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# Mesenchymal stem cell-derived exosomes: an emerging therapeutic strategy for hepatic ischemia-reperfusion injury

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**Abstract**

Hepatic ischemia-reperfusion injury (HIRI) severely threatens the success rates of liver surgery and transplantation. Its complex pathological process involves multiple factors such as oxidative stress, inflammatory responses, and ferroptosis, creating an urgent need for new therapeutic strategies. Exosomes derived from mesenchymal stem cells (MSCs) are emerging as a next-generation acellular therapeutic approach. With their outstanding immune-regulatory capabilities, significant reparative functions, and good biocompatibility, they are leading innovations in the field of HIRI treatment. This article provides a systematic comparison of the therapeutic characteristics of MSC-derived exosomes(MSC-EXOs) from four different sources: adipose tissue, bone marrow, umbilical cord, and induced pluripotent stem cells. Although the clinical translation of MSC-EXOs still faces challenges such as variations in isolation methods, large-scale production, and safety assessments, their remarkable therapeutic effects and vast application potential signal the arrival of a new era of precision treatment for HIRI. This review not only provides a comprehensive theoretical foundation to promote the clinical application of MSC-EXOs but also opens up innovative research directions in the field of regenerative medicine.

**Keywords** Hepatic Ischemia-Reperfusion Injury(HIRI), MSC-derived exosomes(MSC-EXOs), Ferroptosis, Therapeutic standardization, Regenerative medicine

## Introduction

In recent years, the high incidence of liver injury, liver tumors, and related chronic diseases (such as viral hepatitis and fatty liver disease) has driven the demand for liver resection surgeries [1–3]. However, the use of portal vein occlusion techniques to reduce intraoperative bleeding inevitably leads to HIRI [4, 5]. Due to the liver's unique dual blood supply and complex anatomical structure, ischemia-reperfusion injury(IRI) has become a common challenge in liver surgery [6, 7]. This issue is particularly severe in patients with insufficient liver function reserve, as they are more susceptible to damage, significantly lowering postoperative prognosis and quality of life [8, 9]. The pathological process of HIRI is mainly divided into two stages: the ischemic phase and

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the reperfusion phase [10–14]. The ischemic phase typically involves a lack of liver blood supply, leading to tissue hypoxia and cellular damage [15]. The reperfusion phase occurs when blood flow is restored, triggering the complement cascade reaction, which subsequently leads to secondary injury [16, 17]. Currently, although the main clinical treatments for HIRI include pharmacological and surgical therapies [18–20], patients may still experience adverse reactions triggered by chemotherapy. Additionally, the high risks and costs associated with surgical treatment may result in unsatisfactory therapeutic outcomes for HIRI [11]. Therefore, the development of safe and effective treatment strategies has become an urgent clinical issue. MSC-EXOs, as a novel acellular therapeutic strategy, have become a research hotspot due to their unique biological properties. This article systematically compares, for the first time, the mechanisms and protective effects of MSC-EXOs from four different sources—adipose tissue, bone marrow, umbilical cord, and induced pluripotent stem cells (iPSCs)—in the treatment of HIRI. Additionally, we focus on the key challenges faced by the clinical translation of MSC-EXOs, such as the standardization of isolation methods, large-scale production, and safety assessment, and propose corresponding optimization strategies to provide new insights for promoting the clinical application of MSC-EXOs in the treatment of HIRI.

#### Mechanisms of HIRI and current therapeutic strategies

HIRI is a severe complication that occurs during surgeries for end-stage liver diseases, such as liver transplantation and liver resection. It can easily lead to acute liver injury, liver failure, and even patient death [11, 21, 22]. Severe HIRI may result in irreversible damage, trigger multiple organ dysfunction, and negatively affect patient prognosis and survival rates. The pathophysiological mechanisms of HIRI are highly complex, and current research has proposed potential mechanisms, including mitochondrial damage, oxidative stress imbalance, abnormal cell death, excessive activation of immune cells, intracellular inflammation dysregulation, and microcirculation dysfunction [11, 22–24]. With the progress of research, developing effective clinical prevention and treatment strategies has become possible. At present, the main treatment methods for HIRI include pharmacological interventions, surgical treatment, and machine perfusion [24–27] (Fig. 1).

In terms of pharmacological interventions, antioxidants (such as N-acetylcysteine), anti-inflammatory drugs (such as steroids), and immunomodulators (such as cyclosporine A) have shown certain therapeutic effects in basic research by scavenging free radicals, inhibiting inflammation, and regulating the immune system [22, 28–32]. However, these drugs lack sufficient validation in clinical trials and have potential side effects, which limits their practical application. Surgical treatment mainly involves traditional surgical procedures, while ischemic preconditioning (IPC) and ischemic postconditioning (IPostC) are commonly used auxiliary interventions during the perioperative period to help alleviate IRI during surgery [20, 33, 34]. Traditional surgery is primarily used to repair liver damage, such as removing the damaged part or improving blood flow. However, these methods have limited long-term protective effects against IRI after surgery. IPC involves a brief period of ischemia and reperfusion of the liver before surgery, which activates the body's self-protection mechanisms to reduce postoperative damage [35]. In contrast, IPostC is performed during the reperfusion phase after ischemia, aiming to reduce reperfusion injury by briefly interrupting blood flow. Although IPostC has shown some benefits in studies, its effectiveness depends on precise timing and implementation conditions.

Despite the benefits shown by IPC and IPostC in studies, they face significant challenges. Their effectiveness is limited by the intervention time window and individual patient factors, such as underlying diseases (e.g., hypertension, diabetes), especially in cases of acute ischemia [36, 37]. Additionally, these strategies are typically more suitable for planned surgeries rather than emergency surgeries or severe injury cases. Improving the effectiveness of these methods remains a key area of research [38–40]. Machine perfusion, as an emerging organ preservation method, helps reduce ischemic damage by simulating physiological conditions. Research has shown that machine perfusion can provide oxygen, nutrients, and remove metabolic byproducts, thereby maintaining organ vitality and prolonging preservation time [41, 42]. However, machine perfusion requires advanced equipment and technology, with high operational costs [43, 44]. Moreover, its long-term stability and standardized processes have not been fully established, limiting its widespread application in clinical settings.

