



The clinical application of mesenchymal stem cells in liver disease: the current situation and potential future

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Abstract: Liver disease is a major health issue which present poor clinical treatment performance. Cirrhosis and liver failure are common clinical manifestations of liver diseases. Liver transplantation is recognized as the ultimate and most efficient therapy to the end stage of liver disease. But it was limited by the shortage of honor organs and high cost. Nowadays, stem cell therapy gained more and more attention due to its attractive efficacy in treating liver disease especially in cirrhosis during the clinical trials. Mesenchymal stem cell (MSC) can be differentiated into hepatocytes, promote liver regeneration, inhibit liver fibrosis and induce liver apoptosis, particularly via paracrine mechanisms. This review will highlight recent clinical applications of MSC, providing the available evidence and discussing some unsolved questions in treating liver disease.

Keywords: Mesenchymal stem cells (MSCs); liver disease; cirrhosis

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Introduction

Liver disease is a major health problem and caused by various etiologies around the world. Acute liver failure (ALF), liver cirrhosis and liver cancer are the main common liver diseases. ALF is a fatal clinical syndrome characterized by extensive hepatocyte necrosis and inflammatory infiltration caused by hepatotoxic drugs, immune-mediated attacks or viral infections (1,2). In the clinical, ALF progressed rapidly with a poor presentation to medical treatment (3). Cirrhosis is the end stage of liver fibrosis and prone to various complications including infection, hemorrhage, hepatic encephalopathy (HE) and spontaneous peritonitis, etc. According to the latest global report, liver cancer ranked sixth for cancer incidence and fourth for

cancer deaths in 2015 (4). Hepatocellular carcinoma (HCC) accounts for 85–90% of primary liver cancer (5). At present, liver transplantation is recognized as the most effective treatment for advanced liver diseases. However, there is a prevailing contradiction between urgent clinical need and the shortage of donor livers. Therefore, new effective methods for treating liver diseases is urgently needed.

In recent years, mesenchymal stem cells (MSCs) have been proposed as an alternative approach to treat liver diseases. MSCs can be defined as pluripotent cells with the capacity of self-renewal, which can give rise to many unique, differentiated mesenchymal cell types (6). At present, the MSCs applied in clinical therapy and basic experimental research are mainly derived from bone marrow, umbilical cord, adipose tissue, amniotic fluid, menstrual blood, etc.

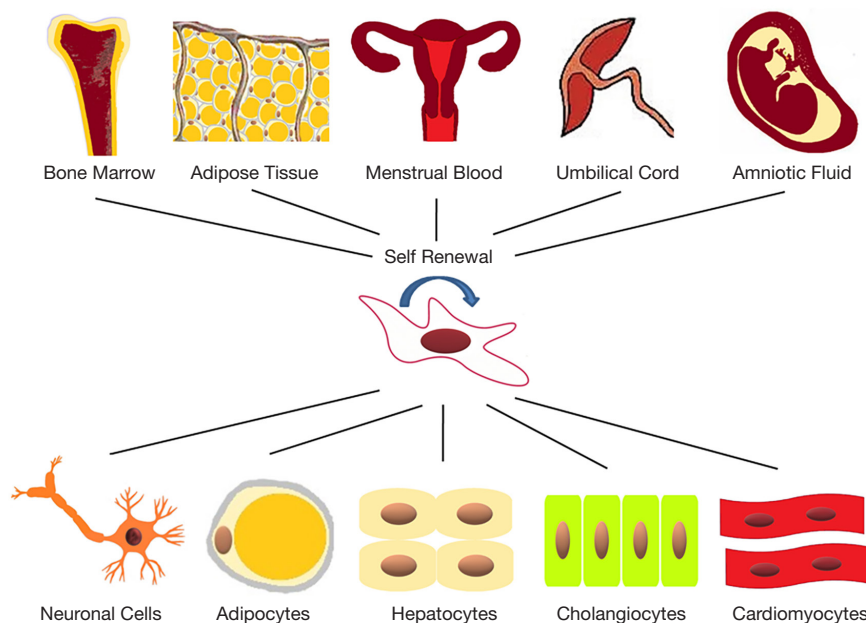


Figure 1 MSCs derived from different tissues develop into multiple cell types *in vitro*. MSCs are most commonly derived from bone marrow, adipose tissue, menstrual blood, umbilical cord and amniotic fluid. MSCs can be induced different into multiple cell types such as neuronal cells, adipocytes, hepatocytes, cholangiocytes and cardiomyocytes.

