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Mesenchymal stem cells: potential application for the treatment of hepatic cirrhosis

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Abstract

Nowadays, orthotopic liver transplantation is considered the most efficient approach to the end stage of chronic hepatic cirrhosis. Because of the limitations of orthotopic liver transplantation, stem cells are an attractive therapeutic option. Mesenchymal stem cells (MSCs) especially show promise as an alternative treatment for hepatic cirrhosis in animal models and during clinical trials. Nevertheless, the homing of transplanted MSCs to the liver occurs in limited numbers. Therefore, we review the strategies for enhancing the homing of MSCs, mainly via the delivery routes, optimizing cell culture conditions, stimulating the target sites, and genetic modification.

Keywords: Mesenchymal stem cells, Cirrhosis, Homing

Background

Cirrhosis is the end stage of progressive fibrosis that is caused by various reasons and that responds poorly to medical conservative treatment. Chronic damage to the liver leads to the extensive accumulation of extracellular matrix (ECM) among the hepatocytes. Epidemiological data state that 1.03 million cirrhotic patients worldwide die each year from severe associated complications [1].

Currently, liver transplantation is the most effective therapy for advanced hepatic diseases. Among those fortunate enough to receive liver transplantation, the survival rates at 3, 12, and 36 months are 94%, 88%, and 79%, respectively [2]. However, we should be take into account the lack of donor organs, the high costs, and the long-term use of immunosuppressants after transplantation. Thus, there is an urgent need to find alternative therapeutic strategies. Recent studies have shown that hepatocytes in the cirrhotic liver still have the potential to regenerate, but there is an imbalance between regeneration and necrosis [3]. A potential hypothesis states that a fully functioning part of the liver could be created through the proliferation of the infused cells that will remodel the injured liver. It is doubtful whether increasing the number of hepatocytes alone would be an effective treatment for the patients.

Based on the proof-of-concept, hepatocytes were transplanted to treat liver-related diseases [4]. Because of the limited number of hepatocytes and the lack of their proliferation and stability in vitro, the efficacy of grafted hepatocytes decreased progressively. Hence, it is crucial to find another readily available cell source.

This review aims to highlight all currently available evidence regarding the use of stem cells for treatment of liver cirrhosis and to determine whether there is any factual basis for their potential.

Stem cells in regenerative medicine

Stem cells, termed as clonogenic undifferentiated cells, cannot just self-renew indefinitely but can differentiate into a variety of cell lineages, including pluripotent embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), hematopoietic stem cells (HSCs), hepatic stem cells, mesenchymal stem cells (MSCs), and so forth (Fig. 1).

Splenic teratomas could be formed after infusion of ESCs [5]. The application of ESCs is therefore limited because of their potential for malignancy. iPSCs are artificially derived from a nonpluripotent cell and thus ethical issues remain the major obstacle to their clinical administration. Furthermore, the only available source of HSCs is the hematopoietic system, and this restricts their clinical application. Hepatic stem cells have been identified in fetal as well as mature liver. During embryonic development, the cells within the liver bud are recognized as hepatoblasts which are bipotent, giving

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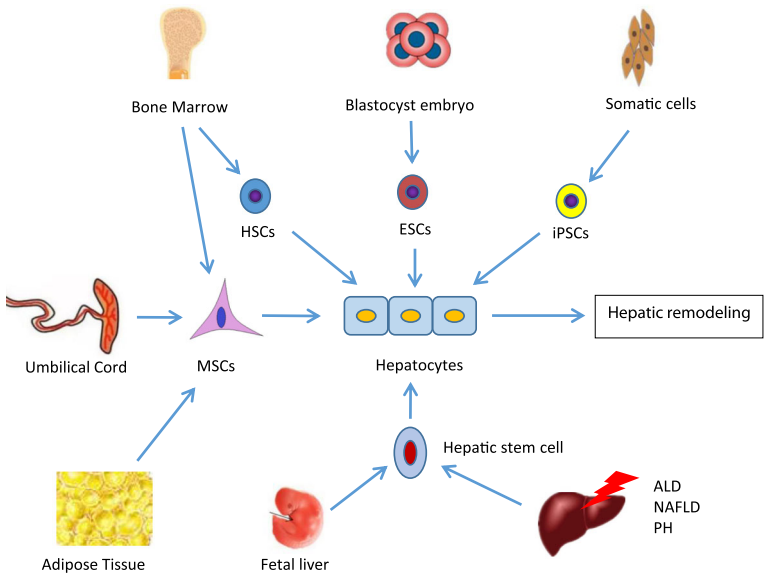

