

## Review Article

# The plusses and minuses of bone marrow-derived mesenchymal stem cells in the treatment of liver cirrhosis

Yipu Zhao<sup>1,2</sup>, Shuai Huang<sup>1,2</sup>, Rongtao Zhu<sup>1,2</sup>, Yuling Sun<sup>1,2</sup>

<sup>1</sup>Department of Hepatobiliary and Pancreatic Surgery, The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, Henan, China; <sup>2</sup>Institute of Hepatobiliary and Pancreatic Diseases, School of Medicine, Zhengzhou University, Zhengzhou 450052, Henan, China

Received February 21, 2017; Accepted April 6, 2017; Epub June 15, 2017; Published June 30, 2017

**Abstract:** Liver transplantation is the most effective treatment for advanced liver disease, but its application is restricted. Cell therapy provides a fresh approach for treating liver cirrhosis. The immunological superiority and stem cell characteristics of mesenchymal stem cells (MSCs) from bone marrow, umbilical cord, adipose tissue, or dental tissues might allow them to perform well as alternative cell therapy treatments. Many previous animal experiments and clinical studies of liver disease have been reported and have demonstrated the efficacy and safety of MSCs therapy; no serious side effects or complications were noted, but not all trials have shown efficacy. Potential mechanisms of action, for example, secreting cytokines and growth factors, promoting liver regeneration, inhibiting inflammation in the liver, facilitating the degradation of excessive extracellular matrix (ECM) and differentiating into multi-lineage cells, could account for how MSCs therapy helps improve liver function. However, exploring the mechanism of action still requires further study, and a multitude of problems still await solutions in clinical practice. The use of MSCs in treating liver disease shows broad potential as well as undoubted challenges. In this paper, we will focus on the current possible mechanisms by which bone marrow mesenchymal stem cells (BM-MSCs) improve liver function, show the relationship between the application of MSCs and the occurrence of liver tumors and hepatic fibrosis, and present recent controversies and prospects for the treatment of liver cirrhosis.

**Keywords:** Bone marrow, mesenchymal stem cells, liver cirrhosis, stem cell therapy

## Introduction

Liver cirrhosis is the final pathological result of a wide variety of chronic liver diseases. The formation of pseudolobuli and tubercles and the loss of liver function at different levels are the representative pathological characteristics of liver cirrhosis [1, 2]. As the disease progresses, it becomes life threatening. According to current treatment schemes, liver transplantation is the most efficient method of treatment for advanced liver cirrhosis caused by multiple factors. However, an imbalance between donor availability and the high demand, severe post-operative mortality, long-term side effects and high cost gravely limit its application [3]. Cell-based therapies offer a choice for patients with advanced liver cirrhosis. Mesenchymal stem cells (MSCs), which can be readily obtained and

cultured in vitro, have been known for many years and have been reported to provide benefits in liver disease. Moreover, they are ethically more acceptable to patients and exhibit low inherent immunogenicity [4]. Bone marrow-derived mesenchymal stem cells (BM-MSCs) are suitable candidates for use in therapeutic stem cell strategies. Various animal studies and clinical trials on BM-MSCs have revealed the benefit and feasibility of using these cells to treat liver cirrhosis and even liver failure. However, risky aspects of these applications should be carefully considered.

## Properties of bone marrow-derived mesenchymal stem cells

MSCs are derived from a wealth of sources, such as bone marrow, adipose tissue, skeletal

muscle, and synovium [5]. Bone marrow is an important source of stem cells. MSCs have self-renewal capability and multiple differentiation potentials, including the ability to develop into hepatocytes [6]. These properties indicate an intrinsic role in regeneration and tissue repair. BM-MSCs do not express major histocompatibility complex (MHC) class II antigens [7] and can escape immune recognition through inhibition of immune cells, such as T cells, B cells, antigen presenting cells (APCs) and natural killer cells, during the process of activation and differentiation [8-10], thus improving the body's tolerance and reducing the incidence of serious adverse reactions. These features show that BM-MSCs are conducive to tissue repair and reconstruction and present a new approach for treatment of liver disease.

### *How BM-MSCs are proposed to improve liver function: possible mechanisms*

In general, elucidation of the mechanism by which BM-MSCs improve liver function is still a long way off. Currently, the possible mechanisms include (1) the secretion of cytokines and growth factors that promote liver regeneration; (2) the inhibition of inflammation and the activation of hepatic stellate cells (HSCs); and (3) the inhibition of the production and promotion of the degradation of excessive extracellular matrix; (4) their multipotent characteristics. First, BM-MSCs can secrete many growth factors and cytokines, and this is probably the most important mechanism. For example, BM-MSCs secrete the well-known hepatocyte growth factor (HGF) [11], which has demonstrated anti-apoptotic properties in hepatocytes and plays an essential role in promoting the regeneration of the liver. HGF has been applied in several experimental investigations to attenuate fibrosis [12]. Moreover, van Poll's research [13] suggested that systemic administration of MSC-derived molecules could visibly inhibit hepatocyte apoptosis, while the expression of interleukin-1 $\beta$  and tumor necrosis factor alpha (TNF- $\alpha$ ) were decreased. According to Wang X, administration of HGF could promote recovery in carbon tetrachloride (CCl<sub>4</sub>)-induced liver injury [14]. Transforming growth factor (TGF)- $\beta$ 1 plays a significant role in the process of liver fibrosis; TGF- $\beta$ 1 can activate the Smad3 signaling pathway, which greatly contributes to liver fibrosis progression [15, 16]. MSCs transplan-

