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Stem cell therapies for liver failures and cirrhosis

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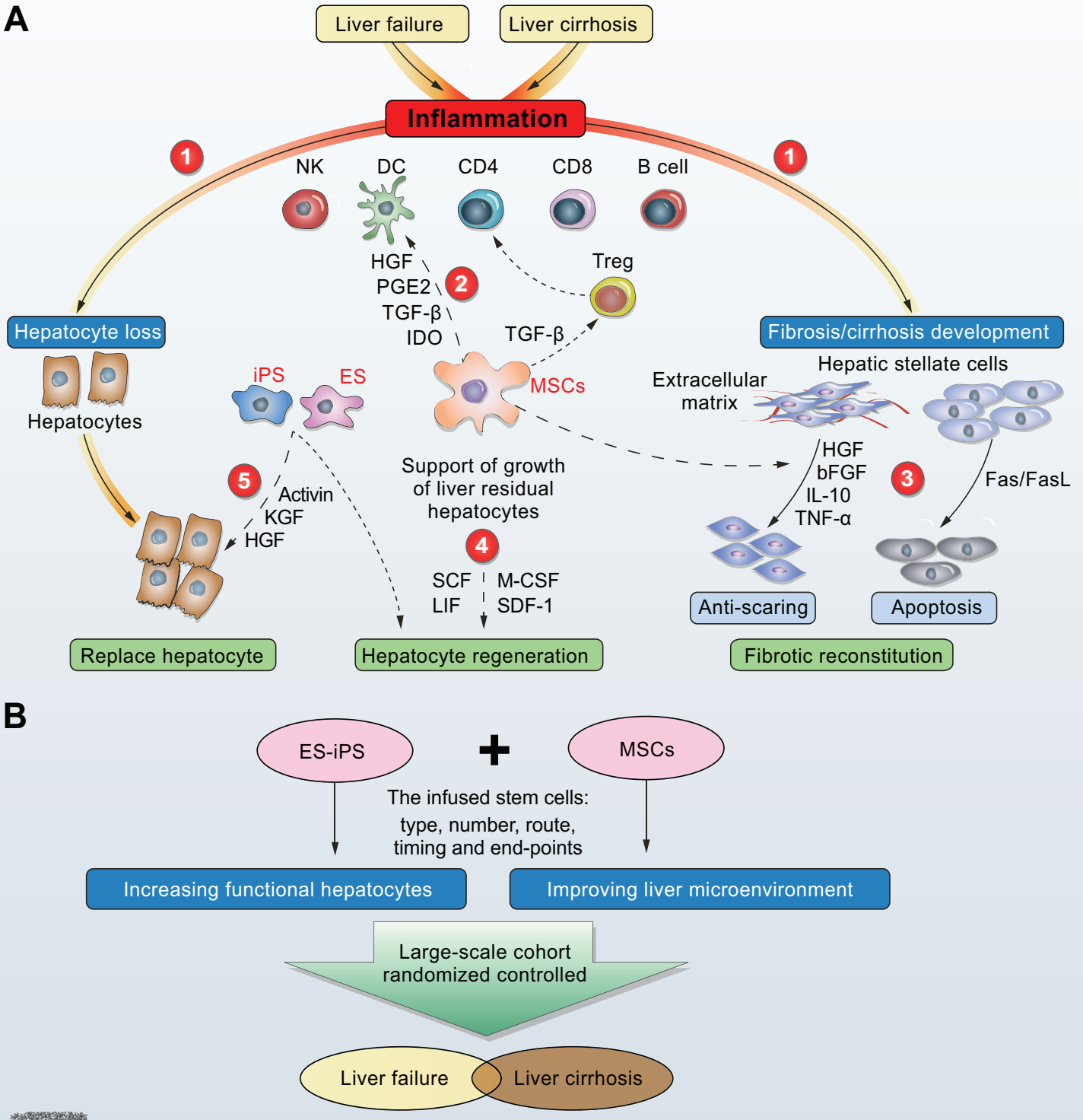

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Table. Clinical study using stem cells/MSC treatment for patients with liver failure or cirrhosis.

