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Research Progress on the Application of Human Umbilical Cord Mesenchymal Stem Cells in Acute Liver Failure

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Abstract: Acute liver failure (ALF), a severe clinical syndrome marked by high mortality rates and limited conventional treatments, urgently requires innovative therapeutic strategies. In recent years, human umbilical cord mesenchymal stem cells (hUC-MSCs) have emerged as a research hotspot due to their unique differentiation potential, remarkable regenerative capacity, and significant immune regulatory properties. Studies demonstrate that it can improve liver function through multiple mechanisms, promote hepatocyte regeneration, and reduce hepatic injury. Additionally, their role in regulating inflammatory responses provides new therapeutic approaches for ALF. This review systematically examines the latest research progress on hUC-MSCs in ALF treatment, focusing on their mechanisms of action, therapeutic efficacy, and clinical application prospects, aiming to provide valuable references for future research and clinical practice.

Keywords: Human umbilical cord mesenchymal stem cells; Acute liver failure; Clinical application; Research progress; Therapeutic mechanism

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1. Introduction

Acute liver failure (ALF) is a severe clinical syndrome caused by multiple factors that lead to rapid loss of liver function, accompanied by complications such as coagulation disorders and hepatic encephalopathy [1]. Traditional treatments primarily include liver transplantation and symptomatic support, but clinical outcomes are often limited due to donor shortages and surgical complication risks [2]. The advent of regenerative medicine brings to light a silver lining to the treatment of ALF, among which, human umbilical cord mesenchymal stem cells (hUC-MSCs) have gradually grabbed people's attention with their more accessible sources and immunogenetics, superior regenerative functions, making hUC-MSCs an effective choice in treating ALF [3].

Human umbilical cord mesenchymal stem cells demonstrate remarkable advantages through their multi-

directional differentiation potential and excellent immune regulatory capabilities, making them crucial for liver regeneration and repair. Experimental studies have shown that hUC-MSCs can promote hepatocyte survival and regeneration while suppressing hepatic inflammatory responses by secreting various cytokines and bioactive substances, thereby improving liver function [4, 5]. Additionally, hUC-MSCs exhibit low immunogenicity, which ensures excellent safety and tolerance during allogeneic transplantation [6].

In animal models of acute liver failure, the application of hUC-MSCs has demonstrated remarkable therapeutic efficacy. In certain cases, the therapeutic effects of hUC-MSCs even surpass those of conventional drug treatments [5, 7]. Furthermore, exosomes derived from hUC-MSCs are recognized as crucial mediators in their therapeutic mechanisms, capable of exerting anti-inflammatory and regenerative effects by modulating intercellular signaling pathways [8].

Although hUC-MSCs have shown promising potential in treating acute liver failure, further clinical studies are needed to verify their efficacy and safety. Currently, multiple clinical trials are underway to evaluate the application of hUC-MSCs in patients with acute liver failure [9, 10]. Future research should focus on optimizing the preparation and application protocols of hUC-MSCs, exploring optimal administration routes and dosages, aiming to achieve better therapeutic outcomes in clinical practice [5].

In conclusion, hUC-MSCs have shown broad application prospects in the treatment of acute liver failure. With the deepening of research and technological progress, hUC-MSCs are expected to become a safe and effective treatment option, bringing new hope to patients with acute liver failure.

2. The subject

2.1. Basic characteristics of human umbilical cord mesenchymal stem cells

2.1.1. Cell origin and characteristics

Human umbilical cord mesenchymal stem cells, a crucial stem cell type derived from human umbilical cord tissue, demonstrate superior proliferative capacity and multi-directional differentiation potential compared to other mesenchymal stem cell sources (e.g., bone marrow or adipose tissue). Research indicates that hUC-MSCs can self-renew under in vitro conditions and differentiate into various cell types, including osteoblasts, chondrocytes, and adipocytes when properly induced [11]. Furthermore, their immunological profile exhibits low immunogenicity through reduced expression of major histocompatibility complex (MHC) class I molecules and absence of MHC class II molecule expression, which provides significant advantages for clinical applications [12].

