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LETTER TO THE EDITOR

Mechanism of mesenchymal stem cells in liver regeneration: Insights and future directions

Yu-Xin Jin, Hang-Qi Hu, Jia-Cheng Zhang, Xi-Yan Xin, Yu-Tian Zhu, Yang Ye, Dong Li

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Abstract

Mesenchymal stem cells (MSCs) are a prevalent source for stem cell therapy and play a crucial role in modulating both innate and adaptive immune responses. Non-alcoholic fatty liver disease (NAFLD) is characterized by the accumulation of triglycerides in liver cells and involves immune system activation, leading to histological changes, tissue damage, and clinical symptoms. A recent publication by Jiang *et al*, highlighted the potential of MSCs to mitigate in NAFLD progression by targeting various molecular pathways, including glycolipid metabolism, inflammation, oxidative stress, endoplasmic reticulum stress, and fibrosis. In this editorial, we comment on their research and discuss the efficacy of MSC therapy in treating NAFLD.

Key Words: Mesenchymal stem cells; Liver regeneration; Non-alcoholic fatty liver disease; Immune cells; Therapeutic strategy

Core Tip: This editorial discusses a recent article published in the *World Journal of Stem Cells*, which presents mesenchymal stem cells as a promising therapeutic approach for non-alcoholic fatty liver disease/non-alcoholic steatohepatitis. The study emphasizes targeting key molecular pathways such as glycolipid metabolism, inflammation, oxidative stress, endoplasmic reticulum stress, and fibrosis. We provide insights into their findings and explore relevant topics in this field.

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TO THE EDITOR

The liver, a central metabolic organ and a key component of the human immune system, is highly susceptible to pathogen-induced acute or chronic liver injury[1]. It harbors a dense population of myeloid and lymphoid immune cells, and disruption of liver immune homeostasis is frequently associated with various liver diseases[2]. Following liver injury, different subsets of innate immune cells such as - macrophages, natural killer (NK) cells, NKT cells, γδ T cells, dendritic cells, innate lymphoid cells, neutrophils, and eosinophils - and adaptive immune cells, including T lymphocytes, regulatory T cells, B lymphocytes, and T helper cells, become activated[3]. End-stage liver disease is marked by extensive damage to the liver parenchymal cells, resulting in liver dysfunction and irreversible liver failure. Conventional liver therapies are often fall short in treating these conditions, making liver transplantation the only effective treatment option for end-stage liver disease[4]. However, the clinical utility of liver transplantation is limited by high costs, organ shortages, surgical risks, potential immune rejection post-transplantation, and relatively low success rates. Moreover, even in cases of successful transplant cases, patients must take immunosuppressive drugs for life, which imposes significant economic and emotional burdens.

Mesenchymal stem cells (MSCs) are pluripotent stem cells capable of homing to target tissues and releasing various factors that can modify or enhance damaged tissue function[5]. MSCs can be isolated from multiple sources, including bone marrow, adipose tissue, peripheral blood, synovial membrane tissue, and cartilage[6]. These cells can differentiate into mesodermal lineages, such as adipocytes, osteocytes, and chondrocytes[7]. MSCs exhibit self-renewal, pluripotent differentiation, and low immunogenicity, making them pivotal for tissue repair. MSCs transplantation, as well as the use of MSC derivatives such as exosomes or conditioned medium, has proven effective in resolving inflammation, oxidative stress, fibrosis, and the accumulation of fatty acids and triglycerides in various non-alcoholic fatty liver disease (NAFLD) mouse models[8-11]. Recent clinical studies have demonstrated that MSC therapy alleviates liver damage, improves liver function, and promotes liver tissue regeneration[12,13]. Furthermore, liver stem cell transplantation, which can generate mature hepatocytes with self-proliferation capabilities, is currently considered a potential adjuvant treatment for end-stage liver diseases[14]. Numerous studies have confirmed the effectiveness of stem cells, particularly MSCs and induced pluripotent stem cells, in treating liver failure[15]. For auto-immune hepatitis, MSCs are especially effective due to their immune regulatory properties and significant repair capabilities[16]. One study has shown that MSC-mediated modification of the fiber domain allows the virus to replicate effectively in a hepatocellular carcinoma vector, while the hypoxic response of viruses weakens cancer cell growth, ultimately enhancing the antitumor efficacy against hepatocellular carcinoma[17].

