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LETTER TO THE EDITOR

Innovative mesenchymal stem cell treatments for fatty liver disease

Fei-Qiong Gao, Jia-Qi Zhu, Xu-Dong Feng

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Abstract

The incidence of non-alcoholic fatty liver disease (NAFLD) and alcohol-associated liver disease (ALD) is increasing year by year due to changes in the contemporary environment and dietary structure, and is an important public health problem worldwide. There is an urgent need to continuously improve the understanding of their disease mechanisms and develop novel therapeutic strategies. Mesenchymal stem cells (MSCs) have shown promise as a potential therapeutic strategy in therapeutic studies of NAFLD and ALD. NAFLD and ALD have different triggers and their specific mechanisms of disease progression are different, but both involve disease processes such as hepatocellular steatosis and potential fibrosis, cirrhosis, and even hepatocellular carcinoma. MSCs have metabolic regulatory, anti-apoptotic, antioxidant, and immunomodulatory effects that together promote liver injury repair and functional recovery, and have demonstrated positive results in preclinical studies. This editorial is a continuum of Jiang *et al*'s review focusing on the advantages and limitations of MSCs and their derivatives as therapeutics for NAFLD and ALD. They detail how MSCs attenuate the progression of NAFLD by modulating molecular pathways involved in glucolipid metabolism, inflammation, oxidative stress, endoplasmic reticulum stress, and fibrosis. Based on recent advances, we discuss MSCs and their derivatives as therapeutic strategies for NAFLD and ALD, providing useful information for their clinical application.

Key Words: Alcohol-associated liver disease; Non-alcoholic fatty liver disease; Mesenchymal stem cells; Cell therapy; Inflammation

Core Tip: Mesenchymal stem cells (MSCs) and their derivatives are a promising therapeutic approach for non-alcoholic fatty liver disease and alcohol-associated liver disease. MSCs, which come from diverse sources and are of low immunogenicity, can attenuate disease progression by modulating key molecular pathways, such as glycolipid metabolism, inflammation, oxidative stress, and fibrosis. In addition, derivatives of MSCs are also considered as a therapeutic strategy due to their ability to retain some of the beneficial effects of MSCs while reducing the risks inherent in cell therapy. However, further studies are needed to emphasize their important mechanistic role in liver injury repair. Refining protocols for the clinical application of MSCs under the prerequisite of a well-defined mechanistic understanding may allow utilizing the full benefits of MSCs in the treatment of liver disease to enhance liver reparability and provide new hope for the treatment of non-alcoholic fatty liver disease and alcohol-associated liver disease.

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TO THE EDITOR

Liver disease is responsible for 2 million deaths per year, about 4% of all deaths (1 in 25 deaths worldwide), and deaths are mainly attributed to complications of cirrhosis and hepatocellular carcinoma, with cirrhosis most commonly associated with viral hepatitis, and alcoholic and non-alcoholic fatty liver disease (NAFLD)[1]. The epidemiology and burden of NAFLD and alcohol-associated liver disease (ALD) are changing due to the rising prevalence of obesity and increased alcohol consumption. Age-standardized death rates for NAFLD-associated cirrhosis increased between 2012 and 2017, while age-standardized death rates for cirrhosis of other etiologies declined[2]. Although NAFLD and ALD share fatty liver/steatosis, steatohepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma, the two diseases are different in many ways, including risk factors, mechanisms of lipotoxicity, gut microbiome, mitochondrial dysfunction, and other pathogenic pathways[3]. Both NAFLD and ALD, as common chronic liver diseases, may eventually progress to end-stage liver disease, for which liver transplantation remains the only effective treatment but is limited by donor organ shortages, lifelong immunosuppression, and expensive treatment. Currently, cellular therapies have been investigated as a novel alternative treatment for chronic steatosis and inflammatory and fibrotic liver diseases.

