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Review Article

# Adipose Tissue-derived Mesenchymal Stem Cells in Regenerative Medicine Treatment for Liver Cirrhosis – Focused on Efficacy and Safety in Preclinical and Clinical Studies

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**Abstract**

Stem cell therapy, including mesenchymal stem cell (MSC) therapy, is a promising therapeutic option for treating several diseases. Adipose tissue-derived mesenchymal stem cells (AT-MSCs) have been identified as a candidate for stem cell therapy. Sources of MSCs include bone marrow, umbilical cord, amniotic fluid, and adipose tissue. Adipose tissue can be easily harvested using procedures that are minimally invasive compared with those used to obtain the other sources, and it is suitable for regenerative medicine treatments.

End-stage cirrhosis and chronic liver failure are life-threatening liver diseases. Liver transplantation is an effective therapy for end-stage liver disease, but most patients are unable to undergo liver transplantation because of the limited supply of donors, the complex surgical procedure, rejection, pre-existing disease recurrence, and high costs.

AT-MSCs are a promising candidate for regenerative medicine to treat liver cirrhosis. Over the past decade, the literature on non-clinical studies and clinical trials for liver diseases has been accumulating, and we can speculate on the efficacy and safety of MSC therapy. The mechanisms of the curative effects of AT-MSCs have been clarified insufficiently. However, a large number of reports indicate that the hepato-protective effect of AT-MSCs is related to a paracrine effect of soluble mediators rather than the differentiation potency of the cells. In this review, we summarize the efficacy and safety of AT-MSC use and the current preclinical studies and clinical trials of AT-MSCs.

## ABBREVIATIONS

**AT-MSCs:** Adipose-Tissue derived Mesenchymal Stem Cells; **BM-MSCs**: Bone Marrow-derived Mesenchymal Stem Cells; **$CCl_4$:** Carbon Tetrachloride; **ECM:** Extracellular Matrix; **HGF**: Hepatocyte Growth Factor; **HLA**: Human Leukocyte Antigen; **HSCs:** Hepatic Stellate Cells; **IL**: Interleukin; **MELD**: Model for End-Stage Liver Disease; **MMP:** Matrix Metalloproteinase; **MSCs:** Mesenchymal Stem Cells; **NASH:** Non-Alcoholic Steatohepatitis; **PDGF-β:** Platelet-Derived Growth Factor-β;

**TGF-β:** Transforming Growth Factor-β; **TIMP:** Tissue Inhibitor of Matrix Metalloproteinase; **UC-MSCs**: Umbilical Cord-derived Mesenchymal Stem Cells;

## INTRODUCTION

End-stage cirrhosis and chronic liver failure are life-threatening liver diseases. The most effective therapy for patients with advanced cirrhosis is liver transplantation. However, most patients are unable to undergo liver transplantation because of the limited availability of donors, the complex surgical procedure, rejection, pre-existing liver disease recurrence, and high costs [1,2].

Stem cell therapies, including those using mesenchymal stem cells (MSCs), are promising for the treatment of end-stage liver disease [3]. The tissue origins of MSCs include bone marrow [4], umbilical cord [5], amniotic fluid [6,7], and adipose tissue [8,9].

Adipose tissue can be easily harvested through a less invasive procedure than used to obtain MSCs from other sources, and it is a promising source of MSCs to be used as a regenerative medicine treatment for various diseases, including hepatic failure [10-12]. There is accumulating evidence for hepato-curative effects of adipose tissue-derived mesenchymal stem cells (AT-MSCs). In this review, we summarize the efficacy and safety of AT-MSC use and the clinical trials of AT-MSCs.

## AT-MSCs

MSCs are a promising candidate for regenerative medicine. According to recommendation, International Society for Cell Therapy, the criteria to define human MSCs are that they must adhere to plastic in standard culture conditions and that the cells must express the markers CD105, CD90 and CD73 but not the markers CD45, CD34, CD14, CD11b, CD79a, CD19 and human leukocyte antigen (HLA) -DR. Moreover, the cells must have osteogenic, adipogenic and chondrogenic differentiation potential under standard in vitro differentiation conditions [13]. Bone marrow was the first organ reported to be a source of MSCs, but the isolation procedure for bone marrow is the most invasive procedure of all of the MSC sources.

