Perioperative Precision Medicine
ISSN: 2957-5443

Zentime

Review Article https://doi.org/10.61189/167468gjipte

Research progress of bone marrow mesenchymal stem cells in the treatment of acute liver failure

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Acknowledgement: This work was supported by Key Project Research Fund of Wannan Medical College (WK2022Z10); Anhui Province College Student Innovation and Entrepreneurship Training Program Project (S202410368031); Anhui Province College Student Innovation Training Program Project (S202510368032).

Declaration of conflict of interest: None.

Received April 15, 2025; Accepted July 25, 2025; Published December 31, 2025

Highlights

- This review focuses on the research of bone marrow mesenchymal stem cells (BM-MSCs) in treating acute liver failure (ALF).
- BM-MSCs are a heterogeneous subset of stromal stem cells that can be isolated from various adult tissues.
- BM-MSCs have the ability to migrate toward damaged tissues and differentiate into hepatocytes. They effectively suppress pro-inflammatory cytokine release and promote hepatocyte proliferation.
- BM-MSCs are a promising target for clinical treatment of acute liver failure.
- BM-MSCs provide a new therapeutic direction for patients with acute liver failure during the perioperative period.

Abstract

Acute liver failure (ALF) is a severe hepatic injury characterized by rapid progression and multifactorial etiology. Clinical manifestations predominantly include severe gastrointestinal symptoms, altered consciousness, coagulopathy, jaundice, and hepatic encephalopathy. Currently, no specific pharmacological agents or established therapeutic regimens exist for ALF. While liver transplantation remains the primary clinical intervention, its application is limited by the shortage of donors. Advances in medical technology and research have led to accumulating experimental evidence suggesting that mesenchymal stem cells (MSCs) can alleviate liver inflammation, improve hepatic histology and function, and enhance survival rates in ALF. MSCs have advanced to clinical trials, with ongoing exploration into the mechanisms underlying their efficacy, highlighting their substantial potential in regenerative medicine. In the future, BM-MSCs may become an important treatment option for patients with acute liver failure during the perioperative period. This review provides a comprehensive overview of the therapeutic mechanisms and key findings associated with stem cells, particularly BM-MSCs, in the treatment of ALF.

Keywords: Acute liver failure, mesenchymal stem cells, therapeutics

Introduction

Acute liver failure (ALF) is a severe hepatic injury caused by factors such as drugs, hepatotoxic substances, viruses, and alcohol, characterized by extensive hepatocyte death and rapid deterioration of liver function. Clinical manifestations include hepatic encephalopathy, intracranial hypertension, infections, coagulation disorders, and hemorrhage. Without timely intensive care or liver transplantation, ALF can lead to multiple organ failure and death [1]. Allogeneic

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Table 1. MSCs from different sources

Feature	BMSCs	UCMSCs	ADSCs	hPMSCs
Full Name	Bone Marrow Mesenchymal Stem Cells	Umbilical Cord Mesenchymal Stem Cells	Adipose-Derived Mesenchymal Stem Cells	Human Placental Mesenchymal Stem Cells
Source	Bone Marrow	Umbilical Cord	Adipose Tissue	Placenta
Immunogenicity	Low (potential for mild rejection in allogeneic transplantation)	Very low	No rejection in autologous transplantation	Low
Immunomodulation	Suppresses inflammation via HO-1 and inhibits pyroptosis via IL-10	Significantly mitigates inflammatory responses and modulates macrophage polarization	Suppresses excessive immune responses and ameliorates the inflammatory microenvironment	Not reported
Paracrine Factors	HO-1 activates autophagy	Highly secretes HGF to promote hepatic regeneration	Secretes growth factors promoting angiogenesis	Improves liver function indicators
Differentiation Potential	Multipotent differentiation	Multipotent differentiation (notably strong hepatic differentiation potential)	Multipotent differentiation (moderate hepatic differentiation capacity)	Exhibits prominent anti-fibrotic differentiation potential
Clinical Accessibility	Invasive harvesting, slow expansion kinetics, high cost	Non-invasive source, high yield, rapid expansion	Minimally invasive harvesting, high yield	Non-invasive source

Note: HO-1, heme oxygenase 1; IL-10, Interleukin-10; HGF, hepatocyte growth factor.

liver transplantation remains the only effective treatment for liver failure; however, alternative therapies are urgently needed due to the severe shortage of donors [2]. Numerous studies have shown that transplantation of hepatic stem cells or pluripotent stem cell-derived hepatocyte-like cells in experimental liver disease models can lead to liver repopulation by donor cells and improved survival rates [3].