tation inhibited Smad3 phosphorylation, which restricted the downstream components of the TGF- $\beta$ 1 signaling pathway and specifically counteracted many profibrotic actions of TGF- $\beta$ 1 [17, 18]. MSCs can express hepatocyte growth factor (HGF) and the cognate receptor HGFR/c-met and then stimulate chemotactic migration [19, 20]. Interestingly, HGF has been reported to induce tolerance and to reduce T-cell proliferation and antigen presentation of dendritic cells [21, 22], which might provide synergistic effects in human immunological tolerance. BM-MSCs can secrete vascular endothelial growth factor (VEGF), which attenuates myocardial reperfusion injury and significantly reduces cell injury in vitro, in part through the activation of the PI3K signaling pathway [23]. Recent research has indicated that stem cells increase the levels of VEGF, Angpt1 and Angpt2, which could be propitious for vascular regeneration, and other paracrine growth factors, such as platelet-derived growth factor (PDGF), fibroblast growth factor (FGF) and epidermal growth factor (EGF), which jointly improve hepatocyte and bile duct proliferation [24]. Similarly, in ischemia-reperfusion-induced liver injury, allogeneic BM-MSCs attenuate the oxidative stress response, and higher expression levels of the anti-apoptotic protein Bcl-2 and lower expression levels of the pro-apoptotic proteins Casp3 and Bax were also observed during the process; these results indicate that improvement mainly occurs via a paracrine mechanism [25]. This result was consistent with another study of the antioxidant properties of MSCs [26], and other related factors secreted by MSCs, such as interleukin-10 and TNF- $\alpha$ , were also shown to alleviate fibrosis and decrease collagen synthesis, as well as inhibit inflammation [27]. Second, activated hepatic stellate cells (HSCs) are major participants in collagen deposition, and they even transdifferentiate into fibrogenic myofibroblast-like cells [28]. MSCs may exert inhibitory effects on the transition of hepatic stellate cells from a quiescent state to an activated state, in part, by reducing the phosphorylation of extracellular signal-regulated kinase (ERK) 1/2 and decrease the gene expression of collagen types I and III [27, 29]. FGF-treated MSCs were shown to reinforce apoptosis of hepatic stellate cells through JNK-p53 signaling [30]. MSCs regulate the function of HSCs through secretion of IL-10 and nerve growth factor (NGF), exerting a therapeutic effect on

inflammation and liver fibrosis [31, 32]. Yue Yu et al. observed that the HGF expression level increased and TGF- $\beta$ 1 secretion from activated HSCs decreased by using genetically modified HGF-expressing MSCs. This illustrates that MSCs exhibit an antifibrosis effect by modulating the function of HSCs to a certain extent [33]. In addition, in CCl<sub>4</sub>- or dimethylnitrosamine (DMN)-treated rats, not only was  $\alpha$ -smooth muscle actin ( $\alpha$ -SMA) expression reduced but collagen deposition also decreased after MSCs administration. This indicated the role of MSCs in inhibiting fibrosis formation and the progression of fibrosis [29]. BM-MSCs migrate into the fibrous area of cirrhotic livers, where they express matrix metalloproteinases such as MMP-9 and MMP-13, which contribute to extra cellular matrix degradation, tissue remodeling and the desired curative effects on liver function, thus affecting the survival rate [34, 35].

In addition, the liver has a potentially powerful regenerative capacity, although in advanced liver disease, the regenerative capacity is insufficient to compensate for the injured tissue. MSCs from human, mouse and rat bone marrow, as well as from other sources, can be induced to express hepatocyte differentiation markers in vitro [6, 36-40] and in vivo [41-43]. Hepatocyte nuclear factor 4 alpha (HNF4 $\alpha$ ) [44] and fibroblast growth factor 2 (FGF2) [45] might facilitate the differentiation of transplanted bone marrow cells into hepatocytes. However, it is still not clear what percentage of the cells can be induced to differentiate into hepatocytes. Di Bonzo et al. [46] intravenously transplanted purified active BM-MSCs into immune-deficient mice with or without acute or chronic liver injury and found that transplanted MSCs could move to both normal and damaged liver parenchyma, particularly in conditions of chronic liver injury; however, as evidenced by very low or undetectable levels of the hepatocyte markers serum albumin alpha fetal protein (AFP), CK18 and CK19, differentiation into hepatocytes rarely occurred. Houlihan DD et al. observed that the production of bone marrow-derived hepatocytes is very rare in most cases of liver injury [47]. In spite of direct injection into the liver, differentiation of MSCs into hepatocytes did not occur [48]. Therefore, hepatocytes from bone marrow are not likely to be responsible for the healing function of MSCs in the liver during the course of liver da-

mage. It is difficult to explain the differences between the above views, and it seems that MSCs exert their influence predominantly by indirect mechanisms rather than through hepatocyte differentiation. Pluralistic and integrated responses were perceived to hamper the progressive deterioration of hepatic architecture. Although BM-MSCs therapy for liver cirrhosis has demonstrated an improvement in liver function, the therapeutic mechanisms responsible for the beneficial effects are still far from clear.

*Tests and effects in animal experiments and clinical trials:* The use of BM-MSCs transplantation as an alternative treatment for hepato-cirrhosis has been widely studied in animal models. Its effectiveness has been demonstrated both in carbon-tetrachloride-treated cirrhotic mice [49] and in a thioacetamide-induced cirrhotic rat model. In the latter rat model,  $\alpha$ -SMA, collagen-1 and TGF- $\beta$ 1 expression decreased markedly after BM-MSCs treatment. Furthermore, the hepatic hydroxyproline content and the percentage of the collagen proportionate area were also decreased significantly [17]. However, not all the results are coincident. Using a severe chronic liver injury rat model, Carvalho et al. found that BM-MSCs did not generate benefits or improve liver function after repeated infusions of BM-MSCs, and no obvious differences were observed in collagen content, immunofluorescence analysis, biochemical assays and ultrasound imaging [50]. This result was in contrast to the aforementioned study, suggesting that the therapeutic results of MSCs are still controversial. Meanwhile, we determined explicitly that both the route and dosage of BM-MSCs led to significant differences in performance due to the experimental design.

In the last couple of years, researchers worldwide have continued to expand the scope of clinical research, while studies have exhibited conflicting or even contradictory results regarding the validity of MSCs. In November 2003, Terai S conducted a clinical study of autologous bone marrow cell infusion therapy for advanced liver cirrhosis and presented its safety and availability [51]. Mervat El-Ansary performed a phase II trial on a total of 25 HCV-related patients with decompensate liver cirrhosis. In the 15 patients in the MSCs group, BM-MSCs were either undifferentiated (n=9) or differentiated

## Mesenchymal stem cells and liver cirrhosis

**Table 1.** Several clinical studies used bone marrow cells in the treatment of liver disease

Type of cells	Injection route and dosage	Etiology and patient number	Support validity	Complications	Follow-up period	Trials
BM-MNCs	Peripheral vein; $5.2 \pm 0.63 \times 10^9$	9; LC (3 HBV, 5 HCV and 1 unknown)	Yes	None	24 weeks	Terai S et al. [51] 2006
BM-MSCs	Peripheral or portal vein; $3-5 \times 10^7$	8; LC (4 HBV, 1 HCV, 1 alcoholic and 2 unknown)	Yes	None	24 weeks	Kharaziha P et al. [53] 2009
BM	Hepatic artery; $3.4-3.8 \times 10^8$	53; LF due to HBV	Yes	None	192 weeks	Peng L et al. [54] 2011
BM(G-CSF)	Peripheral vein; $1 \times 10^6$ /kg body weight	20; End-stage liver disease (HCV)	Yes	None	At least 26 weeks	Salama H et al. [67] 2014
BM-MSCs	Intrasplenic; $10 \times 10^6$	20; LC (HCV)	Yes	None	6 mo	Amin MA et al. [68] 2013
BM-MSCs	Peripheral vein; Median of 195 million	15; Decompensated LC (RCT)	No	None	12 mo	Mohamadnejad M et al. [56] 2013
BM-MSCs	Hepatic artery; $5 \times 10^7$ (twice)	11; Alcoholic cirrhosis	Yes	None	12 mo	Jang YO et al. [63] 2014

