ISSN 1948-0210 (online)

World Journal of *Stem Cells*

World J Stem Cells 2024 August 26; 16(8): 773-826

Published by Baishideng Publishing Group Inc

World Journal of Stem Cells

Contents

Monthly Volume 16 Number 8 August 26, 2024

World Journal of Stem Cells

Monthly Volume 16 Number 8 August 26, 2024

Contents

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RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Stem Cells

ISSN
ISSN 1948-0210 (online)

LAUNCH DATE
December 31, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Carlo Ventura, Shengwen Calvin Li

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1948-0210/editorialboard.htm

PUBLICATION DATE
August 26, 2024

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World J Stem Cells 2024 August 26; 16(8): 780-783

DOI: 10.4252/wjsc.v16.i8.780

ISSN 1948-0210 (online)

EDITORIAL

Mesenchymal stem cells: A promising therapeutic avenue for non-alcoholic fatty liver disease

Chun-Han Cheng, Wen-Rui Hao, Tzu-Hurng Cheng

Specialty type: Cell and tissue engineering

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification
Scientific Quality: Grade C
Novelty: Grade B
Creativity or Innovation: Grade B
Scientific Significance: Grade B

P-Reviewer: Hu HS

Received: June 28, 2024
Revised: July 24, 2024
Accepted: August 9, 2024
Published online: August 26, 2024
Processing time: 59 Days and 2.4 Hours

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is a pressing global health concern that is associated with metabolic syndrome and obesity. On the basis of the insights provided by Jiang *et al*, this editorial presents an exploration of the potential of mesenchymal stem cells (MSCs) for NAFLD treatment. MSCs have numerous desirable characteristics, including immunomodulation, anti-inflammatory properties, and tissue regeneration promotion, rendering them attractive candidates for NAFLD treatment. Recent preclinical and early clinical studies have highlighted the efficacy of MSCs in improving liver function and reducing disease severity in NAFLD models. However, MSC heterogeneity, long-term safety concerns, and unoptimized therapeutic protocols remain substantial challenges. Addressing these challenges through standardized protocols and rigorous clinical trials is essential to the safe and successful application of MSCs in NAFLD management. Continued research into MSC mechanisms and therapeutic optimization is required to improve treatments for NAFLD and related liver diseases.

Key Words: Mesenchymal stem cells; Non-alcoholic fatty liver disease; Therapeutic potential; Liver fibrosis; Regenerative medicine; Stem cell therapy; Inflammation; Clinical trials

Core Tip: Mesenchymal stem cells (MSCs) constitute a promising therapy for non-alcoholic fatty liver disease. Expanding upon insights from the forthcoming study by Jiang *et al*. MSCs demonstrate potent immunomodulatory and anti-inflammatory effects and can promote liver tissue regeneration. Addressing challenges such as MSC heterogeneity and ensuring long-term safety through standardized protocols are crucial to harnessing the full therapeutic potential of MSCs in clinical settings.

Citation: Cheng CH, Hao WR, Cheng TH. Mesenchymal stem cells: A promising therapeutic avenue for non-alcoholic fatty liver disease. *World J Stem Cells* 2024; 16(8): 780-783
URL: https://www.wjgnet.com/1948-0210/full/v16/i8/780.htm
DOI: https://dx.doi.org/10.4252/wjsc.v16.i8.780

