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REVIEW ARTICLE

Stem Cell Transplant for Advanced Stage Liver Disorders: Current Scenario and Future Prospects

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Abstract: ***Background:*** Chronic liver disorders (CLD), caused by the lifestyle patterns like alcoholism or by non-alcoholic fatty liver disease or because of virus-mediated hepatitis, affect a large population fraction across the world. CLD progresses into end-stage diseases with a high mortality rate. Liver transplant is the only approved treatment available for such end-stage disease patients. However, the number of liver transplants is limited due to the limited availability of suitable donors and the extremely high cost of performing the procedure. Under such circumstances, stem cell (SC) mediated liver regeneration has emerged as a potential therapeutic alternative approach.

Objective: This review aims to critically analyze the current status and future prospects of stem cell-based interventions for end-stage liver diseases. The clinical studies undertaken, the mechanism underlying therapeutic effects and future directions have been examined.

Method: The clinical trial databases were searched at https://clinicaltrials.gov.in and http://www.isrctn.com to identify randomized, non-randomized and controlled studies undertaken with keywords such as "liver disorder and mesenchymal stem cells (MSCs)", "liver cirrhosis and MSCs" and "liver disorder and SCs". Furthermore, https://www.ncbi.nlm.nih.gov/pubmed/ database was also explored with similar keywords for finding the available reports and their critical analyses.

Results: The search results yielded a significant number of studies that used bone marrow-derived stem cells, MSCs and hepatocytes. The studies clearly indicated that SCs play a key role in the hepato-protection process by some mechanisms involving anti-inflammatory, auto-immune-suppression, angiogenesis and anti-apoptosis. Further, studies indicated that SCs derived paracrine factors promote angiogenesis, reduce inflammation and inhibit hepatocyte apoptosis.

Conclusion: The SC-based interventions provide a significant improvement in patients with CLD; however, there is a need for randomized, controlled studies with the analysis of a long-term follow-up.

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1. INTRODUCTION

Chronic liver disorder (CLD) is emerging as one of the major health problems, afflicting nearly 844 million people across the world (1) and its mortality rate is comparable to those of other chronic diseases like diabetes, cardiovascular and pulmonary disorder but still, its impact is underestimated. The disease kills nearly 2 million people every year (2, 3). In western countries, non-alcoholic fatty liver disease is more prevalent whereas in Asia, Africa and Latin America, virus-induced hepatitis is the leading cause of CLD (3). Viral hepatitis alone kills more people than either HIV or malaria but has historically received less global attention. The initial liver damage caused by alcohol toxicity or virus infection or by fatty acid deposition leads to inflammation, hepatocyte necrosis, fibrosis and end-stage liver cirrhosis progressively. Other factors driving the hepatocyte necrosis involve hepatotoxicity by various everyday drugs and autoimmune attacks (4). The mechanism leading to the progression of the disease

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mechanism leading to the progression of the disease involves abnormal innate and adaptive immune response. In order to restore injured liver homeostasis, the immune system recruits $CD4^+$, $CD8^+$, natural killer (NK) cells and macrophages at the site of liver damage leading to secretion of a number of pro-inflammatory and pro-apoptotic cytokines like tumor necrosis factor (TNF-α), interferon (IFN-γ), interleukin (IL-2) and granulocyte-macrophage colony-stimulating factor (GMCSF) leading to hepatocyte death, inflammation, necrosis and immune-mediated liver injury (5,6,7,8). Furthermore, when hepatic stellate cells, which are a source of extracellular proteins, are activated to the proliferative state, they also start synthesizing collagen. The deposition of collagen and extracellular matrix (ECM) proteins leads to fibrosis. The stage further deteriorates due to an imbalance in matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) equilibrium, which is responsible for matrix remodeling (9). After attaining the cirrhosis stage, the damaged liver cannot be reversed. However, the standard treatment regimen aims at slowing down the disease progression and avoiding complications. The treatment involves the use of interferon, corticosteroids and antibiotics (10, 11). The end-stage liver failure can be managed only by orthotropic liver transplantation (OLT) which is the sole and widely accepted treatment. However, due to a number of constraints like limited availability of donors, staggering financial cost and the possibility of immune rejection, liver transplant remains a less viable option in many cases (12). In recent years, researchers have explored other possible treatment regimes for chronic liver disorders including a possibility of promoting self – regeneration of liver by using autologous or allogeneic transplant of cells or cell-based products with the aim to alter the mechanisms responsible for damaging hepatocytes, replenish the lost cells, reduce the fibrosis and stimulate the generation of hepatocytes. In this review, the SC-based approaches are analyzed in the area of regenerative medicine for liver diseases.

2. REGENERATIVE STRATEGIES FOR TREAT MENT OF LIVER DISORDERS

2.1. Transplantation of Hepatocytes

Mature hepatocytes are functional units of the liver and their infusion provides a better therapeutic alternative where organ transplant is unviable. Primary hepatocytes transplant aims to improve liver function by providing exogenous hepatocytes. During the last few decades, the approach made the transition from bench to bedside. Over a certain period of time, hepatocyte isolation, culture, storage and transplant procedures have been standardized. The three-step collagenase perfusion technique is the most widely used method for isolation (13 - 15). Freshly isolated hepatocytes can be transplanted directly in patients or could be cryo-stored for later use. The major sources of hepatocytes are liver tissues rejected for transplant or liver segments after split liver transplant. The quality of hepatocytes isolated from rejected tissues is considered unsuitable for transplant. The hepatocyte functionality can be retained by cell isolation from steatotic donors with the inclusion of an antioxidant, N-acetylcysteine, into the perfusion solution. This may greatly improve the viability of hepatocytes (16, 17). Another possible approach promising for future treatments involves *in vitro* expansion of isolated hepatocytes received from healthy donors. Replication of hepatocyte micro-environment can provide a cue for the development of hepatocyte culture platform. The selection of extracellular matrix, co-culture of supportive cells like liver biliary epithelial cells or sinusoidal endothelial cells, the addition of growth factors, amino acids and hormones can significantly enhance the survival and retain the function of cultured hepatocytes. Furthermore, culture in the 3D spheroid form can improve intercellular signaling and functionality due to the mimicking of the liver constitution (18).

