Review Article on Stem Cell and Clinical Application

Mesenchymal stem cells to treat liver diseases

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Abstract: Mesenchymal stem cells (MSCs) are being developed for stem cell therapy and can be efficiently used in regenerative medicine. To date, more than 1,000 clinical trials have used MSCs; of these, more than 80 clinical trials have targeted liver disease. MSCs migrate to damaged liver tissues, differentiate into hepatocytes, reduce liver inflammatory responses, reduce liver fibrosis, and act as antioxidants. According to the reported literature, MSCs are safe, have no side effects, and improve liver function; however, their regenerative therapeutic effects are unsatisfactory. Here, we explain, in detail, the basic therapeutic effects and recent clinical advances of MSCs. Furthermore, we discuss future research directions for improving the regenerative therapeutic effects of MSCs.

Keywords: Cell therapy; liver disease; mesenchymal stem cells (MSCs); regenerative medicine

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Introduction

Mesenchymal stem cells (MSCs) were initially identified in the bone marrow by Friedenstein and coworkers (1), and, since then, they have been isolated from various organs, including the adipose tissue, umbilical cord and cord blood, brain, peripheral blood, synovial membranes, muscle, dermis, and liver (2-6). The International Society for Cellular Therapy (ISCT) defines MSCs as cells that can adhere to plastic; express CD73, CD90, and CD105 as cell surface antigens (≥95% positive); and differentiate into adipocytes, chondroblasts, and osteoblasts under *in vitro* differentiation conditions (7). MSCs are being actively studied for the regenerative treatment of incurable diseases via homing to damaged sites, differentiation into damaged target cells, or alleviation of the death of dying cells. According to ClinicalTrials.Gov, more than 1,000 clinical trials using MSCs have been registered; of these, more than 80 have targeted liver disease.

The liver has a high regenerative potential; however, long-term chronic injury, such as that due to viral hepatitis, alcohol, toxic drugs, and autoimmune attacks, lacks a complete remedy apart from liver transplantation. Since Theise *et al.* (8) found Y chromosome-positive hepatocytes in autopsied livers of women after therapeutic bone marrow allografts, bone marrow-derived cells, including unsorted bone marrow cells (BMCs), hematopoietic stem cells, and MSCs, have been investigated for the treatment of chronic liver diseases (9-14). In addition, the primary hepatocytes or hepatocyte-like cells derived from pluripotent stem cells are being actively explored to develop cell-based regenerative therapies for liver diseases. In this review, we focus only on MSCs that treat liver disease and discuss the potential therapeutic mechanisms, brief recent clinical advances, and future study perspectives to develop more efficient therapeutics.

