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REVIEW

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Advances in the treatment of liver injury based on mesenchymal stem cell-derived exosomes

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Abstract

Mesenchymal stem cells (MSCs) have shown a great potential role in treating liver injury. MSCs can promote liver regeneration by differentiating into hepatocytes, and can also secrete exosomes to participate in the repair of liver injury. Increasing evidence has shown that mesenchymal stem cell-derived exosomes (MSC-EXOs) play an important role in treating liver injury. In this review, the biogenesis and function of exosomes and the characteristics of MSC-EXOs were analyzed based on recent research results. MSC-EXOs are significant in liver injuries such as liver fibrosis, liver failure, hepatocellular carcinoma, oxidative stress, and lipid steatosis, and participate in the process of liver regeneration.

Keywords Mesenchymal stem cells, Exosomes, Liver injury, Liver regeneration

Introduction

Liver disease claims the lives of 2 million individuals annually, representing approximately four percent of global mortality, with fatalities predominantly stemming from complications such as cirrhosis and hepatocellular carcinoma. [1] Cirrhosis and liver cancer together account for 3.5% of all deaths in the world, ranking as the 11th and 16th most prevalent causes of mortality worldwide. [2] Chronic liver disease (CLD) and related cirrhosis are responsible for approximately 1 million deaths each year, imposing substantial mortality, morbidity, and economic burdens. [3]Due to the increase in obesity, metabolic-associated CLD has increased and shown an increasing trend. [4] Liver transplantation often serves as the final option in end-stage liver disease. Liver transplantation accounts for the second largest proportion of solid organ transplantation, but the current rate of transplantation can only meet a small amount of the global demand [5]. Therefore, new therapeutic measures are needed in the face of the occurrence and development of liver diseases.

MSCs possess inherent capabilities for self-renewal, pluripotency, and support a dynamic equilibrium, facilitating regeneration and immune modulation among numerous physiological functions. [6, 7] There are several studies that have found that MSCs are significant in the treatment of acute or chronic liver injury. However, MSC therapy encounters constraints, such as the inability to continuously supply cells with stable phenotypes and high production costs. [8] In addition, MSCs have potential problems related to immune rejection and have the possibility of tumorigenesis. [9, 10] In contrast, MSC-EXOs have unique advantages. Compared with MSCs, exosomes are easier to produce and store, and due to their cell-free characteristics, they can avoid immune rejection problems and tumorigenesis. [11, 12]And because of their nano size and lipid bilayer structure, easier to target organs through biological barrier treatment. [13] Currently, MSC-EXOs

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have shown therapeutic potential in various kinds of diseases, including myocardial injury, lung injury, kidney injury, and others [14–16].

As a kind of natural nanomaterials, exosomes can be used as delivery vectors for treatment after engineering modification based on the physiological structure characteristics of exosomes. Unlike conventional nanomaterials, exosomes can enhance their endocytosis due to their membrane proteins and promote drug therapeutic effects [17]. In a murine model of transient middle cerebral artery occlusion (MCAO), curcumin-loaded exosomes can cross the blood–brain barrier and inhibit inflammation and apoptosis in the lesion area [18]. Natural exosomes contain a variety of nucleic acids. Exosomes can deliver nucleic acids to play a characteristic gene therapy effect and improve the targeting by modifying the surface motif of the vector [19]. Various methods can be used to load nucleic acids into exosomes, such as electroporation, cellular nanoporation, transfection with specific reagents, and exosome-lipid hybrid systems. [20] Proteins regulate many physiological functions in the human body and efficiently catalyze various physiological reactions in the human body. Protein-related nanotherapy is of great significance. Multiple investigations on exosomes as natural nanomaterials, which play a targeted therapeutic role by combining with proteins [21]. Therefore, MSC-EXO has a broad prospect in the treatment of liver injury.

