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STEM CELL THERAPY FOR LIVER DISEASES: CURRENT PERSPECTIVES

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Objective: To evaluate the current status of stem cell therapy in the treatment of liver diseases, including efficacy, challenges, and future perspectives based on recent advances and ongoing clinical studies. **Methodology**: Bibliographic review through the PubMed database applying the following search strategy: "((Liver Cirrhosis) OR (Human Viral Hepatitis) OR (Acute Liver Failure)) AND (Stem Cells) AND (Treatment)", generating a total of 710 articles published between 2014 and 2024, 24 of which were selected for this review. **Review**: It is noteworthy that mesenchymal stem cells are capable of modulating the immune system, inducing tissue repair and reducing liver fibrosis, due to their ability to differentiate into different cell types and release bioactive factors. **Final considerations**: There is a need for more clinical studies to overcome limitations related to the standardization of the stem cell preparation process, in order to guarantee the efficacy and safety of the treatment.
Keywords: Stem cells; Liver Regeneration; Liver Diseases.

INTRODUCTION

According to Jangra et al. (2022), liver diseases represent a significant burden on the public health system, fatally affecting the global population. Its etiologies are varied, including viral infection, alcoholism and excess fat, which contribute to an inflammatory process and progressive liver fibrosis. The final stage of this process is cirrhosis, which triggers severe systemic responses. When the pathology evolves into irreversible organ dysfunction, liver transplantation appears as the only effective therapy. However, the high demand for this procedure and the shortage of donors prolongs the waiting time, often resulting in the death of the patient before the intervention (Dwyer, Macmillan, Brennan and Forbes, 2021).

In this context, stem cells have been shown to be effective and promising therapeutic agents in the treatment of liver fibrosis and cirrhosis (Lu et al., 2023).

Due to their multipotentiality, capacity for cell proliferation and differentiation, low immunogenic response, production of chemokines, immunomodulatory effects, as well as anti-fibrotic, anti-apoptotic and antioxidant activities, stem cells are increasingly considered for the development of techniques that restore the microarchitecture of the liver. Its bioavailability in various tissues, such as bone marrow, adipose tissue, muscles and fetal tissues, also contributes to this advancement (Cao, Ji and Lu, 2020; Guo et al., 2019).

However, despite the promising potential of these treatments for serious liver diseases, significant challenges still need to be overcome before this approach becomes a practical reality. These include the need to ensure long-term safety, prove efficacy, and overcome obstacles related to engraftment and survival of stem cells in the liver. In recent years, strategies such as cryopreservation and cell encapsulation have been developed to improve cell replacement. However, randomized and controlled clinical studies with longer follow-up periods are needed to increase the reliability of clinical safety and treatment efficacy (Cao, Ji, and Lu, 2020).

The characteristics of immunomodulation, cell proliferation and differentiation and anti-inflammatory capacity of stem cells stand out as advantages of this method. These approaches offer the opportunity to effectively regenerate the liver parenchyma, potentially eliminating the need for organ transplantation (Miguel et al., 2019). Therefore, the objective of the present study is to evaluate the current status of stem cell therapy in the treatment of liver diseases, including efficacy, challenges, and future perspectives based on recent advances and ongoing clinical studies.

METHODOLOGY

Bibliographic review developed following the PVO strategy, an acronym for Population or Research Problem, Variables and Outcome. The strategy was used to guide the formulation of the guiding research question: "How are stem cell-based therapies evolving in the treatment of liver diseases and what are the current and future perspectives of this field?" The searches were carried out in the PubMed - MEDLINE (Medical Literature Analysis and Retrieval System Online) databases, using combinations of search terms with Boolean operators "AND" and "OR". Specific terms were used using the following search strategy: "((Liver Cirrhosis) OR (Human Viral Hepatitis) OR (Acute Liver Failure)) AND (Stem Cells) AND (Treatment)". This initial search resulted in 710 articles. The inclusion criteria adopted were: articles in English, published between 2014 and 2024, that addressed the themes proposed for this research. Review studies, meta-analyses, observational and experimental studies, such as randomized clinical trials, were considered for inclusion, as long as they were made available in full.

The exclusion criteria eliminated duplicate articles, available only in summary form, that did not directly address the proposal studied or that did not meet the other inclusion criteria. After applying the selection criteria, 24 articles were selected from the PubMed database to compose the collection of this study.