Potential therapeutic mechanisms of MSCs for hepatic fibrosis

Despite reports revealing that cell therapies using BMCs,

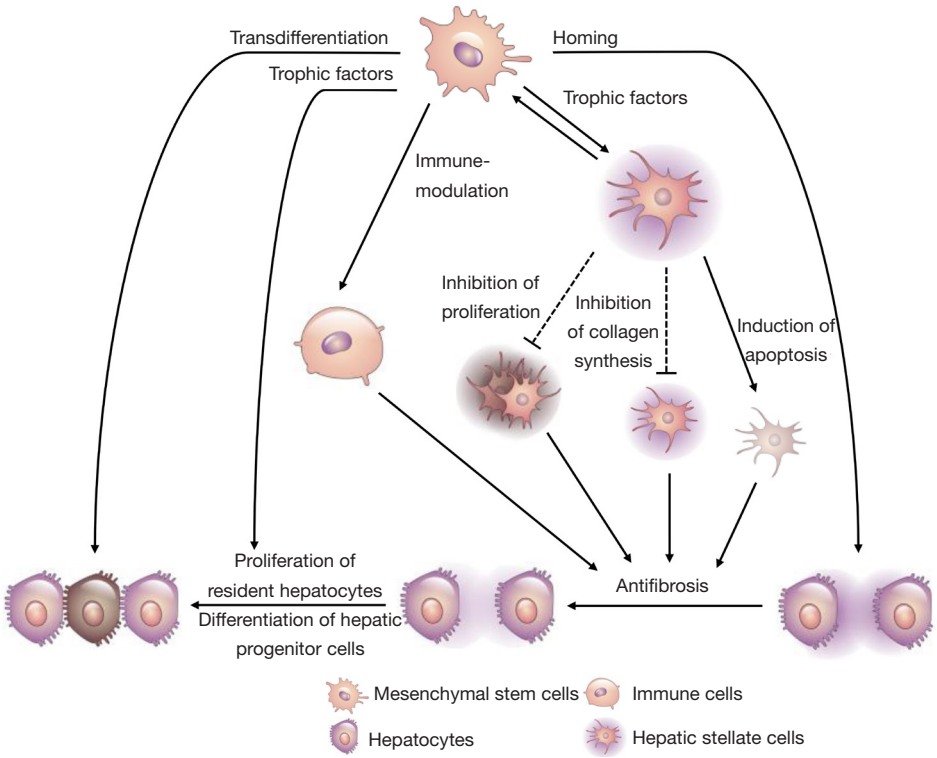

Figure 1 Potential therapeutic mechanisms of MSCs in hepatic fibrosis. The potential protective mechanisms of MSCs include the following: (I) homing into damaged sites; (II) transdifferentiation into hepatocyte-like cells; (III) suppression of immune reactions; (IV) secretion of trophic factors to suppress the activated hepatic stellate cells and increase the proliferation of both resident hepatocytes and hepatic progenitor cells; and (V) antifibrotic action that results from the regulation of activated hepatic stellate cells and immune cells. The shadows represent the ECM that is secreted from the hepatic stellate cells. Modified from Eom *et al.* (15). MSCs, mesenchymal stem cells; ECM, extracellular matrix.

HSCs, and MSCs can improve liver function and alleviate hepatic fibrosis, their precise therapeutic mechanisms remain unclear. In this section, we summarize the potential therapeutic mechanisms underlying the effects of MSCs (*Figure 1*), which have been reported to have relatively diverse therapeutic roles compared to BMCs and HSCs.

Homing of MSCs

Homing is the active migration of HSCs or lymphocytes from the BM or blood toward different organs, antigens, or cytokines via the vasculature. Recently, this term has also been applied to MSCs, considering their ability to migrate to and engraft in the injured tissues (16). Stress signaling from injured tissues triggers the migration of locally or systemically infused MSCs to the damaged site (17). Several molecules that are expressed on the MSC surface facilitate MSC rolling, adhesion, and migration into the tissue. Importantly, MSCs can be detected in the injured tissues after systemic transfusion. Green fluorescent protein (GFP)-labeled MSCs were detected in C-C motif ligand (CCL) 4-treated rat livers after infusion via peripheral or portal veins (18). Adhesion molecules (e.g., integrins, selectins, and endoglin) and chemokine receptors (CCR1, CCR7, and CCR9) are involved in MSC homing (19).

Hepatocyte-like differentiation of MSCs

MSCs possess multilineage differentiation potential for cells of all three germ layers. They can differentiate into hepatocyte-like cells both *in vivo* and *in vitro* in the presence of specific cytokines and growth factors {such as hepatocyte growth factor (HGF), oncostatin M, epidermal growth factor (EGF), insulin-like growth factor (IGF), fibroblast growth factor (FGF)-2/-4, and leukemia inhibitory factor] and chemical compounds [such as dexamethasone,

insulin-transferrin-selenium, retinoic acid, nicotinamide, norepinephrine, sodium butyrate, and dimethyl sulfoxide (20)]}. Moreover, MSCs can also differentiate into the hepatocyte-like cells upon culturing with liver cells in prohepatogenic conditions (21) or in pellet cultures (22). Functionally transformed cells express hepatocyte nuclear factors (HNF)-3, GATA4, cytokeratin (CK) 19, transthyretin, alpha-fetoprotein, albumin, and CK18, which can be analyzed via flow cytometry, reverse transcription polymerase chain reaction, immunostaining, and western blotting (20).