2.1.2. Differentiation potential and regeneration mechanism

The differentiation potential of hUC-MSCs holds significant promise for regenerative medicine applications. Not only can hUC-MSCs differentiate into hepatocyte-like cells (HLCs), but they also promote the regeneration of damaged liver tissues by secreting exosomes and cytokines [14]. Research indicates that hUC-MSCs regulate their differentiation through multiple signaling pathways such as Wnt/β-catenin and TGF-β, which play crucial roles in liver cell regeneration and repair [5]. Furthermore, exosomes from hUC-MSCs have been demonstrated to carry various miRNAs and proteins that modulate biological functions in target cells, promote cell proliferation and anti-apoptosis, thereby accelerating liver repair processes [15].

In conclusion, hUC-MSCs have become a key research focus for treating acute liver failure due to their unique origin, potent immune regulatory capabilities, and remarkable differentiation potential. With a deeper

understanding of their biological characteristics, hUC-MSCs are poised to play an increasingly significant role in regenerative medicine applications.

2.2. Research on human umbilical cord mesenchymal stem cells in acute liver failure

2.2.1. Progress of animal model research

Research on human umbilical cord mesenchymal stem cells in acute liver failure, particularly in animal models, has been gaining momentum. Studies demonstrate that hUC-MSCs can protect and repair the liver through multiple mechanisms. For instance, in mouse models, hUC-MSCs injection significantly suppresses hepatic inflammation, improves liver function, and enhances survival rates [16]. Additionally, hUC-MSCs have been found to regulate immune responses and reduce hepatocyte apoptosis, thereby mitigating liver damage [17]. In one study, hUC-MSCs improved hepatic histology and systemic homeostasis by inhibiting monocyte aggregation and maturation, further boosting survival rates [13]. These animal model studies have laid the groundwork for clinical applications of hUC-MSCs in treating acute liver failure.

2.2.2. Clinical trial data analysis

Clinical trial data on human umbilical cord mesenchymal stem cells in treating acute liver failure are being increasingly reported. Although the current number of clinical studies remains relatively limited, existing results demonstrate hUC-MSCs' potential to improve patients' liver function and survival rates. For instance, a study on critically ill liver failure patients found that those receiving hUC-MSCs treatment showed significant improvements in both survival rates and liver function indicators [18]. Additionally, research indicates that hUC-MSCs can effectively reduce serum levels of liver enzymes, improve jaundice, and enhance coagulation function [19]. Nevertheless, the scale and design of clinical trials still require further optimization to ensure the reliability and reproducibility of the results.

2.2.3. Evaluation of therapeutic effect and safety

When evaluating the efficacy and safety of hUC-MSCs in treating acute liver failure, researchers primarily focus on their improvement of liver function and the incidence of adverse reactions. Current studies indicate that hUC-MSCs therapy demonstrates favorable outcomes in improving liver function with relatively low rates of adverse events [20]. For instance, one study found no severe adverse events following hUC-MSC application, and patients showed significant improvement in liver function indicators post-treatment [21]. However, given the current limited clinical data, more randomized controlled trials are needed to further confirm the therapeutic effects and safety of hUC-MSCs in acute liver failure management. Additionally, researchers should explore optimal administration routes, dosage regimens, and long-term efficacy of hUC-MSCs to develop more effective treatment strategies for acute liver failure patients.

2.3. Discussion on therapeutic mechanism

2.3.1. Cell migration and directed differentiation

Research on the application of hUC-MSCs in acute liver failure demonstrates that cell migration and directed differentiation constitute crucial components of their therapeutic mechanisms. hUC-MSCs exhibit strong migratory capacity, enabling them to migrate to damaged tissues through chemokines such as CXCL12 in both in vivo and in vitro environments. Studies indicate that hUC-MSCs can promote migration to liver injury areas by

secreting various cytokines and chemokines in acute liver failure models, thereby exerting reparative effects [22]. Additionally, under the influence of the hepatic microenvironment, hUC-MSCs can differentiate into hepatocyte-like cells, enhancing liver regeneration capacity. Relevant research shows that hUC-MSCs interact with hepatocytes to promote their proliferation and functional recovery, ultimately improving liver function [23].