In particular, it is thought that AT-MSCs are ideal for developing regenerative medicine. The advantages of using adipose tissue as a source of MSCs include its abundance and easy access for harvesting [10,14]. Furthermore, a comparative analysis of MSCs from bone marrow, umbilical cord and adipose tissue has been reported [15]. According to this report, adipose tissue contains MSCs at the highest frequency, and there are no morphological or immune phenotypic differences among bone marrow, umbilical cord and adipose tissue as sources.

Many reports indicate that AT-MSCs have more therapeutic effects than other sources of MSCs. MSCs have immunomodulatory effects on various immune cells such as T-cells [16], B-cells [17], natural killer cells [18] and dendritic cells [19]. These properties of MSCs make it possible to control the autoimmune diseases and graft-versus-host-disease [20]. Many studies indicate that AT-MSCs have more pronounced immunomodulatory effects compared with other MSCs sources such as bone marrow and umbilical cord [21,22]. Furthermore, other pre-clinical studies demonstrated that treatment of AT-MSCs are more effective on hindlimb ischemia [23], wound healing [24] and spinal cord injury [25] than bone-marrow derived MSCs (BM-MSCs).

### Pathogenesis of liver cirrhosis

Liver cirrhosis is characterized by extensive fibrosis caused by chronic hepatic injury. The major causes of liver fibrosis are infection with hepatitis B virus, infection with hepatitis C virus, alcoholic steatohepatitis and nonalcoholic steatohepatitis (NASH). Liver fibrosis is the excessive accumulation of extracellular matrix (ECM) in the space of Disse following both the increased synthesis and decreased degeneration of ECM [26,27].

Hepatic stellate cells (HSCs) are the key source of ECM synthesis in the damaged liver. Quiescent HSCs, which synthesize a small amount of ECM, are activated by soluble mediators and differentiate into myofibroblasts, which are the main source of ECM. It is well known that augmented tissue inhibitor of matrix metalloproteinase (TIMP1) expression derived from hepatic myofibroblasts plays a pivotal role in tipping the balance between the production and the degradation of ECM components [28]. TIMP1 promotes the accumulation of ECM in damaged liver through the inhibition of matrix metalloproteinases (MMPs), a family of enzymes that degrade ECM components.

HSCs are activated by soluble mediators, such as transforming growth factor-β (TGF-β) [29,30] and platelet-derived growth factor-β (PDGF-β) [31]. TGF-β is considered to play a pivotal role in the progression of liver fibrosis through the augmentation of ECM synthesis by HSCs. In addition, TGF-β suppresses ECM degeneration through not only the blockade of MMP expression but also the facilitation of TIMP1 expression [29]. In contrast, it is thought that PDGF-β is the most potent mitogen for HSCs. PDGF-β is upregulated in the fibrotic liver, and PDGF-β inhibition attenuates liver fibrosis in vivo [31] (Figure 1).

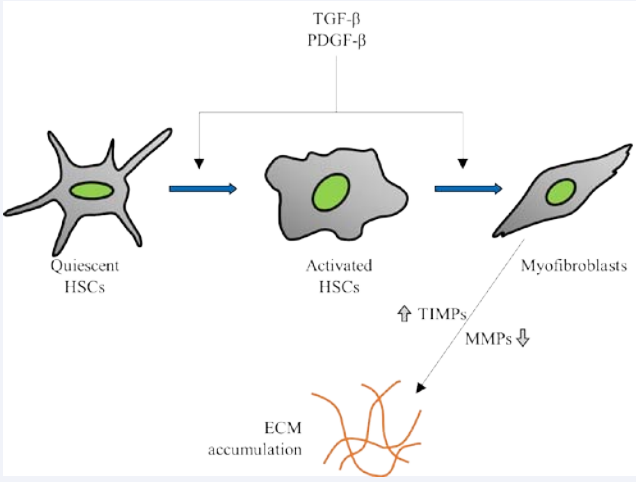


**Figure 1** Quiescent hepatic stellate cells (HSCs) are activated by soluble mediators such as transforming growth factor-β (TGF-β) and platelet-derived growth factor-β (PDGF-β). The activated HSCs are further activated by soluble mediators and differentiate into myofibroblasts. These myofibroblasts up-regulate the expression of tissue inhibitor of matrix metalloproteinases (TIMPs) in damaged liver. TIMPs promote the accumulation of extra celler matrix (ECM) in damaged liver through the inhibition of ECM degradation by matrix metalloproteinases (MMPs) activity [17].