(7-9). As shown in *Figure 1*, MSCs have the potential to differentiate into chondrocytes, osteocytes, and adipocytes, which show significant effect in regenerative medicine (10). Furthermore, MSCs have low inherent immunogenicity and can modulate immune responses by interacting with various immune cells (11). The homing capacity is the key to the effective application of MSC in clinical treatment, which was defined as blocking MSCs in the tissue vasculature and then migrating across the endothelium (12). The present study demonstrated that stem cell therapy was a therapeutic strategy in liver disease.

In this review, we aim to discuss available evidence and highlight some unsolved questions of stem cells for treating liver disease. This work will focus on the clinical application of MSCs in liver disease.

The mechanism of MSC in tissue repair and regeneration medicine

In previous study, stem cell therapy for liver disease has been proved to be effective in both basic and clinical research. MSCs were mostly applied in liver cirrhosis and shown a better therapeutic effect in compensatory period of liver disease. According to present studies,

stem cell therapy shown significant improvement in liver function through anti-apoptosis and immune regulation. MSC can differentiate into hepatocytes *in vivo* and play a key therapeutic role in the treatment of liver fibrosis by secreting various immunomodulatory factors. After MSCs therapy, antiapoptotic factors including hepatocyte growth factor (HGF) and insulin-like growth factor (IGF-1) were elevated with the same promotion in angiogenetic and mito-genetic factors (13).

In vitro experiments, MSCs can promote apoptosis of hepatic stellate cells and inhibit collagen synthesis. Direct coculture of endothelial progenitor cells (EPCs) and MSCs *in vitro* enhanced cell proliferation and angiogenic capacity, PDGF and Notch signaling pathways were involved in this effect (14). In indirect coculture experiment, MSCs inhibited LX2 (hepatic stellate cell line) proliferation through secretion of inflammatory factors [interleukin-6 (IL-6), IL-8, HGF, growth-related oncogene and osteoprotegerin] (15). MSCs participated in the cell communication directly or indirectly through paracrine function.

Hepatic progenitor cells (HPCs), also named hepatic stem cell, possess an extremely low percentage in adult liver. When liver injured, HPCs can differentiate into both

hepatocytes and cholangiocytes.

The application of MSCs in ALF

In the clinical, ALF progressed rapidly with a poor presentation to medical treatment (3). In recent years, the incidence of liver failure caused by herbal medicine has increased significantly.

It has been demonstrated that excessive inflammatory response plays a key role in pathogenesis and prognosis of ALF (16). During the progress of ALF, the domestic Kupffer cells (KCs), dendritic cells (DCs), and natural killer (NK) cells are highly activated, simultaneously the monocytes/macrophagocytes and the neutrophils are recruited in liver tissue (17). Another report demonstrated that activated KCs released high levels of TNF- α , IL-1, and IL-6 in LPS induced ALF models (18). The systemic inflammation could stimulate hepatocytes necrosis and apoptosis.

Many studies have confirmed the role of MSCs in the treatment of ALF animal models. MSCs can reduce the mortality, improve liver functions, inhibit hepatocytes apoptosis and promote proliferation (19,20). Previous studies demonstrated that MSCs showed therapeutic effect in ALF by immunoregulation. Firstly, MSCs can inhibit inflammation and alleviate liver injury by regulating inflammatory cytokine levels. Chen *et al.* indicated that MenSC could down-regulate the expression of TNF- α , IL-6, and IL-1 β in mice models (21). Zhu *et al.* showed that BM-MSCs reduced the levels of TNF- α , IFN- γ and IL-4 (22). Secondly, MSCs inhibit the levels of inflammatory cytokine released by T cells, B cells, DCs and NKs cells (23-25). On the other hand, MSCs can enhance hepatocyte proliferation in liver failure models. Liu *et al.* showed that PGE₂ secreted by MSCs enhanced hepatocyte proliferation by YAP and mTOR signaling (19). Shi *et al.* demonstrated that the DLL-4 secreted by Human BM-MSC promoted the proliferation of biliary epithelium cells in ALF pigs and rats (26). Although multiple MSCs can differentiate into hepatocyte-like cells *in vitro* (27-29), only few part (<4.5%) of transplanted MSCs differentiated into hepatocyte-like cells in ALF pigs (26).

Currently, the application of MSCs in ALF is limited to basic research. But it is obvious that MSCs have the capacity of promoting liver regeneration and suppressing inflammation. Comparing to control group, BM-MSCs effectively reduced the levels of ALT and ALB after 1 week of treatment (30). All these studies indicated the broad prospects of MSCs application in the clinical treatment of ALF.