With the development of regenerative medicine, cell therapy has gradually become a hotspot in HIRI research. Among these studies, MSCs have gained widespread attention due to their anti-inflammatory, anti-apoptotic, and tissue-repair-promoting effects. However, cell therapy still faces many challenges in clinical translation, including low graft cell survival, poor functional stability, and potential immune rejection issues [45–48]. In this context, MSC-EXOs have emerged as a novel acellular therapeutic strategy, offering new hope for the treatment of HIRI.

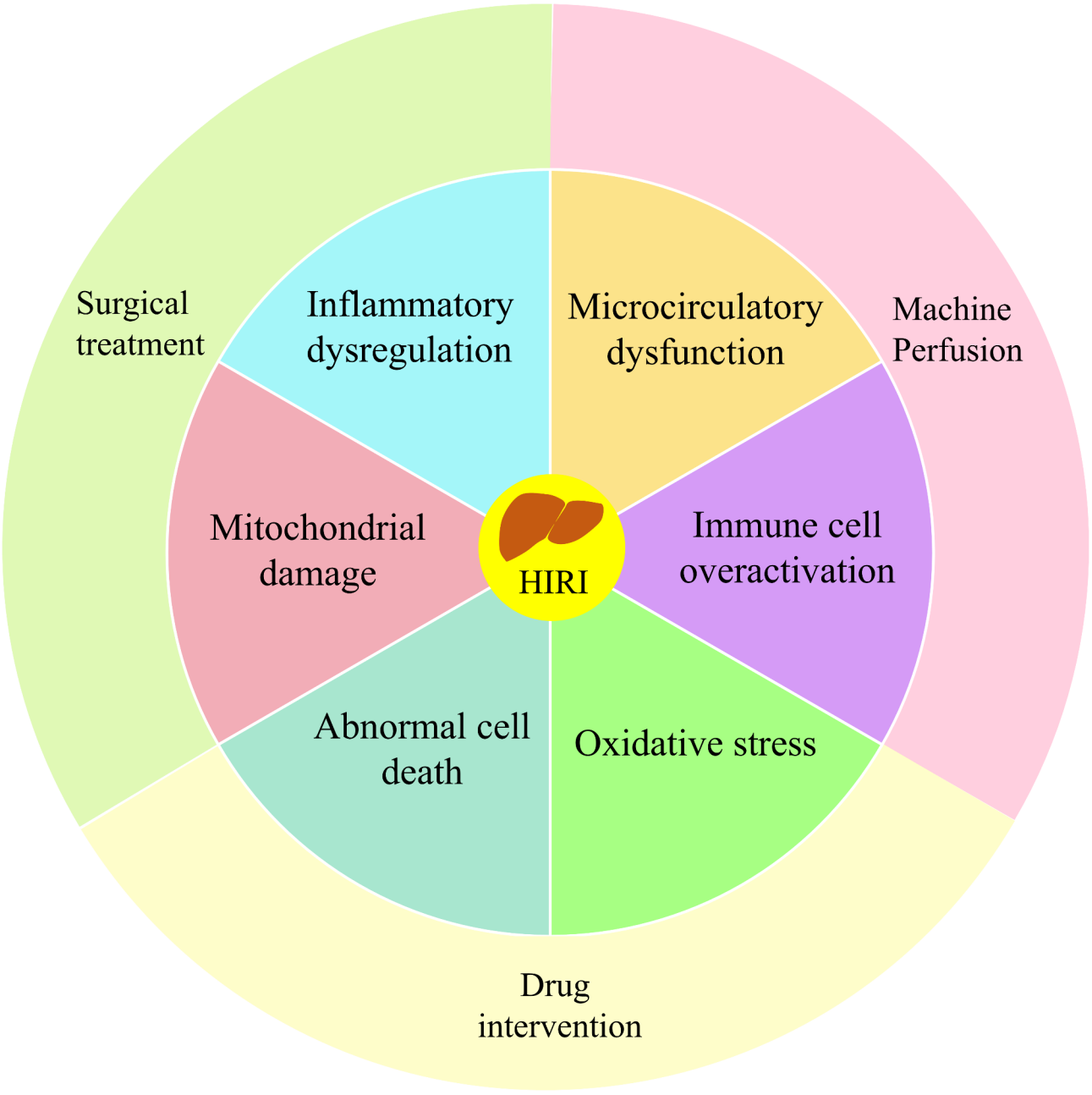


**Fig. 1** The diagram shows the main factors and interventions related to HIRI. The core factors of HIRI include inflammatory dysregulation, microcirculatory dysfunction, mitochondrial damage, immune cell overactivation, oxidative stress, and abnormal cell death. Meanwhile, interventions for HIRI include surgical treatment, machine perfusion, and drug intervention

### Functions and application potential of MSCs and their derived exosomes

MSCs are a type of stem cell with multi-lineage differentiation potential and strong immune-regulatory functions [49–51]. In recent years, they have become an emerging therapeutic option to mitigate IRI due to their secretion of paracrine factors and promotion of tissue repair [52–54]. In particular, exosomes secreted by MSCs, as an important subtype of extracellular vesicles, exhibit unique therapeutic advantages. MSC-EXOs are nanovesicles with a diameter ranging from 30 to 200 nanometers [55], rich in specific surface markers (such as CD9, CD63, and CD81) [56], and carrying various bioactive molecules, including proteins, nucleic acids (e.g., miRNA, lncRNA), lipids, and metabolites [57, 58]. These exosomes can precisely deliver bioactive substances through endocytosis, ligand-receptor binding, or membrane fusion [59–62].