Abbreviations: BM: Bone marrow; BM-MNCs: Bone marrow mononuclear cells; BM-MSCs: Bone marrow mesenchymal stem cells; G-CSF: Granulocyte-colony-stimulating factor; HBV: Hepatitis B virus; HCV: Hepatitis C virus; LC: Liver cirrhosis; LF: Liver failure; RCT: Randomized controlled trials.

into hepatocytes (n=6). However, in all 15 patients, the symptoms of jaundice and limb edema were alleviated significantly both 3 and 6 months later, serum albumin and serum bilirubin levels were ameliorated, and the model for end stage liver disease (MELD) score declined. Moreover, there was not a distinct difference regarding laboratory tests and clinical results between patients with undifferentiated MSCs and those with MSCs that differentiated into hepatocytes [52]. This was consistent with the results of Kharaziha et al. [53], who transplanted autologous MSCs into 8 patients with end-stage liver disease via peripheral or portal veins. In China, Peng et al. performed a clinical study on autologous MSCs transplantation in 53 liver failure patients and confirmed its short-term efficacy, but no significant improvement was observed in the long-term [54]. Recently, 10 patients with ursodeoxycholic acid-resistant primary biliary cirrhosis underwent allogeneic BM-MSCs transplantation, and serum levels of  $\gamma$ -GT, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and IgM significantly decreased. In addition, the quality of life was improved throughout the 12-month follow up [55], thus verifying the validity of the treatment to a certain extent.

In contrast to the above research results, Mehdi Mohamadnejad et al. carried out a randomized placebo-controlled trial regarding MSCs transplantation, and parameters such as the MELD score, Child-Pugh score, serum albumin level, international normalized ratio (INR), and total bilirubin level did not exhibit significant changes compared to the control group by both the 3 and 12 month follow-ups, which is not

consistent with the previous report [56]; this indicates that there is still controversy about whether MSCs infusion is effective. Therefore, further studies are warranted to probe the true effect of MSCs infusion in liver cirrhosis. In recent years, part of the clinical experimental results are presented in **Table 1**.

*The relationship between BM-MSCs transplantation and liver cancer:* It remains uncertain whether the anti-apoptotic and immunomodulatory properties of BM-MSCs play a role in promoting the occurrence of tumors. In vitro culture of BM-MSCs, particularly with longer culture times, might increase the risk of phenotypic alterations and genetic abnormalities in BM-MSCs [57]. Liver cirrhosis itself is a pre-malignant condition, and we should also be concerned about the potential of promoting tumor growth in vivo. The relationship between BM-MSCs and cancer has not yet reached a broad consensus. Adult MSCs undergo spontaneous transformation following long culture times in vitro, supporting the idea of malignant transformation, particularly for poorly differentiated hepatocellular carcinoma [58, 59], which raises important safety issues. However, several reports have found that BM-MSCs do not affect the incidence of tumors [60]. The formation of tumors resulting from the introduction of long-term cultured human MSCs into nude mice has not been reported. In addition, MSCs from the bone marrow of children expressed normal levels of p16, p53, RB and H-RAS in an in vivo model [61] and, thus, were consistent with a recent study, suggesting that the spontaneous transformation of MSCs leading to tumorigenesis was rare over a relatively short time period [62].

Jang YO et al. [63] and Mehdi Mohamadnejad et al. [56] also observed that there was no evidence that the application of stem cells promoted tumor development during the follow-up period. Peng's results revealed no significant differences in the incidence of hepatocellular carcinoma between patients with and without MSCs transplantation after a 192-week follow-up. Furthermore, for patients with cirrhosis, the application of autologous BM-MSCs might, to some extent, offer protection with respect to the occurrence of hepatocellular carcinoma and mortality [54]. Another report suggests that frequent BM-MSC infusion was conducive to inhibiting tumor promotion during stages of hepatocarcinogenesis in an N-nitrosodiethylamine (DEN)/green fluorescent protein (GFP)-carbon tetrachloride (CCl<sub>4</sub>) model; however, the inhibitory mechanism requires further analysis [64]. Recently, Zhao et al. reported that MSCs from transgene-free human induced pluripotent stem cells were less likely to promote tumors because the contributors of pro-tumor effects, such as receptors for interleukin-1, TGF- $\beta$  and hyaluronan, were expressed at very low levels [65]. The results from a number of clinical studies tend to be consistent: BM-MSCs are more likely to reduce liver carcinogenesis than increase it.

### *Effects of splenectomy on BM-MSCs transplantation*

MSCs can migrate into specific sites in the liver in response to tissue damage homing signals. Based on this migratory advantage, peripheral vein [56, 66, 67], hepatic artery [54, 63], intrasplenic [68] or portal-venous [53] delivery, and even direct injection into the liver [48], have all been demonstrated to carry MSCs to the liver, although the reported outcomes of the preceding injection approaches showed slight differences. Liver cirrhosis is often accompanied by symptoms of splenomegaly as well as hypersplenism, in which the circulating cells are subject to varying degrees of damage. Takuya Iwamoto, in both a mouse model and a clinical study, demonstrated that infusion of autologous bone marrow cells to treat cirrhosis exhibited a more effective performance after splenectomy. In the clinical trial, significantly greater increases in the serum albumin level and the HGF level were observed after splenectomy compared to the application of BM-MSCs alone at 4 and 24 weeks. Other indicators, such as

the Child-Pugh score, the PT-INR and the serum level of type III pro-collagen-N-peptide (PIIIP), presented a desired improvement throughout the 24 weeks of observation. In addition, higher expression levels of MMP-9 and increased delivery of GFP-positive BM-MSCs into the injured liver in the splenectomy group were observed compared to the non-splenectomy group, and decreases in TGF- $\beta$ 1 mRNA and  $\alpha$ -SMA expression, which enhanced liver regeneration, were also described [69]. Another clinical trial showed a similar effect and demonstrated a significant increase in the numbers of circulating hematopoietic stem cells and platelets after splenectomy [70]. This may be related to the absence of captured BM-MSCs and a reduction of BM-MSC damage in the spleen. The change in intrahepatic blood flow after splenectomy slightly decreases hepatic fibroproliferation as well [71].