## Therapeutic potential of AT-MSCs

Many pre-clinical studies have demonstrated that AT-MSCs have a hepato-curative effect in animal models of acute and chronic liver diseases [32-43]. AT-MSCs attenuate impaired liver function and tissue damage in rodent models of acute hepatitis induced by carbon tetrachloride ($CCl_4$) [32], concanavalin A [33,34], acetaminophen [35], ischemia reperfusion [36,37] and combination of retrorsin and allylalcohol [38]. Furthermore, AT-MSCs ameliorate the liver dysfunction and the histological changes that occur with the fibrogenesis induced by $CCl_4$ [39,40], thioacetamide [41] and NASH [42] in mice. It has also been reported that AT-MSCs have therapeutic efficacy in the acute-on-chronic liver failure rabbit model [43].

The mechanisms of the protective effects of AT-MSCs on hepatic injury are not fully understood, but they can be ascribed to several possible mechanisms. However, there is still debate about these potential mechanisms. MSCs have a homing capacity to injured organs [44,45]. MSCs home to the endothelial cells through interactions with integrins and vascular cell adhesion molecule-1 [46]. Additionally, MSCs display rolling and adhesion behavior on endothelial cells, where CXC-chemokine receptors-4 and its ligand stromal-derived factor-1 play a crucial role in this behavior [47]. MSCs then migrate across the endothelium and invade the injured organ. Tracking AT-MSCs with an in vivo imaging system has revealed that AT-MSCs accumulate in damaged livers in mice [14].

Many studies have demonstrated that MSCs secrete various molecules, such as cytokines, chemokines and growth factors [48]. AT-MSCs secrete many soluble factors, such as interleukin (IL) -1RA, IL-6, IL-8, hepatocyte growth factor (HGF), nerve growth factor, monocyte chemoattractant protein-1, granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor. AT-MSCs secrete these factors more abundantly than either BM-MSCs or normal human dermal fibroblasts [22]. In particular, it is thought that HGF has hepato-protective effects through the inhibition of HSC activation [49]. HGF has preventive and therapeutic effects on liver cirrhosis in rats through growth inhibition and apoptosis induction in myofibroblasts that are activated in cirrhosis. HGF also has a suppressive effect on collagen I and IV synthesis in HSCs [50]. Furthermore, HGF enhances MMP expression and activity [51].

In the case of BM-MSCs, TIMP1 and MMP expression is affected by BM-MSC administration in liver fibrosis models. According to these studies, the application of BM-MSCs suppresses the upregulated expression of TIMP1 in mice with liver fibrosis [52,53]. In contrast, MMP expression is promoted by the administration of BM-MSCs in liver fibrosis models [53-55]. AT-MSCs are also expected to regulate TIMP1 and MMP expression in cirrhosis.

Taken together, it is suggested that AT-MSCs home to damaged livers, where they secrete various molecules, such as HGF. These molecules suppress the activation of myofibroblasts in fibrotic livers, resulting in the degeneration of ECM, which most likely occurs through the suppression of TIMP1 expression and the promotion of MMP expression.

## Safety issues of AT-MSCs

Preclinical toxicity and tumorigenicity tests of AT-MSCs conducted under Good Laboratory Practice conditions have been reported [56]. Toxicity symptoms were found not to occur for 13 weeks in mice, even at the highest dose of AT-MSCs ($2.5\times10^8$ cells/kg) administered via the tail vein. Similarly, with a subcutaneous injection at the same dose, no evidence of tumorigenicity was found for 26 weeks using the toxicity test in immunodeficient mice. For large animals, a 6-week toxicity study using an intravenous administration route for $2x10^6$ and $1x10^7$ cells/kg umbilical cord-derived MSCs (UC-MSCs) in cynomolgus monkeys has been reported, and this report suggested that the transplantation of UC-MSCs does not affect the general health of cynomolgus monkeys [57]. Moreover, the intravenous infusion of AT-MSCs in cats has no complications during or after administration [58].

In contrast, several reports have indicated that transplanted cells may be entrapped in the lungs during their first pass through systemic organs. The intravenous injection of neural progenitor stem cells results in death immediately after administration to mice [59]. Another study has reported that blood microcirculation is interrupted in mice when AT-MSCs are injected into the aorta owing to the large cell diameter [60]. The tissue factor has a critical role in promoting MSC-mediated coagulation in mice, and its expression likely leads to thromboembolism. An anti-coagulant agent has also been suggested to be useful for avoiding embolism [61]. Recently, another group has indicated that cell size and infusion velocity are critical factors for developing safe protocols for intracarotid stem cell transplantation in rats [62].