DISCUSSION

Human mesenchymal stem cells (hMSC) are multipotent cells capable of differentiating into different cell types. In in vivo environments, these cells represent potent sources of factors capable of modulating the immune system and inducing tissue repair through intrinsic modulation of the microenvironment. This is due to their low immunogenicity, since they do not express the major histocompatibility complex II (CMH-II) receptors, CD40, CD80 and CD86, but only the CHM-I receptor, which characterizes them as non-immunogenic (Nevens and Van Der Merwe, 2022). Jia et al. (2020) mentions that treatment with hMSC, originating from the umbilical cord and administered by peripheral infusion, is capable of inhibiting monocyte activation and interrupting the inflammatory cascade in monkeys with acute liver failure, corroborating its immunomodulatory effect.

According to Dwyer, Macmillan, Brennan and Forbes (2021), a new aspect within the field of mesenchymal stem cells is in vogue. Human allogeneic liver-derived progenitor cells, which are hMSCs derived from liver tissue, have the intended effect of therapies aimed at treating acute liver failure. They receive this name because they have the ability to differentiate into hepatocyte and cholangiocytic lineages. In cases of severe loss or when replication of the liver parenchyma is compromised, these cells differentiate and proliferate into the most affected cell type. These cells do not engraft liver tissue, acting only at sites of inflammation, where they release cytokines for inflammatory control.

For Gupta et al. (2019), bone marrow-derived mesenchymal stem cells (MSCs) demonstrated significant ability to regenerate the liver, promoting differentiation into healthy hepatocytes in a rat model of thioacetamide-induced liver fibrosis. This process occurs mainly through the modulation of the inflammatory environment and the reduction of hepatic inflammatory cells, in addition to the remodeling of collagen fibers and the reduction of the expression of α-SMA, a marker of activated hepatic stellate cells (Gupta et al., 2019). Studies have indicated that such cells play a crucial role in immune modulation, mainly through the reduction of pro-inflammatory cytokines or interleukins (IL), such as IL-17 and IL-6, and the increase in anti-inflammatory cytokines such as IL-10. Modulation of these cytokines is essential for the control of liver inflammation and subsequent fibrosis (Al-Dhamin et al., 2020; De Miguel et al., 2019).

In addition to mesenchymal stem cells themselves, exosomes play a fundamental role in liver repair, as described by Elzainy, El Sadick, and Altowayan (2024). They transport regenerative and anti-inflammatory factors to liver tissue, helping to repair damage and promote liver regeneration. This is particularly evident in the treatment of acute liver injury and fibrosis (Zhou et al., 2020). According to Povero et al. (2019), MSC culture under hypoxic conditions can enhance their regenerative and immunomodulatory properties. Pre-treatment or co-treatment with specific substances, such as melatonin, has shown promise in increasing the therapeutic efficacy of MSCs, highlighting the importance of culture conditions and manipulation of these cells before their application. Hu et al. (2020) highlight that, despite advances, there are significant challenges, such as variation in results due to different sources of MSC, such as adipose tissue and bone marrow.

Furthermore, Yang et al. (2023) mention that several pre-clinical and clinical studies show that mesenchymal stem cells derived from bone marrow, adipose tissue and umbilical cord have high medicinal potential for chronic and acute liver injuries. However, this theme still lacks effectiveness in terms of

its efficacy and safety. According to Yuan et al. (2023), new approaches are being explored, including the genetic modification of MSCs to improve their therapeutic properties and the use of cell-based products, such as the previously mentioned exosomes, which present fewer risks associated with the use of living cells. These strategies aim to improve liver regeneration and immune modulation without the risks of tumorigenicity or cellular rejection. These findings highlight the significant potential of MSCs and their derivatives in the treatment of liver diseases, offering new perspectives for regenerative and immunomodulatory therapies (Yuan et al., 2023).

Treatment using mesenchymal stem cells has been promising and has demonstrated therapeutic potential in relation to liver function, especially in patients with chronic liver disease (Liu et al., 2022). It is understood that liver transplantation cannot currently be widely used due to some limitations, such as the number of donors and the use of immunosuppressive therapy over the years. Therefore, the study with MSC opened a new area of therapeutic possibility. However, mesenchymal stem cells originate from several unique biological characteristics, which complicates the standardization and production process (Gao, Yin, & Ren, 2022).

Furthermore, some limitations addressed in the studies consist of issues related to the ability to produce results, long-term tolerability, safety and adverse effects of the therapy, such as immunological reactions. Other components, such as the origin, purity, density and quality of stem cells, also influence this process (Liu et al., 2022; Zhou et al., 2020).