### *Whether BM-MSCs ameliorate the symptoms of liver fibrosis*

BM-MSCs can transform into liver cells and improve liver function. However, BM-MSCs have a variety of differentiation potentials; they can also be converted into myofibroblasts, which promote the development of liver cirrhosis, leading to the opposite effect.

Forbes SJ observed 7 male patients who developed liver fibrosis after liver transplants from female donors and found karyotype Y chromosome-positive cells in the fibrotic region. These Y chromosome-positive cells had a myofibroblast phenotype, which is positive for  $\alpha$ -SMA, vimentin and fibulin-2 and negative for CD45. Moreover, the myofibroblasts of BM-MSCs origin made up a high proportion of the cell population [72]. Russo et al. [73] used female mice receiving male bone marrow transplants and observed significant myofibroblast populations derived from bone marrow. In contrast, minor contributions of bone marrow-derived cells to parenchymal regeneration were observed. Furthermore, the total numbers of myofibroblasts derived from bone marrow were higher in the presence of liver cirrhosis than in the absence of liver damage, and it should be noted that the researchers also investigated stellate cells from bone marrow. BM-MSC differentiation into myofibroblast-like cells expressing  $\alpha$ -SMA was also described in mouse fibrotic liver [74], and the increase in TGF- $\beta$ 1 is

responsible for the differentiation of BM-MSCs to myofibroblasts [75, 76]. Tatiana Kisseleva [77] also reported that fibrocytes of bone marrow origin could produce collagen in chimeric mice with bile duct ligation-induced liver injury, indicating a potentially destructive effect on liver function.

No sufficiently compelling theory can explain the contradictory results, and they may be related to the design of the scientific research and the research focus. The microenvironment of the liver might have an effect on the differentiation direction of BM-MSCs. Studies exploring this potential double-edged sword need to be further refined to draw on the advantages and avoid the disadvantages of BM-MSCs.

### Conclusion

The only current therapy modality for liver failure is liver transplantation, but its application is limited. In recent years, cell therapy has been a popular area of research. The widespread application of hepatocyte transplantation is also restricted because human hepatocytes are not easily cultured *in vitro*; they tend to dedifferentiate in culture, and the viability and function of hepatic cells present different degrees of loss [78, 79]. The immunological superiority and stem cell characteristics of MSCs allow them to perform better as alternative cell therapy treatments. Other sources of stem cells, such as human adipose tissue [80] and umbilical cord tissue [81], have been shown to migrate well into the liver parenchyma, and they appear to ameliorate impaired liver function.

A systematic review and meta-analysis involving 1012 participants summed up the safety of systemic MSCs administration and suggested that the administration of MSCs was safe, and no severe side effects or complications were noted, although transient fever was described [53, 60]. Many pre-clinical and clinical studies have tried to demonstrate the viability of BM-MSC applications, and with more in-depth study, BM-MSCs still have the potential to become a favorable treatment strategy.

However, we should clearly understand that the effectiveness of MSCs treatment is still controversial because many disputed and unanswered questions still exist. As of now, although a large amount of preclinical and clinical evi-

dence has confirmed the feasibility and promise of bone marrow cells in disease modification and BM-MSCs present a relatively safe and impactful approach for alleviating fibrosis, there are many unknown factors that still need to be studied and assessed before clinical application. The mechanisms by which MSCs produce specific secretory effects, the detailed signaling pathways involved, and the differentiation and anti-fibrotic or potential profibrotic activity remain unclear. This brings risks and uncertainties to the clinical application of BM-MSCs, and major breakthroughs are needed regarding this critical knowledge and the potential problems. Better comprehension concerning the effects underlying each step in the proliferation and lineage differentiation of MSCs will immensely expand the scope of possible therapeutic applications of both native and cultured MSCs *in vitro* [82].

There are still a multitude of problems awaiting solution in clinical practice, including the determination of the most effective number of cells, the best route of administration, the activity of the transplanted cells, the times of injections and the patients who will most benefit from treatment [83, 84]. Previous clinical research designs were also lacking in norms and require further perfection of therapeutic evaluation and monitoring schemes for long-term evaluation of treatment efficacy, the lifespan of MSCs, the homing ability and the ideal time point for BM-MSCs transplantation, which may also affect the efficacy of transplantation [29, 85]. Even donor age might influence the differentiation potential [48].

### Future prospects

Cell therapy developed for the treatment of liver cirrhosis has been officially approved as an "Advanced medical technology B" in Japan [86]. In addition, other sources of MSCs such as umbilical cord blood or adipose tissue show similar benefits in the treatment of liver disease [87].

As previously described, there are many controversies regarding BM-MSCs transplantation for the treatment of liver cirrhosis. Chronic liver diseases can be caused by factors such as viral hepatitis, alcohol, drugs, and metabolic and autoimmune diseases. Hence, differences in etiology might result in different consequ-

ences of MSCs therapy and lead to selection bias, although the process of fibrosis is similar regardless of the original cause.

The administration of MSCs in a randomized trial with cirrhotic patients resulting from various etiologies did not show improvement over the placebo, while most of the other trials have shown efficacy. We might find the best possible beneficiaries of the therapy for a specific etiology through continuous in-depth study. In the meantime, the remaining unresolved issues need to be addressed. Satisfactory positive results do not always appear in clinical trials. In addition, we should be alert to the pro-fibrogenic potential of MSCs due to the differentiation of myofibroblasts, and determining how to avoid this unwanted differentiation is also a significant task. However, overall, the administration of BM-MSCs as a hopeful new therapeutic strategy to treat liver disease remains possible. Thus, a better understanding of the mechanism would be beneficial for the evolution of more available treatment options. Nevertheless, the relevant clinical research has only been performed for a little over a decade and is still immature. Moreover, well-designed randomized clinical trials are scarce. We need a larger sample size, a longer period of time and multicenter clinical trials to achieve a greater understanding of the pluses and minuses of stem cell therapies.

### Disclosure of conflict of interest

None.

### Authors' contribution

Yipu Zhao and Shuai Huang searched the literature, analyzed the data, and accomplished the first draft; they contributed equally to this work. Rongtao Zhu and Yuling Sun designed the review; all authors contributed to this paper with drafting and critical revision, and final approval of the final version.