Mesenchymal stem cells (MSCs) are a heterogeneous subset of stromal stem cells that can be isolated from various adult tissues. MSCs interact with both the innate and adaptive immune systems, modulating effector functions [4]. A growing body of animal studies suggests that MSCs significantly mitigate acute liver injury in ALF through their migratory capacity, hepatogenic differentiation potential, immunomodulatory effects, and paracrine actions [5]. Due to their ability to migrate to injured tissues, differentiate into hepatocytes, suppress inflammatory cytokine release, and promote hepatocyte proliferation, MSCs have emerged as a key focus of research in ALF treatment [6]. The specific characteristics of mesenchymal stem cells from different sources are shown in **Table 1**.

Clinical challenges in allogeneic liver transplantation for ALF

Determining the suitability of allogeneic liver transplantation for ALF presents significant clinical challenges, primarily in the timely identification of transplant indications and contraindications. A critical challenge is precise indication assessment, requiring clinical evaluation to confirm irreversible hepatic injury and distinguish reversible from irreversible etiologies. The latter, characterized by extensive hepatocyte necrosis without regenerative potential, typically necessitates urgent transplantation [7]. While established prognostic scoring systems such as the Model for End-Stage Liver Disease (MELD) help identify patients at highest mortality risk, their predictive accuracy remains limited [2]. Furthermore, the dynamic assessment of contraindications is challenging: absolute contraindications must be rigorously excluded, while managing relative contraindications (e.g., advanced age) requires highly individualized evaluation [3, 8]. The clinical complexity is compounded by the potential for rapid deterioration within hours, necessitating continuous monitoring and dynamic reassessment of transplant eligibility. Additionally,

establishing transplant criteria in special populations is significantly influenced by distinct etiological profiles. Post-transplant outcomes exhibit substantial heterogeneity among these subgroups, even after successful transplantation. A particularly salient challenge is pediatric ALF, especially cases triggered by specific metabolic disorders (e.g., mitochondrial hepatopathies) [6, 9]. Evidence from large registries like the European Liver Transplant Registry (ELTR) indicates significantly reduced long-term survival in these children compared to adult ALF recipients or pediatric patients transplanted for more common metabolic indications [10]. This underscores the unique clinical challenges and heightened post-transplant management requirements associated with metabolic etiologies in pediatric ALF.

Advances in the mechanisms underlying bone marrow-derived mesenchymal stem cell (BMSC) therapy for ALF

BMSCs were first identified in adult mouse bone marrow by Friedenstein AJ et al. during in vitro colony assays in 1976. Recent studies have demonstrated their self-renewal, multipotent differentiation, low immunogenicity, and immunomodulatory functions. BMSCs have recently been applied in clinical trials, while the underlying mechanisms of their efficacy are being extensively investigated [11].

BMSCs ameliorate ALF via modulation of autophagy through the HO-1/PI3K/AKT signaling pathway