Regarding the modulation of microenvironmental factors, the formation of secretomes is observed, which release proteins and bioactive molecules capable of reducing liver fibrosis (Povero et al., 2019). According to Elzainy, El Sadick and Altowayan (2024), these vesicles act as carrier molecules due to their potential to cross the blood-brain barrier, long half-life in circulation and biocompatibility. Furthermore, the same authors cite studies that demonstrate the repair of damaged liver tissue and fibrosis in mice with non-alcoholic fatty liver disease, as well as the improvement of glucose metabolism in mice with type 2 diabetes, activating autophagy.

According to Yang et al. (2023), such hMSC secretomes have been shown to increase the genetic expression of the fatty acid oxidation process in hepatocytes of type 2 diabetic rats with obesity, promoting the oxidation of fatty acids in the liver after liver failure and regulating the oxidation of fatty acids in cases of breast cancer and gastrointestinal tract. Studies show the inhibition or reduction of apoptosis and the inflammatory response, in addition to the growth of liver cells. And also in the context of the repair of rat models with liver fibrosis induced by Carbon Tetrachloride (CCl4), Nevens and Van Der Merwe (2022) describe that umbilical cord hMSC (cuhMSC), in addition to improving biochemical and histopathological changes, are capable of reducing the expression of fibrosis factors, collagens, metalloproteinases, Transforming Growth Factor beta (TGFb) and SMAD proteins in the TGFb signaling pathway.

For Yao, Wang, Zhu and Rong (2020), intravenous injection of CTMcuh was able to decrease liver fibrosis, apoptosis and attenuate liver damage induced by CCl4 in mice and rats. However, in addition to the use of hMSC, the use of Human Fetal Liver-Derived Mesenchymal Stem Cells (hMSC) was more effective than the cuhMSC secretome in the treatment against fibrosis, including repairs of collagen, malondialdehyde (MDA), hydroxyproline, total bilirubin and gamma-glutamyl transferase (γ-GT). The differences in efficacy between CTMcuh and CTMffh

secretomes can be explained by the fact that the latter contains more biological activity factors than the former. The MSCffh secretome is an alternative to be considered for the treatment of liver fibrosis.

According to Sattwika, Indrarti and Bayupurnama (2021), the increase in cell rejection by immune-mediated processes occurs due to the use of reagents processed from animal origin in the stem cell preparation process. Certain preparation techniques aim at the possibility of developing a "xeno-free" culture system, however, this system cannot yet be widely disseminated, since, in the initial stage of cell preparation, several growth hormones of origin are required. animal.

It is worth noting that, according to Liu, Yuan and Wang (2022), there is a lack of standardized and rigorous clinical trials to systematically facilitate a unified treatment. Furthermore, many patients with acute liver failure, indicated for treatment with hepatocyte transplantation or bioartificial livers, are in an advanced, life-threatening stage of the disease and require urgent treatment. Therefore, it becomes difficult to formulate procedures and treatments with multiple details in time, making it difficult to reach a consensus on treatment. Additionally, in relation to the limitation of the use of pluripotent stem cells, there is the issue of the immunological response induced by transplantation. It has been reported that even genetically identical autologous cells pose risks of being immunogenic, even in syngeneic hosts (Pareja, Gómez-Lechón & Tolosa, 2019; Kakinuma; Watanabe, 2019). Ultimately, to understand more about the immune response process, more in vivo studies are needed, since treatment with induced pluripotent stem cell technology is still in its infancy and for it to become feasible, several obstacles need to be overcome. be overcome (Pareja, Gómez-Lechón & Tolosa, 2019).

FINAL CONSIDERATIONS

The findings demonstrate that stem cell therapies have proven to be effective and promising in the intervention of liver fibrosis and cirrhosis, due to their characteristics of immunomodulation, cell proliferation and differentiation and anti-inflammatory capacity, which allow the repair of liver tissue; a fact of extreme importance, since liver diseases considerably affect the general population. However, there are limitations highlighted in the studies, such as topics related to the competence to achieve results, long-term tolerability, safety and adverse effects of the therapy. Therefore, there is a need for randomized and controlled clinical studies to overcome limitations related to the standardization of the stem cell preparation process, in order to guarantee the efficacy and safety of the treatment, in addition to exploring newer aspects, such as the use of products based on in exosomes, which present fewer risks related to the use of living cells; and the genetic modification of MSCs with the aim of improving their therapeutic characteristics, offering an alternative to liver transplants and improving patients' quality of life.

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