**Address correspondence to:** Dr. Yuling Sun, Department of Hepatobiliary and Pancreatic Surgery, The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, Henan, China; Institute of Hepatobiliary and Pancreatic Diseases, School of Medicine, Zhengzhou University, Zhengzhou 450052, Henan, China. Tel: +86-371-67967126; Fax: +86-371-67967127; E-mail: ylsun@zzu.edu.cn

### References

- [1] Wanless IR, Nakashima E, Sherman M. Regression of human cirrhosis. Morphologic features and the genesis of incomplete septal cirrhosis. *Arch Pathol Lab Med* 2000; 124: 1599-1607.
- [2] Zhou W, Zhang Q, Qiao L. Pathogenesis of liver cirrhosis. *World J Gastroenterol* 2014; 20: 7312-7324.
- [3] Kim WR, Therneau TM, Benson JT, Kremers WK, Rosen CB, Gores GJ, Dickson ER. Deaths on the liver transplant waiting list: an analysis of competing risks. *Hepatology* 2006; 43: 345-351.
- [4] Eom YW, Kim G, Baik SK. Mesenchymal stem cell therapy for cirrhosis: present and future perspectives. *World J Gastroenterol* 2015; 21: 10253-10261.
- [5] Barry FP, Murphy JM. Mesenchymal stem cells: clinical applications and biological characterization. *Int J Biochem Cell B* 2004; 36: 568-584.
- [6] Lee KD, Kuo T, Whang-Peng J, Chung YF, Lin CT, Chou SH, Chen JR, Chen YP, Lee O. In vitro hepatic differentiation of human mesenchymal stem cells. *Hepatology* 2004; 40: 1275-1284.
- [7] Tse WT, Pendleton JD, Beyer WM, Egalka MC, Guinan EC. Suppression of allogeneic T-cell proliferation by human marrow stromal cells: implications in transplantation. *Transplantation* 2003; 75: 389-397.
- [8] Aggarwal S, Pittenger MF. Human mesenchymal stem cells modulate allogeneic immune cell responses. *Blood* 2005; 105: 1815-1822.
- [9] Inoue S, Popp FC, Koehl GE, Piso P, Schlitt HJ, Geissler EK, Dahlke MH. Immunomodulatory effects of mesenchymal stem cells in a rat organ transplant model. *Transplantation* 2006; 81: 1589-1595.
- [10] Sotiropoulou PA, Perez SA, Gritzapis AD, Baxevanis CN, Papamichail M. Interactions between human mesenchymal stem cells and natural killer cells. *Stem Cells* 2006; 24: 74-85.
- [11] Matsuda-Hashii Y, Takai K, Ohta H, Fujisaki H, Tokimasa S, Osugi Y, Ozono K, Matsumoto K, Nakamura T, Hara J. Hepatocyte growth factor plays roles in the induction and autocrine maintenance of bone marrow stromal cell IL-11, SDF-1 alpha, and stem cell factor. *Exp Hematol* 2004; 32: 955-961.
- [12] Ueki T, Kaneda Y, Tsutsui H, Nakanishi K, Sawa Y, Morishita R, Matsumoto K, Nakamura T, Takahashi H, Okamoto E, Fujimoto J. Hepatocyte growth factor gene therapy of liver cirrhosis in rats. *Nat Med* 1999; 5: 226-230.
- [13] van Poll D, Parekkadan B, Cho CH, Berthiaume F, Nahmias Y, Tilles AW, Yarmush ML. Mesen-

## Mesenchymal stem cells and liver cirrhosis

- chymal stem cell-derived molecules directly modulate hepatocellular death and regeneration in vitro and in vivo. *Hepatology* 2008; 47: 1634-1643.
- [14] Wang XL, Ge SD, McNamara G, Hao CL, Crooks GM, Nolte JA. Albumin-expressing hepatocyte-like cells develop in the livers of immune-deficient mice that received transplants of highly purified human hematopoietic stem cells. *Blood* 2003; 101: 4201-4208.
- [15] Dooley S, Ten Dijke P. TGF-beta in progression of liver disease. *Cell Tissue Res* 2012; 347: 245-256.
- [16] Friedman SL. Mechanisms of hepatic fibrogenesis. *Gastroenterology* 2008; 134: 1655-1669.
- [17] Jang YO, Kim MY, Cho MY, Baik SK, Cho YZ, Kwon SO. Effect of bone marrow-derived mesenchymal stem cells on hepatic fibrosis in a thioacetamide-induced cirrhotic rat model. *BMC Gastroenterol* 2014; 14.
- [18] Matsumoto K, Nakamura T. Hepatocyte growth factor: renotropic role and potential therapeutics for renal diseases. *Kidney Int* 2001; 59: 2023-2038.
- [19] Neuss S, Becher E, Woltje M, Tietze L, Jahnen-Dechent W. Functional expression of HGF and HGF receptor/c-met in adult human mesenchymal stem cells suggests a role in cell mobilization, tissue repair, and wound healing. *Stem Cells* 2004; 22: 405-414.
- [20] Son B, Marquez-Curtis LA, Kucia M, Wysoczynski M, Turner AR, Ratajczak J, Ratajczak MZ, Janowska-Wieczorek A. Migration of bone marrow and cord blood mesenchymal stem cells in vitro is regulated by stromal-derived factor-1-CXCR4 and hepatocyte growth factor-c-met axes and involves matrix metalloproteinases. *Stem Cells* 2006; 24: 1254-1264.
- [21] Okunishi K, Dohi M, Nakagome K, Tanaka R, Mizuno S, Matsumoto K, Miyazaki J, Nakamura T, Yamamoto K. A novel role of hepatocyte growth regulator through suppressing factor as an immune dendritic cell function. *J Immunol* 2005; 175: 4745-4753.
- [22] Ito W, Kanehiro A, Matsumoto K, Hirano A, Ono K, Maruyama H, Kataoka M, Nakamura T, Gelfand EW, Tanimoto M. Hepatocyte growth factor attenuates airway hyperresponsiveness, inflammation, and remodeling. *Am J Respir Cell Mol Biol* 2005; 32: 268-280.
- [23] Angoulvant D, Ivanov F, Ferrera R, Matthews PG, Nataf S, Ovize M. Mesenchymal stem cell conditioned media attenuates in vitro and ex vivo myocardial reperfusion injury. *J Heart Lung Transplant* 2011; 30: 95-102.
- [24] Adas G, Koc B, Adas M, Duruksu G, Subasi C, Kemik O, Kemik A, Sakiz D, Kalayci M, Purisa S, Unal S, Karaoz E. Effects of mesenchymal stem cells and VEGF on liver regeneration following major resection. *Langenbecks Arch Surg* 2016; 401:725-740.
- [25] Jin G, Qiu G, Wu D, Hu Y, Qiao P, Fan C, Gao F. Allogeneic bone marrow-derived mesenchymal stem cells attenuate hepatic ischemia-reperfusion injury by suppressing oxidative stress and inhibiting apoptosis in rats. *Int J Mol Med* 2013; 31: 1395-1401.
- [26] Quintanilha LF, Takami T, Hirose Y, Fujisawa K, Murata Y, Yamamoto N, Dos Santos Goldenberg RC, Terai S, Sakaida I. Canine mesenchymal stem cells show antioxidant properties against thioacetamide-induced liver injury in vitro and in vivo. *Hepatol Res* 2014; 44: E206-E217.
- [27] Wang J, Bian C, Liao L, Zhu Y, Li J, Zeng L, Zhao RC. Inhibition of hepatic stellate cells proliferation by mesenchymal stem cells and the possible mechanisms. *Hepatol Res* 2009; 39: 1219-1228.
- [28] Moreira RK. Hepatic stellate cells and liver fibrosis. *Arch Pathol Lab Med* 2007; 131: 1728-1734.
- [29] Zhao D, Lei J, Chen R, Yu W, Zhang X, Li S, Xiang P. Bone marrow-derived mesenchymal stem cells protect against experimental liver fibrosis in rats. *World J Gastroenterol* 2005; 11: 3431-3440.
- [30] Tang W, Akahoshi T, Piao J, Narahara S, Murata M, Kawano T, Hamano N, Ikeda T, Hashizume M. Basic fibroblast growth factor-treated adipose tissue-derived mesenchymal stem cell infusion to ameliorate liver cirrhosis via paracrine hepatocyte growth factor. *J Gastroenterol Hepatol* 2015; 30: 1065-1074.
- [31] Parekkadan B, van Poll D, Megeed Z, Kobayashi N, Tilles AW, Berthiaume F, Yarmush ML. Immunomodulation of activated hepatic stellate cells by mesenchymal stem cells. *Biochem Biophys Res Commun* 2007; 363: 247-252.
- [32] Lin N, Hu K, Chen S, Xie S, Tang Z, Lin J, Xu R. Nerve growth factor-mediated paracrine regulation of hepatic stellate cells by multipotent mesenchymal stromal cells. *Life Sci* 2009; 85: 291-295.
- [33] Yu Y, Lu L, Qian X, Chen N, Yao A, Pu L, Zhang F, Li X, Kong L, Sun B, Wang X. Antifibrotic effect of hepatocyte growth factor-expressing mesenchymal stem cells in small-for-size liver transplant rats. *Stem Cells Dev* 2010; 19: 903-914.
- [34] Sakaida I, Terai S, Yamamoto N, Aoyama K, Ishikawa T, Nishina H, Okita K. Transplantation of bone marrow cells reduces CCl4-induced liver fibrosis in mice. *Hepatology* 2004; 40: 1304-1311.
- [35] Li T, Zhu J, Ma K, Liu N, Feng K, Li X, Wang S, Bie P. Autologous bone marrow-derived mes-