2.2. Stem Cells Derived Hepatocytes

Investigators, in pursuit of finding additional types of cells which could be used for treating hepatic malfunctioning, found that MSCs could serve the purpose. Several studies have demonstrated that MSCs derived from the umbilical cord (UC-MSCs), adipose tissue (AT-MSCs), bone marrow (BM-MSCs) and amniotic fluids could be differentiated into hepatocyte-like cells (HLCs) in culture medium using specific combination and concentration of growth factors. The procedure involves initial differentiation followed by the maturation step. Prior to differentiation, MSCs are cultured in serum-deprived media supplemented with epidermal growth factor (EGF) and fibroblast growth factor (FGF). The differentiation step involves culture in the presence of hepatocyte growth factor (HGF), nicotinamide (NTA), FGF and insulin-transferrin-selenium (ITS) The maturation step is driven by oncostatin M and dexamethasone in the presence of HGF, FGF and ITS. The addition of histone deacetylase inhibitors in the maturation step promotes the expression of hepatocyte-specific genes and related functions. Several studies have reported *in vivo* differentiation of MSCs into HLCs which was marked by albumin, alpha-fetoprotein and cytokeratin 18 stainings (19 -

alpha-fetoprotein and cytokeratin 18 stainings (19 - 22).

Induced pluripotent stem cells (iPSCs) constitute another category of stem cells that can be differentiated into hepatocytes. The generated HLCs share significant features like mature hepatocytes. The method involves the generation of hepatocyte endoderm using Wnt3a/ Activin A and DMSO; expansion of hepatoblast by HGF and hepatocyte maturation in the presence of Oncostatin M (23). The HLCs are comparable to primary hepatocytes but they express low levels of albumin and cytochrome P450, have incomplete urea cycle and have high levels of alpha-fetoprotein. Furthermore, the iPSC -hepatocyte differentiation also generates partially mature phenotypes that are required to be removed along with undifferentiated cells. The presence of undifferentiated iPSCs in clinical transplant can potentially lead to teratoma formation and immune reactions (24). However, a fraction of undifferentiated cells can be reduced by implicating hepatocyte microenvironment like conditions including matrix-like structure, soluble factors, cellular interactions and inter-cellular signaling (25 - 27). Though considerable research has been done for the generation of functional hepatocytes from iPSCs, no methodology has successfully demonstrated the development of fully mature hepatocytes. Future studies may develop strategies incorporating 3D hepatic micro-environment conditions into SC differentiation.

2.3. Bone Marrow-derived Stem Cells

Bone marrow-derived stem cells comprise hematopoietic $CD34^+$ stem cells (HSCs), endothelial progenitor cells (EPCs) and BM-MSCs. HSCs are marked by the presence of specific cell markers like c-kit, Sca-1, Thy-1, CD34, CD45 and CD133 (28). HSCs exert a therapeutic effect in liver cirrhosis by trans-differentiating into hepatocytes, secreting a number of growth factors, as well as by angiogenic- and anti-apoptotic-effects. Several reports have demonstrated the hepatocytic differentiation of HSCs, but the mechanism is poorly understood. Studies, trying to decipher the underlying mechanisms, suggest that HSCs fuse with mature hepatocytes and transfer the genetic material into the cytosol of resident cells leading to stimulation in cell multiplication (29-30). However, a concern over the trans-differentiation mechanism has been raised, citing doubts over the methods adopted for collecting the data (31). HSCs, in general, secrete a number of paracrine factors like HGF, FGF-2 and insulin-like growth factor-1 (IGF-1) stimulating regeneration of damaged liver (32-33). Besides, HSCs drive repair of damaged vasculature through secretion of angiogenic factors like vascular endothelial growth factor (VEGF). HSCs also mediate hepatic repair through recruiting macrophages as they phagocytose cellular debris of damaged hepatocytes and release Wnt3a which stimulate hepatocytic differentiation of progenitor cells. Additionally, macrophages, through the release of interleukin-6 (IL-6), mediate hepatic regeneration (34-35). EPCs are derived from precursor cells, hemangioblasts, which are common precursors of HSCs and EPCs. EPCs are characterized, in general, by the presence of a CD34 cell marker. However, depending on the tissue of origin, they can display other markers also. EPCs play significant roles in neovascularization in damaged tissues. The EPCs exhibiting neoangiogenic properties are marked by the presence of CD34-Flk-1CD133. Further, EPCs improve hepatocyte regeneration and decrease matrix content through improved metalloproteinase activity (36 - 37). MSCs constitute a significantly low percentage of bone marrow-derived stem cells population. Functionally, they are capable of hepatocyte regeneration directly through differentiation into the hepatic cells and by the secretion of various paracrine factors. MSCs modulate hepatic environment through immunosuppressive activities also by altering the maturation of DCs, and by inhibiting the recruitment of T cells and NK cells (38-40). A diagrammatic representation of hepatic regeneration with the help of transplanted SCs has been summarized in Fig. (**1**).