Mesenchymal stem cells (MSCs) can be derived from a wide range of biological tissues, including bone marrow, adipose, umbilical cord, and placenta, and have a wide range of proliferative capacity and pluripotent biological properties[4]. They are promising for therapeutic applications due to their easy accessibility and proliferation in culture, genetic stability, low immunogenicity, and therapeutic properties in tissue repair and immunomodulation. MSCs treatment for NAFLD and ALD provides hepatoprotection, modulates inflammatory processes and angiogenesis, and may benefit liver disease by restoring liver function and reducing inflammation and fibrosis[5]. Furthermore, numerous preclinical studies have demonstrated that extracellular vesicles released from MSCs (MSC-EVs) have considerable potential in the treatment of liver diseases, and optimization of MSC-EVs culture conditions or modification of MSC-EVs further facilitates their development and clinical application in the treatment of liver diseases[6]. The minireview by Jiang *et al*[7] provides valuable insights into the advances in the study of MSCs therapy for the alleviation of NAFLD. Our editorial examines the in-depth mechanisms of MSCs and their derivatives in the treatment of NAFLD and ALD, with the aim of helping to understand and refine the protocols for the clinical application of MSCs and providing new hope for the treatment of NAFLD and ALD.

MSCs-based therapy and NAFLD

Numerous preclinical studies have demonstrated that MSCs from different sources have a role in attenuating obesity, glucose metabolism, hepatic steatosis, inflammation, and fibrosis, which is becoming increasingly prominent in cell therapy for NAFLD[8-10] (Table 1). This may also be realized by their effects on gut microecology[11]. Immunomodulation is an important factor influencing MSC transplantation, and it has been suggested that MSCs may show clinical value in the treatment of NAFLD/non-alcoholic steatohepatitis (NASH) through their ability to inhibit CD4+ T cell activation[12,13]. MSCs can also play a therapeutic role in ameliorating hepatic steatotoxicity and metabolic disturbances in the context of NAFLD by regulating endoplasmic reticulum stress and calcium homeostasis through sarco(endo)plasmic reticulum Ca(2+)-ATPase[14]. Hepatocyte growth factor was identified as a key functional cytokine secreted by menstrual-derived endometrial stem cells, which reduces hepatic Rnf186 expression and regulates glycolipid metabolism through the AMP-activated protein kinase/mechanistic target of rapamycin pathway to alleviate NAFLD [15]. Not only through the action of secreted factors, MSCs can also rescue dysfunctional mitochondria by transferring mitochondria, thus alleviating steatosis, liver function, and glucolipid metabolism disorders in NAFLD[16,17]. Due to the pluripotency of MSCs, their differentiated hepatocyte-like cells may serve as a source of replacement cells for primary hepatocytes, which, together with their anti-inflammatory and regeneration-promoting properties, could contribute to the

Table 1 Mesenchymal stem cell treatments for non-alcoholic fatty liver disease/non-alcoholic steatohepatitis and alcohol associated liver disease

Ref.	Cell source	Secretome	Model	Disease	Function and mechanism
Du *et al*[15]	MenSCs	HGF	Mouse	NAFLD	Rnf186 regulated glucose and lipid metabolism through the AMPK/mTOR pathway HGF decreased the expression of hepatic Rnf186
Wang *et al*[13]	Mouse BM-MSCs	-	Mouse	NAFLD	Suppressed the activation of CD4+ T cells
Hu *et al*[9]	Human UC-MSCs	-	Mouse	NASH	Alleviated obesity, glucose metabolism, hepatic steatosis, inflammation, and fibrosis Regulated lipid metabolism and the PPAR signaling pathway
Yang *et al*[11]	Human UC-MSCs	-	Mouse	NASH	Alleviated hepatic steatosis, inflammation, and fibrosis Reversed the microbiome and metabolome disorders
Li *et al*[14]	Rat BM-MSCs	-	Mouse/HepG2 cells	NAFLD	Regulation of ER stress and the calcium homeostasis *via* SERCA
Bi *et al*[16]	BM-MSCs	Mitochondria	Mouse/hepatocytes	NAFLD	Mitochondrial transfer from BMSCs rescued dysfunction mitochondria
Nickel *et al*[17]	Human BM-MSCs	Mitochondria	Mouse	NASH	Resolution of NASH in mouse livers involved the donation of human mitochondria to the mouse hepatocytes
Domingues *et al*[19]	Antioxidant-upregulated human AD-MSCs	-	Mouse	Diet-induced obese	Reduced oxidative stress post-antioxidant-upregulated MSC delivery, intraperitoneally, and reduced systemic inflammation and fat accumulation in the liver
Winkler *et al*[18]	Human BM-MSCs	-	Mouse	NASH	Transplantation of MSC-derived human hepatocyte-like cells corrects NASH in mice by restoring triglyceride depositions, reducing inflammation and augmenting the regenerative capacity of the liver
Cai *et al*[32]	BM-MSCs	-	Mouse	Chronic alcoholic hepatitis	Through the PI3K/NF-κB and PI3K/mTOR pathways Modulation of natural killer B cells and follicular helper T cells
Huai *et al*[37]	Human UC-MSCs	FGF21	Mouse	ALD	Enabled macrophages to exhibit anti-inflammatory inclination
Li *et al*[38]	Lysophosphatidic acid receptors and sphingosine-1-phosphate receptors-co-treated human AD-MSCs	-	Mouse	ALD	Ameliorated histological damage, oxidative stress, inflammation, fibrosis, and lipid metabolism dysfunction, and enhanced alcohol metabolizing enzyme activity
Ge *et al*[39]	BM-MSCs/BM-MSCs pre-activated with TLR3	-	Mouse	Chronic-binge alcohol	Protection against alcohol-induced intestinal and hepatic injury and immune dysfunction
Hernandez *et al*[40]	Human UC-MSCs	-	Mouse	Alcohol binge drinking	Activated stem cells resulted in marked improvement in survival and in recovery of hepatic chemistries
Chung *et al*[34]	Sk-MSCs	HGF	Mouse/human colonic Caco-2/tc7 cells	Alcoholic liver damage	Reduced inflammatory responses in the liver and gut