AT-MSCs have advantageous characteristics that allow allogeneic transplantation without immune rejection. AT-MSCs are immunoprivileged because they have intermediate expression levels of HLA-I and undetectable expression levels of HLA-II and because they do not express co-stimulatory molecules, such as CD80, CD86 and CD40 [63,64].

In summary, most of the pre-clinical toxicity reports indicate no side effects resulting from the administration of MSCs, including AT-MSCs. However, there is a risk of embolism induced by the intravenous injection of MSCs in accordance with the studies using rodents. Hence, we should be careful to avoid embolism when clinical trials are conducted.

## Clinical trials

In this review, we summarized some of the clinical trials in which MSCs have been used to treat liver cirrhosis. In the clinical trial database (ClinicalTrials.Gov), 47 protocols using MSCs to treat patients with liver cirrhosis are ongoing in the clinical setting (Table 1). Most of these trials are using BM-MSCs or UC-MSCs.

Clinical trials of BM-MSC administration to treat patients with liver failure have been reported. Kharaziha P et al. conducted clinical trials using BM-MSC administration to treat several patients with end-stage liver disease, including hepatitis B and hepatitis C induced disease and alcoholic and cryptogenic cirrhosis [65]. The augmented Model for End-Stage Liver Disease (MELD) score and prothrombin activity in these patients were

**Table 1:** A summary of the clinical trials of MSCs in cirrhosis.

| Source of MSCs | Indication | Phase | Enrolment | Clinical Trials. Gov Identifier | References |
|---|---|---|---|---|---|
| adipose | Cirrhosis | - | 4 | NCT01062750 | |
| bone marrow | Alcoholic cirrhosis | 2 | 11 | NCT01741090 | [67] |
| | Chronic hepatitis B-induced liver failure | 1/2 | Treatment: 53 Control: 105 | NCT00956891 | [66] |
| | Cirrhosis(Hepatitis B, Hepatitis C, alcoholic, cryptogenic) | 1/2 | 8 | NCT00420134 | [65] |
| umbilical cord | Primary Biliary Cirrhosis | 1/2 | 7 | NCT01662973 | [71] |
| | Cirrhosis(Chronic Hepatitis B) | 1/2 | Treatment: 30 Control: 15 | NCT01220492 | [69] |
| | Acute-on-chronic liver failure | 1/2 | Treatment: 24 Control: 19 | NCT01218464 | [70] |

Abbreviations: MSCs: Mesenchymal Stem Cells

decreased by treatment with BM-MSCs. Peng L et al. and Jang YO et al. reported a curative effect when BM-MSCs were used to treat chronic hepatitis B-induced liver failure and alcoholic cirrhosis [66,67]. Terai et al. reported that bone marrow cell infusions caused a significant amelioration of serum levels of albumin and total protein, and they reported that the Child-Pugh scores in these patients were not adversely affected [68].

Several clinical trials using UC-MSCs to treat cirrhotic patients have been performed. Zhang Z et al. administered UC-MSCs to chronic hepatitis B patients with decompensated liver cirrhosis and ascites [69], and they reported a reduction in ascites volume as well as an improvement in liver functions and MELD scores resulting from treatment with UC-MSCs. Other studies have shown that UC-MSCs improve the survival rate, MELD score and various liver functions in acute-on-chronic liver failure patients [70].

A clinical trial using adipose tissue-derived stromal cells to treat four patients with eligible liver cirrhosis has recently started. This is the first clinical trial using AT-MSCs in cirrhotic patients. In this trial, patients will receive autologous adipose tissue stromal cells through intrahepatic arterial administration, and the endpoint for this trial is safety (ClinicalTrials.Gov NCT01062750).

## CONCLUSION

Stem cell therapies, including those using MSCs, are promising alternatives to liver transplantation. AT-MSCs are especially promising because adipose tissue is an abundant and easily accessible source in the body. There is accumulating evidence that AT-MSCs have curative effects on acute and chronic liver failure in animal models. In addition, many toxicological studies have confirmed the safety of AT-MSCs.

Whereas clinical studies of BM-MSC and UC-MSC treatments for patients with serious liver disease have been conducted, clinical trials using AT-MSCs have not yet been conducted, although clinical trials using AT-MSCs are anticipated. According to the clinical trials using BM-MSCs and UC-MSCs, these cells are effective for treating patients with severe liver disease and do not have obvious side effects. AT-MSCs may also have therapeutic potential for liver cirrhosis.