The safety and clinical efficacy of bone marrow-derived stem cells have been evaluated in several studies. In a systematic meta-analysis, Moore et al. (41), critically analyzed findings of 1,668 studies recorded in several publications and databases. Out of those, 33 were selected for further evaluation. Based on the median cohort size of at least 10 and a follow-up time of 6 months, a significant improvement in liver function test was observed in 16 studies. They ascertained that the SC-treatment was safe in most of the cases when the peripheral administration route was used. Other routes of administration including portal vein and hepatic artery were recorded to be associated with a higher risk of provoking variceal bleeding or by increasing portal hypertension and disruption. In a multicenter, randomized, open-labeled phase II trial, Suk et al. (42) investigated the safety and efficacy of autologous bone marrow-derived stem cells with the primary end-point of improvement in fibrotic content based on picrosirius red staining. The secondary end-points were Child Pugh score and Model for end-stage Liver disease (MELD) score based on liver function tests. Reductions

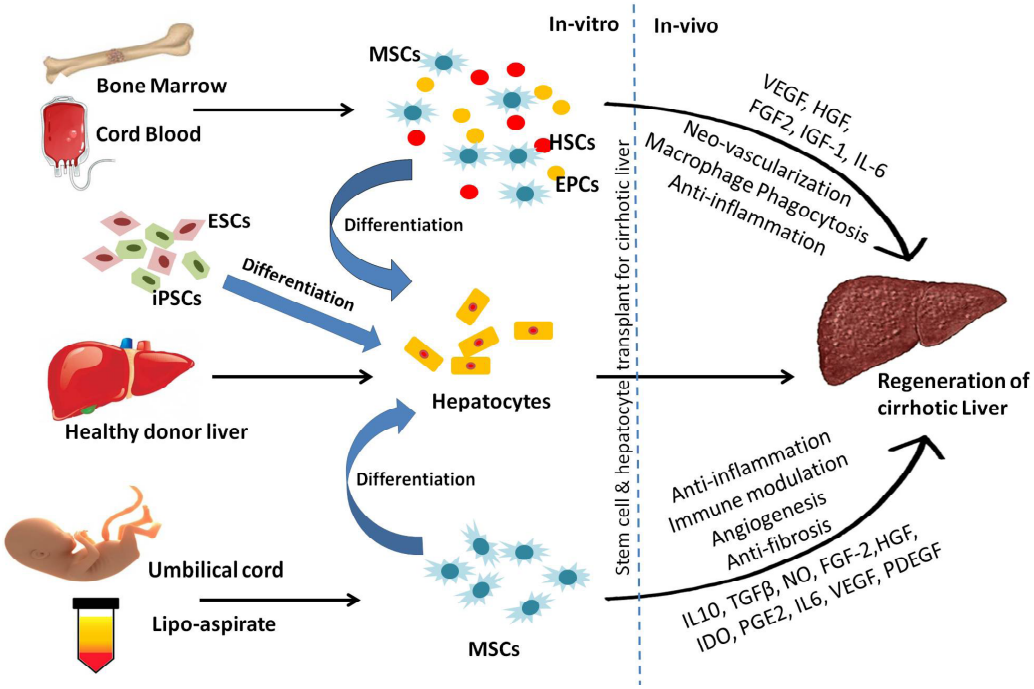

Fig. (1). Diagrammatic representation of source, isolation and mode of action of stem cells on cirrhotic liver. (MSCs - Mesenchymal stem cells; HSCs- Hematopoietic stem cells; EPCs-Endothelial progenitor cells).

in fibrotic contents by 25% after one transplant and that by 37% after two transplants were observed. The Child Pugh score and biochemical parameters improved in the group receiving SC-transplantation compared to control; however, the MELD score, which predicts end-stage liver disease survival, remained unchanged. In another report, the combinatorial effect of stem cells with antihepatitis B virus drugs was investigated. Patients with hepatitis B and decompensated liver cirrhosis were treated with lamivudine, adefovir dipivoxil and autologous bone marrow cells. The control group was treated with the drugs only. After 4 weeks of treatment, liver function indicators and clinical symptoms improved more significantly in the group receiving combinatorial treatment in comparison to other groups (43).

Several researchers have considered the MELD score as a more reliable evaluation criterion and have carried out their studies using this as the primary endpoint marker. In a multicentric, open-label, randomized and controlled phase 2 trial, the safety and efficacy of G-CSF and CD133 positive hematopoietic stem cells were evaluated. The study found that G-CSF alone or in combination with hematopoietic stem cells did not improve the primary endpoint MELD score in patients with compensated liver cirrhosis (44-46). In a double-blind, randomized, controlled trial, Mohamadnejad et al. (47) investigated the effect of autologous bone marrow mononuclear cells or CD133 positive cells transplant in patients with decompensated cirrhosis. The transplant did not result in any significant improvement in the MELD score after six months. However, a transient improvement was observed at 3 months in the group of patients receiving CD133 positive cells. The inconsistent clinical outcomes can be attributed to a number of factors like the degree of variation in primary end-points of the studies, randomization practices, disease state of the recruited patients, quality of cells infused, degree of selection of mononuclear cells or purified cells, dosage and frequency, and the route of administration. Also, poor understanding of the mechanism underlying therapeutic effect could have considerably affected the design of the clinical study, final aim and evaluation methodology and consequently, the outcome inferred.