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a pressing global health concern that is closely associated with metabolic syndrome, obesity, and type 2 diabetes mellitus[1-3]. NAFLD involves a spectrum of liver conditions characterized by excessive hepatic fat accumulation without substantial alcohol intake; these conditions include nonalcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and hepatocellular carcinoma[3-5]. Treatment approaches for NAFLD primarily focus on lifestyle modifications and managing metabolic conditions but often fail to halt disease progression[6]. Therefore, novel therapeutic strategies are urgently required; mesenchymal stem cells (MSCs) constitute a promising option for NAFLD treatment[7]. The pathogenesis of NAFLD involves insulin resistance, oxidative stress, chronic inflammation, and genetic predisposition[8]. On the basis of insights from research, this editorial presents an exploration of the potential of MSCs for NAFLD treatment. MSCs are multipotent stromal cells capable of differentiating into various cell types and exerting strong immunomodulatory effects[1]. Studies have demonstrated that MSCs can ameliorate liver fibrosis and inflammation in preclinical NAFLD models[9,10]. MSCs exert their therapeutic effects through the paracrine secretion of anti-inflammatory cytokines such as interleukin (IL)-10 and transforming growth factor (TGF)-β, which modulate hepatic lipid metabolism and promote hepatocyte mitophagy, thereby reducing liver steatosis and oxidative stress[9,11,12]. However, translating MSC-based therapies from experimental settings to clinical applications presents substantial challenges, including the lack of standardized isolation protocols, uncertainty regarding their long-term safety, and lack of optimized delivery methods[1]. Overcoming these challenges is essential to the clinical application of MSC-based therapies and leveraging the regenerative and immunomodulatory properties of MSCs to address multiple facets of NAFLD pathology [1]. Jiang *et al*[1] demonstrated that MSCs have potential for NAFLD treatment because of their immunomodulatory, anti-inflammatory, and regenerative properties. Continued research into the mechanisms of action of MSCs and the refinement of therapeutic protocols may transform the management of NAFLD and related liver conditions. Accordingly, this editorial emphasizes the requirement for further investigation to overcome current challenges and realize the potential of MSCs in treating NAFLD.

THERAPEUTIC EFFECTS OF MSCs ON NAFLD

MSCs are multipotent stromal cells that can differentiate into various cell types, such as osteoblasts, chondrocytes, and adipocytes[1]. They can modulate immune responses, reduce inflammation, and promote tissue regeneration; they thus constitute an attractive option for treating liver diseases[4]. MSCs can be isolated from several tissues, including bone marrow, adipose tissue, and umbilical cord blood, and are thus highly accessible for therapeutic use[7]. Recent studies have demonstrated the potential of MSCs in ameliorating NAFLD. For example, one study revealed that human umbilical cord MSCs could effectively reduce diet-induced obesity and NASH-related fibrosis in mice by promoting fatty acid oxidation and reducing fatty acid synthesis[7]. Other studies have also demonstrated that MSC-derived exosomes could ameliorate experimental NASH through the nuclear factor erythroid 2-related factor/NAD(P)H: Quinone oxidoreductase 1 pathway, mediating anti-inflammatory and antifibrotic effects without the risks associated with direct stem cell transplantation[10,13]. Therefore, MSCs constitute a promising strategy for treating NAFLD through the targeting of key pathways involved in NAFLD pathogenesis. The primary mechanism of action of MSCs involves their ability to modulate hepatic lipid metabolism. Specifically, MSC-derived exosomes enhance fatty acid oxidation and suppress *de novo* lipogenesis in liver cells, thus effectively reducing hepatic steatosis[11,12]. This finding is consistent with those of studies demonstrating that interventions targeting metabolic pathways can restore lipid homeostasis in NAFLD models[14]. Moreover, MSCs exert potent anti-inflammatory effects within the liver by secreting cytokines such as IL-10 and TGF-β, which suppress Kupffer cell activation and hepatic inflammation; this is crucial for mitigating NAFLD progression[9]. A study on immune checkpoint blockade also highlighted the role of inflammatory pathways in NAFLD pathogenesis and suggested potential therapeutic avenues[15]. Additionally, MSCs can modulate the immune environment within the liver, shifting macrophage polarization and ameliorating the proinflammatory environment that exacerbates NAFLD. For

example, exosomes derived from human umbilical cord MSCs polarize profibrotic M2 macrophages without exacerbating liver fibrosis[16]. MSCs also secrete bioactive molecules such as hepatocyte growth factor and various microRNAs, which are crucial to liver regeneration and repair[17]. Furthermore, MSC-secreted miR-24-3p and miR-627-5p ameliorate NAFLD by targeting key pathways involved in lipid metabolism and inflammation[17,18]. MSCs also mitigate oxidative stress and endoplasmic reticulum stress in NAFLD by scavenging reactive oxygen species and enhancing antioxidant defenses, thereby protecting hepatocytes from oxidative damage and apoptosis[7,19,20]. Finally, MSCs are crucial to inhibiting the hepatic fibrosis associated with NAFLD; they can inhibit hepatic stellate cell activation and promote the breakdown of extracellular matrix components, which is essential for fibrosis resolution[9,13].