Fig. 1 The different types of stem cells isolated from different tissues differentiate into hepatocytes. ALD alcoholic liver disease, ESCs embryonic stem cells, HSCs hematopoietic stem cells, iPSCs induced pluripotent stem cells, MSCs mesenchymal stem cells, NAFLD nonalcoholic fatty liver disease, PH partial hepatectomy

rise to both hepatocytes and bile-duct epithelial cells. Moreover, cells in the ductal plates in fetal and neonatal livers are also hepatic stem cells. Their capacity to repopulate the liver upon transplantation is also well studied in animal models [6, 7]. Hepatic progenitor cells (HPCs), also defined as hepatic stem cells, are rare in normal adult livers (0.01%), located in the Canals of Hering, and all regenerative responses are mainly granted by mature hepatocytes except in certain disease states [7].

HPCs are activated after liver injury, such as alcoholic liver disease (ALD) and nonalcoholic fatty liver disease (NAFLD) [8]. Oxidative stress, which plays the main role in the pathogenesis of ALD and NAFLD, promotes the accumulation and differentiation of HPCs into hepatocytes [9, 10]; furthermore, HPCs can differentiate into hepatocytes in vivo and promote liver regeneration after partial hepatectomy or acute toxic liver injury [11]. This suggests that infusion of the progenitor cells may alleviate the damage of hepatocytes which is caused by long-lasting oxidative stress or partial hepatectomy.

The proliferation of HPCs as a response to chronic liver damage is minimal [11] and is correlated with the severity and localization of the inflammatory infiltrate [12]. Manipulation of the HPC microenvironment may be used as a therapeutic approach for the alleviation of liver insufficiency [11, 12].

In addition, evidence has suggested that mesenchymal cells through the processes of mesenchymal-epithelial or epithelial-mesenchymal transition (MET/EMT) may contribute to adult liver regeneration during chronic liver injury [13]. Mesenchymal cells in the liver may be derived not only from their own progenitor cells but also from the bone marrow (BM) by migrating to the injured liver [14, 15], although this statement is controversial. This suggests that not only HPCs but also mesenchymal cells simultaneously contribute to the initiation and development of liver diseases, although the mechanisms remain unclear [16]. This indicates that the interaction between HPCs and mesenchymal cells is important for remodeling of injured liver. The accumulating evidence suggests that HPCs could be the best alternative treatment for hepatic damage; however, HPCs may cause carcinogenesis and fibrogenesis, as has been shown in vitro [6]. Before thorough viewing of their therapeutic potential, a better knowledge of the factors that determine HPC differentiation and their possible malignant transformation is necessary.

The therapeutic potential of MSCs has been extensively investigated as well as their differentiation, immunoregulatory properties, and secretion of trophic factors. In contrast to ESCs, iPSCs, and HPCs, MSCs do not have any ethical problems and have become the ideal alternative.

During the past few years, MSCs have been mainly isolated from the bone marrow (BM-MSCs). Alternative sources of MSCs have been proposed, such as from adipose tissue (AD-MSCs), umbilical cord blood (CB-MSCs), umbilical cord (UC-MSCs), and amniotic fluid.

The application of MSCs

BM-MSCs are capable of undergoing differentiation into hepatic cells and recovering liver function, indicated by

the apoptosis of hepatic stellate cells, decreased transforming growth factor (TGF)-β1, and alpha-smooth muscle actin (α-SMA) gene expression [17]. AD-MSCs, which are more immunocompatible and easier to isolate than BM-MSCs, have a protective role against liver fibrosis [18]. UC-MSCs show a more beneficial immunogenic profile and stronger overall immunosuppressive potential than BM-MSCs [19].