Direct intrahepatic administration of human MSCs resulted in the differentiation of the majority of MSCs into hepatocyte-like cells in allyl alcohol-treated rat livers (23). Furthermore, although the MSC-derived hepatocyte-like cells are morphologically and functionally similar to hepatocytes, sufficient data suggesting that MSCs completely mimic hepatocytes *in vivo* are lacking. Moreover, studies have indicated that, in addition to their transdifferentiation into hepatocytes or hepatocyte-like cells, MSCs are able to secrete trophic factors that facilitate liver regeneration and strong immune suppression, which is important for engraftment (24).

Immunosuppressive potential of MSCs

MSCs can exhibit potent anti-inflammatory properties, such as downregulating immune cells and enhancing the secretion of immunomodulatory factors (25). They can directly inhibit the adaptive immune cells, can suppress B and T cell proliferation and function, induce apoptosis of T cells via programmed death 1, and upregulate regulatory T cell (Tregs) proliferation and functionality. Additionally, MSCs can control innate immunity by inhibiting monocyte differentiation, dendritic cell (DC) activation, and natural killer (NK) cell activation (25).

Furthermore, MSCs can secrete immunomodulatory factors, such as nitric oxide (NO), prostaglandin E2 (PGE2), indoleamine 2,3-dioxygenase (IDO), human leukocyte antigen (HLA)-G, and IL-6 and -10 (25). Murine MSC-derived NO can inhibit T cell proliferation (26). PGE2 plays multifaceted roles in cell proliferation, apoptosis, tissue repair, angiogenesis, inflammation, immune surveillance, and cancer (27-29). It augments the synthesis of the anti-inflammatory cytokine IL-10 and decreases the production of the proinflammatory cytokines TNF-α, IFN-γ, and IL-12 by DCs and macrophages. Moreover, it suppresses the proliferation and differentiation of T cells, macrophages, and monocytes as well as the cytotoxic activity of NK cells and cytotoxic T lymphocytes (30-32). PGE2 directly inhibits the synthesis of IL-2, thereby promoting Th2 immune responses rather than Th1 responses, and induces differentiation and expansion of Treg cells (33). IDO and HLA-G are important for immune tolerance; they suppress the proliferation of B cells and effector T cells, maturation of DCs, and cytotoxicity of NK cells (34,35). MSCs can potentiate macrophage polarization and generation of tolerogenic DCs (26). IL-6 secreted by MSCs can inhibit T cell-mediated immunity by disrupting monocyte differentiation into DCs (36,37). In addition, IL-6 secreted by MSCs protects the lymphocytes and neutrophils against apoptosis (26,38). Thus, MSCs play a crucial role in immunosuppression, which makes them an attractive therapeutic candidate for hepatic fibrosis.

MSC therapy may trigger tissue regeneration, repair, and remodeling. MSCs exert their effects by secreting bioactive molecules that are responsible for tissue regeneration, repair, and angiogenesis. These soluble factors, known as trophic factors, are associated with not only regeneration but also reductions in inflammation, apoptosis, and fibrosis in the injured tissues (39). MSC-derived trophic factors, including growth factors [brain-derived neurotrophic factor (BDNF), glial cell-derived neurotrophic factor, EGF, FGF-2/-4/-7/-9/-17, HGF, IGF-1, nerve growth factor, and platelet-derived growth factor (PDGF)], cytokines (IFN-γ, TNF-α, and IL-1α/β, -2, -6, -8, -10, -12, and -13), chemokines (various CCLs and C-X-C motif ligands), and antiapoptotic and angiogenic factors (VEGF), facilitate the regeneration of specific tissues (40).