In a recent publication titled "Current perspectives on mesenchymal stem cells as a potential therapeutic strategy for non-alcoholic fatty liver disease", the authors elucidated how MSCs can attenuate the progression of NAFLD[18]. The review offers a comprehensive overview of the therapeutic potential of MSCs in NAFLD, addressing various aspects such as the mechanisms of action, therapeutic potential, and the roles of MSCs in treating different facets of NAFLD by regulating molecular pathways related to glycolipid metabolism, inflammation, oxidative stress, endoplasmic reticulum stress, and fibrosis. Despite extensive documentation of MSC effects on liver regeneration, our understanding of the mechanisms through which MSCs promote hepatocyte regeneration remains limited.

Mechanism of MSCs in liver regeneration

It has been demonstrated that culturing MSCs with specific growth factors enables their differentiation into hepatocyte-like cells (HLCs) with liver-specific morphology and functions. These HLCs exhibit several characteristics, including the ability to uptake low-density lipoproteins and indocyanine green, secrete albumin and urea, store glycogen, and display cytochrome P450 activity[19]. Moreover, HLCs target the injury site by releasing exosomes, which help restore liver homeostasis and enhance hepatocyte function[20]. Studies have shown that MSCs migrate to the site of liver injury sites and secrete growth factors and cytokines with paracrine effects, thereby promoting liver regeneration. MSCs release various anti-apoptotic growth factors, such as stromal cell-derived factor-1, basic fibroblast growth factor, vascular endothelial growth factor, hepatocyte growth factor, and insulin-like growth factor-I, to prevent hepatic stellate cell activation and subsequent liver fibrosis[21,22]. MSCs also express numerous chemokine receptors that facilitate their localization to inflammatory sites through interaction with inflammatory chemokines and cytokines. Additionally, the presence of CD44 on the surface of MSCs enables their binding to E-selectin on endothelial cells, facilitating their migration to injury sites to promote regeneration of damaged liver cells[23]. Furthermore, MSCs enhance angiogenesis through paracrine effects, which improve venous endothelial cell proliferation, migration, and angiogenesis, while also enhancing the oxygen and nutrient supply and growth factor release in damaged tissues to support regeneration[24].

MSCs also regulate immune responses by inhibiting the activation of innate immune cells, such as macrophages, NK cells, NKT cells, dendritic cells, and monocytes, while modulating the activity of adaptive immune cells. They suppress the activation of T cell, B cell, and NK cells, reduce the expression of NK group 2, member D, decrease alanine aminotransferase and pro-inflammatory cytokine levels, and alleviate inflammatory cell infiltration in the liver[25]. Additionally, MSCs inhibit T cell and B cell proliferation, induce immunotolerance, promote regulatory T cell deve-

lopment, and suppress antibody production, secretion, and activated B cell proliferation in the adaptive immune system [26].

CONCLUSION

The study conducted by Jiang *et al*[18] is significant not only for highlighting the potential of MSCs as a therapeutic approach for NAFLD, a prevalent and complex liver condition with limited treatment options. It provides a comprehensive overview of how MSCs can mitigate the progression of NAFLD through various mechanisms, including modulation of glycolipid metabolism, inflammation, oxidative stress, endoplasmic reticulum stress, and fibrosis. However, the review could benefit from a more detailed comparison of MSCs from different sources in treating NAFLD. While it is noted that the therapeutic properties of MSCs vary with their origin, more comprehensive studies comparing efficacy are needed. A more detailed analysis would be valuable. Additionally, discussions on integrated strategies, such as combining MSCs with pharmacotherapy, lifestyle modifications, gene therapy, cell therapy, and biomaterials, should be more extensive.

Given the current understanding of MSCs - regarding their classification, characteristics, and versatile roles in regenerative medicine - they hold great promise for treating NAFLD. Their ability to differentiate into various cell types and release factors that support tissue repair and regeneration makes them a compelling option for therapeutic interventions. Overall, MSCs are crucial for facilitating liver regeneration and repairing liver damage. Further research is required to address existing limitations and uncertainties. Future studies should focus on conducting more comprehensive comparisons of the efficacy of MSCs from different sources, exploring their detailed mechanisms of action, and performing well-designed clinical trials to validate the safety and efficacy of MSC-based therapies in combination with other treatment modalities. Additionally, efforts should be made to standardize isolation and culture protocols for MSCs to ensure the consistency and reliability in therapeutic effects. The development of new MSC-based therapies for liver ailments requires further research to elucidate the molecular mechanisms governing MSC - immune cell interactions. More studies and clinical validation are necessary to develop more effective and safer therapeutic strategies utilizing MSCs for NAFLD treatment.

FOOTNOTES

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