The application of MSCs in cirrhosis

Liver fibrosis is a chronic disease caused by various etiologies, including viral infection, drug damage, alcohol abuse and immunological diseases. Chronic liver damage leads to excessive extracellular matrix (ECM) deposition through cycles of hepatocytes apoptosis, inflammation and repetitive damage repair. Cirrhosis is the end stage of progressive fibrosis that lack of effective comprehensive medical treatment. MSCs have the capacity of differentiating into hepatocyte-like cells and secreting factors to regulate immune. Thus, MSCs participate in tissue repair through direct and indirect approach.

It has been reported that MSCs alleviate the processes of epithelial-mesenchymal transition (EMT) and contribute to liver regeneration through differentiation, immune regulation and secretion (31). At present, BM-MSCs are the most widely used in clinical application.

A few clinical trials have been conducted to evaluate the curative effect of MSCs treating liver diseases (*Table 1*). Autologous BM-MSCs transplantation was effective in improving liver function and Child-Pugh scores in patients with liver cirrhosis (32). Autologous BM-MSCs were investigated to improve histologic fibrosis and liver function in patients with alcoholic cirrhosis (34,35). Comparing to one-time transplantation, there was no improved results in fibrosis quantification in two-time BM-MSC transplantation (34). After autologous BM-MSCs therapy, serum albumin levels and total protein were elevated. In SHUJI TERAI's study, α -Fetoprotein (AFP) and proliferating cell nuclear antigen (PCNA) expression was significantly elevated in liver biopsy tissue after autologous BM-MSCs therapy (32). It was reported that AFP and PCNA participate in the process of hepatocyte proliferation (42). MSCs can differentiate into hepatocytes, effectively promoting liver regeneration. In another clinical trial, regulation of Treg/Th17 cell balance was investigated in treating liver cirrhosis (36). Present evidences demonstrated that autologous BM-MSCs can activate T cell receptors and rebuild immunological tolerance (43). Paracrine function of MSCs regulates immune response and promotes liver regeneration. In Mehdi Mohamad Nejad's research (37), autologous BM-MSC transplantation probably has no beneficial effect in decompensated cirrhotic patients. Meaningfully, repeated autologous BM-MSCs therapy improved liver function of patients with decompensated liver cirrhosis after splenectomy (44). In HCV-related end-stage liver disease, MSCs therapy also shown a satisfactory tolerability and beneficial effects on liver synthetic functions

Table 1 MSCs in clinical trials treating liver diseases

Cell source	patient population	Number of patients	Follow-up	Efficacy	Discussion on mechanism	Limitations	Publication year and references
Autologous BM-MSCs	Liver cirrhosis	9 treatment	24W	Improved serum albumin levels, total protein levels and Child-Pugh scores	A-Fetoprotein and PCNA elevated	Without control; no track of MSCs	2006 (32)
Autologous BM-MSCs	Chronic HBV-induced liver failure	53 treatment; 105 control	192W	Short-term efficacy was favorable, but no long-term improvement; Reducing incidence of HCC and mortality	Not elucidated	The precise mechanism was not elucidated	2011 (33)
Autologous BM-MSCs	Alcoholic cirrhosis	11 treatment	12W	Induces a histological and quantitative improvement	Tgf- β 1, collagen I and α -SMA decreased	Without control; no track of MSCs	2012 (34)
Autologous BM-MSCs	Alcoholic cirrhosis	37 treatment (18 one-time, 19 two-time); 18 control	6M	Improved histologic fibrosis and liver function	Not elucidated	The precise mechanism was not elucidated	2016 (35)
Autologous BM-MSCs	HBV-related cirrhosis	20 treatment; 19 control	24W	Improved liver function	Regulation of Treg/Th17 cell balance	The effect of BMSCs from health not elucidated	2014 (36)
Autologous BM-MSCs	Decompensated cirrhosis	15 treatment; 12 received placebo	12M	No beneficial effect	Meld scores in the span of 1 year might be related to the natural course of cirrhosis	The number of enrolled patients was limited	2014 (37)
Autologous BM-MSCs	HCV-related ESDL	20 treatment; 20 control	3M	Improved liver synthetic functions and hepatic fibrosis	Combination of G-CSF enhanced the effect	Need further study	2014 (38)
UC-MSC	HBV- decompensated cirrhosis	30 treatment; 15 control	1Y	Improved liver function, reduce ascites	Higher level of serum HGF in treatment group	Need further study	2012 (39)
UC-MSC	HBV-related ACLF	24 treatment; 19 control	72W	Increased the survival rates; reduced MELD scores	Promote proliferation and enhance the resident hepatocyte function	No histological alterations	2012 (40)
UC-MSC	PBC	7 treatment	48W	Alleviated symptoms such as fatigue and pruritus; down-regulated serum ALP and γ -GT levels	Not elucidated	The number of enrolled patients was limited	2012 (41)