2.4. Mesenchymal Stem Cells

MSCs constitute a category of cells widely investigated for liver cirrhosis treatment. MSCs are tissue-specific adult progenitor cells marked by their surface adherence property, positive for the expression of CD44, CD90, CD73, CD105, CD106, CD49 and Stro-1 and by the absence of CD45, CD14, CD34, CD11b, CD19 and HLA-DR surface markers (48). Though MSCs are distributed throughout body, including adipose tissue (AT-MSCs), bone marrow (BM-MSCs), dental pulp, placenta, amniotic fluid, liver, lung, gut and umbilical cord (UC-MSCs) tissue, for clinical us-

age, cells have been isolated primarily from bone marrow, adipose tissue and umbilical cord (49-51). Early studies showed that MSCs have multi-lineage differentiation capacity as they can potentially differentiate into chondrocyte, osteoblast, adipocyte, hepatocyte and cardiomyocytes like cells. However, recent findings suggest that MSCs do not have a common embryonic origin and they do not trans-differentiate outside their lineage, rather they are tissue-specific progenitor cells (52). Some researchers are of the view that MSCs are signaling cells, which exert therapeutic effects through paracrine signaling molecules (53). Our current knowledge about MSCs may contradict their stem cell characteristics but there are consensuses on regenerative and immunomodulatory properties, which are significant for the therapeutic efficacy.

MSCs are the most studied for the purpose of cell-mediated interventions among stem cells thanks to their ease of availability, low tumorigenicity, and immunosuppressive as well as immune evasive characters. Some of the recent investigations on liver disease models are enlisted in Table **1** (54-65). A search for studies in clinical databases https://clinicaltrials.gov.in and http://www.isrctn.com using the keywords combinations like "liver failure and mesenchymal stem cells", "liver cirrhosis and mesenchymal stem cells" and "liver disorder and mesenchymal stem cells", gathered 13 completed and 11 ongoing studies at the time when this article was under preparation. We found additional studies, not registered in the above databases but reported at https://www.ncbi.nlm.nih.gov/pubmed/. Researchers have reported clinical benefits of using MSCs alone or in combination with conventional therapies for treating hepatic disorders. Zhang et al. (66) investigated the effect of UC-MSCs on 45 patients with decompensated liver cirrhosis. The infusion resulted in a reduction in the volume of ascites and improved level of liver biochemical parameters. Similarly, M. Shi et al. (67) reported survival benefits in patients with acute-on-chronic liver failure. The UC-MSCs infusion significantly reduced the MELD score, serum total bilirubin (TBiL), and alanine aminotransferase (AAT). Furthermore, it improved serum albumin (ALB), cholinesterase (CHE) and prothrombin activity (PTA). In a randomized study, 20 hepatitis C positive patients with end-stage liver disease were treated with autologous bone marrow-derived MSCs. In the control group, 20 patients received conventional liver supportive treatments. Post-treatment liver function parameters and the fibrosis level improved in the treatment group. However, the controlled group did not show any significant improvement (68). Yu et. al. (69) reported the treatment of hepatitis B virus-related decompensated liver cirrhosis with UC-MSCs along with the standard treatment. In comparison to the control group (receiving standard treatments only), the treatment group demonstrated an increase in CHE, globulin and alkaline phosphatase (ALP) and reduced Child-Pugh score. In their meta-analysis, Zhao et al., (70) revisited the findings of trials performed using MSCs as a therapeutic intervention for treating liver disorders. Altogether 13 randomized and 11 nonrandomized controlled trials were analyzed. Their examination revealed that MSCs infusion was safe which improved liver functions in the initial 6 months. Also, the MSC treatment improved the MELD score, ALB, ALT, and TBiL levels and prothrombin time (PT) of patients. No improvement was observed in PTA, international normalized ratio (INR) and cholinesterase (CHE) levels. The study unfolded some interesting and significant findings. The intra-arterial administration of MSCs was found to be superior over other routes of delivery and displayed higher efficacy, which co-related with enhanced homing of MSCs into the sites of injury. Also, BM-MSCs were found to exhibit better therapeutic efficacy than UC-MSCs. Furthermore, a single administration of MSCs exhibited a more beneficial effect in terms of improved MELD score and ALT level in comparison to multiple injections. In another study, on patients with acute-on-chronic liver failure, the clinical effect of stem cells was analyzed. The study found that treatment with UC-MSCs provided short term benefit with an improvement in TbiL, ALT amd MELD score (71). The therapeutic role of MSCs infusion in liver cirrhosis caused by autoimmune disease was assessed by Liang et al. (72). Peripheral infusion of allogeneic umbilical cord-derived MSCs resulted in improved liver serum parameters and MELD scores at 6 months, 1 year and 2 years follow-ups. In another open labeled, randomized, controlled 24-week follow up study, patients of hepatitis B-related acute-on-chronic disease were treated with BM-MSCs and were assessed against standard treatment in the control group. The treatment resulted in survival benefits to patients after 24 weeks, which was evident by improving liver function and low incidence of infection (56). Similarly, Yu-Hua Li *et al*. (73) reported the infusion of umbilical cord-derived MSCs with a follow-up period of 24 months and determination of survival rate. Patients suffering from hepatitis B

Table 1. Recent pre-clinical studies demonstrating role stem cells treatment in liver disease models.