Antifibrotic activities of MSCs

Fibrosis is a cardinal feature of chronic inflammation. Hepatic fibrosis results from chronic liver injury caused by alcohol, drugs, viral infection, and metabolic or inherited diseases. It is characterized by excessive ECM deposition; hepatic stellate cells are key fibrogenic cells in this process. Activated hepatic stellate cells stimulate the neighboring cells and initiate inflammatory responses. MSCs are effective in treating fibrosis due to their antifibrotic and immunosuppressive properties (41-44). Recently, MMPs, which can be inhibited by tissue inhibitor of MMP (TIMP), have been demonstrated to reduce liver fibrosis. MSCs can upregulate the expression of MMPs (43), which can degrade ECM, and downregulate TIMP expression (44); thus, MSCs regulate the balance between MMPs and TIMP to control

ECM remodeling and reduce liver fibrosis. Additionally, MSCs can suppress the proliferation and activation of hepatic stellate cells via indirect mechanisms or direct cell–cell contact, inhibit collagen synthesis, and suppress overactive immune reactions; MMPs can breakdown the ECM, resulting in the apoptosis of hepatic stellate cells (42). Collectively, these mechanisms alleviate liver fibrosis.

Antioxidant activities of MSCs

Owing to their immunosuppressive, antifibrotic, and trophic properties, MSCs have also been evaluated for their antioxidant activity. Several studies have suggested that MSCs mediate strong antioxidant effects in various animal models (45-48). Typically, carbon tetrachloride (CCl_4), tert-butyl hydroperoxide, paracetamol, alcohol, and thioacetamide (TAA) are used to induce oxidative stress in experimental animal models. In this process, reactive oxygen species (ROS), reactive nitrogen species, and free radicals act as mediators to initiate inflammation, hepatocellular damage, and fibrosis, although the small amount of ROS produced via the oxidation–reduction chain (cellular respiration) in the cell is crucial in cell signaling and homeostasis (49,50). MSCs can alleviate chemically induced (CCl_4 and TAA) oxidative stress *in vitro* and *in vivo* (46,48). Transplantation of MSCs suppresses oxidative stress and enhances antioxidant activity by increasing the expression of superoxide dismutase, thereby reducing hepatocyte apoptosis (46,48). MSCs can surmount oxidative stress in not only hepatic fibrosis but also other diseases, such as dextran sulfate sodium-induced colitis and neurodegenerative diseases (e.g., Friedreich's ataxia) (51). Collectively, these data highlight the efficacy of MSC infusion for the treatment of liver disease.

Clinical application of MSCs to treat liver diseases

According to ClinicalTrials.Gov, more than 80 clinical trials evaluating the treatment of liver disease using MSCs have been completed or are in progress. In *Table 1*, clinical studies, focusing on the patient group, source of MSC, injection route, and main improvements, are summarized (52-71). Despite differences in patient group, injection cell dose, MSC source, graft type, administration route, and study design, no significant side effects were observed in the reported clinical studies. Patient groups included acute-on-chronic liver failure (ACLF) and cirrhosis due to alcohol, HBV or HCV, primary biliary cholangitis (PBS), and autoimmune diseases-induced cirrhosis. In early studies, autologous bone marrow-derived MSCs have mainly been used; however, recently, umbilical cord, umbilical cord blood, and bone marrow-derived allogenic MSCs have also been used. Peripheral veins are mainly used for stem cell transplantation along with the portal vein and intrasplenic, intrahepatic, and hepatic arteries. Except for two other clinical outcomes, MSC transplantation typically resulted in improvement in liver functions, including AST, ALT, GGT, serum albumin, and bilirubin levels and histological score.