References	Types of stem cell infused	Number of patients	Improvement after cell infusion
Mesenchymal stem cells			
Zhang Z, *et al.,* J Gastroenterol Hepatol, 2012	Umbilical cord-MSC	30 treatment, 15 control	Improved liver function, MELD and reduced ascites
Shi M, *et al.,* Stem Cell Transl Med, 2012	Umbilical cord-MSC	24 treatment, 19 control	Improved liver function, MELD and reduced survival rates
MoHamadnejad M, *et al.,* Arch Iran Med, 2007	BM-MSC	3 cryptogenic, 1 AIH	Improved MELD
Kharaziha P, *et al.,* Eur J Gastroenterol Hepatol, 2009	BM-MSC	4 HBV, 1 HCV, 1 alcoholic, 2 cryptogenic	Improved MELD and liver function
Peng, *et al.,* Hepatology, 2011	BM-MSC	53 treatment, 105 control	Improved ALB, TBIL and MELD
Bone marrow-derived precursors			
Lyra AC, *et al.,* World J Gastroenterol, 2007	BMNC	3 HCV, 3 alcoholic, 4 others cryptogenic	Decreased TBIL and INR and improved ALB
Amer, *et al.,* Eur J Gastroenterol Hepatol, 2011	BMNC	10 intrasplenic, 10 intrahepatic, 20 control	Improved ascites and MELD
Terai S, *et al.,* Stem cell, 2006	BMNC	5 HCV, 3 HBV, 1 unknown	Improved ALB and CP
Kim JK, *et al.,* Cell Transpl, 2012	BMNC	10 HBV	Increased liver volume and CP score
Saito T, *et al.,* Stem Cell Dev, 2011	BMNC	5 treatment, 5 control	Improved ALB, PT and CP score
Lyra AC, *et al.,* Gut, 2007	BMNC	15 treatment, 15 control	Improved ALB and CP score
Hematopoietic stem cells			
Gordon MY, *et al.,* Stem Cells, 2006	$CD34^+$ cells	5 treatment	Improved ALB
MoHamadnejad M, *et al.,* World J Gastroenterol, 2007	$CD34^+$ cells	1 HBV, 1 AIH, 1 PBC, 1 cryptogenic	Improved MELD
Pai M, *et al.,* Am J Gastroenterol, 2008	Cultured $CD34^+$ cells	9 treatment	Improved ALB and CP score
Garg V, *et al.,* Gastroenterol, 2012	G-CSF mobilized $CD34^+$ cells	23 treatment, 24 placebo	Increased survival, reduced MELD scores
Han Y, *et al.,* Cytotherapy, 2008	PBMCs from G-CSF mobilized PB	20 treatment, 20 control	Improved ALB and CP score
Am Esch JS, *et al.,* Stem Cells, 2005	$CD133^+$ cells	3 treatment, 3 control	Improved liver volume after liver resection

MSC, mesenchymal stem cell; BMNC, bone marrow mononuclear cells; PB, peripheral blood; G-CSF, granulocyte colony-stimulating factor; CP, Child-Pugh score; MELD, model for end-stage liver disease; AIH, autoimmune hepatitis.

Introduction

Liver failure and cirrhosis occur as a result of a variety of chronic hepatic injuries. They display sequential and overlapping severe pathogenic processes that include severe inflammation, hepatocyte necrosis, and fibrosis/cirrhosis, and carry a high mortality rate [1]. There is a prevailing contradiction between the urgent need for liver transplants and a severe shortage of donor livers, which highlights the need to develop new therapeutic strategies for these conditions. Recent studies have shown that stem cell-based therapies may reduce liver inflammation, and subsequently improve scarring and replenish hepatocytes, which could be a promising strategy for patients with liver failure and cirrhosis [2]. By November 1st, 2012, more than 170 clinical trials had been registered or were in proof when ClinicalTrials.gov was searched for the terms “stem cells AND liver diseases”. In particular, mesenchymal stem cells (MSCs) are a heterogeneous subset of stromal stem cells that mainly express CD105, CD73, CD44, CD90, and CD71, rather than hematopoietic markers such as CD45, CD34, and CD14, or co-stimulatory molecules, such as CD80 and CD86. They can be obtained from a variety of tissues including bone marrow, adipose tissue, placenta, and Wharton jelly of the umbilical cord. Importantly, MSCs can not only differentiate into cells of the mesodermal lineage and other embryonic lineages, but can also functionally mediate immune modulation *in vivo* [3]. The administration of MSCs in small-sample size clinical trials has also been reported to be well tolerated and safe, and confers beneficial effects in patients with liver failure, by enhancing liver function and reducing Child-Pugh and MELD scores, ascites, and overall mortality (Table) [4–8]. However, some concerns and critical issues remain unanswered regarding the long-term safety and efficacy of clinical stem cell therapies.