Diseases Model	Source of stem cells / conditioned media (CM)	Therapeutic benefit	Mechanism	Reference
Carbon tetra chloride induced liver model in C57BL/6J mice	BM-MSCs	Fibrosis reduced	M2 macrophage activation and M1 macrophage inhibition	[54]
Carbon tetra chloride induced liver model in mice	Heterogenic BM-MSCs rhesus macaques	Ameliorate liver fibrosis; improved biochemical parameters		[55]
Human , Hepetitis B virus related acute or chronic liver failure	Allogenic BM-MSC	Improved liver function and 24 week survival rate		[56]
Thioacetamide induced injured liver mice model	Human placental amnion membrane derived MSCs	Ameliorate liver fibrosis and restore liver function.		[57]
Hepatic stellate cells (HSCs) cell line and Carbon tetra chloride induced liver model in mice	AD-MSCs transfected with modified miRNA122 expression lentivirus. Over-expression of miR122	Ameliorate liver fibrosis	Inhibition of proliferation of hepatic stellate cells (HSCs) and collagen maturation. Alteration of gene expression related to collagen deposition.	[58]
Carbon tetra chloride induced liver fibrosis model in C57BL/6J mice	Human umbilical cord derived MSCs	Attenuated liver fibrosis, reduced portal hypertension and sodium retention	Upregulation of keratinocyte growth factor and suppression of miRNA -199.	[59]
Hepatic stellate cells (HSC) cell line and Wistar-Han rats	Human liver derived MSCs/ progenitor cells.	Proliferation of HSCs inhibited	Pro-collagen-1 synthesis inhibited; Enhanced secretion of HGF, IL-6, MMP-1 and MMP-2.	[60]
Thioacetamide induced liver FHF in mice model and Carbon tetra chloride induced liver fibrosis model	Murine bone marrow derived MSCs and conditioned media	Induction of hepatocyte proliferation; reduced inflammation and fibrosis; reduced hepatocyte apoptosis.		[61]
D-galactosamine-induced acute liver failure in Rats	BM-MSCs + Hepatocytes derived CM	AST, ALT, total Bilirubin level improved		[62]
Carbon tetra chloride induced liver model in C57BL/6 mice	AD-MSCs engineered to express miRNA 181-5p in exosomes.	Reduced fibrosis; AST, ALT, total Bilirubin level improved.	Downregulation of STAT-3 and Bcl-2 pathway and activated autophagy.	[63]
lipopolysaccharide and D-galactosamine induced acute liver failure Mice model C57BL/6J.	AD-MSCs secreted exosomes	AST and ALT level decreased.	miRNA-17 mediated inhibition of NLRP3 inflammasomes.	[64]
70 % partial Hepatectomized rat	AD-MSCs transfected with miRNA 27b	Suppressed liver inflammation, hepatic proliferation and regeneration.	Heme-oxygenase (HO-1) mediated hepatic regeneration regulated by miRNA 27b	[65]
70 % partial Hepatectomized BALB/c mice.	Human AD-AMSCs derived CM	Hepatocyte proliferation; increased level of IL-6, TNF-α, VFGF and HGF	Activation of JAK/STAT-3 pathway.	[100]

related acute- on- chronic disease were treated with plasma exchange, Entecavir and stem cells in the treatment group and only with plasma exchange in the control group. The biochemical parameters, INR, PT and MELD score improved at 4 weeks. At 24 months ALB level, INR and PT remained improved along with the cumulative high survival rate (74). However, in a separate randomized controlled trial, Mohamadnejad et

al., (75) found different results of MSCs administration in patients with decompensated cirrhosis. Out of 27 patients, 15 received MSCs and 12 received placebo. At 12 months follow-up, no significant improvement in the MELD score, Child-Pugh scores and biochemical parameters was observed. Overall, these studies indicated that MSC infusion is safe in most cases and hepatic regeneration has been observed, though benefits DID not sustain over a very long period. The improvements in biochemical parameters were not translated into survival benefits or improved MELD scores, either. It is worth keeping in mind that the inference deducted mentioned above is based on only a very limited number of studies that assessed the survival benefit for longer duration in controlled and properly randomized clinical trials.

3. MECHANISM UNDERLYING THERAPEUTIC EFFECT OF STEM CELLS

The SCs-mediated hepatic regenerative and therapeutic effects involve a plethora of mechanisms that include immune-modulatory, anti-inflammatory, anti-apoptotic, anti-oxidative, angiogenic, anti-fibrotic activities and their differentiation into hepatocyte-like cells. The imbalanced innate and adaptive immune activity in response to damages in the liver is reversed by MSCs through immune modulation. MSCs promote the induction of $CD4^+CD25^+Foxp3^+$ regulatory T cells and inhibition of proliferation of dendritic cells (DC), T and B cells, leading to immune tolerance. MSCs also down-regulate the expression of DC surface markers CD40, CD80, CD83, CD86 and MHC molecules, thereby, diminishing their antigen-presenting ability. Furthermore, NK cell and NKT cytotoxicity are also inhibited. MSCs down-regulate the proinflammatory T helper 17 cells (Th17) (76-77). MSCs promote FAS-ligand/FAS-mediated T cell apoptosis, which in turn, promote $CD4^+CD25^+Foxp3^+$ regulatory T cell activity. MSCs secrete FAS regulated monocyte chemotactic protein-1 (MCP-1) to attract T cells for FASL mediated apoptosis. The immunosuppressive characters of MSCs are associated with secretion of interleukin-10 (IL-10), transforming growth factor-β (TGF-β), nitric oxide (NO), indoleamine 2,3-dioxygenase (IDO), and prostaglandin E2 (PGE2) (78). TGF- β1 is an effective immunosuppressant secreted by MSCs and leukocytes. TGF-β1 inhibits antigen presentation activity of DCs, T cell proliferation, activation of B cells and cytotoxicity of NK cells. In addition, TGF β1 also drives the conversion of naïve T cells into $CD4^+CD25^+Foxp3^+$ regulatory T cells which further promote immune suppression (79). MSCs control the differentiation of human monocyte-derived DCs by IL-10 secretion and cellular contact. Further, they also down-regulate T lymphocyte proliferation ability of DCs. (80). Similarly, monocytes in the presence MSCs secrete IL-6, IDO and PGE2 and polarize towards anti-inflammatory macrophages (M2) (81).