Wan *et al*[35]	BM-MSCs	TSG-6	Mouse	Alcoholic hepatitis	Secreted TSG-6 to inhibit STAT3 activation and to reduce liver injury
Wan *et al*[33]	BM-MSCs	-	Mouse	Alcoholic hepatitis	Inhibited hepatic neutrophil and macrophage infiltration, and alleviated oxidative stress

MenSCs: Menstrual-derived endometrial stem cells; HGF: Hepatocyte growth factor; NAFLD: Non-alcoholic fatty liver disease; BM-MSCs: Bone marrow mesenchymal stem cells; UC-MSCs: Umbilical cord mesenchymal stem cells; NASH: Non-alcoholic steatohepatitis; AD-MSCs: Adipose-derived mesenchymal stem cells; ALD: Alcohol associated liver disease; Sk-MSCs: Skeletal muscle satellite cell-derived mesenchymal stem cells; SERCA: Sarco(endo)plasmic reticulum Ca(2+)-ATPase; AMPK: AMP-activated protein kinase; PI3K: Phosphoinositide 3-kinase; mTOR: Mechanistic target of rapamycin; NF-κB: nuclear factor kappa B; TSG-6: Tumor necrosis factor-stimulated gene-6; STAT3: Signal transducer and activator of transcription 3; FGF21: Fibroblast growth factor 21; TLR3: Toll-like receptor 3; PPAR: Peroxisome proliferator-activated receptor; ER: Endoplasmic reticulum; BMSC: Bone marrow mesenchymal stem cell; MSC: Mesenchymal stem cell.

recovery of NASH-injured liver after transplantation[18]. MSCs with different special pretreatment protocols may play similar beneficial roles in the treatment of different kinds of diseases. For example, antioxidant-up-regulated modified MSCs play an important role in reducing oxidative stress, improving glucose tolerance, reducing systemic inflammation, and ameliorating fatty liver disease[19]. MSC exosomes also showed similar enhancement effects after pretreatment, *e.g.*, curcumin[20] pretreatment and pan-peroxisome proliferator-activated receptor agonist induction[21].