In conclusion, AT-MSCs are a promising regenerative medicine candidate for treating liver cirrhosis. Researchers are exploring the clinical potential of AT-MSCs while considering the safety issues.

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## REFERENCES

1. Muraca M. Cell therapy as support or alternative to liver transplantation. Transplant Proc. 2003; 35: 1047-1048.
2. Lorenzini S, Gitto S, Grandini E, Andreone P, Bernardi M. Stem cells for end stage liver disease: how far have we got? World J Gastroenterol. 2008; 14: 4593-4599.
3. Zhang Z, Wang FS. Stem cell therapies for liver failure and cirrhosis. J Hepatol. 2013; 59: 183-185.
4. Pittenger MF, Mackay AM, Beck SC, Jaiswal RK, Douglas R, Mosca JD, et al. Multilineage potential of adult human mesenchymal stem cells. Science. 1999; 284: 143-147.
5. Kim JW, Kim SY, Park SY, Kim YM, Kim JM, Lee MH, et al. Mesenchymal progenitor cells in the human umbilical cord. Ann Hematol. 2004; 83: 733-738.
6. Tsai MS, Lee JL, Chang YJ, Hwang SM. Isolation of human multipotent mesenchymal stem cells from second-trimester amniotic fluid using a novel two-stage culture protocol. Hum Reprod. 2004; 19: 1450-1456.
7. Tsai MS, Hwang SM, Tsai YL, Cheng FC, Lee JL, Chang YJ. Clonal amniotic fluid-derived stem cells express characteristics of both mesenchymal and neural stem cells. Biol Reprod. 2006; 74: 545-551.
8. Zuk PA, Zhu M, Ashjian P, De Ugarte DA, Huang JI, Mizuno H, et al. Human adipose tissue is a source of multipotent stem cells. Mol Biol Cell. 2002; 13: 4279-4295.
9. Zuk PA, Zhu M, Mizuno H, Huang J, Futrell JW, Katz AJ, et al. Multilineage cells from human adipose tissue: implications for cell-based therapies. Tissue Eng. 2001; 7: 211-228.
10. Konno M, Hamabe A, Hasegawa S, Ogawa H, Fukusumi T, Nishikawa S, et al. Adipose-derived mesenchymal stem cells and regenerative medicine. Dev Growth Differ. 2013; 55: 309-318.

11. PikuÅ,a M, Marek-Trzonkowska N, Wardowska A, Renkielska A, Trzonkowski P. Adipose tissue-derived stem cells in clinical applications. Expert Opin Biol Ther. 2013; 13: 1357-1370.

12. izuno H. Adipose-derived stem and stromal cells for cell-based therapy: current status of preclinical studies and clinical trials. Curr Opin Mol Ther. 2010; 12: 442-449.

13. Oedayrajsingh-Varma MJ, van Ham SM, Knippenberg M, Helder MN, Klein-Nulend J, Schouten TE, et al. Adipose tissue-derived mesenchymal stem cell yield and growth characteristics are affected by the tissue-harvesting procedure. Cytotherapy. 2006; 8: 166-177.

14. Ochiya T, Yamamoto Y, Banas A. Commitment of stem cells into functional hepatocytes. Differentiation. 2010; 79: 65-73.

15. Kern S, Eichler H, Stoeve J, Klüter H, Bieback K. Comparative analysis of mesenchymal stem cells from bone marrow, umbilical cord blood, or adipose tissue. Stem Cells. 2006; 24: 1294-1301.

16. Di Nicola M, Carlo-Stella C, Magni M, Milanesi M, Longoni PD, Matteucci P, et al. Human bone marrow stromal cells suppress T-lymphocyte proliferation induced by cellular or nonspecific mitogenic stimuli. Blood. 2002; 99: 3838-3843.

17. Glennie S, Soeiro I, Dyson PJ, Lam EW, Dazzi F. Bone marrow mesenchymal stem cells induce division arrest anergy of activated T cells. Blood. 2005; 105: 2821-2827.

18. Spaggiari GM, Capobianco A, Becchetti S, Mingari MC, Moretta L. Mesenchymal stem cell-natural killer cell interactions: evidence that activated NK cells are capable of killing MSCs, whereas MSCs can inhibit IL-2-induced NK-cell proliferation. Blood. 2006; 107: 1484-1490.