MSCs provide protection to hepatocytes through paracrine secretion. Their secretome contains various cytokines and growth factors exhibiting the hepato-protective effects. The factors improve hepatocyte function; promote hepatocyte proliferation and angiogenesis, and reverse fibrotic condition (82). Moreover, MSCs mediate the polarization of monocytes from pro-inflammatory M1 macrophages to anti-inflammatory M2 macrophages resulting in the secretion of anti-inflammatory cytokines like IL-10 and CCL-1 and reduced inflammation (83).

Hepatic stellate cells, comprising 5% to 8% of total hepatic cells, stay in the quiescent stage and are involved in vitamin A storage as retinol ester. Hepatic stellate cells are also reported to work as antigen-presenting cells. Under hepatic inflammatory conditions, stellate cells transform into the active proliferative state, and start synthesizing collagen. The excessive synthesis and deposition of collagen ECM result in fibrosis (84). The process is mediated *via* TGF-β-signaling pathway. TGF-β1 is one of the prime regulators of extracellular matrix assembly and remodeling. Furthermore, TGF-β1 stimulates the secretion of endogenous TIMPs, which inhibits the activity of MMPs, causing imbalanced ECM remodeling. High TGF-β levels result in the activation of hepatic stellate cells to myofibroblasts, collagen deposition, hepatocyte death, fibrosis and consequently, liver cirrhosis (85). MSCs transplantation, under such conditions, promotes collagen and ECM degradation through the activation of MMP-9 and MMP-13 and inhibition of TIMP-1. Further, MSCs also inhibit stellate cells' activity through cell-cell contact in Notch-dependent manner and promote apoptosis through nerve growth factor (NGF) secretion (86).

Besides exhibiting the hepato-protection, MSCs mediate regeneration also through differentiating into hepatocytes. Adult and fetal liver progenitor / stem cells which are termed as oval cells and hepatoblast, respectively, are a potential source of hepatic cells. They can differentiate into hepatocytes and bile duct cells. The transplantation of oval cells and hepatoblasts has demonstrated successful liver regeneration and repopulation in a liver model (87). The use of *ex vivo* cultured hepatocytes for transplantation poses issues

like limited survival, loss of hepatocyte-specific genes and freeze-thaw related damages. However, co-culturing them with MSCs allows a sustainable culture of hepatocytes and their improved functional activities (88). Additionally, co-administration of MSCs can immuno-modulate the host environment towards successful engraftment of cells and enhance hepatocyte viability (89).

As previously discussed, adult progenitor cells, pluripotent embryonic stem cells (ESCs) and iPSCs are potentially able to differentiate into HLCs and integrate into liver at the injury site. ESCs and iPSCs can generate HLCs consistently on a large scale (90- 91). Another iPSCs based approach involves the development of hepatocytes followed by the creation of 3D structured liver buds. These are functionally and morphologically similar to liver tissues (92). However, pluripotent stem cell-based methodologies involve major issues like teratoma formation and provoking antibody development against genetically modified cells in the recipient. Though several protocols have been evaluated to optimize differentiation procedure, new approaches are required which can eliminate risks and can help in a safe transplant.

4. THERAPEUTIC POTENTIAL OF STEM CELLS DERIVED SECRETOMES

4.1. Composition of Secretomes

SCs secrete a number of growth factors, cytokines, exosomes and other molecules in surrounding media in which they are cultured, therefore, the media is termed as conditioned media (CM) and it provides a cell-free platform which offers therapeutic effects with no risk of tumorigenicity and transplant rejection. The CM is comprised of growth factors, like cytokines, other secreted proteins, miRNAs, DNAs and lipid vesicles. The secretion profile, also referred to as secretome, primarily depends on cell source and culture conditions. The secretome of stem cells generally comprises a vast number of angiogenic factors, (VEGF, bFGF, placenta growth factor (PLGF), platelet-derived growth factor (PDGF), HGF, GMCSF, stromal cell-derived factor (SDF-1), EGF, FGF-7 and heparin-binding epidermal growth factor (HB-EGF)), anti-inflammatory cytokines (IL-10, IL-17E, IL-27. IL-13, IL-12p70, TGF-β1), pro-inflammatory cytokines (IL-1b, IL-8 and IL-9), chemokines, angiogenin, MCP-1, thrombospondins and brain-derived neurotrophic factor (BDNF) (93-96). Besides the paracrine factors, MSCs also release extracellular vesicles (EVs) which are categorized into exosomes (30-100 nm), microvesicles (100-1000 nm) and apoptotic bodies (500-2000 nm). Exosomes are therapeutically potential candidates as they are cell-free structures loaded with secretory proteins, RNAs, DNA and lipid. They are lipid bilayer vesicles with a membrane rich in cholesterol, sphingomyelin and ceramide. The proteome analysis of MSC-derived exosomes revealed the presence of a substantial number of proteins. Significant quantities of these proteins are also shared by exosomes of other cell origins (96). The proteome content of exosomes primarily comprises heat shock proteins, tetraspanins, clathrins, signaling molecules, cytokines, chemokines, and growth factors. Further, exosomes were also reported to carry miRNA with a size of 10-100 nucleotides (97). The miRNA composition of exosomes depends on the source of MSCs. The exosomes of adipose-derived MSCs-origin have been found to be rich in miR-486-5p, miR-191-5p, and miR-222-3p, whereas those of bone marrow-derived MSCs were found to be rich in miR-143-3p, miR-10b-5p, miR-486-5p, miR-22-3p, and miR-21-5p (98). However, the miRNA profiles were found to be significantly variable in different studies (99).