Although MSC differentiation into hepatocytes has been demonstrated in vivo, evidence suggests that various trophic and immunomodulatory factors play a key therapeutic role in the treatment of liver fibrosis. The trophic factors, which are secreted by MSCs, prevent apoptosis of hepatocytes with the help of antiapoptotic factors (hepatocyte growth factor (HGF) and insulin-like growth factor (IGF-1)), angiogenetic factors (vascular endothelial growth factor (VEGF)), mitogenetic factors (epidermal growth factor (EGF), HGF, and nerve growth factor (NGF)), and TGF-α [20, 21]. Because of the smaller and less complex immunogenic potency, MSC-free therapy might constitute a better alternative treatment.

Further clinical trials have evaluated the efficiency of transplanted MSCs for treating patients with liver fibrosis. Several clinical trials have been designed to evaluate their therapeutic potential in hepatic cirrhosis treatment [22–26] (Table 1). The results of the studies seem to be promising, with improvements in model for end-stage liver disease (MELD) score and metabolic parameters, but data on histological improvement are weak. Long-term outcomes after UC-MSC treatment would be preferable for patients with liver cirrhosis [22, 23], although the short-term efficacy of infused BM-MSCs is favorable [24–26]. It should be noted that the number of infused cells, the delivery route, and the frequency of injection per patient vary in the studies. Different sources of MSCs and various populations of patients may be more convincing for any therapeutic effect. Moreover, AD-MSCs and UC-MSCs have better immunocompatibility, and they are more vitalized and much easier to isolate than BM-MSCs from older patients [18, 19]. The efficacy of autologous BM-MSCs may suffer from aging differentiation and deficiency in vitality [18, 22]. In contrast, allogeneic UC-MSCs are free from these limitations [19, 22]. Furthermore, for prognosis and better analysis on the difference between stem cells, the follow-up time of patients should be prolonged with the creation of time points. The results are also limited because of small sample sizes and absence of control groups [22–26]. Currently, there are no standardized protocols for clinical trials and it is not possible to monitor whether the infused MSCs home to the targeted organs or not.

Gholamrezanezhad et al. [27] have shown that there was no significant improvement in liver function after a

Table 1 MSCs in clinical trials treating liver fibrosis

Cell source	Delivery route	No. of cells	Patient population	No. of patients	Follow-up period	Efficacy	Limitations	Reference
UC-MSCs	Intravenous	5×10^5/kg, three times	Chronic hepatitis B	30 treatment, 15 control	12 months	Improvement of liver function and MELD score; reduced ascites	No track of the infused UC-MSCs and the histological evidence in the studied patients	[22]
UC-MSCs	Intravenous	5×10^5/kg, three times	Primary biliary cirrhosis	7 treatment	48 weeks	Decrease in serum ALP and γ-GGT; alleviation of fatigue and pruritus	No track of the infused UC-MSCs and histological evidence alterations in the studied patients; less detailed follow-up time points	[23]
BM-MSCs	Intravenous infusion	1×10^7/kg	Liver cirrhosis due to hepatitis C virus	15 treatment, 10 control	6 months	Improvement in the frequency of encephalopathy, jaundice, ascites, bleeding tendency, and lower limb edema	Less detailed follow-up time points	[24]
Autologous BM-MSCs	Hepatic artery	$0.75 \pm 0.50 \times 10^6$/patient	Hepatitis B virus cirrhosis	27 treatment, 29 control	24 weeks	Significant improvement in liver function	During follow-up, patients were lost about 1/3	[25]
Autologous BM-MSCs	Peripheral vein	1×10^6/kg	End-stage liver disease due to hepatitis C virus	20 treatment, 20 control	6 months	Significant improvement in liver function	No histological evidence; less detailed follow-up time points	[26]