In the treatment of HIRI, MSC-EXOs significantly improve liver damage through anti-inflammatory,

antioxidative, cell death regulation, and tissue repair-promoting effects(Fig. 2). Compared with traditional MSC therapy, MSC-EXOs have notable advantages: as an acellular therapeutic option, they avoid the risks associated with cell transplantation (e.g., tumorigenesis) [63, 64], exhibit lower immunogenicity [65, 66], can be produced on a large scale [67, 68], and offer flexible routes of administration [69, 70], making them suitable for clinical use. MSC-EXOs have broad application prospects in HIRI treatment, applicable to both acute and chronic liver injuries [71–73], and can be combined with other therapeutic strategies [65, 74–76]. Through engineering modifications, the targeting ability of MSC-EXOs can be further enhanced, paving the way for the development of novel drug delivery systems and smart drug delivery strategies.

Recent studies have shown that Huc-MSC-exosomes(hucMSC-EXOs) modified with HSTP1 can specifically bind to activated hepatic stellate cells (aHSC), thereby improving liver fibrosis [77]. Additionally, exosomes derived from adipose-derived mesenchymal stem cells(AMSCs), modified with miR-122, also play a significant role in controlling liver injury [78]. Another study pointed out that by engineering MSC-Exos and adding quercetin and vitamin A, the therapeutic effects of exosomes were enhanced, achieving selective targeting of the liver and effectively reducing the senescence response induced by acute liver injury [79].

In personalized treatment, appropriate exosome sources can be selected based on the patient's specific condition, and administration schemes can be optimized to achieve precise therapy. However, the clinical application of MSC-EXOs still faces challenges, such as the need to establish standardized preparation processes and quality control systems, and to assess their long-term safety and efficacy. Future research should focus on addressing these key issues to promote the clinical translation of MSC-EXOs in HIRI treatment. By analyzing the characteristics, functions, and application potential of MSC-EXOs, their unique value as a novel therapeutic strategy is gradually emerging. With further research and technological advancements, MSC-EXOs are expected to provide safer and more effective treatment options for HIRI patients.

## The protective effects of exosomes derived from different sources of MSCs on HIRI

In recent years, exosomes derived from different sources of MSCs have shown significant therapeutic effects in the treatment of HIRI. This section will focus on the mechanisms and protective effects of exosomes from four sources of MSCs—adipose tissue, bone marrow, umbilical cord, and iPSCs—in the treatment of HIRI.

### Protective effects of exosomes derived from AMSCs on HIRI

Research has shown that AMSCs significantly alleviate HIRI by secreting exosomes and various bioactive factors.