4.2. Stem Cell-derived Secretome for Treating Hepatic Disorders

Overall, the composition of CM secretome determines the hepatoprotective effects in fibrosis. The repair is mediated by secreted growth factors, cytokines and chemokines. The anti-inflammatory cytokines reduce hepatic inflammation, promote wound healing and modulate the immune system. The growth factors, on the other hand, promote hepatocyte proliferation, reduce apoptosis, enhance angiogenesis, reverse fibrosis and protect surviving hepatocytes. The recruitment of other progenitor stem cells and angiogenesis is mediated through chemokines. Furthermore, exosomes promote hepatic regeneration through loaded miRNAs, regulating certain pathways. The functional and therapeutic role of SC-derived condition medium has been investigated in damaged liver model studies. In a comparative analysis, the transplantation of adipose-derived stem cells (ADSCs) or administration of ADSC-derived conditioned media (ADSC-CM) in partially hepatectomized mice, showed a similar level of hepatocyte regeneration (100). In a proof of concept study, the exosome rich fractionated secretome improved the cell viability, reduced cytotoxicity and oxidative stress (101). Similarly, conditioned media from ESC derived MSCs provided protection to hepatocytes and improved biochemical and histopathological parameters in thioacetamide-induced liver failure model of mice (102). Lee et al. (103), analyzed the effects of hypoxic

conditions on the secretion profile of adipose-derived SCs. The hypoxic stress resulted in elevated levels of IL-6, TNF-α, VEGF and HGF in conditioned media and also in the induction of proliferation of hepatocytes. The infusion of conditioned media activated phosphorylation of STAT3 protein and inhibited SOCS3 expression in injured hepatocytes. The study further demonstrated that beneficial effects of conditioned media were abolished when IL-6 siRNA transfected cells were used. Overall, the IL-6 mediated therapeutic effect was generated via JAK/STAT-3 signaling pathway.

As previously discussed, MSCs derived exosomes are loaded with a number of cytokines, growth factors, chemokines, proteins and miRNAs. These biomolecules play significant roles in maintaining homeostasis, biochemical processes, metabolism, immune regulation, and organ regeneration. These molecules, in general, are major components responsible for intercellular communications. Exosomes can communicate to local and remote cellular micro-environment through paracrine signaling. However, under damaged hepatic conditions, when hepatic homeostasis is disturbed, MSC derived exosomes can suppress inflammation, reduce oxidative stress, inhibit fibrosis and trigger hepatocyte regeneration through cytokines and growth factors. In a report, CCl4-induced liver fibrosis in mice model was treated with human umbilical cord-derived MSCs-exosomes. The exosome transplant resulted in decreased collagen deposition, reduced inflammation, inhibition of epithelial to mesenchymal transition and hepatic regeneration (104). miRNA are other key molecules present in exosomes that mediate hepatic regeneration through the activation or suppression of signaling pathways. In a CCl4-induced liver fibrosis mouse model, the infusion of miR-125b loaded MSC derived exosomes ameliorated fibrosis through the suppression of activated Hedgehog signaling (105). Similarly, the treatment of liver fibrosis model with miR-122 expressing MSC derived exosomes improved the condition by inhibiting activation of HSCs (106).

A number of studies have been carried out for deciphering the effects of preconditioning the cells with different physical or chemical factors. In a similar pursuit, Sukho et al. (107) analyzed the effect of cell seeding density and TNF-α and IFN-γ concentration on adipose-derived stem culture. The pre-conditioning of the cells increased secretion of VEGF and FGF while decreasing the expression of pro-inflammatory genes TNF-α and prostaglandin synthase 2. A naturally-occurring antimicrobial peptide LL-37 stimulated adipose-derived stem cells to enhance secretion of VEGF, thymosin β-4, MCP-1 and stromal cell-derived factors. Furthermore, LL-37 enhanced the expression of early growth response-1 (EGR-1) gene. The release of these factors is associated with cell migration, paracrine actions and tissue regeneration (108). Similarly, cultures involving hypoxic pre-conditions promoted VEGF-A, angiogenin secretions and increased cell viability under ischemia (109 -110). Preconditioning with SDF-1α significantly improved cell homing, proliferation and differentiation in diseased mice model (111). The findings of some of the recent studies have been summarized in Table **2** (112-120).

5. FUTURE DIRECTIONS

As discussed above that the transplantation of naive SCs significantly modulates diseased hepatic microenvironment leading to reduced inflammation and increased regeneration. However, the efficacy of infused SCs remains inconsistent due to a number of variables like partial homing of transplanted cells in hepatic sites, their poor survival under stressed microenvironment and their low proliferation rates. Recent investigations aim to address these issues in order to improve the therapeutic value of transplanted cells. One of such approaches involved SCs pre-conditioning by treating with one or more factors like hypoxic conditions, growth factors, cytokines, antibiotics or lipopolysaccharides. The approaches aim to modulate specific signaling pathways which are either up-regulated or down-regulated resulting in differential gene expression. The altered secretome due to increased secretion of anti-inflammatory cytokines and growth factors, enhances cell viability, cell homing and proliferation. The approach has been evaluated in several liver disease models.

Genetic manipulation of SCs offers an alternative approach to enhance their therapeutic value by increasing their regenerative capacity. Incorporation of certain genes in SCs *via* lentivirus or adenovirus-mediated transduction could make a number of variations like their migration to injured hepatic sites, increase in the secretion of MMPs, inhibition of hepatic stellate cells, collagen deposition, and proliferation of hepatocellular carcinoma cells. The targeted enhancement in the secretion of certain cytokines which are known to associate with specific functions could dramatically increase the therapeutic value of SCs. For example, the transplantation of MSCs overexpressing HGF, which is responsible for the amelioration of hepatic fibrosis, in a rat model resulted in decreased secretion of fibrogenic

Table 2. Summary of studies demonstrating effect of pre-conditioning or gene transfer on stem cell treatment in liver disease model.