Possible risks of MSC therapy

Although MSCs have been reported to improve hepatocyte and liver function in laboratory, preclinical, and clinical trials, there are some considerations that must be noted. As described earlier, MSCs can migrate to the damaged liver and, thus, exert immunosuppressive, antifibrotic, and antioxidant effects to repair this damaged organ; however, these MSCs may exhibit fibrogenic activity. When MSCs were cocultured with the human hepatoma cell line HuH-7 in a hepatogenic differentiation medium, the MSCs expressed alpha-smooth muscle actin (α-SMA), a marker for myofibroblast differentiation. Moreover, after intrahepatic administration of MSCs into partially hepatectomized NOD/SCID mice, the MSCs expressed vimentin and α-SMA in the absence of hepatic markers (72). The transplanted MSCs exhibited very low engraftment rates in normal and acutely injured NOD/SCID mice, compared to chronically injured mice; a significant number of the MSCs injected into the site of acute liver injury exhibited a myofibroblast-like morphology (73). Collectively, these results suggest that the fibrogenic potential of MSCs could result in increased hepatic fibrosis under certain circumstances. Therefore, prior to the use of MSCs for the treatment of hepatic fibrosis, the issue of MSC-induced fibrosis needs to be evaluated in depth.

MSCs can migrate to tumors and, then, incorporate into the tumor stroma (74,75). They promote the proliferation of pre-existing tumor cells via differentiation into tumor-associated fibroblasts (TAFs) in the tumor microenvironment, inhibition of the antitumor immune response, promotion of neovascularization and tumor metastasis, and inhibition of tumor cell death (76). Transforming growth factor-β (TGF-β), commonly secreted by tumor cells, induces differentiation of MSCs into myofibroblasts, which express α-SMA, tenascin C, and

Table 1 Clinical studies of MSCs in liver diseases

Study	Patient group	MSC source	Injection route	Main improvement
Mohamadnejad [2007]	Decompensated liver cirrhosis (n=4)	Autologous BM	Peripheral vein	Creatinine and MELD score
Kharaziha [2009]	Liver cirrhosis (n=8)	Autologous BM	Portal vein (n=6) Peripheral vein (n=2)	Creatinine, prothrombin time, and MELD score
El-Ansary [2010]	Decompensated liver cirrhosis due to HCV or HBV (n=12)	Autologous BM	Intrasplenic (n=6) Peripheral vein (n=6)	Creatinine, prothrombin time, albumin, bilirubin, and MELD score
Amer [2011]	Decompensated liver cirrhosis due to HCV (n=40)	Autologous BM	Intrasplenic (n=10) Intrahepatic (n=10)	Ascites, peripheral edema, albumin, MELD score, and Child-Pugh score
Peng [2011]	ACLF caused by HBV (n=158)	Autologous BM	Hepatic artery	Prothrombin time, albumin, bilirubin, and MELD score
El-Ansary [2012]	Decompensated liver cirrhosis due to HCV (n=25)	Autologous BM	Peripheral vein	Albumin and MELD score
Shi [2012]	ACLF-associated HBV (n=43)	Allogeneic UC	Peripheral vein	Albumin, prothrombin time, bilirubin, ALT, survival rates, and MELD score
Zhang [2012]	Decompensated liver cirrhosis due to HBV (n=45)	Allogeneic UC	Peripheral vein	Albumin, bilirubin, MELD score, and ascites
Amin [2013]	Post-HCV (n=20)	Autologous BM	Intrasplenic	Albumin, prothrombin time, bilirubin, AST, ALT, and MELD score
Mohamadnejad [2013]	Decompensated liver cirrhosis (n=25)	Autologous BM	Peripheral vein	None
Wang [2013]	UDCA-resistant PBC (n=7)	Allogeneic UC	Peripheral vein	Alkaline phosphatase and γ-glutamyltransferase (GGT) levels
Jang [2014]	Alcohol-related liver cirrhosis (n=11)	Autologous BM	Hepatic artery	MELD score and liver histology
Salama [2014]	Post-HCV end-stage liver disease (n=40)	Autologous BM	Peripheral vein	MELD score and Child-Pugh score
Wang [2014]	UDCA-resistant PBC (n=10)	Allogeneic BM	Peripheral vein	ALT, AST, GGT, and IgM
Suk [2016]	Alcohol-related liver cirrhosis (n=72)	Autologous BM	Hepatic artery	Histologic fibrosis and Child-Pugh score
Detry [2017]	Liver transplant recipients	Allogenic BM	Peripheral vein	No difference in rate of infection or de novo cancer
Lanthier [2017]	Decompensated alcoholic hepatitis (n=58)	Autologous BM	Hepatic artery	None
Lin [2017]	ACLF-associated HBV (n=110)	Allogeneic BM	Peripheral vein	Bilirubin, MELD score, and survival rates
Liang [2017]	Autoimmune diseases-induced cirrhosis (n=26)	Allogeneic UC (n=23), UCB (n=2), or BM (n=1)	Peripheral vein	Bilirubin, albumin, prothrombin, and MELD score
Xu [2019]	ACLF-associated HBV (n=110)	Allogeneic UC	Peripheral vein	Bilirubin, ALT, AST, and MELD score