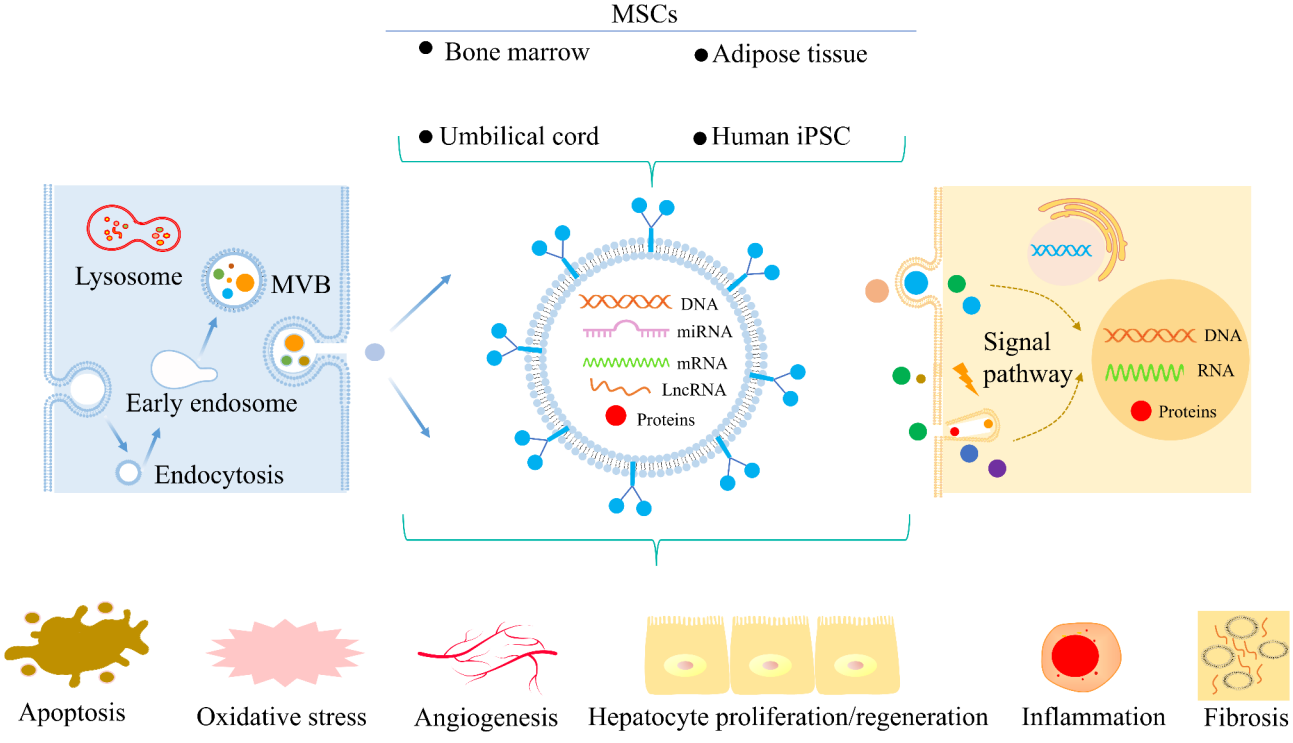


**Fig. 2** MSC-EXOs and their mechanisms in HIRI

In a rat model, Zhang et al. [80] induced liver injury by occluding the hepatic portal triad for 30 min and intervened with tail vein injection of AMSC-derived exosomes (AMSC-EXOs). The results indicated that AMSC-EXOs significantly improved liver function, reduced hepatocyte damage, primarily by inhibiting oxidative stress and apoptosis, while promoting mitochondrial dynamics and biosynthesis. In another rat study, Piao et al. [81] induced liver injury by blocking hepatic blood flow for 30 min and found that AMSC-EXOs reduced the expression of pyroptosis-related proteins (such as caspase-1 and GSDMD) by inhibiting the NLRP3 inflammasome and NF-κB pathway, activated the Wnt/β-catenin pathway, and promoted the expression of liver regeneration factors (such as Cyclin D1 and VEGF), thereby significantly reducing liver injury and promoting liver tissue repair. In a further study using a miniature pig model, Wang et al. [82–84] investigated the role and mechanisms of AMSC-EXOs in liver injury treatment. The study found that AMSC-EXOs significantly improved liver function and reduced tissue damage by inhibiting pro-inflammatory factors (such as TNF-α, IL-6, and CRP) and upregulating anti-inflammatory factors (such as IL-10). Additionally, AMSC-EXOs effectively protected hepatocytes from damage by inhibiting the endoplasmic reticulum stress pathways (such as GRP78, IRE1α, and PERK/eIF2α) and reducing the expression of anti-regenerative factors (SOCS3 and TGF-β), thus promoting liver regeneration (Fig. 3).

**Protective effects of exosomes derived from BMSCs on HIRI**

In recent years, exosomes derived from bone marrow mesenchymal stem cells (BMSCs) have gained increasing attention for their protective effects in HIRI. Wu et al. [18] used a rat liver transplant model to induce HIRI by transplanting severe fatty liver and intervened with heme oxygenase-1-modified BMSC-derived exosomes (HM-EXOs). The study found that HM-EXOs significantly reduced the necrotic area and neutrophil infiltration in liver tissue, inhibited the increase of ferroptosis-related markers ($Fe^{2+}$ and MDA), and enhanced the expression of the antioxidant protein GPX4, protecting mitochondrial structure. In vitro experiments showed that HM-exos delivered miR-124-3p to inhibit STEAP3 expression, reduced lipid ROS and iron ion levels, suppressed lipid peroxidation, and decreased ferroptosis. This research offers a novel strategy for exosome-based organ transplantation protection.

In another mouse I/R model, Li et al. [85] induced liver injury by occluding hepatic vessels and simulated in vitro ischemia-reperfusion injury (H/R) in cells. The experiment showed that tail vein injection of BMSC-Exos enriched with miR-25-3p reduced hepatocyte apoptosis and tissue necrosis and alleviated injury by inhibiting the

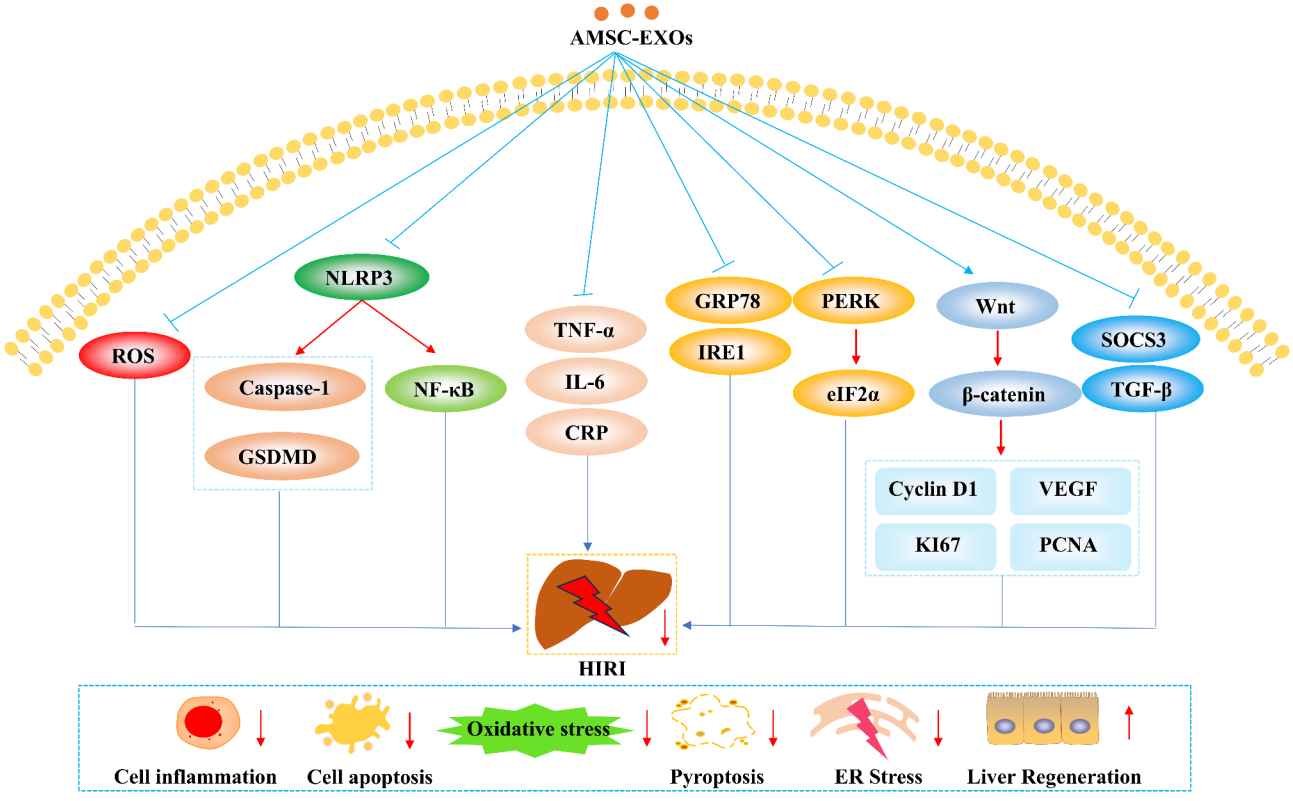


**Fig. 3** Illustration of the protective mechanism of AMSC-EXOs in HIRI

PTEN and p53 signaling pathways. In vitro experiments further confirmed that miR-25-3p, by targeting PTEN, alleviated hypoxia-induced apoptosis and enhanced cell viability. This study revealed that BMSC-Exos modulate the p53 signaling pathway by delivering miR-25-3p, providing new mechanistic support for the treatment of HIRI(Fig. 4).