Diseases Model	Source of Stem Cells	Conditioning Agent / Gene Incorporated	Therapeutic Benefit	Reference
Liver I/R model C57BL/6J mice.	Human UC-MSCs	Rapamycin	Elevated levels of IL-10, TGF-β1, IDO and prostaglandin E2. Reduced ALT and AST. Inhibition of cell apotosis. Improved cell homing.	106
Carbon tetra chloride induced liver model in mice	BM-MSCs	Melatonin	Low collagen deposition, high glycogen storage, Low ALT level, low expression of TGF-β1, High expression of MMPs, Higher homing ability.	107
Common bile duct ligation induced liver cirrhosis model in rat.	BM-MSCs	SDF-1α and resveratrol.	High expression of CXCR4 and MMP-9. Improved liver homing.	108
70 % partial Hepatectomized BALB/c mice.	Human AD-MSCs	Lipopolysacchride	Increased mRNA levels of IL-6, TNF-α, HGF, and VEGF.	109
Rat model of liver fibrosis induced by dimethylnitrosamine injection	Human BM-MSCs	HGF gene	Reduced level of fibrogenic cytokines PDGF-bb, and TGF-β1; Hughsecretion of MMPs	110
Carbon tetra chloride induced liver fibrosis model in nude mice.	Human – BM-MSCs	CXC R4 gene	Improved colonization at injured liver site. Reduced hepatocyte apoptosis.	111
Fulminant hepatic failure model in rat developed by galactosamine and lipopolysaccharide injection.	Rat – amniotic fluid derived MSCs	Interleukin -1 receptor antagonist (IL-1Ra) gene	Prevented liver failure and reduced mortality in mice model. Improved liver function.	112
BALB/c mice liver fibrosis model induced by thioacetamide	Mice BM-MSCs	Insulin growth factor like -1 (IGF-1)	Ameliorated liver fibrosis; reduced activation of hepatic stellate cells.	113
Male nude mice model of HCC	Human UC-MSCs	HNF4α gene	Inhibition of hepatoma cell growth and metastasis.	114

cytokines PDGF-bb and TGF-β1 and improved anti-fibrotic activity (116). Similarly, BM-MSCs over-expressing IFN-γ attenuated the proliferation of HCC cells through the inhibition of AKT/ FOXO3a pathway (121). Overexpression of another gene, hepatocyte nuclear factor 4α (HNF4α), is linked with the regulation of hepatocyte differentiation. MSCs secreting HNF4α inhibit hepatoma cell growth and metastasis *via* the down-regulation of Wnt/β-catenin signaling pathway (122). The role of different genes overexpressed in SCs targeting hepatic disorders has been summarized in Table **2**. Though the virus-based approach is the most effective in stable gene transfer in cells, in general, including SCs, the safety of engineered cells in clinical set up needs careful consideration. Several other approaches which hold potential to offer a significant advancement in regenerative medicine include exosome-mediated delivery of genes, drugs, miRNAs and proteins should also be considered. Due to the advantage of cell-free delivery system, the SCs associated risks are minimized. Further, tagging the SCs with hepatocyte-specific receptor ligands could improve the homing of the cells or uptake of exosomes loaded with various molecules.

Targeting resident endogenous stem cells through the administration of small molecules offers another unique opportunity where stem cell fate, function, self renewability and differentiation can be modulated. In comparison to genetic manipulation, the small molecules-mediated approach is comparatively less complicated, cost-effective and controllable. The mechanism is based on either inhibition or activation of signaling pathways or mimetic of biomolecules. Several small molecule-based drugs are already clinically evaluated and approved. Eltrombopag is a thrombopoietin (TPO) mimetic drug used to enhance the platelet count in thrombocytopenia cases. The drug works by enhancing the production of platelets from hematopoietic progeni-

tor cells (123). Furthermore, HSCs' transplant requires mobilization of SCs into peripheral circulation through the application of granulocyte colony-stimulating factor (GCSF). However, the SCs yield is suboptimal. AMD3100 is a molecule which significantly enhances HSCs count even after a single administration. The drug has been approved by FDA in combination with GCSF in Non-Hodgkin's lymphoma and multiple myeloma patients (124). Similarly, BIO5192 and BOP are other molecules which mobilize HSCs into peripheral circulation (125-126). Kartogenin (KGN), another molecular agent, promotes osteogenic differentiation of BM-MSCs and exerts protective and regenerative effects on the cartilage (127-128). Another molecule from isoxazoles family, Isx-1, stimulates cardiac repair post-ischemic injury (129-130).

With the advent of target approaches in regenerative medicine, future research aims towards the development of methodologies which can modulate resident *in vivo* SCs. The keys to develop new molecules which can target endogenous regenerative cells are the identification of signaling pathways, rationale drug designing and screening of compounds against SCs targets. However, other aspects including safety from undesired side effects of molecular drugs and uncontrolled proliferation of progenitor cells must be considered while designing therapeutic molecules.

CONCLUSION

A significant number of studies have demonstrated beneficial effects of SCs for treating major liver degenerative disorders. The intercellular interaction of SCs with damaged hepatocytes in a stressed microenvironment is a dynamic process and regeneration is generated in a sequential and synchronized way. Though the infusions of MSCs are proven to be safe and effective in most of the translational studies; effectiveness remains inconsistent. The inconsistencies in clinical outcomes could be attributed to a number of factors like dosage and frequency of SC implantations, route of administration and source of SCs. The optimization of procedures, careful considerations of clinical parameters during patient selection and robust randomization process can significantly improve the meaningful outcome of clinical studies. Accumulating evidence demonstrates a positive role of SC-based interventions in degenerative hepatic conditions and thus they are becoming more promising and significant.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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