19. Nauta AJ, Kruisselbrink AB, Lurvink E, Willemze R, Fibbe WE. Mesenchymal stem cells inhibit generation and function of both CD34+-derived and monocyte-derived dendritic cells. J Immunol. 2006; 177: 2080-2087.

20. Le Blanc K, Rasmusson I, Sundberg B, Götherström C, Hassan M, Uzunel M, et al. Treatment of severe acute graft-versus-host disease with third party haploidentical mesenchymal stem cells. Lancet. 2004; 363: 1439-1441.

21. Ribeiro A, Laranjeira P, Mendes S, Velada I, Leite C, Andrade P, et al. Mesenchymal stem cells from umbilical cord matrix, adipose tissue and bone marrow exhibit different capability to suppress peripheral blood B, natural killer and T cells. Stem Cell Res Ther. 2013; 4: 125.

22. Keyser KA, Beagles KE, Kiem HP. Comparison of mesenchymal stem cells from different tissues to suppress T-cell activation. Cell Transplant. 2007; 16: 555-562.

23. Kim Y, Kim H, Cho H, Bae Y, Suh K, Jung J. Direct comparison of human mesenchymal stem cells derived from adipose tissues and bone marrow in mediating neovascularization in response to vascular ischemia. Cell Physiol Biochem. 2007; 20: 867-876.

24. Liu X, Wang Z, Wang R, Zhao F, Shi P, Jiang Y, et al. Direct comparison of the potency of human mesenchymal stem cells derived from amnion tissue, bone marrow and adipose tissue at inducing dermal fibroblast responses to cutaneous wounds. Int J Mol Med. 2013; 31: 407-415.

25. Zhou Z, Chen Y, Zhang H, Min S, Yu B, He B, et al. Comparison of mesenchymal stromal cells from human bone marrow and adipose tissue for the treatment of spinal cord injury. Cytotherapy. 2013; 15: 434-448.

26. Bataller R, Brenner DA. Liver fibrosis. J Clin Invest. 2005; 115: 209-218.

27. riedman SL. Mechanisms of hepatic fibrogenesis. Gastroenterology. 2008; 134: 1655-1669.

28. Roderfeld M, Weiskirchen R, Wagner S, Berres ML, Henkel C, Grötzinger J, et al. Inhibition of hepatic fibrogenesis by matrix metalloproteinase-9 mutants in mice. FASEB J. 2006; 20: 444-454.

29. Shek FW, Benyon RC. How can transforming growth factor beta be targeted usefully to combat liver fibrosis? Eur J Gastroenterol Hepatol. 2004; 16: 123-126.

30. Gressner AM, Weiskirchen R, Breitkopf K, Dooley S. Roles of TGF-beta in hepatic fibrosis. Front Biosci. 2002; 7: d793-807.

31. Borkham-Kamphorst E, Stoll D, Gressner AM, Weiskirchen R. Antisense strategy against PDGF B-chain proves effective in preventing experimental liver fibrogenesis. Biochem Biophys Res Commun. 2004; 321: 413-423.

32. Banas A, Teratani T, Yamamoto Y, Tokuhara M, Takeshita F, Osaki M, et al. IFATS collection: in vivo therapeutic potential of human adipose tissue mesenchymal stem cells after transplantation into mice with liver injury. Stem Cells. 2008; 26: 2705-2712.

33. Kubo N, Narumi S, Kijima H, Mizukami H, Yagihashi S, Hakamada K, et al. Efficacy of adipose tissue-derived mesenchymal stem cells for fulminant hepatitis in mice induced by concanavalin A. J Gastroenterol Hepatol. 2012; 27: 165-172.

34. Higashimoto M, Sakai Y, Takamura M, Usui S, Nasti A, Yoshida K, et al. Adipose tissue derived stromal stem cell therapy in murine ConA-derived hepatitis is dependent on myeloid-lineage and CD4+ T-cell suppression. Eur J Immunol. 2013; 43: 2956-2968.

35. Salomone F, Barbagallo I, Puzzo L, Piazza C, Li Volti G. Efficacy of adipose tissue-mesenchymal stem cell transplantation in rats with acetaminophen liver injury. Stem Cell Res. 2013; 11: 1037-1044.

36. Sun CK, Chang CL, Lin YC, Kao YH, Chang LT, Yen CH, et al. Systemic administration of autologous adipose-derived mesenchymal stem cells alleviates hepatic ischemia-reperfusion injury in rats. Crit Care Med. 2012; 40: 1279-1290.