ACLF, acute-on-chronic liver failure; BM, bone marrow; HBV, hepatitis B virus; HCV, hepatitis C virus; PBC, primary biliary cholangitis; RCT, randomized controlled trial; UC, umbilical cord; UDCA, ursodeoxycholic acid

fibroblast surface protein; it also increases the expression and secretion of growth-stimulating factors, such as CCL5/RANTES and stromal cell-derived factor 1 (SDF-1). Recently, researchers found that MSCs can differentiate into carcinoma-associated fibroblasts or TAFs, which express α-SMA and promote tumor growth by inducing neovascularization and expressing tumor-stimulating factors (77-81). In addition, MSCs express various antiapoptotic and prosurvival factors, including VEGF, FGF-2, PDGF, HGF, BDNF, SDF-1α, IGF-1 and -2, TGF-β, and IGF binding protein-2, through which they promote tumor growth by suppressing tumor apoptosis (40,82-86). Hypoxia, which usually occurs in tumor regions and sites of inflammation, can stimulate MSCs to produce VEGF, FGF2, HGF, IGF1, CX3CR1, and CXCR4; these factors are known to be able to protect tumor cells in tumor microenvironments (87-90).

Future prospects of MSC therapy for hepatic fibrosis

MSC priming

MSCs are known to migrate to damaged areas and express various immune cell-regulating factors, such as NO, PGE2, IDO, IL-6 and -10, and HLA-G, upon exposure to inflammatory cytokines, such as IFN-γ, TNF-α, and IL-1β (91); however, depending on the concentrations and types of inflammatory cytokines in the damaged microenvironments, MSCs may mediate myofibroblast activity (72,73). Therefore, to improve the functional activity and reduce the unwanted properties of MSCs, they can be primed with inflammatory cytokines *in vitro* prior to infusion. IFN-γ-primed MSCs inhibit the proliferation of activated T and NK cells by inducing IDO expression (92). In addition, HLA-A, -B, -C, and -E were elevated in IFN-γ-primed MSCs, which were less susceptible to NK cell-mediated killing and increased immunosuppression (93). Moreover, IFN-γ-primed MSCs can induce the expression of TNF-related apoptosis-inducing ligands and, thus, be used to treat cancer. Investigating the interactions of MSCs with the microenvironments of damaged areas in disease models can provide insights into the precise mechanisms underlying the therapeutic effects of MSCs, which can be applied to enhance these effects in regenerative medicine.

MSC-derived exosomes

Paracrine action is one of the key mechanisms that can be evaluated to explore the therapeutic potential of MSCs (94,95). In accordance with the effects of MSC transplantation, MSC-conditioned medium can improve liver function via paracrine factors, which comprise free soluble factors and extracellular vesicles (EVs). EVs are divided into microvesicles (0.1–1 mm in diameter) and exosomes (40–100 nm in diameter) (96,97). Exosomes originate from the inward budding of late endosomes known as multivesicular bodies; they carry various nucleic acids, lipids, and proteins. Most cells secrete EVs in response to triggers or environmental circumstances, to exchange information between the cells (98). More than 850 unique gene products and 150 miRNAs have been identified as the cargo of MSC-derived exosomes; they have been implicated, via mass spectrometry, antibody array, and microarray, in cell-to-cell communication, immune regulation, and tissue repair (99,100). Several studies have reported that MSC-derived exosomes inhibit hepatocyte epithelial-to-mesenchymal transition and collagen production (101), increase hepatocyte proliferation (102) and liver function (103), and stimulate host responses to initiate repair (104-110). Moreover, as exosomes can be more easily produced and stored than MSCs, greater quality control may be possible; exosomes can be repeatedly administered as drug; thus, they could maintain and improve their therapeutic effects more consistently over time than MSC therapy.