Additionally, Zhang et al. [86] used Baicalin-pretreated BMSC-derived exosomes (Ba-EXO) for intervention in a mouse liver injury model. The results showed that Ba-Exo reduced liver tissue necrosis and inflammatory cell infiltration, and improved Th17/Treg cell imbalance. In vitro experiments indicated that Ba-EXO upregulated the expression of FGF21, activated FOXO1, and inhibited the JAK2/STAT3 signaling pathway, effectively alleviating Th17/Treg imbalance and significantly reducing reperfusion injury. This study provides a new strategy for the treatment of reperfusion injury, demonstrating that Ba-EXO regulates immune balance and signaling pathways to exert its protective effects.

**Protective effects of exosomes derived from umbilical cord MSCs(UCMSCs) on HIRI**

In recent years, the role of hUCMSCs in HIRI has also been studied. In a mouse model, Xie et al. [87] induced HIRI by occluding hepatic vessels for 90 min and intervened with tail vein injection of hUCMSC-EXOs. The study found that hUCMSC-EXOs significantly improved liver injury markers, alleviated histological damage, regulated the Th17/Treg cell balance, and exerted their effects through the miR-1246-mediated IL-6-gp130-STAT3 signaling pathway. In further studies, Xie et al. [88] explored the protective effects of hUCMSC-EXOs in both in vivo and in vitro models. In vitro, using LO2 cells to simulate I/R, hUCMSC-EXOs delivered miR-1246, which significantly increased cell viability, reduced apoptosis, and alleviated H/R injury by regulating the GSK3β/Wnt/β-catenin signaling pathway. In in vivo experiments, a mouse I/R model was established by blocking liver blood flow for 90 min and then restoring blood flow. Treatment with hUCMSC-EXOs via portal vein injection significantly improved liver function, reduced hepatocyte damage and necrosis, and decreased apoptosis and pro-inflammatory mediator levels.

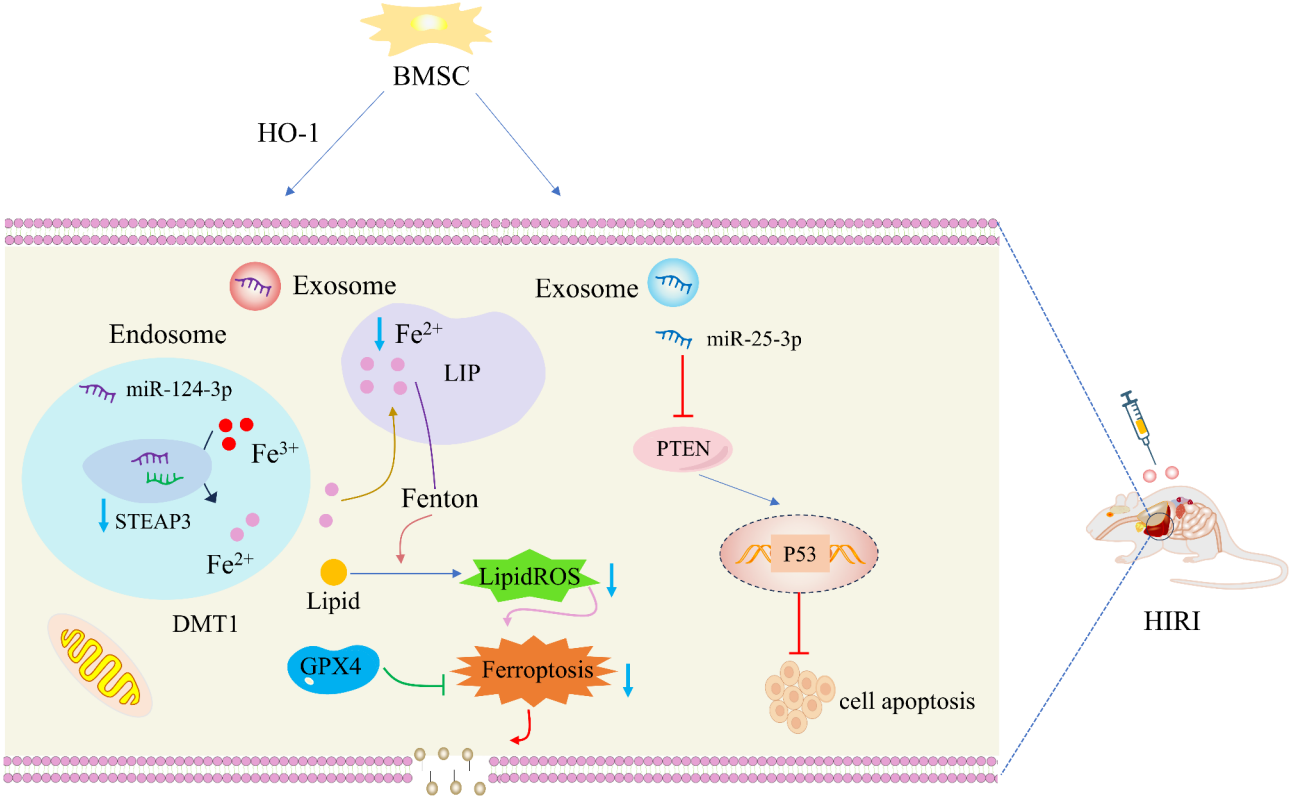


**Fig. 4** Exosomes secreted by BMSCs, modified with HO-1, deliver miR-124-3p. miR-124-3p targets STEAP3, reducing the conversion of $Fe^{3+}$ to $Fe^{2+}$ and promoting the transport of $Fe^{2+}$ via DMT1, thereby regulating the process of ferroptosis. In the Fenton reaction, $Fe^{2+}$ induces lipid peroxidation, increases lipid ROS, and activates ferroptosis, a process that is suppressed by the antioxidant action of GPX4. Additionally, miR-25-3p in the exosomes can inhibit PTEN, thereby regulating the p53 signaling pathway and reducing cell apoptosis