MSC, mesenchymal stem cell; BM-MSCs, bone marrow-derived mesenchymal stem cell; PCNA, proliferating cell nuclear antigen; HBV, hepatitis B virus; TGF- β 1, transforming growth factor β 1; Treg, regulatory T cells; Th, T helper cells; MELD, model for end-stage liver disease; ESDL, end-stage liver disease; GSF, galactosemic fibroblast; UC-MSC, umbilical cord-derived mesenchymal stem cell; HGF, hepatocyte growth factor; ACLF, acute-on chronic liver failure; ALP, alkaline phosphatase; γ -GT, γ glutamyl transferase; W, week, M, month, Y, year.

and hepatic fibrosis (38). The efficacy of autologous BM-MSCs was connected to age and physical condition which make a close relation to differentiative capacity (39,45). Insufficient enrolled patients may be one of the limitations in the study. Future randomized controlled trials need to expand number of enrolled patients to confirm the efficacy of MSCs therapy in liver disease. To be concerned, autologous BM-MSC therapy couldn't achieve acceptable long-term effects on prognosis (33). The reasons for the poor long-term efficacy may be as follows: the number of autologous BM-MSCs were limited; the homing ability is poor that MSCs could not reach the effective amount in liver (46).

UC-MSC can be obtained free and amplify to a large number. It has been reported that UC-MSC transplantation alleviate symptoms of various autoimmune diseases (47,48). In a 1-year follow-up clinical research, UC-MSC transplantation has been proved to be safe and could improve liver function and reduce ascites in patients with decompensated liver cirrhosis (39). Even in ACLF patients, Shi *et al.* (40) have shown that UC-MSC transfusions significantly increased the survival rates. UC-MSCs show a more beneficial immunogenic profile and stronger overall immunosuppressive potential than BM-MSCs (49). After UC-MSC therapy, liver function was improved, that serum albumin levels increased and bilirubin levels decreased. UC-MSC treatment also improved liver function and patient's quality of life in primary biliary cirrhosis (PBC) (41). UC-MSC therapy lowered serum alkaline phosphatase and γ -glutamyltransferase levels and alleviate fatigue and pruritus symptom in PBC patients. Comparing to BM-MSC, adipose-derived stromal cells (ADSCs) can be obtained from healthy donors freely and cultured to expand sufficient numbers. During cell amplification, ADSCs could maintain the characteristics of stem cells without losing their differentiation capacity (50). During the past few years, ADSCs have been used as a therapeutic strategy for tissue repair and immune modulation (51). ADSCs shown anti-inflammatory effect and secrete various factors to promote regeneration. ADSCs have been displayed as a feasible therapeutic strategy to alleviate liver damage (11,52). But there aren't many clinical trials using ADSCs to treat liver disease.

Human menstrual blood-derived stem cells (MenSCs) are isolated from menstrual fluids with the advantage of simple operation, easy obtainment, safe and painless. MenSCs have been used to treat several diseases such as stroke, type 1 diabetes, premature ovarian failure and myocardial infarction (53-56). Previous study described that MenSCs can be differentiated into functional hepatocyte-like cells (57). In mice experiment, MenSCs shown an

antifibrotic effect in liver fibrosis (9). At present, there are few clinical applications of MenSCs in liver disease. More clinical trials should be conducted in the future study.

The application of MSCs in liver cancer

It has been proved that MSCs have the ability of migrating and integrate into the tumor tissue (58). However, the application of multi-origin MSCs in liver cancer is controversial. Different sources of MSCs play diverse roles in liver cancer, which limits the application of MSCs in clinical treatment. Gardin *et al.* proved that AD-MSCs inhibited HepG2 and PLC-PRF-5 proliferation while promoted apoptosis *in vitro* by up-regulating P53 and RB and down-regulating c-Myc and hTER (59). Another report showed that conditioned medium (CMs) delivered from AD-MSCs inhibited hepatoma carcinoma cell proliferation and promoted death *in vitro* by down-regulating Akt signaling (60).