Genetic modification of MSCs

Despite several advantages of MSCs in treating human diseases, MSC therapy is still limited by low cell survival, engraftment, and homing efficiency to the damaged site as well as by insufficient secretion of effector molecules. To overcome these limitations, researchers have investigated genetic modifications in MSCs. Diverse prosurvival genes, such as Akt (111), heat shock protein 20 (112), SDF-1β (113), hypoxia-inducible factor-1α (114), and FGF-2 (115), have been inserted into MSCs, to prolong their survival in the target organ. Moreover, SDF-1- and CXCR4-engineered MSCs exhibited more efficient homing and engraftment in target organs, followed by enhanced regeneration of the liver, kidney, skin, and brain (116-120). To treat hepatic fibrosis, MSCs can be modified using decorin (DCN) (121), urokinase-type plasminogen activator (uPA) (122), and IL-10 (123). DCN-MSCs induce histological improvements in hepatic fibrosis and aid in the recovery of liver function in rats with TAA-induced cirrhosis via suppression of

TGF-β/Smad signaling (121). MSCs expressing uPA exhibited markedly lower expression of α-SMA, TGF-β1, and collagen types I and III but increased expression of MMP-2, -3, and -9, HGF, and proliferating cell nuclear antigen; moreover, they ameliorated hepatic fibrosis (122). In addition, in liver-fibrotic rats, IL-10-MSCs improved liver histopathology and liver function but suppressed inflammation and the activation of hepatic stellate cells (123). Therefore, genetic manipulation of MSCs may greatly enhance their therapeutic functions by increasing their survival and migration to the target organs and inducing their factor expression with high therapeutic potential.

Three-dimensional (3D) culture

To increase their survival and therapeutic potential, MSCs can be cultured in 3D systems with or without biomaterial scaffolds. To date, a variety of scaffolds manufactured from natural ECM components or synthetic materials as well as decellularized organ/tissue matrices have been used to enhance the proliferation and differentiation of stem cells (124-127). Moreover, 3D spheroid MSC cultures without scaffolds have been reported to improve the differentiation efficiency of MSCs (128,129) and enhance their therapeutic potential in liver disease, peritonitis, kidney injury, and myocardial infarction (129-132). Spheroid 3D culture of MSCs increased the expression of antifibrotic factors, such as IGF-1, HGF, and IL-6; furthermore, the MSCs protected the hepatocytes injured with CCl_4 *in vitro* more effectively than 2D cultured cells. In addition, 3D spheroid-derived MSCs ameliorated hepatic fibrosis and improved liver function to a greater extent than 2D-cultured MSCs.

Conclusions

Cell-based therapies with BMCs, HSCs, hepatocytes, and MSCs are being actively used to replace liver transplantation, which is the ultimate treatment for end-stage liver disease. MSCs are being evaluated as a very suitable cell source for cell therapies that have been reported to improve the liver function. They migrate to the damaged liver tissues, differentiate into hepatocytes, reduce liver inflammatory responses and liver fibrosis, and exhibit antioxidant effects. More than 80 clinical studies on the treatment of liver disease with MSCs have been completed or are in progress; the reported clinical results suggest that MSCs are safe, have no side effects, and can improve liver function. However, despite the proven regenerative value of MSCs, their regenerative therapeutic effect is unsatisfactory. Therefore, to improve the regenerative therapeutic effects of MSCs, research on MSC-priming, MSC-derived exosomes, genetic modification, and 3D-culture methods is warranted. In addition, to improve the therapeutic efficacy of MSCs, further robust preclinical and clinical studies are necessary to standardize the optimal number of transplanted MSCs, their delivery route, and their administration frequency.

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Footnote

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