CLINICAL EVIDENCE AND CHALLENGES

NAFLD is characterized by hepatic fat accumulation, inflammation, and varying degrees of fibrosis and poses a substantial global health burden[1]. MSC-derived exosomes ameliorate hepatic steatosis through enhancing fatty acid oxidation and reducing *de novo* lipogenesis in hepatocytes[11]. MSCs also exert anti-inflammatory effects by secreting cytokines such as IL-10 and TGF-β, which suppress Kupffer cell activation and hepatic inflammation[9,16]. Moreover, MSCs mitigate oxidative stress by scavenging reactive oxygen species and inhibiting hepatic stellate cell activation, which is crucial to fibrosis development in NAFLD[13,19]. Clinical evidence supports the potential of MSC therapy to improve liver function and mitigate disease severity through these mechanisms[7,11]. Nevertheless, long-term safety concerns, such as adverse immune responses and tumorigenic risks, require comprehensive evaluation in clinical settings[13]. Additionally, optimizing treatment delivery and dosing strategies tailored to NAFLD pathology is crucial for maximizing therapeutic efficacy and minimizing adverse effects[1]. Future research should focus on elucidating specific mechanisms of MSC-mediated effects, including the role of MSC-derived exosomes in modulating hepatic pathways[10,18]. Robust clinical trials are required to establish the safety and efficacy of MSCs across diverse populations of patients with NAFLD [4]. Preclinical studies and early-phase clinical trials have demonstrated the potential of MSC therapy to ameliorate liver function and mitigate disease progression in NAFLD. However, several challenges remain. For example, the inherent heterogeneity of MSCs causes the therapeutic efficacy of these cells to vary considerably based on their source - bone marrow, adipose tissue, or the umbilical cord - and the methodologies used for their isolation and preparation. To overcome this variability, establishing standardized MSC isolation, culture, and delivery protocols is essential, as Jiang *et al*[1] emphasized and Korkida *et al*[4] indicated. The long-term safety of MSC therapy is also a critical concern. Potential risks, such as differentiation into unintended cell types, tumorigenicity, and immune reactions, must be meticulously evaluated. Rigorous preclinical and clinical studies are required to develop a comprehensive safety profile for MSC therapy[7,9,10]. Furthermore, determining the optimal dose, administration route, and frequency of MSC therapy is crucial to maximizing therapeutic benefits and minimizing risks. Although studies have demonstrated the potential of MSCs to treat NAFLD, optimal treatment protocols have not been established. However, research suggests that the route of administration (*e.g.*, intravenous *vs* direct hepatic injection) and the frequency of dosing considerably influence the efficacy and safety of MSC therapy[3,12]. These variables must be optimized to improve patient outcomes. MSCs exert their effects by secreting anti-inflammatory cytokines and growth factors that help reduce hepatic inflammation and fibrosis[16,17]. Future studies aimed at elucidating these mechanisms are essential to optimize MSC therapy for NAFLD [6]. In summary, although MSC therapy holds promise for the treatment of NAFLD, numerous challenges remain. Specifically, standardizing MSC preparation and delivery methods, ensuring long-term safety, and conducting large-scale clinical trials are essential prerequisites to the clinical application of MSCs to treat NAFLD. These efforts can promote the development of effective MSC treatments for NAFLD, which can improve patient outcomes and therapeutic strategies.

CONCLUSION

On the basis of the comprehensive review of Jiang *et al*[1], this editorial emphasizes the promise of MSCs in addressing the multifaceted pathogenesis of NAFLD. MSCs target critical pathways such as lipid metabolism, inflammation, oxidative stress, endoplasmic reticulum stress, and fibrosis; therefore, they constitute a novel and potent therapeutic option. Despite their therapeutic potential, MSC-based therapies have several challenges, such as a lack of standardized MSC isolation protocols, uncertain long-term safety, and a lack of understanding of the precise mechanisms through which MSCs exert their effects[4]. Nevertheless, integrating MSC therapy into clinical practice can offer new hope for effective treatments and improved patient outcomes for those with NAFLD. This editorial highlights the insights provided by Jiang *et al*[1] and recommends ongoing investigations and clinical trials into the use of MSCs to treat NAFLD.

FOOTNOTES

Author contributions: Cheng CH and Hao WR contributed equally to this editorial; Cheng CH, Hao WR, and Cheng TH have contributed to this editorial; Cheng CH and Hao WR primarily responsible for writing; Cheng TH overseeing revisions. All authors have read and approved the final manuscript.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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S-Editor: Wang JJ
L-Editor: A
P-Editor: Zhang XD

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