During cell migration, the reorganization of the cytoskeleton and intercellular adhesion are crucial factors. hUC-MSCs enhance cellular migration capacity by regulating dynamic cytoskeletal changes. Simultaneously, through interactions with integrins and adhesion proteins that engage surrounding cells or the extracellular matrix, they facilitate directed cell migration and differentiation [24]. This mechanism of cell migration and directed differentiation provides a vital biological foundation for hUC-MSCs in the treatment of acute liver failure.

2.3.2. Analysis of cytokines and signaling pathways

Cytokines play a crucial role in the therapeutic mechanisms of hUC-MSCs. Studies have shown that hUC-MSCs secrete various cytokines such as IL-6, IL-10, and TGF-β, which are key players in regulating inflammatory responses and promoting cell proliferation and differentiation [27]. Additionally, hUC-MSCs activate multiple signaling pathways, including MAPK and PI3K/Akt, to regulate cellular survival and proliferation. The activation of these signaling pathways not only promotes self-renewal of hUC-MSCs but also enhances their repair capacity in acute liver failure [25].

In the treatment of acute liver failure, human umbilical cord mesenchymal stem cells form a complex therapeutic network through cytokine secretion and activation of signaling pathways. The interaction between these cytokines and signaling pathways not only promotes the migration and directed differentiation of hUC-MSCs but also enhances their immune regulatory functions, thereby providing new approaches and methods for treating acute liver failure [26]. Further investigation into these mechanisms will help optimize the clinical application of hUC-MSCs.

2.4. Future research directions

2.4.1. Optimization of cell therapy

Human umbilical cord mesenchymal stem cells show promising applications in ALF, though further optimization of cell therapy protocols is required to enhance therapeutic efficacy. Research indicates that hUC-MSCs possess multiple biological properties such as immune regulation, anti-inflammatory effects, and tissue repair promotion, making them ideal candidates for ALF treatment. However, cell therapy outcomes are influenced by multiple factors, including cell source, preparation methods, administration routes, and dosage [28]. Future studies should focus on standardizing hUC-MSC preparation procedures to ensure consistent cell quality. Additionally, exploring the impact of different administration routes (e.g., intravenous, intraperitoneal, or local injection) on therapeutic outcomes remains a crucial direction. Optimizing cell culture conditions and expansion techniques may improve cell viability and functionality, thereby enhancing treatment effectiveness [29].

Further research should focus on the distribution and survival of hUC-MSCs in vivo. By employing imaging techniques such as bioluminescence or magnetic resonance imaging, the localization and persistence of hUC-MSCs in the liver can be monitored in real time, thereby evaluating their therapeutic efficacy. Additionally, studying the interactions between hUC-MSCs and the host immune system is crucial for optimizing treatment strategies. Modifying the immunological properties of hUC-MSCs may enhance their effectiveness in allogeneic liver transplantation therapy [30].

2.4.2. Potential side effects and countermeasures

While hUC-MSCs show promising potential in treating acute liver failure, their potential side effects warrant close monitoring. Research indicates that these cells may trigger immune responses under specific conditions, potentially leading to adverse reactions [31]. Future studies should therefore prioritize evaluating the safety of hUC-MSCs, with particular attention to their long-term effects in vivo.

To minimize potential side effects, researchers may consider optimizing the cell administration regimen. For instance, administering low-dose doses in divided administrations could reduce adverse reactions while maintaining therapeutic efficacy. Additionally, monitoring patients' immune responses and biochemical markers during treatment is essential to adjust the therapy plan promptly when necessary.

In conclusion, future research should comprehensively consider the therapeutic effect and safety of hUC-MSCs, and achieve better clinical application effects by optimizing treatment regimens, combining other therapies, and strengthening the monitoring and management of side effects [32].

2.5. Clinical application prospect

Human umbilical cord mesenchymal stem cells hold great promise in the treatment of ALF. As research into their therapeutic potential deepens, numerous clinical trials and basic studies have demonstrated that hUC-MSCs can improve liver function, promote hepatocyte regeneration, and reduce liver damage through multiple mechanisms. These cells not only exhibit strong immune regulatory capabilities but also secrete various growth factors and cytokines to facilitate liver repair and regeneration. Additionally, the relatively straightforward acquisition of hUC-MSCs and fewer ethical concerns make them advantageous for clinical applications. With ongoing advancements in related research, hUC-MSCs are poised to become a novel and effective therapeutic approach in managing acute liver failure.