Rationalization for stem cell therapies

Improvements in hepatic inflammatory and fibrotic microenvironments

In patients with liver failure or cirrhosis, inflammation-associated liver damage and fibrosis are usually mediated by abnormal innate and adaptive immune responses. Although many details of the involvement of MSCs with inflammatory and fibrotic processes remain unknown, MSCs have been demonstrated to play an immunomodulatory role through producing inhibitory cytokines or inducing the development of regulatory T cells [9]. Interestingly, MSC therapy appears to be effective

Fig. Stem cell therapies for liver failure and cirrhosis. (A) The rationalization for stem cell therapies in liver failure and cirrhosis. Liver failure and cirrhosis are characterized by massive inflammation and necrosis, and the accumulation of scar tissue, respectively (1). Different stem cell types and their progenies have various putative functional roles. MSCs are endowed with immunomodulatory (2), anti-fibrotic and pro-regenerative capabilities (3), which can support the expansion of regenerating hepatocytes via ameliorating the inflammatory and fibrotic hepatic microenvironments (4). Thus, ES-iPS could help expand the population of functional hepatocytes (5), ultimately improving the liver function of patients with liver failure and cirrhosis. (B) The tailoring of stem cell co-transplantation towards patients with different types and stages of liver disease may offer novel therapeutic interventions for liver failure and cirrhosis. Precise clinical protocols need to be refined and translated into well-designed, randomized controlled clinical trials that are double-blinded. These would optimize the selection of the optimal stem cell type, the number of infused stem cells, the route of administration, timing of interventions and the selection of suitable fixed primary end points.

in regulating the immune response in tissue injury, transplantation, and autoimmunity in both animal models of liver disease and patients in clinical trials [3]. MSCs can also directly inhibit the activation of hepatic stellate cells (HSCs), the main cell source of the extracellular matrix, via MSC-derived IL-10 and TNF-α, and may also induce HSC apoptosis via, in part, the Fas/FasL pathway [10]. Notably, MSCs have the potential to differentiate into myofibroblasts, which act as scar-forming cells within the liver in certain settings. Recent findings showed that use of whole bone marrow as a cell therapy in a rodent model with chronic liver injury led to the development of hepatic fibrosis [11]. Thus, MSCs are considered to act through multiple mechanisms to coordinate a dynamic, integrated response to liver inflammation and fibrosis, which prevents the progressive distortion of hepatic architecture (see Figure, panel A).

Replenish functional hepatocytes

Another realistic target of MSC therapy is to replace damaged hepatocytes with exogenous functional hepatocytes in patients with liver failure or cirrhosis. In this regard, embryonic stem (ES) cells and induced pluripotent stem (iPS) cells have been shown to be the most capable of producing large numbers of functional hepatocyte-like cells (HLCs) in both mice and humans. However, ethical issues and uncertainties regarding their behavior *in vivo* in an appropriate homoeostatic manner have limited their clinical implications [12] (see Figure, panel A). The amelioration of hepatic inflammatory and fibrotic microenvironments via stem cell therapy is likely to promote the generation of residual hepatocytes. In particular, recent studies have indicated that MSCs can produce various growth factors and cytokines, such as hepatocyte growth factor, which exerts a protective role against liver injury and is critical for hepatic regeneration [5,13] (see Figure, panel A). However, it remains to be explored whether and how MSCs can promote liver stem cells to differentiate into hepatocytes or expand the residual hepatocyte population to obtain sufficient numbers and quality *in vivo* for patients with liver diseases. In addition, future studies will need to demonstrate whether stem cell-derived HLCs have the same functionality *in vivo* as endogenous hepatocytes, and ensure that these cells cannot revert to a more primitive state within the recipient.

Current challenges

Several critical issues in clinical protocols require further investigation, such as the optimal type of transfused MSCs, the optimal therapeutic timing, the most effective number of stem cells, the best route of administration and the primary end points (see Figure, panel B). The long-term clinical benefits and safety of stem cell-based therapies should be further confirmed in a large-sized randomized controlled trial. It is currently unknown whether MSC therapy could induce complications such as hepatic artery dissection, tumorigenesis, and fibrogenesis. Additionally, it will be important to document the histological alterations caused by transplanted MSCs in order to track the fate of the infused stem cells *in vivo*, and to elucidate the mechanisms that underlie the bidirectional interactions between infused stem cells and the hepatic inflammatory/fibrotic microenvironments [14]. If these challenges can be resolved, the clinical application of stem cells for the treatment of patients with liver disease, with controllable and feasible standards and recommendations, will be further warranted.

Perspective and strategies

Stem cell therapies present an exciting but challenging frontier in translational hepatology. For patients with liver failure or cirrhosis, iPS/ES cells may be excellent candidates for the production of functional hepatocytes to replenish deficient liver functions. MSCs appear to be the optimal candidates to ameliorate hepatic fibrotic and inflammatory microenvironments. Thus, the co-transplantation of iPS/ES-derived HLCs and MSCs may offer the potential for a range of new therapeutic interventions for liver disease (see Figure, panel B). Notably, liver failure and cirrhosis have variable pathogenic properties and disease severities. Considering the variable characteristics of different stem cells (ES, iPS, and MSCs), it will be highly important to tailor future stem cell therapies to specific patient types.

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Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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