### Protective effects of exosomes derived from iPSC-MSCs on HIRI

iPSCs can differentiate into various somatic cells, demonstrating wide application potential. In recent years, the role of hiPSC-MSC-derived exosomes (hiPSC-MSC-EXOs) in HIRI has also been studied. In a rat model, Nong et al. [89] induced HIRI by occluding the portal vein branches for 60 min, followed by injection of hiPSC-MSC-EXOs. The study found that hiPSC-MSC-EXOs significantly reduced liver injury marker levels, alleviated inflammation and oxidative stress, and inhibited apoptosis. To further investigate the underlying mechanism, Du et al. [90] studied a mouse I/R model and found that after fusion with hepatocytes, hiPSC-MSC-EXOs activated the sphingosine kinase/sphingosine-1-phosphate (SK/S1P) signaling pathway, promoting hepatocyte proliferation and significantly protecting the liver from IRI(Fig. 5).

In conclusion, exosomes derived from various types of mesenchymal stem cells exert therapeutic effects in liver ischemia-reperfusion injury through different molecular mechanisms. AMSC-EXOs primarily regulate inflammation and oxidative stress pathways, BMSC-EXOs mainly influence ferroptosis and apoptosis, hUCMSC-EXOs focus on immune regulation and cell survival, while hiPSC-MSC-EXOs promote cell proliferation and tissue repair.

### Comparative summary of exosomes from different sources

With the development of regenerative medicine, MSC-EXOs from different sources have shown unique advantages and promising application prospects in disease treatment. AMSCs have characteristics such as minimally invasive collection, high purity yield, and low immunogenicity, and are abundant in source, making them suitable for autologous transplantation with good stability [91–93]. However, their extraction efficiency needs improvement, and the activity and functionality of MSCs are influenced by the donor's age [94, 95]. These features make them a potential choice for the treatment of acute liver injury and inflammatory liver diseases. BMSCs have strong resistance to inactivation and a low pathogen infection rate, demonstrating significant advantages in immune regulation and having a broad range of applications [96, 97]. However, the collection process is invasive, and large-scale production is challenging, potentially making them useful for liver transplantation and immune-related disease treatment. UCMSCs have notable advantages such as non-invasive collection, ethical acceptability, and strong proliferative capacity [98, 99]. They are relatively easy to obtain and show excellent potential in tissue damage repair, potentially applicable in the treatment of acute liver failure and neonatal liver diseases. iPSC-MSCs can be controlled for production, manufactured on a large scale, and customized for individual needs, offering unlimited sourcing [100–104]. However, they face challenges such as high costs and

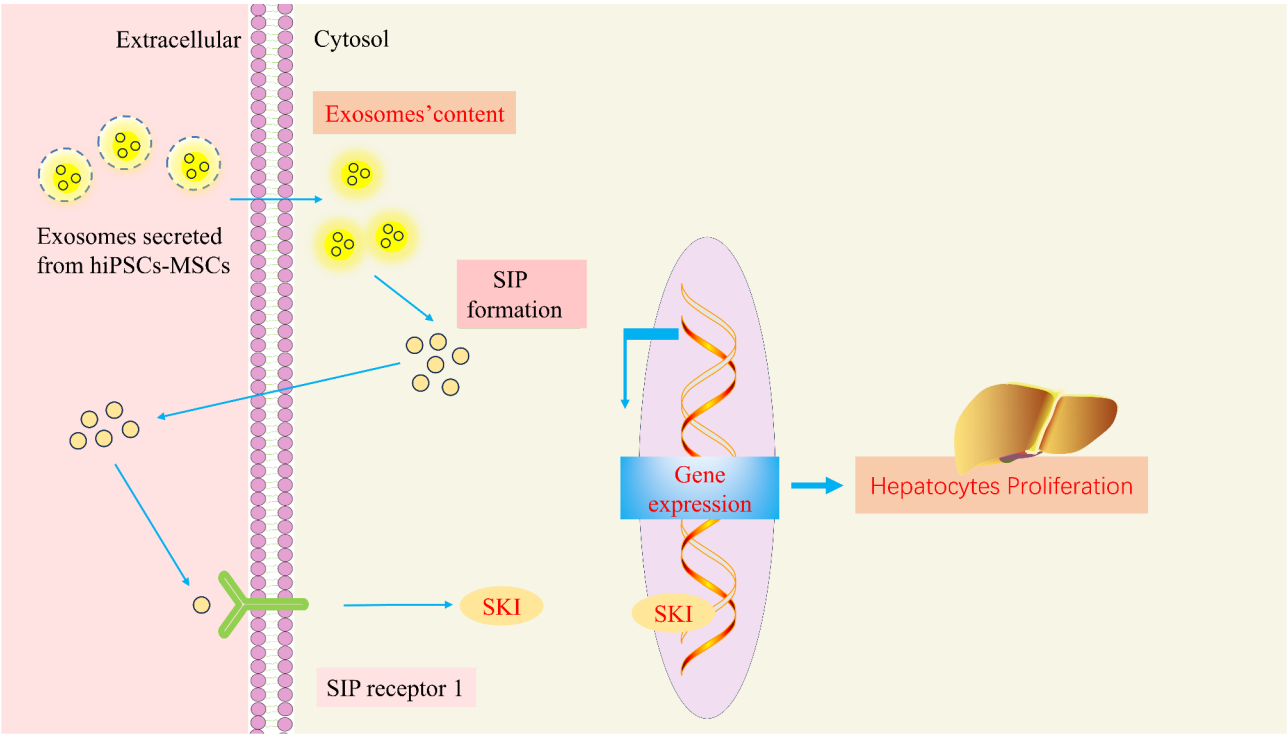


**Fig. 5** hiPSC-MSC-Exos alleviate HIRI by enhancing hepatocyte proliferation by activating the sphingosine kinase/sphingosine-1-phosphate pathway