Heme oxygenase-1 (HO-1) is an inducible enzyme with anti-apoptotic and immunomodulatory properties [12]. Autophagy, a conserved intracellular catabolic process, may be a critical pathway in MSC-mediated therapy for ALF. Zhang et al. isolated and cultured BMSCs from Sprague-Dawley rats [13]. ALF-induced rats were treated with BMSCs, an HO-1 inducer, or an HO-1 activity inhibitor, followed by assessment of hepatic injury markers and HO-1 activity. The results demonstrated that MSC treatment significantly upregulated HO-1 expression while reducing serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (TBIL). In contrast, pharmacological inhibition of HO-1 attenuated the therapeutic efficacy of MSCs and suppressed hepatocellular autophagy. These findings suggest that BMSCs ameliorate ALF through HO-1 upregulation-dependent mechanisms [14]. Wang et al. transplanted BMSCs into D-galactosamine-induced ALF rats. Pharmacological inhibition studies revealed that BMSCs alleviated ALF through HO-1 upregulation, wherein HO-1 activated autophagy via the PI3K/AKT signaling pathway [15]. Amiri F et al. intravenously administered autophagy-impaired BMSCs to mice with ALF [16]. The autophagy-modulated MSC transplantation group exhibited significantly reduced hepatic enzyme activity and lower necrotic scores compared to sham-operated controls (receiving no cell therapy). At 72 hours post-transplantation, mice receiving autophagy-inhibited MSCs demonstrated restoration of hepatic enzyme levels to baseline values. These data indicate that autophagy inhibition in BMSCs enhances their paracrine-mediated hepatic regenerative potential, suggesting a novel strategy to optimize cell-based therapy for ALF [16]. MSCs possess remarkable metabolic and functional supportive capacities in inflammatory diseases [17].

BMSCs mitigate inflammatory responses in ALF through modulation of underlying immune mechanisms

NOD-like receptor protein 3 (NLRP3) plays a pivotal role in inflammatory and immune responses. Wang et al. administered exogenous recombinant rat interleukin (IL)-10, small interfering RNA (siRNA), and the NLRP3 inhibitor MCC950 to mice, demonstrating that either IL-10 injection or BMSC transplantation ameliorated elevated total bilirubin, NH3, inflammatory cytokines, and related enzymes in ALF, suggesting that IL-10 secreted by BMSCs alleviates ALF through inflammasome suppression [18]. Wang JL et al. assessed hepatocyte proliferation using immunohistochemical (IHC) staining, examined key Wnt signaling proteins and cell surface factor expression, and employed IL-4 silencing to explore IL-4's role in BMSC bioactivity [18]. Results indicated that BMSCs ameliorate ALF through IL-4-dependent macrophage polarization toward the M2 anti-inflammatory phenotype [19]. Jiang et al. inhibited the PI3K/AKT/mTOR signaling pathway in vitro with the specific inhibitor LY294002, followed by intravenous BMSC administration into rats

to observe transdifferentiation dynamics [20]. BMSCs migrated to intestinal injury sites and transdifferentiated into intestinal epithelial cells. Compared to the ALF control group, this treatment significantly reduced intrahepatic pro-inflammatory cytokine levels. Additionally, intestinal permeability, mortality rates, and histopathological lesions in the gut were markedly reduced. These findings suggest that BMSC transplantation may serve as a potential therapeutic candidate for endotoxemia in ALF [20]. High mobility group box chromosomal protein 1is a crucial proinflammatory molecule in various inflammatory diseases. Wang et al. demonstrated that soluble receptor for advanced glycation end-products (sRAGE) administration significantly prolonged survival time, improved liver function, reduced inflammatory cytokine levels, and mitigated hepatocyte necrosis in ALF rats [21]. Xiu et al. revealed that CXCR4 overexpression in BMSCs enhanced their migration capacity through PI3K/Akt signaling pathway activation downstream of CXCR4, elucidating the molecular mechanisms and providing novel insights for the clinical application of BMSCs in ALF treatment [22].

Interaction between HO-1 and NLRP3

In ALF, HO-1 (heme oxygenase-1) and the NLRP3 inflammasome are closely interconnected through oxidative stress, endotoxemia, and inflammatory cascades, jointly participating in the pathological process of ALF. HO-1 inhibits NLRP3 activation [23]. The HO-1 metabolic product, carbon monoxide, inhibits NLRP3 inflammasome assembly, while bilirubin inhibits NLRP3 ubiquitination, reducing its binding efficiency with the adaptor protein. In experiments using BMSCs to treat ALF, high HO-1 expression significantly reduced NLRP3 activity [24]. The integrative role of autophagy: HO-1-induced autophagy can selectively degrade NLRP3 inflammasome components, forming a negative feedback loop. When autophagy is inhibited, the protective effect of BMSCs against ALF diminishes, and levels of inflammatory factors in liver tissue increase. HO-1 and NLRP3, acting as central regulators for antioxidant stress and pro-inflammatory responses, form an interactive regulatory network through the “oxidative stress-endotoxin-inflammation” axis in ALF. Therapeutic strategies targeting both may offer new approaches to ALF treatment [25, 26].