## Mesenchymal stem cells and liver cirrhosis

- enchymal stem cell transplantation promotes liver regeneration after portal vein embolization in cirrhotic rats. *J Surg Res* 2013; 184: 1161-1173.
- [36] Jiang YH, Jahagirdar BN, Reinhardt RL, Schwartz RE, Keene CD, Ortiz-Gonzalez XR, Reyes M, Lenvik T, Lund T, Blackstad M, Du JB, Aldrich S, Lisberg A, Low WC, Largaespada DA, Verfaillie CM. Pluripotency of mesenchymal stem cells derived from adult marrow. *Nature* 2002; 418: 41-49.
- [37] Hong SH, Gang EJ, Jeong JA, Ahn CY, Hwang SH, Yang IH, Park HK, Han H, Kim H. In vitro differentiation of human umbilical cord blood-derived mesenchymal stem cells' into hepatocyte-like cells. *Biochem Biophys Res Commun* 2005; 330: 1153-1161.
- [38] Schwartz RE, Reyes M, Koodie L, Jiang YH, Blackstad M, Lund T, Lenvik T, Johnson S, Hu WS, Verfaillie CM. Multipotent adult progenitor cells from bone marrow differentiate into functional hepatocyte-like cells. *J Clin Invest* 2002; 109: 1291-1302.
- [39] Ong S, Dai H, Leong KW. Hepatic differentiation potential of commercially available human mesenchymal stem cells. *Tissue Eng* 2006; 12: 3477-3485.
- [40] Banas A, Teratani T, Yamamoto Y, Tokuhara M, Takeshita F, Osaki M, Kato T, Okochi H, Ochiya T. Rapid hepatic fate specification of adipose-derived stem cells and their therapeutic potential for liver failure. *J Gastroenterol Hepatol* 2009; 24: 70-77.
- [41] Zhan Y, Wang Y, Wei L, Chen H, Cong X, Fei R, Gao Y, Liu F. Differentiation of hematopoietic stem cells into hepatocytes in liver fibrosis in rats. *Transplant Proc* 2006; 38: 3082-3085.
- [42] Kia R, Sison RL, Heslop J, Kitteringham NR, Hanley N, Mills JS, Park BK, Goldring CE. Stem cell-derived hepatocytes as a predictive model for drug-induced liver injury: are we there yet? *Br J Clin Pharmacol* 2013; 75: 885-896.
- [43] Seo MJ, Suh SY, Bae YC, Jung JS. Differentiation of human adipose stromal cells into hepatic lineage in vitro and in vivo. *Biochem Biophys Res Commun* 2005; 328: 258-264.
- [44] Hang H, Yu Y, Wu N, Huang Q, Xia Q, Bian J. Induction of highly functional hepatocytes from human umbilical cord mesenchymal stem cells by HNF4 alpha transduction. *PLoS One* 2014; 9: e104133.
- [45] Ishikawa T, Terai S, Urata Y, Marumoto Y, Aoyama K, Sakaida I, Murata T, Nishina H, Shinoda K, Uchimura S, Hamamoto Y, Okita K. Fibroblast growth factor 2 facilitates the differentiation of transplanted bone marrow cells into hepatocytes. *Cell Tissue Res* 2006; 323: 221-231.
- [46] Di Bonzo LV, Ferrero I, Cravanzola C, Mareschi K, Rustichelli D, Novo E, Sanavio F, Cannito S, Zamara E, Bertero M, Davit A, Francica S, Novelli F, Colombatto S, Fagioli F, Parola M. Human mesenchymal stem cells as a two-edged sword in hepatic regenerative medicine: engraftment and hepatocyte differentiation versus profibrogenic potential. *Gut* 2008; 57: 223-231.
- [47] Houlihan DD, Newsome PN. Critical review of clinical trials of bone marrow stem cells in liver disease. *Gastroenterology* 2008; 135: 438-450.
- [48] Baertschiger RM, Serre-Beinier V, Morel P, Bosco D, Peyrou M, Clement S, Sgroi A, Kaelin A, Buhler LH, Gonelle-Gispert C. Fibrogenic potential of human multipotent mesenchymal stromal cells in injured liver. *PLoS One* 2009; 4: e6657.
- [49] Iwamoto T, Terai S, Hisanaga T, Takami T, Yamamoto N, Watanabe S, Sakaida I. Bone-marrow-derived cells cultured in serum-free medium reduce liver fibrosis and improve liver function in carbon-tetrachloride-treated cirrhotic mice. *Cell Tissue Res* 2013; 351: 487-495.
- [50] Carvalho AB, Quintanilha LF, Dias JV, Paredes BD, Mannheimer EG, Carvalho FG, Asensi KD, Gutfilen B, Fonseca LM, Resende CM, Rezende GF, Takiya CM, De Carvalho AC, Goldenberg RC. Bone marrow multipotent mesenchymal stromal cells do not reduce fibrosis or improve function in a rat model of severe chronic liver injury. *Stem Cells* 2008; 26: 1307-1314.
- [51] Terai S, Ishikawa T, Omori K, Aoyama K, Marumoto Y, Urata Y, Yokoyama Y, Uchida K, Yamasaki T, Fujii Y, Okita K, Sakaida I. Improved liver function in patients with liver cirrhosis after autologous bone marrow cell infusion therapy. *Stem Cells* 2006; 24: 2292-2298.
- [52] El-Ansary M, Abdel-Aziz I, Mogawer S, Abdel-Hamid S, Hammam O, Teaema S, Wahdan M. Phase II Trial: undifferentiated versus differentiated autologous mesenchymal stem cells transplantation in egyptian patients with HCV induced liver cirrhosis. *Stem Cell Rev Rep* 2012; 8: 972-981.
- [53] Kharaziha P, Hellstrom PM, Noorinayer B, Farzaneh F, Aghajani K, Jafari F, Telkabadi M, Atashi A, Honardoost M, Zali MR, Soleimani M. Improvement of liver function in liver cirrhosis patients after autologous mesenchymal stem cell injection: a phase I-II clinical trial. *Eur J Gastroenterol Hepatol* 2009; 21: 1199-1205.
- [54] Peng L, Xie D, Lin B, Liu J, Zhu H, Xie C, Zheng Y, Gao Z. Autologous bone marrow mesenchymal stem cell transplantation in liver failure patients caused by hepatitis B: short-term and long-term outcomes. *Hepatology* 2011; 54: 820-828.
- [55] Wang L, Han Q, Chen H, Wang K, Shan G, Kong F, Yang Y, Li Y, Zhang X, Dong F, Wang Q, Xu D,