Exosome biogenesis

With the progress in the study of extracellular vesicles, there are three main types according to their release mechanism and size: exosomes, microvesicles (MVs)/shedding particles, and apoptotic bodies. (Fig. 1) [22–24] Initially, exosomes were thought to represent cellular waste products. But as the research progresses, these vesicles are thought to mediate intercellular communication function, and adjust various physiological and pathological states. [25, 26]

Late endosomes/multivesesomes (MVBs) can form exosomes after being released into the extracellular environment after fusion with the plasma membrane. [27] The biogenesis of exosomes begins in the endosome system, and early endosomes can be formed through internalization. The early endosome develops and matures into MVBs. [28] Within this process, membrane invagination occurs, leading to the formation of MVBs that house numerous nanoscale intraluminal vesicles (ILVs) containing specific proteins, lipids, and cytoplasmic components [22]. MVBs reach the plasma membrane with the help of the cytoskeleton and microtubule network, and subsequently undergo exocytosis by fusion with the cell surface, and ILV is secreted in the form of exosomes. [29] Some MVBs can be directly degraded after fusion

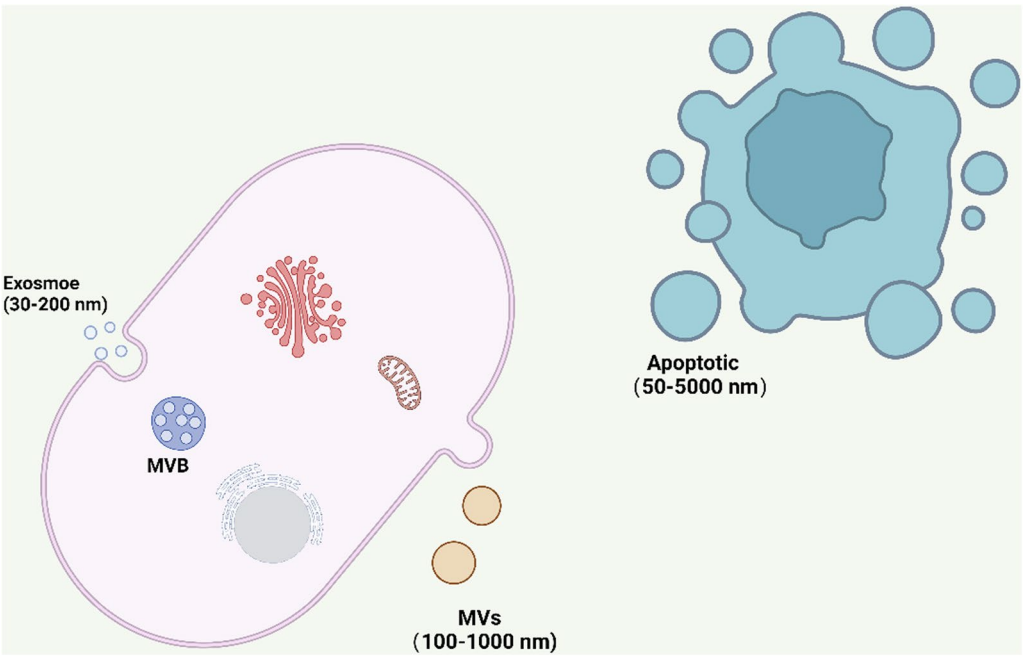

Fig. 1 According to the release mechanism and size, extracellular vesicles can be divided into three types: exosomes (30–200 nm), microvesicles/shedding particles (100–1000 nm), and apoptotic bodies (50–5000 nm). Created in BioRender. ZY, C. (2024)