Small extracellular vesicles derived from MSCs have shown promise in animal models for the treatment of NAFLD, which has led to consideration of their clinical translation[22,23] (Table 2). Kang *et al*[24] demonstrated that human umbilical cord MSCs exosomes (hUC-MSC-Exos) attenuated hepatocellular steatosis, reduced inflammatory macrophages as well as tumor necrosis factor-α and interleukin-6 to inhibit hepatic inflammatory response, and suppressed oxidative stress to alleviate NASH through the nuclear factor erythroid 2-related factor 2/NAD(P)H quinone oxidoreductase-1 antioxidant signaling pathway. In addition, hUC-MSC-Exos can prevent NAFLD by modulating lipid homeostasis through transferring calcium/calmodulin-dependent protein kinase 1 to improve lipid accumulation, inhibit fatty acid synthesis, and enhance fatty acid oxidation[25]. In addition, MSC-Exos are rich in nucleic acids that play important roles in inhibiting lipid accumulation, reactive oxygen species generation, inflammation, and liver fibrosis, which provide potential therapeutic value for NAFLD treatment, such as miR-24-3p[26], miR-223-3p[27], miR-627-5p[28], and miR-96-5p [29]. MSCs not only promote mitochondrial homeostasis in hepatocytes through mitochondrial transfer. Furthermore, it was shown that RNF31 transport *via* MSCs-derived small extracellular vesicles has a substantial impact on the regulation of hepatocyte mitochondrial homeostasis, hepatic steatosis, and recovery of liver function[30]. MSCs release a large number of molecules in conditioned medium, which may have similar beneficial effects in ameliorating NAFLD without pitfalls such as cellular obstruction, and have the potential for clinical application[31]. Clinical trials regarding MSCs therapy for NAFLD are also being conducted progressively and are expected to provide new therapeutic options for clinical application in patients[8].

MSCs-based therapy and ALD

Despite numerous studies dedicated to demonstrating the therapeutic potential of MSCs in the management of acute and chronic liver diseases, the field of utilizing MSCs in the treatment of ALD has not yet been sufficiently reported in the scientific literature (Table 1). Cai *et al*[32] previously reported that the combination of bone marrow-derived MSCs (BM-MSCs) and *Lactobacillus plumosus* culture supernatant may ameliorate the symptoms of alcoholic hepatitis through modulation of the phosphoinositide 3-kinase/nuclear factor kappa B and phosphoinositide 3-kinase/mechanistic target of rapamycin pathways, as well as modulation of natural killer B cells and follicular helper T cells. MSCs have been used to treat many inflammatory diseases, and studies have shown that MSCs are effective in treating alcoholic hepatitis through their ability to inhibit hepatic neutrophil and macrophage infiltration and attenuate oxidative stress[33]. Skeletal muscle satellite cell-derived MSCs exert anti-inflammatory effects through the secretion of prostaglandin E2 and hepatocyte growth factor, which may attenuate alcoholic liver injury by decreasing the inflammatory response in the liver and intestine[34]. Tumor necrosis factor-stimulated gene-6 secreted by BM-MSCs is able to inhibit signal transducer and activator of transcription 3 activation, thereby reducing liver injury and treating alcoholic hepatitis[35]. Application of tumor necrosis factor-stimulated gene-6 alone attenuates alcohol-induced liver injury and fibrosis by blocking the cleavage of CD44 to form the CD44 intracellular domain[36]. Pretreated MSCs likewise had enhanced therapeutic effects on ALD, and fibroblast growth factor 21-overexpressing MSCs promoted the immunomodulatory function of MSCs on macrophages through metabolic regulation of oxidative phosphorylation, causing macrophages to exhibit anti-inflammatory tendencies and thus alleviating ALD[37]. Lysophosphatidic acid receptor and sphingosine-1-phosphate receptor-co-treated human adipose-derived MSCs exhibit significant therapeutic efficacy that could enhance their efficacy in the future treatment of ALD[38]. Toll-like receptor 3-preactivated BM-MSCs can be used to protect against alcohol-induced intestinal and hepatic injury[39]. Activated hUC-MSCs significantly improved hepatocyte survival and recovery of hepatocyte chemical function compared with non-activated stem cells, which has important clinical applications[40].

BM-MSCs transplantation has been recognized as an effective treatment for liver cirrhosis, and there are clinical trials investigating the efficacy and safety of autologous BM-MSCs transplantation for alcoholic cirrhosis[41,42]. Chronic high intake of ethanol can lead to a variety of metabolic changes in the body and increased levels of ethanol and its metabolites in the body's microenvironment. It has been shown that ethanol inhibits BM-MSCs-mediated hepatocyte renewal in rats,

Table 2 Mesenchymal stem cell derivatives for treatment of non-alcoholic fatty liver disease/non-alcoholic steatohepatitis