## Mesenchymal stem cells and liver cirrhosis

- Hu Z, Wang S, Keating A, Bi Y, Zhang F, Zhao RC. Allogeneic bone marrow mesenchymal stem cell transplantation in patients with UDCA-resistant primary biliary cirrhosis. *Stem Cells Dev* 2014; 23: 2482-2489.
- [56] Mohamadnejad M, Alimoghaddam K, Bagheri M, Ashrafi M, Abdollahzadeh L, Akhlaghpour S, Bashtar M, Ghavamzadeh A, Malekzadeh R. Randomized placebo-controlled trial of mesenchymal stem cell transplantation in decompensated cirrhosis. *Liver Int* 2013; 33: 1490-1496.
- [57] Prockop DJ, Keating A. Relearning the lessons of genomic stability of human cells during expansion in culture: implications for clinical research. *Stem Cells* 2012; 30: 1051-1052.
- [58] Serakinci N, Guldberg P, Burns JS, Abdallah B, Schrodder H, Jensen T, Kassem M. Adult human mesenchymal stem cell as a target for neoplastic transformation. *Oncogene* 2004; 23: 5095-5098.
- [59] Wu X, Chen D. Origin of hepatocellular carcinoma: Role of stem cells. *J Gastroenterol Hepatol* 2006; 21: 1093-1098.
- [60] Lalu MM, McIntyre L, Pugliese C, Fergusson D, Winston BW, Marshall JC, Granton J, Stewart DJ; Canadian Critical Care Trials Group. Safety of cell therapy with mesenchymal stromal cells (SafeCell): a systematic review and meta-analysis of clinical trials. *PLoS One* 2012; 7: e47559.
- [61] Kim J, Kang JW, Park JH, Choi Y, Choi KS, Park KD, Baek DH, Seong SK, Min H, Kim HS. Biological characterization of long-term cultured human mesenchymal stem cells. *Arch Pharm Res* 2009; 32:117-126.
- [62] Pan Q, Fouraschen SM, de Rooter PE, Dinjens WN, Kwekkeboom J, Tilanus HW, van der Laan LJ. Detection of spontaneous tumorigenic transformation during culture expansion of human mesenchymal stromal cells. *Exp Biol Med* 2014; 239: 105-115.
- [63] Jang YO, Kim YJ, Baik SK, Kim MY, Eom YW, Cho MY, Park HJ, Park SY, Kim BR, Kim JW, Kim HS, Kwon SO, Choi EH, Kim YM. Histological improvement following administration of autologous bone marrow-derived mesenchymal stem cells for alcoholic cirrhosis: a pilot study. *Liver Int* 2014; 34: 33-41.
- [64] Maeda M, Takami T, Terai S, Sakaida I. Autologous bone marrow cell infusions suppress tumor initiation in hepatocarcinogenic mice with liver cirrhosis. *J Gastroenterol Hepatol* 2012; 272: 104-111.
- [65] Zhao Q, Gregory CA, Lee RH, Reger RL, Qin L, Hai B, Park MS, Yoon N, Clough B, McNeill E, Prockop DJ, Liu F. MSCs derived from iPSCs with a modified protocol are tumor-tropic but have much less potential to promote tumors than bone marrow MSCs. *Proc Natl Acad Sci U S A* 2015; 112: 530-535.
- [66] Shi M, Zhang Z, Xu R, Lin H, Fu J, Zou Z, Zhang A, Shia J, Chen L, Lv S, He W, Geng H, Jin L, Liu Z, Wang FS. Human mesenchymal stem cell transfusion is safe and improves liver function in acute-on-chronic liver failure patients. *Stem Cell Transl Med* 2012; 1: 725-731.
- [67] Salama H, Zekri AN, Medhat E, Al Alim SA, Ahmed OS, Bahnassy AA, Lotfy MM, Ahmed R, Musa S. Peripheral vein infusion of autologous mesenchymal stem cells in Egyptian HCV-positive patients with end-stage liver disease. *Stem Cell Res Ther* 2014; 5: 70.
- [68] Amin MA, Sabry D, Rashed LA, Aref WM, El-Ghobary MA, Farhan MS, Fouad HA, Youssef YA. Short-term evaluation of autologous transplantation of bone marrow-derived mesenchymal stem cells in patients with cirrhosis: Egyptian study. *Clin Transplant* 2013; 27: 607-612.
- [69] Iwamoto T, Terai S, Mizunaga Y, Yamamoto N, Omori K, Uchida K, Yamasaki T, Fujii Y, Nishina H, Sakaida I. Splenectomy enhances the antifibrotic effect of bone marrow cell infusion and improves liver function in cirrhotic mice and patients. *J Gastroenterol* 2012; 47: 300-312.
- [70] Masuya M, Shiraki K, Sugimoto K, Yamamoto N, Yoneda M, Kanayama K, Nishikawa K, Ino K, Tawara I, Ohishi K, Sakurai H, Usui M, Shiraishi T, Isaji S, Takei Y, Katayama N. Splenectomy increases the number of circulating hematopoietic stem/progenitor cells in patients with hepatitis C virus-associated liver cirrhosis. *Hepatology* 2014; 44: E376-E385.
- [71] Wang Q, Duan Z, Du J, Guo S, Sun X, Liu Z. Heme oxygenase/carbon monoxide pathway inhibition plays a role in ameliorating fibrosis following splenectomy. *Int J Mol Med* 2013; 31: 1186-1194.
- [72] Forbes SJ, Russo FP, Rey V, Burra P, Ruge M, Wright NA, Alison MR. A significant proportion of myofibroblasts are of bone marrow origin in human liver fibrosis. *Gastroenterology* 2004; 126: 955-963.
- [73] Russo FP, Alison MR, Bigger BW, Amofah E, Florou A, Amin F, Bou-Gharios G, Jeffery R, Iredale JP, Forbes SJ. The bone marrow functionally contributes to liver fibrosis. *Gastroenterology* 2006; 130: 1807-1821.
- [74] Li C, Kong Y, Wang H, Wang S, Yu H, Liu X, Yang L, Jiang X, Li L, Li L. Homing of bone marrow mesenchymal stem cells mediated by sphingosine 1-phosphate contributes to liver fibrosis. *J Hepatol* 2009; 50: 1174-1183.
- [75] Yang L, Chang N, Liu X, Han Z, Zhu T, Li C, Yang L, Li L. Bone marrow-derived mesenchymal stem cells differentiate to hepatic myofibroblasts by transforming growth factor-beta 1 via sphingosine kinase/sphingosine 1-phos-