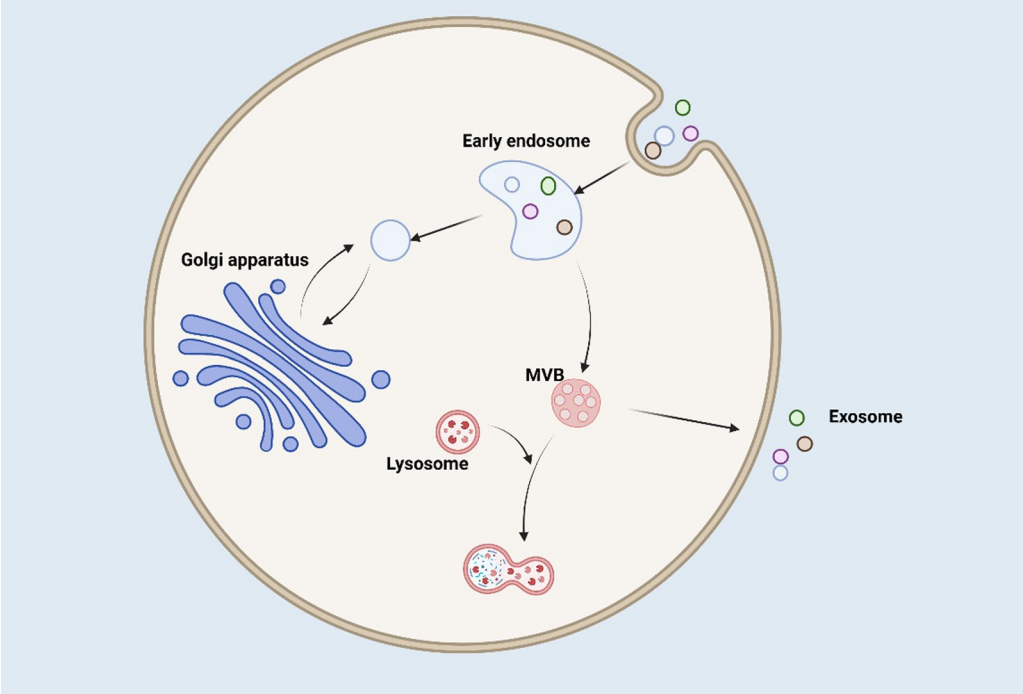

Fig. 2 Early endosomes are formed through internalization, which can communicate with organelles including Golgi apparatus, and then mature into MVBs. Some MVBs fuse with the cell surface and undergo exocytosis to form exosomes. Another fraction of MVBs can bind to lysosomes for degradation. Created in BioRender. ZY, C. (2024)

with lysosomes, while the other part of exosome fuse with autophagosomes first and then degrade after fusion with lysosomes. (Fig. 2) [30] Mechanisms either ESCRT-dependent or ESCRT-independent mediate exosome biogenesis [31].

ESCRT mechanism relies on the five core ESCRT complexes: ESCRT—0,—I, II, III, and Vps4. [32] The ESCRT mechanism governs exosome secretion, and seven ESCRT proteins were found to increase or decrease the secretion of exosomes by RNAi screening. For example, the secretion of exosomes was significantly increased after knocking down ESCRT-III and related proteins CHMP4C, VPS4B, VTA1, and ALIX. [33]

The generation of MVBs can also occur independently of ESCRT, wherein the silencing of key subunits from all ESCRT complexes simultaneously does not impede ILV formation within MVBs, suggesting an ESCRT-independent pathway. [34] Tetra transmembrane protein is an exosome-rich transmembrane protein that mediates exosome release in an ESCRT-independent mechanism. [35] For example, the increased exosomal release of β-catenin in HEK293 cells was found to be mediated through the expression of tetraspanin CD9 and CD82. [36]In addition to proteins, lipids also play an important role in the biogenesis of exosomes. Lipids are important participants in vesicle trafficking and cooperate closely with proteins in the process of vesicle trafficking. [22, 37] Neutral sphingomyelinase 2 (nSMase2) activation facilitates ceramide generation, promoting an ESCRT-independent pathway through ceramide microdomain formation. [38] In addition, phosphatidic acid activation via phospholipase D2, due to its small head group, may promote membrane invagination by inducing negative membrane curvature [39].

Characteristics of MSC-EXOs

MSC-EXOs contain complex biomolecules, such as proteins, lipids, nucleic acids, etc. [30] The exosomes contain not only tetraspanin protein family, heat shock protein, ALIX and TSG101, which are similar to most types of exosomes, but also many specific biological molecules, such as MSCs surface markers CD44, CD73, CD90 and MSC-specific adhesion factors CD73, CD44 and CD29. (Fig. 3) [40–42] 850 specific proteins and 150 miRNAs can be identified in MSC-EXOs, which are involved in many physiological processes [8, 43]. MSC-EXOs contained a large number of pre-form miRNAs. By comparing the miRNAs in exosomes secreted by MSCs and MSCs-derived miRNAs, they were not consistent. Some miRNAs were found in MSCs, but not in MSCs exosomes, indicating that MSCs do not randomly distribute miRNAs to exosomes. They are selected by regulating