ALP alkaline phosphatase, *BM-MSC* bone marrow-derived mesenchymal stem cell, *γ-GGT* glutamyl transpeptidase, *MELD* model for end-stage liver disease, *MSC* mesenchymal stem cell, *UC-MSC* umbilical cord-derived mesenchymal stem cell

1-month period of follow-up because the homing ability of BM-MSCs into the liver occurred in just a limited number of infused cells. Peng et al. [28] also mentioned that the homing ability of MSCs is the main cause why autologous MSC transplantation did not achieve acceptable long-term effects on the prognosis of a patient. The lingering problem of cell-based therapies is whether the delivered cells home within the injured sites or not and how to increase their homing ability.

Homing

Migration or homing within the injured tissues is influenced by multiple factors including the delivery route, the number of infused cells, culture conditions, and others. We review various factors that are related to the migration of MSCs.

Administration routes of MSCs

The delivery route for MSCs seems to be crucial for therapeutic efficiency. Traditional administration of MSCs is mainly via intrahepatic injection, intrasplenic injection, and by intravenous infusion. Systemic delivery of cells may cause a large number of rapid losses of cells within the capillaries, especially in the lungs, which creates a short lifespan for remaining MSCs [29]. Furthermore, infusion of cells with heparin significantly decreases the number of entrapped AD-MSCs within the lungs and increases the number of cells which are accumulated in the liver [30]. The vascular patency may be an essential factor for MSCs flowing into the targeted tissue. Intrahepatic injection appeared to be the ideal way to administer stem cells, with less entrapment of cells in the circulation, and more MSCs differentiating into hepatocytes [31]. Furthermore, administration of the MSCs via the portal vein or hepatic artery shows homing efficacy less than 5% and 20–30%, respectively [32, 33]. The hepatic artery thus seems to be the best delivery route and shows better homing efficacy; however, the vascular patency should be checked before infusion.

Optimizing cultivation conditions

During expansion, freshly isolated MSCs lose ligands or receptors which respond to migratory signals [34]. Migration is a passage-dependent process; with a higher number of passage there is a decrease in efficacy of homing. Also, high culture confluence impairs the migration of MSCs due to upregulation of tissue inhibitor of metalloproteinase (TIMP)-3 [35]. Moreover, hypoxia induces the expression of leptin which is associated with activation of both the STAT3/hypoxia-inducible factor-1α (HIF-1α)/VEGF and stromal cell-derived factor (SDF)-1/CXCR4 signaling pathways [36]. It is suggested that hypoxic preconditioning augments the recruitment of MSCs.

Stimulating the target site to recruit MSC mobilization

In the acute phase of injury, inflammatory cytokines which were released from the damaged tissues recruit monocytes for tissues repair. Compared with unirradiated mice, more MSCs homed in mice that received total body irradiation [37], suggesting that infused MSCs are moved first to injured sites. However, in patients with a subchronic or chronic phase of the disease, some indispensable chemokines for homing may be minimal or absent; therefore external stimuli may provide a simple and available novel approach for homing.

Perry et al. [38] used degenerate electrical waveforms for patients with skin scars and showed that electrical stimulation significantly reduced scar scores and may guide cell migration. Furthermore, the physiological electrical field induced MSCs to graft to the anode in vitro, which had no influence on cell senescence and phenotype [39]. Meanwhile, pulsed focused ultrasound noninvasive local pressure waves deposit energy within the targeted tissues that change the level of local chemoattractants and enhance the efficacy of homing [40]. Mechanical stretching could also enhance engrafted MSC homing within injured tissues via hypoxia, vascularization, and proliferation [41]. In summary, external stimuli may be used to control or induce direct migration of MSCs.

Genetically modified MSCs

Because of the presence of specific integration between ligand and receptor, one hypothesis is that changing the level of the receptor/ligand on MSCs may improve the efficiency of homing within the targeted tissues.