## Mesenchymal stem cells and liver cirrhosis

- phate (S1P)/S1P receptor axis. *Am J Pathol* 2012; 181: 85-97.
- [76] Jeon ES, Moon HJ, Lee MJ, Song HY, Kim YM, Cho M, Suh D, Yoon M, Chang CL, Jung JS, Kim JH. Cancer-derived lysophosphatidic acid stimulates differentiation of human mesenchymal stem cells to myofibroblast-like cells. *Stem Cells* 2008; 26: 789-797.
- [77] Kisseleva T, Uchinami H, Feirt N, Quintana-Bustamante O, Segovia JC, Schwabe RF, Brenner DA. Bone marrow-derived fibrocytes participate in pathogenesis of liver fibrosis. *J Hepatol* 2006; 45: 429-438.
- [78] Gramignoli R, Vosough M, Kannisto K, Srinivasan RC, Strom SC. Clinical hepatocyte transplantation: practical limits and possible solutions. *Eur Surg Res* 2015; 54: 162-177.
- [79] Dhawan A. Clinical human hepatocyte transplantation: current status and challenges. *Liver Transplant* 2015; 211: S39-S44.
- [80] Koellensperger E, Niesen W, Kolbensschlag J, Gramley F, Germann G, Leimer U. Human adipose tissue derived stem cells promote liver regeneration in a rat model of toxic injury. *Stem Cells Int* 2013; 2013: 534263.
- [81] Zhang Z, Lin H, Shi M, Xu R, Fu J, Lv J, Chen L, Lv S, Li Y, Yu S, Geng H, Jin L, Lau GK, Wang FS. Human umbilical cord mesenchymal stem cells improve liver function and ascites in decompensated liver cirrhosis patients. *J Gastroenterol Hepatol* 2012; 272: 112-120.
- [82] Liu Z, Zhuge Y, Velazquez OC. Trafficking and differentiation of mesenchymal stem cells. *J Cell Biochem* 2009; 106: 984-991.
- [83] Kim G, Eom YW, Baik SK, Shin Y, Lim YL, Kim MY, Kwon SO, Chang SJ. Therapeutic effects of mesenchymal stem cells for patients with chronic liver diseases: systematic review and meta-analysis. *J Korean Med Sci* 2015; 30: 1405-1415.
- [84] Ezquer F, Bruna F, Calligaris S, Conget P, Ezquer M. Multipotent mesenchymal stromal cells: a promising strategy to manage alcoholic liver disease. *World J Gastroenterol* 2016; 22: 24-36.
- [85] Sakaida I, Terai S, Yamamoto N, Aoyama K, Ishikawa T, Nishina H, Okita K. Transplantation of bone marrow cells reduces CCl4-induced liver fibrosis in mice. *Hepatology* 2004; 40: 1304-1311.
- [86] Terai S, Takami T, Yamamoto N, Fujisawa K, Ishikawa T, Urata Y, Tanimoto H, Iwamoto T, Mizunaga Y, Matsuda T, Oono T, Marumoto M, Burganova G, Quintanilha LF, Hidaka I, Marumoto Y, Saeki I, Uchida K, Yamasaki T, Tani K, Taura Y, Fujii Y, Nishina H, Okita K, Sakaida I. Status and prospects of liver cirrhosis treatment by using bone marrow-derived cells and mesenchymal cells. *Tissue Eng Part B Rev* 2014; 20: 206-210.
- [87] Kern S, Eichler H, Stoeve J, Klueter H, Bieback K. Comparative analysis of mesenchymal stem cells from bone marrow, umbilical cord blood, or adipose tissue. *Stem Cells* 2006; 24: 1294-1301.