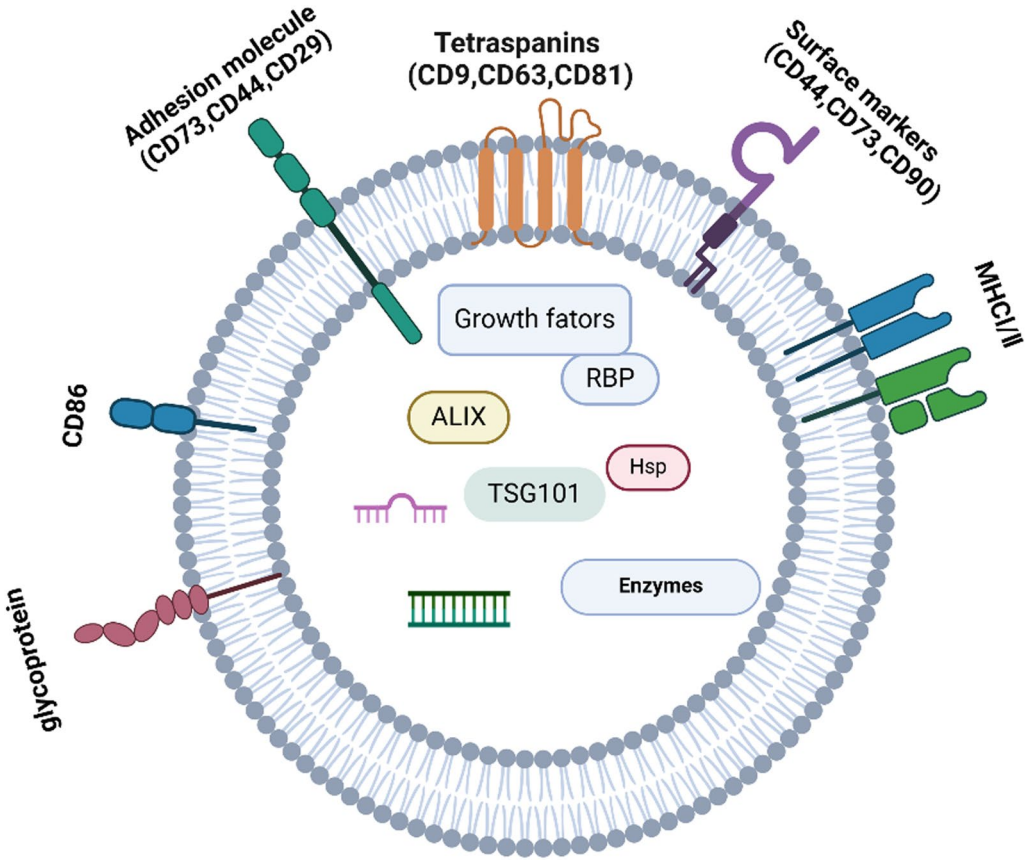

Fig. 3 MSC-EXOs contain different types of proteins, lipids and nucleic acids. These exosomes contain not only glycoproteins, antigen-presenting proteins, tetraspanins and MHCI/II structures similar to most exosomes, but also MSC-EXOs-specific adhesion proteins(CD73, CD44 and CD29) and surface markers(CD44, CD73, CD90). Created in BioRender. ZY, C. (2024)

secretion [44, 45]. It has been established that a close relationship exists between RNA and RNA-binding proteins (RBPs) in the extracellular space. RBPs play a crucial role in the transfer and maintenance of RNA outside cells, as well as in the sorting of miRNAs into exosomes [46, 47].

MSC-EXOs have complex functions, in addition to being carriers of intercellular communication, regulating and mediating intercellular communication. At the same time, it can maintain the microenvironment of interstitial cells and play a physiological role similar to that of MSCs. [40, 48] MSC-EXOs can play an immunomodulatory role through a variety of cytokines, such as TGF, IL-6, IL-10, HGF, etc. [49] It has been found that MSC-EXOs are significant in stimulating angiogenesis through VEGF, MMP and EMMPRIN [50]. MSC-EXOs contain various miRNAs, which are significant in immune regulation, tumor occurrence and progression, and epigenetic regulation, and mediate the progression of a variety of diseases. [51] In addition, MSC-EXOs contain various enzymes required to mediate normal physiological reactions and can play a role in normal human physiological reactions. For example, in energy metabolism, MSC-EXO can detect all five enzymes responsible for ATP production during glycolysis. In addition, MSC-EXOs were also involved in energy metabolism in other aspects. For example, MSC-EXOs have been found to mediate benign remodeling after myocardial ischemia/reperfusion injury by enhancing myocardial viability, mainly by increasing ATP level, reducing oxidative stress and activating the PI3K/Akt pathway. [52] The quantitative changes of nucleic acids and proteins in exosomes can accurately reflect the physiological state of the body. Exosomes can be used as diagnostic biomarkers to identify many diseases at the early stage and reflect the effect of treatment effect in real time [53]. Various miRNAs and proteins in blood-derived exosomes of Alzheimer's disease (AD) patients serve as biomarkers for AD diagnosis. [54]