37. Seki T, Yokoyama Y, Nagasaki H, Kokuryo T, Nagino M. Adipose tissue-derived mesenchymal stem cell transplantation promotes hepatic regeneration after hepatic ischemia-reperfusion and subsequent hepatectomy in rats. J Surg Res. 2012; 178: 63-70.

38. Koellensperger E, Niesen W, Kolbenschlag 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.

39. Kamada Y, Yoshida Y, Saji Y, Fukushima J, Tamura S, Kiso S, et al. Transplantation of basic fibroblast growth factor-pretreated adipose tissue-derived stromal cells enhances regression of liver fibrosis in mice. Am J Physiol Gastrointest Liver Physiol. 2009; 296: 157-167.

40. Wang Y, Lian F, Li J, Fan W, Xu H, Yang X, et al. Adipose derived mesenchymal stem cells transplantation via portal vein improves microcirculation and ameliorates liver fibrosis induced by CCl4 in rats. J Transl Med. 2012; 10: 133.

41. Harn HJ, Lin SZ, Hung SH, Subeq YM, Li YS, Syu WS, et al. Adipose-derived stem cells can abrogate chemical-induced liver fibrosis and facilitate recovery of liver function. Cell Transplant. 2012; 21: 2753-2764.

42. Seki A, Sakai Y, Komura T, Nasti A, Yoshida K, Higashimoto M, et al. Adipose tissue-derived stem cells as a regenerative therapy for a mouse steatohepatitis-induced cirrhosis model. Hepatology. 2013; 58: 1133-1142.

43. Zhu W, Shi XL, Xiao JQ, Gu GX, Ding YT, Ma ZL. Effects of xenogeneic adipose-derived stem cell transplantation on acute-on-chronic liver failure. Hepatobiliary Pancreat Dis Int. 2013; 12: 60-67.

44. Yagi H, Soto-Gutierrez A, Parekkadan B, Kitagawa Y, Tompkins RG, Kobayashi N, et al. Mesenchymal stem cells: Mechanisms of immunomodulation and homing. Cell Transplant. 2010; 19: 667-679.

45. Kang SK, Shin IS, Ko MS, Jo JY, Ra JC. Journey of mesenchymal stem cells for homing: strategies to enhance efficacy and safety of stem cell therapy. Stem Cells Int. 2012; 2012: 342968.

46. Segers VF, Van Riet I, Andries LJ, Lemmens K, Demolder MJ, De Becker AJ, et al. Mesenchymal stem cell adhesion to cardiac microvascular endothelium: activators and mechanisms. Am J Physiol Heart Circ Physiol. 2006; 290: H1370-1377.

47. Ryu CH, Park SA, Kim SM, Lim JY, Jeong CH, Jun JA, et al. Migration of human umbilical cord blood mesenchymal stem cells mediated by stromal cell-derived factor-1/CXCR4 axis via Akt, ERK, and p38 signal transduction pathways. Biochem Biophys Res Commun. 2010; 398: 105-110.

48. Matsuda Y, Matsumoto K, Yamada A, Ichida T, Asakura H, Komoriya Y, et al. Preventive and therapeutic effects in rats of hepatocyte growth factor infusion on liver fibrosis/cirrhosis. Hepatology. 1997; 26: 81-89.

49. Kim WH, Matsumoto K, Bessho K, Nakamura T. Growth inhibition and apoptosis in liver myofibroblasts promoted by hepatocyte growth factor leads to resolution from liver cirrhosis. Am J Pathol. 2005; 166: 1017-1028.

50. Kwiecinski M, Noetel A, Elfimova N, Trebicka J, Schievenbusch S, Strack I, et al. Hepatocyte growth factor (HGF) inhibits collagen I and IV synthesis in hepatic stellate cells by miRNA-29 induction. PLoS One. 2011; 6: e24568.

51. Wang H, Keiser JA. Hepatocyte growth factor enhances MMP activity in human endothelial cells. Biochem Biophys Res Commun. 2000; 272: 900-905.

52. Sakaida I, Terai S, Yamamoto N, Aoyama K, Ishikawa T, Nishina H, et al. Transplantation of bone marrow cells reduces CCl4-induced liver fibrosis in mice. Hepatology. 2004; 40: 1304-1311.

53. Rabani V, Shahsavani M, Gharavi M, Piryaei A, Azhdari Z, Baharvand H. Mesenchymal stem cell infusion therapy in a carbon tetrachloride-induced liver fibrosis model affects matrix metalloproteinase expression. Cell Biol Int. 2010; 34: 601-605.