Yet BM-MSCs showed the opposite effect in HCC. A recent work demonstrated that BM-MSCs stimulated migration and invasion of HCC cells which could be hampered by AQP1 inhibitor (61). BM-MSCs-mediated upregulation of CXCL4 also plays critical role in promoting HCC cell migration and invasion *in vitro* (62). Interestingly, genetically modified BM-MSCs, which expressed high levels of stTRAIL, could migrate to heat-shocked HCC cells and induce apoptosis in nude mice (63).

Despite the original effect of MSCs on tumors, MSCs are potential tools for transporting drugs or anti-tumor virus due to their ability of tumor chemotaxis, immunosuppressive properties and low immunogenicity. It was reported that oncolytic measles virus infected BM-MSCs could homing to HCC tumors and transfer the virus to HCC via heterofusion to significantly inhibit tumor growth (58). What's more, MenSCs infected with oncolytic adenovirus also showed their ability to migrate to variety kinds of tumors and suppress tumor growth *in vivo*. These studies show that using MSCs as gene vehicle could be a novel strategy for tumor-targeted clinical application in the future.

The transduction of secretory substance released by MSCs

It has been reported CM from MSCs show similar protective effects in tissue damage. CM contained paracrine soluble factors and extracellular vesicles (EVs) promoting tissue repair and regeneration (64). EVs can be released by MSCs

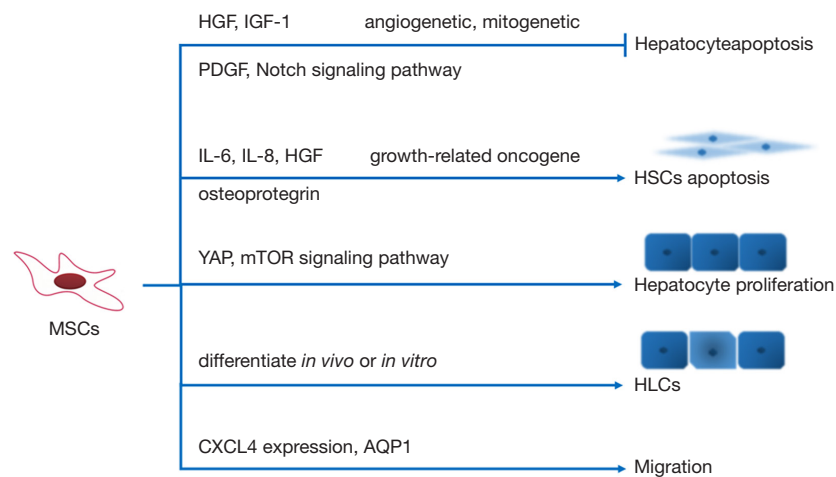


Figure 2 The mechanism of therapeutic effect of MSCs and related signaling pathways. MSCs play a therapeutic role in liver diseases through a variety of ways, a large number of signal pathways are involved.

and transport lipids, proteins, DNA, miRNA, and non-coding RNA. EVs can be classified into three subtypes including exosomes, microvesicles and apoptotic bodies. We partly summarized the cytokines secreted by MSCs and the signal transduction involved in the therapy pathway (Figure 2). In mice experiment, MenSC derived exosomes alleviated fulminant hepatic failure induced by D-GalN/LPS (21). MenSC derived exosomes provided an anti-apoptotic capacity with higher levels of cytokines including ICAM-1, angiopoietin-2, Axl, angiogenin, IGFBP-6, osteoprotegerin, IL-6 and IL-8 (21). MSCs exosomes were proposed as an ideal ‘cell-free’ therapeutic alternative to replace stem cell therapy. Combined with the homing capacity of stem cells, exosomes can be used as vectors for targeted therapy. However, exosome is currently limited to be widely used by the complicated extraction. And it is of great significance to clarify the components of exosomes for further research.

The potential application of MSCs in bioartificial liver (BAL) system

BAL support system incorporating cell source in bioreactor has been proposed as an effective means to treat end-stage liver diseases. With the application of BAL, it suggested to improve the survival time of fulminant hepatic failure pigs (65). Cell source used in BAL should possess the capacity of extensive amplification and maintenance of cellular characteristics. Cell lines derived from hepatomas and genetically engineered hepatocyte-like cells hepatoid cells have been widely used for BAL. Lv *et al.* study shown

that the efficacy of BAL can be enhanced by co-culturing of liver cells with MSCs (65). It suggested that MSCs can modulate cell properties to achieve a better curative effect in BAL application. Adding secretory substance released by MSCs to BAL may enhance the capacity to improve the therapeutic potential.