As an ideal molecular carrier, exosomes not only contain a variety of miRNAs themselves, but also can be modified to deliver a variety of miRNAs, which are applied to the treatment of diseases (Table 1) [55]. Due

Table 1 MSC-EXOs-related miRNAs for the treatment of liver diseases

Diseases	MiRNA	Model	Mechanism
Liver fibrosis	miR-27b-3p	CCl_4-induced mouse model	Inhibit LOXL2 as the downstream target gene of YAP [63]
Liver fibrosis	miR-148a	CCl_4-induced mouse model	Target KLF6 to control the STAT3 signaling pathway [64]
Liver fibrosis	miR-125b	CCl_4-induced mouse model	Inhibiting Smo expression and Hh signaling activation [65]
Liver fibrosis	miR-122	CCl_4-induced mouse model	Targeting the binding site located in the 3'-UTR of P4HA1 mRNA [66]
Liver fibrosis	miR-181-5p	CCl_4-induced mouse model	Inhibit STAT3/Bcl-2/ Beclin-1 pathway [67]
ALF	miR-455-3p	CCl_4/LPS-induced mouse model	Inhibit inflammatory responses by targeting PIK3r1 [68]
HCC	miR-199a-3p	Orthotopic HCC mouse model	Reversed the reduced phosphorylation of 4EBP1 and 70S6K in HCC cells and the reduced chemoresistance of HCC cells treated [69]
HCC	miR-451a	human HCC cell lines Hep3B, MHCC-97 H, HB611, HepG2 and SMMC-7721	Delay the progression of EMT by inhibiting ADAM10 [70]
HCC	miR-15a	human HCC cell lines Hep3B and Huh7	Downregulation of SALL4 inhibits the proliferation, migration and invasion of HCC cells [71]
HCC	miR-122	HepG2 cell xenograft model	Enhance the chemosensitivity of HCC [72]
Liver oxidative stress	miR-26a-5p	cecal ligation puncture (CLP) and lipopolysaccharide (LPS) plus D-galactosamine (D-gal) as sepsis-induced ALI model	Targeting MALAT1 reduces oxidative stress [73]
Liver oxidative stress	miR-200a	DEN-induced LF model	Preventing oxidative stress, inflammation, necroptosis and anti-fibrosis [74]
Liver steatosis	miR-96-5p	HFD-induced mouse model	Inhibits caspase-2, thereby hindering fatty acid synthesis and lipid uptake, and upregulates fatty acid oxidation [75]
Liver steatosis	miR-627-5p	HFHF-induced mouse model	Enhanced lipid and glucose metabolism and decreased liver damage by blocking FTO expression [76]

to their characteristics, exosomes can be preferentially absorbed by the damaged tissue to play a more efficient therapeutic role in tissue damage. [56, 57] In addition, due to their cell-free characteristics, exosomes can effectively avoid the risks such as tumor susceptibility that exist in MSC therapy. [8] MSC-EXOs can be used to inhibit the phagocytosis of macrophages and show long-term circulation ability through their immunosuppressive properties, thereby improving the delivery ability. [58] And exosome-derived drug delivery vectors are well tolerated, which prolongs their circulation half-life and enhances the therapeutic effect [59]. Moreover, due to the membrane proteins and other structures on the surface of exosomes, they can specifically target damaged tissues, and exosomes have therapeutic effects by binding to target cells [60, 61]. Among the various cells that are known to produce exosomes, MSCs are the most productive and suitable for the manufacture of large-scale production of exosomes for carriers. [62]

MSC-EXOs for the treatment of liver diseases

Liver-related injuries are prevalent and profoundly affect global health. Currently, numerous studies indicate that MSC-EXOs play a crucial role in liver injury management. The application of MSC-EXOs in addressing liver injuries primarily involves naturally occurring or engineered exosomes. The specific findings regarding the role of MSC-EXOs in five types of liver injury are summarized below. (Fig. 4).

