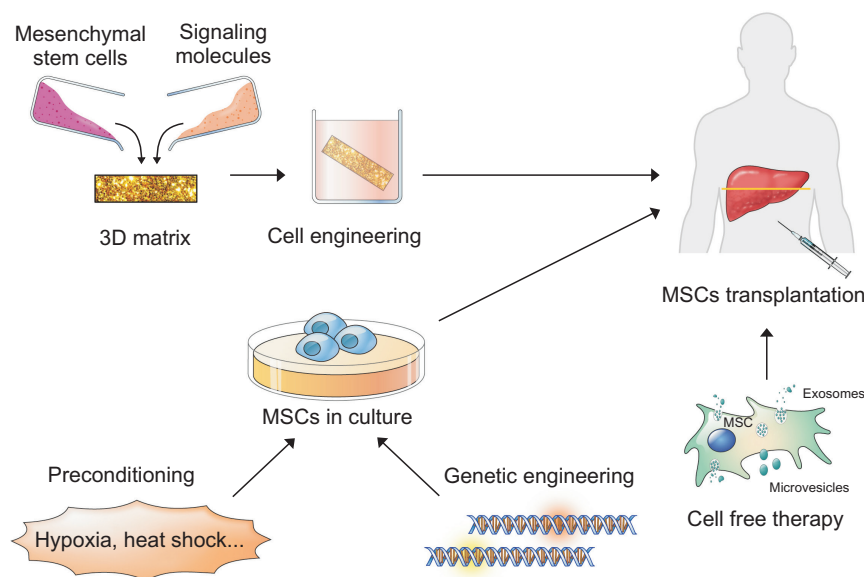


Fig. 2. Strategies for improving the efficacy of mesenchymal stem cell (MSC) therapies. 3D, 3-dimensional.

acid (PLGA), and natural materials such as collagen, have been assessed for their ability to increase the expression of hepatocyte-specific genes in MSCs during hepatic differentiation.⁶⁴ Indeed, modulation of liver function was shown in co-culture of BM-derived MSCs and isolated fresh hepatocytes on a PLGA scaffold. The greatest effect was observed in performance using a 1:5 ratio of MSCs to hepatocytes *in vitro* and *in vivo*.⁶⁵ In addition to scaffold-based 3D systems, the roles of biological scaffolds, such as decellularized tissue, have been evaluated by several groups. Decellularized liver tissue forms an ECM scaffold that can improve MSC engraftment by providing a more physiological environment.⁶⁶

2. Preconditioning to improve cell resistance

During treatment, MSCs are transplanted into pathological disease conditions. In other words, pathological conditions put implanted cells in severe acidic, oxidative, and nutritional stresses.⁶⁷ In this regard, modifying donor cells before transplant helps those cells resist harsh conditions, resulting in improved cell function. Several strategies for preconditioning include promoting a broad pro-survival response through exposing cells to a physical or environmental shock and pharmacological modulators of targeted molecules.^{68,69}

First, thermal preconditioning at 42°C for 1 to 2 hours before transplantation has been demonstrated to promote cell survival *in vivo*. This effect is related to the induction of heat shock protein expression, which inhibits apoptotic pathways.^{70,71} Next, hypoxia, an important feature of MSCs, has been shown to play a crucial role in maintaining stem cell fate, self-renewal, and multi-potency, and cultivating MSCs under hypoxia is an important preconditioning step because it mimics the natural microenvironment of BM.⁷² In this respect, hypoxic precon-

ditioning strategies have been developed to promote defense mechanisms against oxidative stress. Priming MSCs in 0.5% to 3% low oxygen may help to increase engraftment success by inhibiting apoptotic pathways including Akt, B-cell lymphoma (Bcl)-2, and hypoxia-inducible factor (HIF)-1 α and the upregulation of chemokine receptors (i.e., CXCR4 and CX3CR1).⁷²⁻⁷⁴ Although some data have been accumulated by preclinical studies, the response of MSCs to hypoxic conditions is rather contradictory, indicating both damaging and ameliorating effects. Pharmacologic preconditioning of cells before transplantation is another emerging strategy to maintain cell viability after transplantation. For example, antioxidants and HIF-1 α stabilizers contribute to cell survival, while antimycin and mitochondrial electron transport inhibitors have also been described to promote cell survival by activating mitochondrial death pathways.⁷⁵

3. Genetic engineering

Several approaches have been investigated to promote the expression of proteins involved in homing of donor cells.⁷⁶ MSCs have been shown to express low levels of molecules including the homing factor stromal cell-derived factor-1 and chemokine receptors (i.e., CXCR4 and CCR1 receptors).⁷⁷ Genetic manipulation of pro-survival or anti-apoptotic genes including Bcl-2, protein kinase B (Akt/PBK), HGF, and survivin increased MSC survival *in vivo*.⁷⁸⁻⁸¹ It is also known that miRNA can regulate mRNAs, modulating the cellular gene networks, including those involved in cell survival. miRNA overexpression has been shown to enhance MSC survival.^{82,83} However, several problems, including the risk of carcinogenesis, must be carefully considered when applying genetic manipulations.

4. Extracellular vesicles as cell-free therapy

MSCs can secrete soluble molecules with a paracrine effect or release more complex structures called extracellular vesicles (EVs).⁸⁴ EVs exert many of their effects by interaction with the cell surface, internalization, or fusion with the cell membrane. These EVs can be engineered to improve the expression of anticipated activities or introduce specific effector molecules.^{85,86}

MSC-derived EVs improved hepatic injury and inflammation by inactivating the TGF- β /Smad signaling pathway in a CCl₄-induced fibrosis model.⁸⁷ Moreover, EVs derived from human MSCs preserve at least some of the immunomodulatory properties of the cells. A recent study also showed that MSC-derived induced pluripotent stem cell (iPSC)-EVs retain the characteristics of EVs that are usually obtained from tissue-derived MSCs, regardless of origin.⁸⁸ It has been reported that MSC-iPSC-EVs can directly fuse with hepatocytes, increasing the activity of sphingosine kinase-1 and sphingosine-1-phosphate levels and affecting hepatocyte proliferation.⁸⁹ From this perspective, EVs could be a more encouraging therapeutic strategy because they characterize a physically different fraction and transport signals with more predictable effects. However, the complex functions of EVs are still largely unknown. Moreover, further studies are needed to determine how long circulating MSC-EVs survive after administration and what recognition pathways are used by target cells.

CONCLUSIONS

MSC regenerative therapy in chronic liver disease has been shown to be effective via their immunomodulation, differentiation, and anti-fibrosis properties. Many clinical studies have demonstrated the efficacy of MSCs in treating injured hepatocytes by ameliorating tissue fibrosis and improving liver function. However, several concerns remain, including the low migration, poor cell survival, and the risk of carcinogenesis and viral transmission. We reviewed several strategies to enhance their efficacy, including modifying the culture environment and/or priming MSCs along with genetic engineering of cells. In addition, EVs produced by MSCs seem to have therapeutic benefits as a cell-free cell therapy in MSC-based transplantation by preserving at least some of the immunomodulatory properties of the cells.

The prospects of MSC-based cell therapy for chronic liver disease will be determined by standardizing the cell source, culture conditions, administration route, and the outcomes of future large-scale clinical trials.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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