Advances in the therapeutic mechanisms of umbilical cord mesenchymal stem cells (UCMSCs) for ALF

Human UCMSCs are derived from the umbilical cord and exhibit broad tissue sources, multilineage differentiation potential, low immunogenicity, and strong self-renewal capacity, showing significant promise in regenerative medicine [27]. In vitro cultured UCMSCs have been shown to attenuate hepatic inflammation in a co-culture model of liver inflammation following preconditioning [28]. Jia et al. conducted a clinical investigation involving patients diagnosed with liver failure and cirrhosis who received stem cell infusions. Peripheral infusion of UCMSCs demonstrated significant therapeutic efficacy in hepatitis B virus-related liver failure, significantly reducing serum levels of ALT, AST, and TBIL. Extended treatment courses were associated with improved therapeutic outcomes [29]. Tao et al. transplanted UCMSCs into ALF mice, observing reduced serum ALT and AST levels along with attenuated inflammatory responses, suggesting UCMSCs alleviate ALF by modulating hepatocyte apoptosis and macrophage polarization, making UCMSC-based therapy a viable alternative for ALF patients [30]. Yu et al. administered HNF4α-overexpressing UCMSCs via tail vein injection into ALF model mice [31]. The HNF4α-UCMSCs group exhibited significantly improved inflammatory responses compared to the CON-UCMSCs group, with reduced inflammatory cell infiltration, diminished apoptosis, and markedly improved survival rates. HNF4α-UCMSCs secreted higher levels of IL-10 than CON-UCMSCs, thereby attenuating macrophage death and promoting M2 macrophage polarization. These findings highlight the superior therapeutic efficacy of HNF4α-UCMSCs over CON-UCMSCs in ALF treatment, providing a novel therapeutic approach for ALF [31]. Yun et al. evaluated UCMSCs in CCl4-induced ALF, assessing toxicity, tumorigenicity, and biodistribution, and found hepatoprotective effects through reduced hepatocyte necrosis and lobular neutrophil infiltration, suggesting that UCMSC therapy could serve as an alternative to liver transplantation [32]. Zhang et al. investigated the therapeutic effects of transplanting passage 5 (P5) and passage 10 (P10) human UCMSCs into rats with ALF [33]. Control group rats died within 48 to 96 hours after saline injection, while the P5-UCMSCs group exhibited a 7-day survival rate of 62.5%, with only 3 mor-

talities. The P10-UCMSCs group showed a 37.5% survival rate, with 3 rats surviving beyond one week. UCMSC transplantation effectively repaired damaged liver tissue, stimulating endogenous liver regeneration and suppressing hepatocyte apoptosis, thereby repopulating the liver and compensating for hepatic function [33]. Guo J et al. administered UMSCs via peripheral infusion to rhesus monkeys (Macaca mulatta) with toxin-induced intraperitoneal injury [34]. Comparative analysis revealed that, relative to the control group, the UMSCs group exhibited significantly decreased levels of proinflammatory cytokines (e.g., TNF-α, IL-1α, IL-1RA, and IL-15) and chemokines (e.g., MCP-1, MIP-1α, and MIP-1β). This suggests that UMSCs effectively suppress the aggregation and maturation of circulating monocytes, concurrently inhibiting their IL-6 secretion. Histological examination demonstrated substantial improvement in liver architecture, restoration of systemic homeostasis, and enhanced survival rates [35].