2.5.1. Ethical issues and social acceptance

While the application of human umbilical cord mesenchymal stem cells faces fewer ethical controversies, public acceptance remains a key consideration. Given that these cells originate from newborns, some groups may harbor reservations about their source. Moreover, the public's understanding and awareness of stem cell research directly influence its acceptance. Therefore, conducting extensive public education campaigns to enhance awareness of hUC-MSCs and dispel misconceptions is crucial. Simultaneously, establishing transparent ethical review mechanisms to ensure compliance and ethical standards in research and clinical applications will further boost societal trust and acceptance of hUC-MSCs utilization.

2.5.2. Economic evaluation

When evaluating the economic benefits of hUC-MSCs for acute liver failure, comprehensive considerations must be integrated, including therapeutic outcomes, patients' quality of life, and long-term healthcare costs. Initial studies indicate that while hUC-MSCs may temporarily increase medical expenditures, they could significantly reduce subsequent treatment expenses in the long run by effectively improving liver function and reducing complication risks. Therefore, conducting a thorough cost-benefit analysis is essential to provide policymakers with scientific evidence for advancing clinical applications of hUC-MSCs. Furthermore, as technology advances and production costs decrease, the economic viability of hUC-MSCs will continue to improve, facilitating their widespread clinical adoption.

3. Conclusion

Human umbilical cord mesenchymal stem cells, as an emerging cell therapy approach, have demonstrated remarkable potential in recent studies on acute liver failure. Current literature indicates that hUC-MSCs not only exhibit promising therapeutic effects but also attract research attention due to their abundant availability and fewer ethical concerns. However, this promising field still faces numerous challenges and uncertainties that require comprehensive exploration from multiple perspectives.

First, the mechanisms of action of hUC-MSCs remain incompletely understood. While existing studies have revealed their roles through immune regulation, cell regeneration, and repair mechanisms, conflicting findings persist across research lines. Some studies emphasize hUC-MSCs' importance in liver protection, while others focus on their role in modulating inflammatory responses. These divergent perspectives not only hinder a comprehensive understanding of hUC-MSCs' mechanisms but also pose challenges for standardizing clinical applications. Therefore, future research should employ larger-scale clinical trials and fundamental studies to further clarify the specific roles of hUC-MSCs in treating acute liver failure, thereby establishing a more robust theoretical foundation for clinical implementation.

Secondly, optimizing treatment protocols remains a pressing challenge. The use of varying stem cell dosages, administration routes, and treatment durations across studies has compromised result comparability. To achieve optimal therapeutic outcomes for hUC-MSCs, researchers must develop comprehensive treatment strategies encompassing cell sourcing, preparation processes, delivery methods, and potential combination therapies. This approach not only enhances efficacy but also minimizes adverse effects while ensuring patient safety.

Furthermore, the clinical feasibility and sustainability of hUC-MSCs require focused attention. While preliminary clinical trials demonstrate promising therapeutic potential for acute liver failure patients, large-scale clinical implementation still faces multiple challenges, including standardized stem cell preparation, standardized clinical protocols, and ethical/legal considerations. To ensure sustainable application of hUC-MSCs, researchers must collaborate closely with clinicians, ethics committees, and regulatory agencies to establish rigorous standards and procedures that guarantee both safety and efficacy in treatment.

In conclusion, human umbilical cord mesenchymal stem cells demonstrate significant potential in treating acute liver failure. However, further research is required to clarify their mechanisms of action, optimize therapeutic approaches, and enhance clinical applicability. Through multidisciplinary collaboration and interdisciplinary communication, the clinical translation of hUC-MSCs can be further advanced, benefiting more patients and offering new hope for acute liver failure treatment. Future studies should balance diverse perspectives and findings to establish more comprehensive and objective conclusions, thereby providing reliable guidance for clinical practice.

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The authors declare no conflict of interest.

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