Table 1 Comparison of preparation characteristics, clinical advantages, technical limitations, and application directions of exosomes from different MSC sources

| Exosome source | Preparation characteristics | Clinical advantages | Technical limitations | Application directions |
|---|---|---|---|---|
| AMSCs | Minimally invasive collection, higher purification yield, lower immunogenicity | Abundant sources, suitable for autologous transplantation, good stability | Donor age impact, unstable extraction efficiency | Acute liver injury, Inflammatory liver disease |
| BMSCs | Not easily inactivated, low pathogen infection rate | Wide application, strong immune regulatory ability | Collection is traumatic, Difficult to mass produce | Liver transplantation, immune-related diseases |
| UCMSCs | Non-invasive collection | No ethical controversy, strong proliferation ability | Relatively easy to obtain, Allogeneic properties | Acute liver failure, neonatal liver diseases |
| iPSC-MSCs | Controllable production, Scalable preparation | Unlimited source, Features can be customized | High cost, Complex quality control | Personalized therapy |

complex quality control, making them suitable for developing personalized treatment strategies.

To provide a comprehensive analysis of the characteristics of MSC-Exos from different sources in the treatment of HIRI, we conducted a systematic comparison of exosomes derived from the four sources mentioned above. The table summarizes the exosome preparation features, clinical advantages, technical limitations, and application directions, highlighting their differentiated potential in liver injury treatment (Table 1).

## Discussion

### Summary of key findings

This article summarizes the protective effects and potential mechanisms of MSC-EXOs from four different sources in HIRI. AMSC-EXOs exert anti-inflammatory effects by regulating multiple signaling pathways, promoting hepatocyte regeneration. However, their key active components and specific mechanisms still require further clarification. BMSC-EXOs improve liver function by reducing ferroptosis, but the exact mechanisms within the liver microenvironment remain unclear. hUCMSC-EXOs regulate signaling pathways by delivering specific molecules, restoring immune balance. However, research on the synergistic effects of other active components is still limited. hiPSC-MSC-EXOs promote hepatocyte proliferation and repair, but their storage stability and long-term safety need further investigation.

### Challenges in clinical translation and potential solutions

#### *Variability in isolation methods and standardization*

Exosome isolation technology is of great significance in biomedical research and clinical applications. However, existing isolation methods still present certain challenges. Although ultracentrifugation is widely regarded as the "gold standard" for exosome isolation [105, 106], it has drawbacks such as sample loss [107], long processing times, high equipment costs [105], and the risk of structural damage to exosomes due to shear forces [105], which limit its application in high-throughput and large-scale production. Density gradient centrifugation offers high purity and no contamination, but the yield of exosomes is low, and the process is complex, making it unsuitable for handling large-volume samples [108–110]. Microfluidic technology, with its high resolution and high-throughput potential, has attracted significant attention, but it is currently mainly used in laboratory research, and its high cost and complexity hinder industrial advancement [111, 112]. To overcome these challenges, integrated isolation solutions can be developed in the future. For example, combining ultracentrifugation with immunoaffinity separation technology, using specific antibodies to recognize exosome markers (such as CD9, CD63, and CD81), can significantly improve the purity and recovery rate of exosomes. Additionally, the precision screening and dynamic monitoring capabilities of microfluidic technology can be utilized to optimize the isolation process. Moreover, optimizing centrifugation conditions (such as flow rate and temperature) using machine learning and artificial intelligence technologies can enhance separation efficiency and the reproducibility of results, thus driving the development of exosome isolation technology toward standardization, scalability, and industrialization.

#### *Large-scale production and quality control*

Currently, large-scale exosome production relies on bioreactor culture systems. However, traditional culture media, such as those containing fetal bovine serum (FBS), have complex components and high costs. These not only limit the yield of exosomes but also may introduce batch-to-batch variability and contamination risks (e.g., endotoxins) [113]. In the future, serum-free media with clearly defined chemical compositions and lower costs could be introduced, and microcarrier technology could be integrated to further optimize the cell culture environment, improving exosome production efficiency and quality.

In terms of quality control, standardized international guidelines should be established, including systematic characterization of particle size distribution (30–150 nm), typical marker expression levels (e.g., CD9, CD63, CD81), purity, and biological functions. Multi-omics analyses,

such as proteomics and metabolomics, should be used to analyze the active components of exosomes, while also assessing their storage stability to provide a scientific basis for long-term preservation and transportation.

#### *Long-term safety and immunogenicity*

Exosomes are considered an ideal strategy for acellular therapy due to their low immunogenicity, but their long-term safety still requires in-depth study. Current research mainly focuses on acute pathological models, with a lack of long-term monitoring under chronic pathological conditions. It is recommended to introduce large animal models to conduct multi-cycle, multi-dose trials to evaluate the accumulation effects and potential toxicity of exosomes under chronic pathological conditions. Additionally, real-time imaging tracking technologies, such as MRI and fluorescence imaging, should be utilized to monitor the distribution and metabolic pathways of exosomes in vivo, providing a comprehensive assessment of their long-term safety.