Advances in adipose-derived mesenchymal stem cell (ADSC) therapy for ALF

ADSCs are typically isolated from a patient's subcutaneous adipose tissue, yielding high cell numbers. ADSCs accumulate at disease sites to suppress excessive immune responses and secrete various growth factors and cytokines. They promote angiogenesis, exert anti-apoptotic effects, and regulate immune cells through cell-cell interactions. ADSCs possess advantages, including high proliferation, clonogenicity, multipotent differentiation, and immunomodulation, making them ideal candidates for ALF therapy [36]. ADSCs have been widely applied in ALF treatment due to their abundant sources, low cost, and simple isolation procedures [37]. Liau et al. established indirect co-culture systems between primary ADSCs and damaged HepG2 cells, observing that ADSCs exhibited early hepatic differentiation markers under the influence of factors released by injured HepG2 cells [37]. Zhang et al. transplanted ADSC-differentiated hepatocytes into mice with liver injury. Histological analysis revealed marked improvement, evidenced by reduced hepatic necrotic areas and significantly decreased serum TBIL levels [37]. Immunofluorescence staining, serological parameters, and biochemical indices showed varying degrees of improvement. These findings indicate that ADSC-derived hepatocytes hold significant promise for therapeutic interventions in liver disease animal models and clinical translation [37]. Chae et al. implanted Foxa2-modified ADSC scaffolds into the dorsal subcutaneous tissue of nude mice. Histopathological damage was significantly alleviated in the treated group. Paracrine cytokines (e.g., IL-10, IL-4, IL-6, and IL-13) were markedly upregulated through paracrine mechanisms, substantially enhancing hepatic regeneration processes. These findings demonstrate the substantial clinical value of ADSCs in treating ALF [38]. Subsequently, Shi et al. isolated porcine ADSCs and transplanted them into rabbits with ACLF, evaluating biochemical parameters, histomorphological scores, ADSC distribution characteristics, and hepatic pathology. Results showed that ADSC transplantation improved survival rates and liver function, demonstrating their therapeutic effects against ALF [39]. Jin et al. engrafted ADSC-differentiated hepatocyte-like cells into ALF model mice. The PBS control group exhibited 100% mortality within 48 hours, whereas the treatment group achieved a 26.7% survival rate, resulting in a significant survival advantage along with effective attenuation of inflammatory responses [40]. Liu et al. transplanted third-passage ADSCs derived from ALF porcine models and healthy donor-derived ADSCs into ALF mice [41]. Both groups exhibited improved hepatic histopathology, liver function, and survival rates, as evidenced by significant reductions in ALT, AST, direct bilirubin, and TBIL, along with attenuated inflammatory cell infiltration and enhanced hepatic lobule regeneration. Notably, the ALF-ADSCs group exhibited elevated expression of porcine hepatocyte-specific genes in recipient livers, suggesting enhanced hepatic differentiation potential in ADSCs isolated from liver-injured porcine donors [41]. Hwang et al. demonstrated that lipid-conjugated heparin-coated ADSCs reduced serum AST and ALT levels more rapidly and alleviated inflammation compared to untreated ADSCs, indicating that this modification significantly enhances therapeutic efficacy against liver injury [42].

Exploratory studies on human placental mesenchymal stem cell (PMSCs) therapy for ALF

In addition to the three common types of MSCs, PMSCs have shown promising potential in treating ALF. Cao et al. established an ALF model in Chinese experimental miniature pigs and trans-

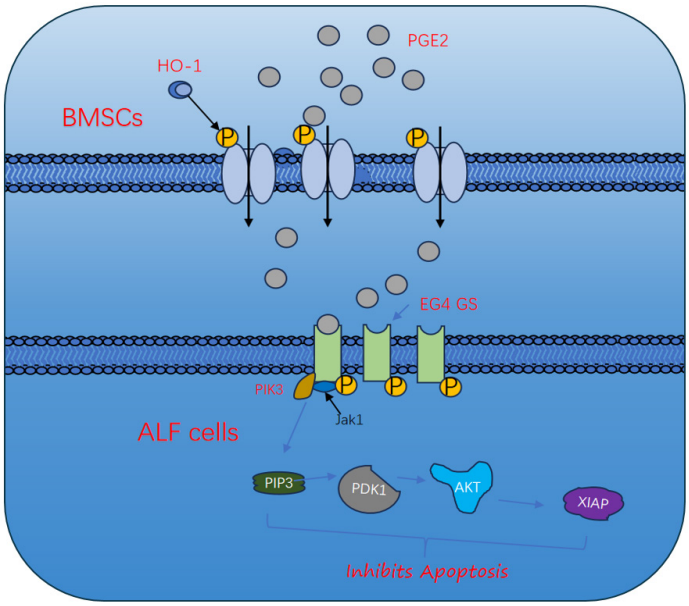

Figure 1. Mechanism of action of BMSCs. HO-1 promotes BMSCs to release PGE2, which binds to EG4 GS on hepatocytes, triggering an enzymatic cascade that activates PIP3, PDK1, and AKT, and subsequently activates XIAP, thereby inhibiting cell apoptosis caused by acute lung injury.

