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From inflammation to regeneration: Advances in stem cell therapy for chronic liver disease.

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Introduction

Chronic Liver Disease (CLD), encompassing conditions such as cirrhosis, Non-Alcoholic Steatohepatitis (NASH), and hepatitis B/C, remains a major cause of morbidity and mortality globally. The pathological trajectory of CLD typically progresses from persistent inflammation, through fibrosis, to irreversible organ failure. Currently, liver transplantation is the only definitive cure for end-stage liver disease. However, organ shortages, immunosuppression complications, and high costs limit its accessibility.In recent years, stem cell therapy has emerged as a promising regenerative strategy to restore liver function, reduce fibrosis, and modulate immune responses. Stem cells particularly Mesenchymal Stem Cells (MSCs) and induced Pluripotent Stem Cells (iPSCs) offer the potential to reverse or arrest the progression of liver disease by targeting inflammation and promoting hepatic regeneration [1].

This article reviews recent advances in stem cell therapy for chronic liver disease, highlighting the mechanisms, clinical applications, and challenges in transitioning from experimental models to standardized treatment protocols. Stem cell therapy aims not only to regenerate hepatocytes but also to modulate the pathological liver microenvironment, which is often dominated by pro-inflammatory cytokines and fibrotic remodeling.MSCs secrete Interleukin-10 (IL-10) and Tumor Necrosis Factor-Stimulated Gene-6 (TSG-6), which suppress liver inflammation by downregulating TNF-α and IL-6.MSCs also reduce infiltration of macrophages and T cells into hepatic tissue, lowering chronic immune activation [2].

Stem cells release Matrix Metalloproteinases (MMPs) that degrade excessive Extracellular Matrix (ECM).They inhibit hepatic stellate cell activation the key driver of fibrosis via paracrine signaling.Under liver-specific cues, stem cells can differentiate into hepatocyte-like cells, producing albumin and metabolic enzymes.More importantly, even undifferentiated MSCs can enhance native hepatocyte survival via secretion of Vascular Endothelial Growth Factor (VEGF) and Hepatocyte Growth Factor (HGF).Derived from bone Aprrow, adipose tissue, and umbilical cord .Most commonly used in clinical trials due to their low immunogenicity and immunomodulatory properties. Administered via peripheral infusion or intrahepatic injection [3].

Reprogrammed from adult somatic cells, iPSCs can be directed to form Hepatocyte-Like Cells (HLCs).Hold promise for personalized liver regeneration, although concerns remain regarding tumorigenicity and genomic instability. Contribute to liver regeneration indirectly by modulating immune responses and promoting angiogenesis. Less efficient than MSCs in hepatocyte-like differentiation.Numerous small-scale human trials have explored the safety and efficacy of stem cell therapy in chronic liver disease:A 2020 phase II study in patients with decompensated cirrhosis found that umbilical cord-derived MSCs significantly improved Model for End-Stage Liver Disease (MELD) scores over 12 weeks, with no major adverse events [4].

Another study demonstrated that MSC infusion reduced serum ALT, AST, and bilirubin levels in hepatitis B-associated cirrhosis, suggesting improved hepatic function. iPSC-derived hepatocyte transplantation in mouse models

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restored synthetic liver functions and improved survival rates, although no large-scale human trials are yet complete. Despite promising outcomes, heterogeneity in protocols, stem cell sources, dosages, and delivery methods limit comparability and scalability of results. Lack of consensus on optimal cell type, dose, and frequency of administration hampers progress. Quality control in stem cell production ensuring viability, purity, and differentiation potential—is a major regulatory hurdleRisks of ectopic tissue formation, fibrosis worsening, and malignancy must be rigorously evaluated. Current follow-ups are typically under 12 months; long-term immunological and oncogenic surveillance is needed [5].

Conclusion

Stem cell therapy represents a transformative frontier in the management of chronic liver disease, shifting the paradigm from damage control to true tissue regeneration. By bridging inflammation suppression and hepatocyte regeneration, stem cells particularly MSCs offer a dual therapeutic approach to halting disease progression and restoring liver function.While early-phase trials confirm safety and modest clinical benefit, further large-scale, standardized studies are essential to validate their role in clinical practice. If challenges in consistency, cost, and long-term monitoring can be addressed, stem cell therapy may soon become a mainstream option for patients with chronic liver disease who currently face limited treatment choices.

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