#### *Clinical application challenges*

MSC-EXOs show potential in clinical applications but also face numerous challenges. Firstly, their composition and function exhibit heterogeneity due to differences in source, culture conditions, and isolation methods [114, 115], leading to inconsistent therapeutic effects. Secondly, MSC-EXOs have poor in vivo stability, are susceptible to environmental factors, and are rapidly cleared from the bloodstream, requiring multiple administrations to maintain efficacy [116–119]. Furthermore, production and storage methods have not been standardized, and there is a lack of unified quality control, which impacts batch-to-batch consistency and the reliability of clinical evaluations. In terms of administration, local injection is difficult to target precisely to the affected area, while intravenous injection faces the issues of rapid clearance and insufficient targeting. Potential solutions to these challenges include the development of efficient delivery systems, such as targeted nanoparticles or liposomes, to precisely deliver MSC-EXOs to the affected areas; optimizing storage and transportation conditions, such as using lyophilization technology to improve exosome stability; and standardizing quality control in production processes to ensure functional consistency and therapeutic efficacy.

## Conclusion and future perspectives

This review demonstrates that MSC-EXOs, as a cell-free therapeutic strategy, shows great potential for the treatment of HIRI. By systematically analyzing current research findings, we have observed that MSC exosomes derived from adipose tissue, bone marrow, umbilical cord, and iPSCs, bone, umbilical cord, and iPSCs each have unique advantages in clinical applications. MSC-EXOs are particularly attractive in therapeutic development due to their cell-free nature, low immunogenicity, and high stability. However, several key challenges must still be overcome to achieve the clinical translation of MSC-EXOs, including the standardization of exosome isolation methods, the establishment of scalable production systems, and comprehensive safety assessments. To address these challenges, we recommend the adoption of advanced isolation technologies combined with standardized quality control systems, as well as systematic safety evaluations. Furthermore, future research should focus on developing engineered MSC-EXOs with enhanced targeting capabilities and therapeutic efficiency. For example, CRISPR-Cas9 gene editing technology can be used to optimize the expression of surface markers on exosomes, enhancing their targeting ability at liver injury sites. Additionally, nanotechnology can be utilized to improve the stability and targeted delivery of exosomes, such as using nanoparticles or liposomes to encapsulate exosomes, thus enhancing their accumulation and therapeutic effects in the liver. Researchers may also use high-throughput screening techniques to quickly evaluate the efficacy of MSC-EXOs from different sources, thereby identifying the most suitable exosome variants for clinical applications. To enable large-scale production of MSC-EXOs, GMP-compliant production platforms should be established, and low-cost, serum-free culture media systems should be explored, alongside the development of precise quality control measures to ensure the stability of exosome quality. Moreover, multi-center clinical trials should be conducted to comprehensively assess the long-term safety and efficacy of MSC-EXOs. These advancements are crucial for translating MSC-EXOs from laboratory research to clinical applications. The success of MSC-EXOs therapy is not only expected to revolutionize the treatment of HIRI but also open up new research directions in regenerative medicine and promote the widespread application of cell-free therapeutic strategies in various diseases.

**Abbreviations**

| | |
|---|---|
| AMSCs | Adipose-derived mesenchymal stem cells |
| BMSCs | Bone mesenchymal stem cells |
| Cas9 | CRISPR-associated protein 9 |
| CRISPR | Clustered regularly interspaced short palindromic repeats |
| CRP | C-reactive protein |
| eIF2α | Eukaryotic translation initiation factor 2α |
| EV | Extracellular vesicle |
| FGF21 | Ibroblast growth factor 21 |
| FOXO1 | Forkhead box protein O1 |
| GPX4 | Glutathione peroxidase 4 |
| GRP78 | Glucose regulated protein 78 |
| GSDMD | Gasdermin D |
| GSK3β | Glycogen synthase kinase-3β |
| hiPSCs | Human induced pluripotent stem cells |
| H/R | Hypoxia/re-oxygenation |
| HIRI | Hepatic ischemia-reperfusion injury |

| | |
|---|---|
| hucMSCs | Human umbilical cord mesenchymal stem cells |
| IL-6 | Interleukin-6 |
| IL-10 | Interleukin-10 |
| lncRNA | Long non-coding RNA |
| IPC | Ischemic preconditioning |
| IPostC | Ischemic postconditioning |
| IRE1α | Inositol-requiring enzyme 1α |
| IRI | Ischemic reperfusion injury |
| IPSC | Induced pluripotent stem cell |
| JAK2 | Janus kinase-2 |
| miRNA | microRNA |
| MSCs | Mesenchymal stem cells |
| MVB | Multivesicular body |
| NF-kB | Nuclear factor kappa-B |
| NLRP3 | Nucleotide-binding oligomerization domain-like receptor protein 3 |
| PCNA | Proliferating cell nuclear antigen |
| PERK | Protein kinase RNA–like endoplasmic reticulum kinase |
| PTEN | Phosphatase and tensin homolog deleted on chromosome ten |
| ROS | Reactive oxygen species |
| SK/S1P | Sphingosine kinase/sphingosine-1-phosphate |
| SOCS3 | Suppressor of cytokine signaling 3 |
| STAT3 | Signal transducer and activator of transcription 3 |
| STEAP3 | Six-Transmembrane epithelial antigen of prostate 3 |
| TBIL | Total bilirubin |
| TGF-β | Transforming growth factor-β |
| Th17/Treg | T helper cell 17/regulatory T cell |
| TNF-α | Tumor necrosis factor-α |
| VEGF | Vascular endothelial growth factor |

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**Author contributions**
Bo Zhao, Jiping Wei, and Zijian Jiang wrote, edited, and revised the manuscript and confirmed the authenticity of the raw data. Yiming Long drew the schematic illustrations. Yan Xu participated in collating article tables. Botao Jiang provided direction and guidance throughout the preparation of this manuscript. All authors read and approved the final version of the manuscript. All authors contributed to the article and approved the submitted version.

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**Data availability**
The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

## Declarations

**Ethics approval and consent to participate**
Not applicable.

**Consent for publication**
Not applicable.

**Generative AI and AI-assisted technologies in the writing process**
During the preparation of this work, the authors used ChatGPT in order to improve the readability and quality of the text. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

**Conflict of interests**
The authors declare that there is no conflict of interest.

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