In the acute phase of injury, the damaged tissue releases numerous stromal cell-derived factors (SDF-1α), but their receptor (CXCR4) is at a low level on the cultured MSCs. MSCs with overexpressed CXCR4 have better migration potential toward SDF-1α and secrete more trophic factors, including HGF and VEGF which stimulate hepatocyte regeneration [42]. Ryu et al. [43] further explained that Akt, ERK, and p38 signal pathways are also related to the SDF-1/CXCR4 axis.

HGF is the most effective mitogen in hepatocyte regeneration and, during tissue injury, its biological effects rely on tyrosine kinase receptor and on cellular mesenchymal to epithelial transition factor (c-met) [44]. Genetic loss of c-met compromises the potential of hepatic oval cells, including their proliferation, migration, and differentiation [45]. Liu et al. [46] demonstrated that the HGF/c-met signaling pathway is crucial for MSC homing within the injured liver and that it facilitates the liver repair. Overexpressed receptor or ligands on the MSCs corresponds with the specific cytokines which are released from the injured organs and could induce homing directly within the targeted tissues.

MicroRNAs or noncoding RNAs target mRNA for degradation or inhibition and may determine the migration of MSCs. More than 60 different microRNAs in MSCs have been recently described and some of them are involved in migration, including let7, microRNA-10b, microRNA-27b, microRNA-335, and microRNA-886-3b [47]. Overexpressed microRNA-211 through the STAT3/microRNA-211/STAT5A signal pathway enhanced migration [48]. Upregulation of microRNA-221 and microRNA-26b enhanced MSC migration via the chemotactic response towards HGF through activation of PI3K/Akt signaling [49]. In addition, some other microRNAs suppressed migration of MSCs—microRNA-27b suppressed the directional migration of MSCs by targeting SDF-1α, and overexpression of microRNA-124 significantly inhibited the chemotactic migration towards HGF by downregulation of Wnt/β-catenin signaling [50]. It is suggested that microRNAs are involved in MSC potential, including their differentiation, paracrine function, proliferation, survival, and migration. Upregulation or downregulation of microRNAs in MSCs could regulate the migration.

Conclusion

The present review demonstrates that stem cell therapy has a favorable therapeutic effect. Currently, the crucial factor that determines the benefit of MSCs is the homing efficacy. The disadvantages of MSC therapy in clinical trials include the risks of iatrogenic tumorigenesis, cellular embolism, and the optimum time for the infusion of cells. Moreover, its safety in clinical trials should be approved by institutional ethics committees. In conclusion, the results on MSCs which were used for the treatment of liver fibrosis are promising, but we need to know the underlying mechanism of their therapeutic effects.

Abbreviations

AD-MSC: Adipose-derived mesenchymal stem cell; ALD: Alcoholic liver disease; BM-MSC: Bone marrow-derived mesenchymal stem cell; CB-MSC: Cord blood-derived mesenchymal stem cell; c-met: Cellular mesenchymal to epithelial transition factor; CXCR4: Chemokine receptor type 4; ECM: Extracellular matrix; EGF: Epidermal growth factor; ESC: Embryonic stem cell; HGF: Hepatocyte growth factor; HIF-1α: Hypoxia-inducible factor-1α; HPC: Hepatic progenitor cell; HSC: Hematopoietic stem cell; IGF-1: Insulin-like growth factor-1; iPSC: Induced pluripotent stem cell; MELD: Model for end-stage liver disease; MSC: Mesenchymal stem cell; NAFLD: Nonalcoholic fatty liver disease; NGF: Nerve growth factor; SDF: Stromal cell-derived factor; TGF: Transforming growth factor; TIMP: Tissue inhibitor of metalloproteinase; UC-MSC: Umbilical cord-derived mesenchymal stem cell; VEGF: Vascular endothelial growth factor

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Availability of data and materials

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Authors' contributions

YZ, YL, LZ, JL, and CZ designed the manuscript and analyzed the literature. YZ, YL, and CZ wrote the manuscript and prepared the table. All authors reviewed and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors consent to the publication of this manuscript.

Competing interests

The authors declare that they have no competing interests.

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