planted PMSCs, observing improved liver function with normalized concentrations of ALT, AST, ALP, CHE, TBIL, and TBA in recipient pigs. Hepatic inflammation and degenerative necrosis were alleviated, while liver regeneration was promoted. The survival time of ALF pigs was significantly prolonged [43]. Yu et al. generated GFP(+) PMSCs through lentiviral GFP (Green Fluorescent Protein) gene transduction, demonstrating that GFP(+) PMSCs expressed multiple liver-promoting factors, and their derived hepatocyte-like cells exhibited typical hepatic phenotypes [44]. Yu et al. administered GFP-labeled PMSCs via tail vein injection to CCl4-induced fibrotic rats, showing improved liver function. This approach also provided insights for the application of adipose-derived stem cell therapy in ALF [45].

Development and prospects

Currently, MSCs exhibit several key capabilities, including homing to injured tissues, targeting damaged sites via inflammatory signals, suppressing cytokine storms, undergoing hepatogenic differentiation, promoting hepatocyte proliferation, and exerting paracrine effects. However, significant challenges remain in the therapeutic application of MSCs for ALF treatment.

Limited research exists on MSC combination therapies, and further investigation is needed to determine whether different delivery vehicles or co-encapsulation strategies could enhance therapeutic efficacy.

Determining the optimal dosage for MSC therapy in ALF remains a critical area for further exploration. The establishment of patient stratification criteria for different transplantation routes (e.g., intravenous vs. intrahepatic injection) in MSC therapy is crucial. Besides, defining the optimal temporal parameters for MSC intervention in ALF is essential for improving clinical outcomes.

Signal path

BMSCs secrete heme oxygenase-1 (HO-1), which exerts anti-inflammatory, antioxidant, and anti-apoptotic effects, thereby ameliorating oxidative stress injury in ALF hepatocytes. Prostaglandin E2 (PGE2) activates G protein-coupled signaling by binding to EP4 receptors on the surface of ALF hepatocytes. This process recruits and phosphorylates Janus kinases (Jaks). Jak1 subsequently phosphorylates phosphatidylinositol 3-kinase (PI3K), which catalyzes the synthesis of phosphatidylinositol (3,4,5)-trisphosphate (PIP3) from phosphatidylinositol (4,5)-bisphosphate (PIP2). PIP3 facilitates phosphoinositide-dependent kinase-1 (PDK1)-mediated phosphorylation of protein kinase B (AKT), generating phosphorylated AKT (p-AKT). Activated AKT suppresses pro-apoptotic factors and upregulates the expression of the X-linked inhibitor of apoptosis protein (XIAP). Collectively, this signaling cascade inhibits apoptotic cell death in ALF hepatocytes. The signaling pathway diagram is shown in **Figure 1**.

Conclusion

This review focuses on elucidating the therapeutic effects of MSCs in ALF. MSCs can be derived from multiple sources, including bone marrow, umbilical cord, adipose tissue, and placenta. They possess the capabilities of self-renewal and multilineage differentiation, coupled with low immunogenicity and immunomodulatory functions. BMSCs can ameliorate ALF by

activating autophagy through the PI3K/AKT signaling pathway via induction of HO-1 expression. In the future, MSCs may potentially become a significant therapeutic alternative to liver transplantation for ALF.

Author contributions: Huan Li performed the conception of the study. Huan Li, Xingchen Yue, Wanning Li, Xin Niu contributed to the literature and collection of materials. Huan Li, Xiaoyu Tang contributed to material analysis and manuscript writing. Huan Li reviewed and refined the manuscript.

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