54. Li T, Zhu J, Ma K, Liu N, Feng K, Li X, et al. Autologous bone marrow-derived mesenchymal stem cell transplantation promotes liver regeneration after portal vein embolization in cirrhotic rats. J Surg Res. 2013; 184: 1161-1173.

55. Chang YJ, Liu JW, Lin PC, Sun LY, Peng CW, Luo GH, et al. Mesenchymal stem cells facilitate recovery from chemically induced liver damage and decrease liver fibrosis. Life Sci. 2009; 85: 517-525.

56. Ra JC, Shin IS, Kim SH, Kang SK, Kang BC, Lee HY, et al. Safety of intravenous infusion of human adipose tissue-derived mesenchymal stem cells in animals and humans. Stem Cells Dev. 2011; 20: 1297-1308.

57. Wang Y, Han ZB, Ma J, Zuo C, Geng J, Gong W, et al. A toxicity study of multiple-administration human umbilical cord mesenchymal stem cells in cynomolgus monkeys. Stem Cells Dev. 2012; 21: 1401-1408.

58. Quimby JM, Webb TL, Habenicht LM, Dow SW. Safety and efficacy of intravenous infusion of allogeneic cryopreserved mesenchymal stem cells for treatment of chronic kidney disease in cats: results of three sequential pilot studies. Stem Cell Res Ther. 2013; 4: 48.

59. Takahashi Y, Tsuji O, Kumagai G, Hara CM, Okano HJ, Miyawaki A, et al. Comparative study of methods for administering neural stem/progenitor cells to treat spinal cord injury in mice. Cell Transplant. 2011; 20: 727-739.

60. Furlani D, Ugurlucan M, Ong L, Bieback K, Pittermann E, Westien I, et al. Is the intravascular administration of mesenchymal stem cells safe? Mesenchymal stem cells and intravital microscopy. Microvasc Res. 2009; 77: 370-376.

61. Tatsumi K, Ohashi K, Matsubara Y, Kohori A, Ohno T, Kakidachi H, et al. Tissue factor triggers procoagulation in transplanted mesenchymal stem cells leading to thromboembolism. Biochem Biophys Res Commun. 2013; 431: 203-209.

62. Janowski M, Lyczek A, Engels C, Xu J, Lukomska B, Bulte JW, et al. Cell size and velocity of injection are major determinants of the safety of intracarotid stem cell transplantation. J Cereb Blood Flow Metab. 2013; 33: 921-927.

63. Le Blanc K, Ringdén O. Immunomodulation by mesenchymal stem cells and clinical experience. J Intern Med. 2007; 262: 509-525.

64. Uccelli A, Moretta L, Pistoia V. Immunoregulatory function of mesenchymal stem cells. Eur J Immunol. 2006; 36: 2566-2573.

65. Kharaziha P, Hellström PM, Noorinayer B, Farzaneh F, Aghajani K, Jafari F, et al. 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: 1199-205.

66. Peng L, Xie DY, Lin BL, Liu J, Zhu HP, Xie C, et al. 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.

67. Jang YO, Kim YJ, Baik SK, Kim MY, Eom YW, Cho MY, et al. Histological improvement following administration of autologous bone marrow-derived mesenchymal stem cells for alcoholic cirrhosis: a pilot study. Liver Int. 2014; 34: 33-41.

68. Terai S, Ishikawa T, Omori K, Aoyama K, Marumoto Y, Urata Y, et al. Improved liver function in patients with liver cirrhosis after autologous bone marrow cell infusion therapy. Stem Cells. 2006; 24: 2292-2298.

69. Zhang Z, Lin H, Shi M, Xu R, Fu J, Lv J, et al. Human umbilical cord mesenchymal stem cells improve liver function and ascites in decompensated liver cirrhosis patients. J Gastroenterol Hepatol. 2012; 27 Suppl 2: 112-120.

70. Shi M, Zhang Z, Xu R, Lin H, Fu J, Zou Z, et al. Human mesenchymal stem cell transfusion is safe and improves liver function in acute-on-chronic liver failure patients. Stem Cells Transl Med. 2012; 1: 725-731.

71. Wang L, Li J, Liu H, Li Y, Fu J, Sun Y, et al. A pilot study of umbilical cord-derived mesenchymal stem cell transfusion in patients with primary biliary cirrhosis. J Gastroenterol Hepatol. 2013; 28 Suppl 1: 85-92.

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