Safety and efficacy of MSCs treatment

Safety, especially potential of tumorigenesis is the most concerned issue in MSCs clinical applications. However, after analyzing previous studies about chromosomal aberrations of MSCs, Sensebe *et al.* argued that genomic stability of cultured adult stem cells, especially MSCs is robust, which indicated that MSCs transplantation was less likely to cause tumor. During a follow-up of 11.5 years after BM-MSCs transplantation, neither tumor nor infections were observed among the 41 patients (66). Chen *et al.* indicated that MSC infusion could significantly reduce the mortality rate of ACLF patients without increasing severe complications (67). According to another meta-analysis, BM-MSCs and UC-MSCs infusion could improve liver function in cirrhosis patients. At the end of the first year, there were no serious side effects or complications.

Fever (37–38 °C) and rash are the most common adverse events reported but recover without additional treatment in clinical trials. Considering that MSCs has the character of low inherent immunogenicity, it may be related to the immune regulation function of MSCs.

Although large amount of studies has demonstrated

the therapeutic effect of different MSCs on various liver diseases both in animal models and patients, there is currently no uniform clinical treatment guideline for efficient therapy strategy.

Determination of cells dose and timing is urgently needed for clinical applications (68). In most clinical indications, the dose of human MSCs is generally 1–2 million cells/kg, and never exceeds 12 million cells/kg (69). However, so far, there are no clinical trials reporting treatment effects comparison in different cell doses. On the other hand, there are very few related studies, especially clinical trials about timing of MSCs transplantation in liver diseases. After comparing effect of MSCs infusion in different time points in hepatic schistosomiasis models, El-Shennawy *et al.* suggested that the earlier injection of MSCs, the better treatment effect (70). These studies suggested necessities for in-depth research of MSCs administration timing in patients.

Optimization and standardization of isolation, culture, expansion and delivering are also key factors to steer MSCs treatment efficacy and safety, which need undergo extensive investigations before applied in the clinical field.

Conclusions

In present studies, stem cells applied in clinical trials varies from different disease. Autologous BM-MSCs is the most widely used in liver diseases. To some extent, autologous MSCs extraction from patients is still a damaging process. The efficacy of autologous BM-MSCs is limited by physician condition including aging differentiation and deficiency in vitality (45). Comparing to BM-MSCs, UC-MSC are free from these limitations (49). ADSCs clinical application is limited by isolation technique. If ADSCs can be isolated more easily, they can be used in greater number than BMSCs.

In conclusion, MSCs therapy couldn't achieve beneficial effect in decompensated cirrhosis and the long-term efficacy is poor. By far, liver transplantation is the most effective and the ultimate treatment for end-stage liver disease. Combined with stem cells in the treatment of liver disease, stem cell therapy can improve liver function in the short-term. Stem cell therapy can prolong the waiting time for liver transplantation in patients with end-stage liver disease and become a bridge between end-stage liver disease and liver transplantation. Repeated stem cell therapy may be an effective approach to achieve long-term therapeutic effects. Further clinical trials are needed to clarify the mechanism of stem cell in liver disease.

It has great significance to further clarify the substances

secreted by MSCs, and to explore the definite substances contributing to immune regulation and tissue regeneration. To better investigate the mechanism involved in MSCs therapy, it is important to identify the protein, DNA and RNA released by MSCs. The proteomics and transcriptomics may play an important role in exploring the under mechanism. Cell communication with the help of EVs transfects key factors to regulate cell differentiation and induce subsequent signal transduction.

Increasing the number of cells homing to the injury site is the key point to improve the therapeutic effect of stem cells. Studying the homing characteristics of stem cells is helpful to improve the effective therapeutic quantity of stem cells. Identifying the differentiation of stem cells *in vitro* micro-environment gave a direction to the targeted regulation of stem cells.

Currently, there are no standardized protocols for stem cells clinical trials. To better analyze the difference between stem cells, more clinical trials should be conducted in the future. The sample size needs to be expanded and it needs to set an effective control group during the study. Therapeutic pathways and effective time points are required to be confirmed. We need to establish standardized protocols for clinical trials.

In summary, it was confirmed that MSCs has a promising therapeutic effect in liver disease therapy. More works are needed to clarify the underlying mechanism of stem cell therapeutic effects. Standardized protocols should be established according to the best time interval and reasonable therapeutic dose. Cell type, injection route and observation time points need to be better formulated in the clinical application of MSCs.

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