Ref.	Cell source	Secretome	Model	Disease	Function and mechanism
Kang *et al*[24]	Human UC-MSC-EV	-	Mouse/HepG2 and AML12 cells	NASH	Nrf2/NQO-1 antioxidant signaling pathway
Yang *et al*[25]	Human UC-MSC-EV	CAMKK1	Mouse/hepatic cells	NAFLD	CAMKK1-mediated lipid homoeostasis regulation
Chen *et al*[30]	MSC-sEV	RNF31	Mouse	NAFLD	Regulation of mitochondrial homeostasis
Du *et al*[26]	Human UC-MSC-Exo	MiRNA-24-3p	Mouse/hepatocytes	NAFLD	MiR-24-3p directly targeted Kelch-like ECH-associated protein 1, and suppressed its expression Restrained lipid accumulation, ROS generation, and inflammation
Niu *et al*[27]	AD-MSC-EV	MiRNA-223-3p	Mouse/hepatocytes	NAFLD	MiR-223-3p displayed suppressive effects on lipid accumulation and liver fibrosis through E2F1 inhibition
Cheng *et al*[28]	Human UC-MSC-Exo	MiRNA-627-5p	Rat/L-02 cells	NAFLD	MiR-627-5p improved glucose and lipid metabolism and alleviated liver damage by repressing FTO expression
El-Derany *et al*[29]	BM-MSC-Exo	MiRNA-96-5p	Mouse	NASH	Caspase-2 signaling inhibition
Tawfeek and Kasem[20]	Curcumin-preconditioned MSC-Exo	-	Mouse/HepG2 cells	NASH	Regulated inflammatory, oxidative stress, and mitochondrial-dependent apoptosis-associated *ASK-JNK-BAX* genes
Kim *et al*[21]	Pan-peroxisome proliferator-activated receptor agonist-primed induced MSC-EV	-	Mouse	NASH	Reduced steatotic changes and ameliorated ER stress and mitochondiral oxidative stress induced by inflammation
Zhang *et al*[23]	MSC-sEV	-	Mouse	NASH	Polarized pro-fibrotic M2 macrophages without exacerbating liver fibrosis
Yang *et al*[31]	MSCs conditional medium	-	Mouse/L-02 cells	NAFLD	Improved mitochondrial function and alleviated inflammation and apoptosis by regulating SIRT1

UC-MSC-EV: Umbilical cord mesenchymal stem cells extracellular vesicle; NASH: Non-alcoholic steatohepatitis; NAFLD: Non-alcoholic fatty liver disease; MSC-sEV: Mesenchymal stem cells small extracellular vesicle; UC-MSC-Exo: Umbilical cord mesenchymal stem cells exosome; AD-MSC-EV: Adipose-derived mesenchymal stem cells extracellular vesicle; BM-MSC-Exo: Bone marrow mesenchymal stem cells exosome; Nrf2: Nuclear factor erythroid 2-related factor 2; NQO-1: NAD(P)H quinone oxidoreductase-1; CAMKK1: Calcium/calmodulin-dependent protein kinase 1; ROS: Reactive oxygen species; MSC: Mesenchymal stem cell.

which may affect the clinical application of MSCs for the treatment of ALD[43], and more research should be invested in exploring the in-depth mechanisms and solutions.

CONCLUSION

NAFLD and ALD are common chronic diseases with a poor prognosis. Finding treatments for these diseases can improve the prognosis and quality of life of patients. Stem cell transplantation is an emerging therapy for the treatment of acute and chronic liver diseases. Both MSCs and their derivatives are attractive therapeutic tools that have been widely explored in preclinical and clinical studies. The incidence of NAFLD and ALD is increasing every year and constantly threatening human health. MSCs secrete molecules and EVs that are considered to have potential as therapeutic agents for NFALD and ALD. However, data from preclinical studies of MSC-derived products for the treatment of animal models of ALD are limited. In addition, a large amount of research data is needed to support the current development of clinical applications of MSCs for NAFLD and ALD, including the optimal therapeutic dose, standardized pretreatment modalities, and therapeutic infusion routes. According to the review by Jiang *et al*[7], MSCs are a promising therapeutic candidate for NAFLD. However, further studies are needed to investigate the relationship between the pathological

events that occur during the development of NAFLD and ALD and the cellular and molecular mechanisms associated with the therapeutic effects of MSCs. In conclusion, MSCs are clearly a promising and attractive resource for the development of liver disease therapies, and further comprehensive studies to develop safer and more effective strategies for the treatment of NAFLD and ALD would be beneficial to realize their therapeutic potential.

FOOTNOTES

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