Therapeutic potential of MSC-EXOs in treating liver fibrosis

CLD manifests as prolonged or repeated injury triggering an excessive wound healing response, abnormal extracellular matrix (ECM) deposition, and perturbations in liver microenvironmental homeostasis [77]. Progressing to cirrhosis, liver fibrosis is a serious complication potentially leading to chronic liver failure and hepatocellular carcinoma [3]. With the rising prevalence of obesity, which correlates with an increase in CLD cases, inhibiting liver fibrosis development is crucial, given the lack of efficacious anti-fibrosis treatments [78]. Numerous persistent liver injuries can result in hepatic fibrosis. MSC-EXOs have been demonstrated in numerous trials to have therapeutic benefits on the liver fibrosis process. Exosomes produced from human mesenchymal stem cells(hucMSC-EXOs) have the potential to treat rats with liver fibrosis brought on by CCl_4. It was discovered that the expression of type II and III collagen in the liver dramatically decreased three weeks following hucMSC-EXOs transplantation. By blocking the TGF-β1/

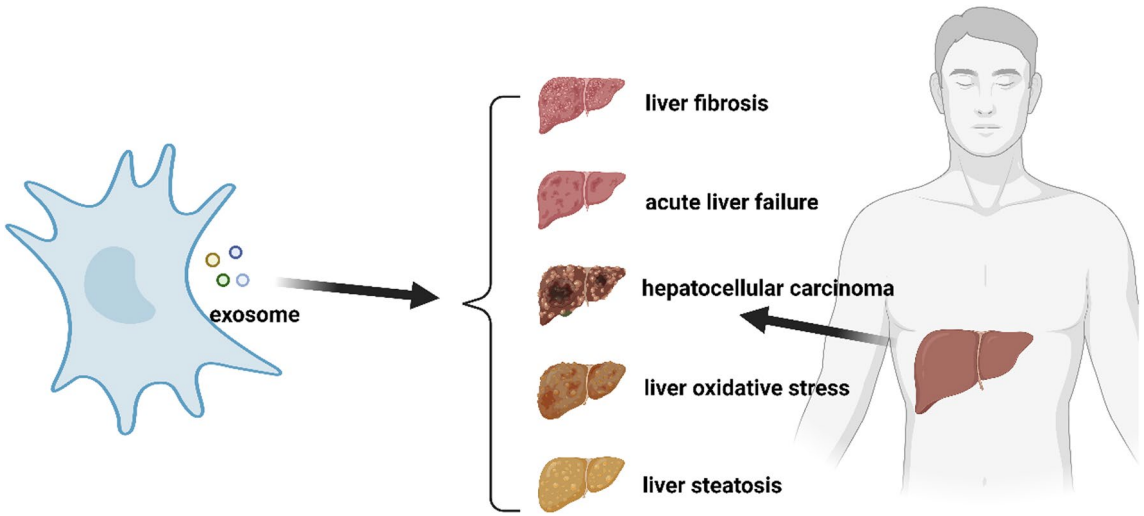

Fig. 4 MSC-EXOs play a significant role in various types of liver injuries, including liver fibrosis, acute liver failure, hepatocellular carcinoma, oxidative stress, and steatosis. Created in BioRender. ZY, C. (2024)

Smad signaling cascade and preventing the epithelial-to-mesenchymal transition (EMT), hucMSC-EXOs reduce liver damage [79]. Furthermore, Wnt/β-catenin signaling was suppressed by human bone mesenchymal stem cell-derived exosomes (hBM-MSC-EXOs), which in turn downregulated hepatic stellate cell (HSC) activation and ultimately decreased CCl_4-induced liver fibrosis. The findings show that hBMSC-EXOs administration may suppress the expression of many Wnt signaling pathway proteins (PPARγ, Wnt3a, Wnt10b, and β-catenin), which in turn can aid in suppressing the expression of downstream genes (WISP1, Cyclin D1). Liver fibrosis is eventually reduced by inhibiting myofibroblast activation and HSCs [80]. A novel form of programmed cell death is ferroptosis. It has been found that ferroptosis induction can improve tissue fibrosis and has the potential for anti-fibrosis therapy. [81] MSC-EXOs can enhance iron death in HSCs, thereby reducing CCl_4-induced liver injury through the exosome /BECN1/xCT/GPX4 pathway. [82] Notably, these findings underscore MSC-EXOs as potential agents that can home in on injured liver sites, modulate Th17 differentiation, and ameliorate liver fibrosis in diseases like Primary sclerosing cholangitis (PSC) by improving the Th17-driven microenvironment. [83] The extracellular copper-dependent enzyme lysyl oxidase-like 2 (LOXL2) catalyzes the deposition and cross-linking of collagen, which results in fibrosis [84].MSC-EXOs can inhibit the expression of Yes-associated protein (YAP) by targeting the 3′ untranslated region of LX-2 with miR-27b-3p and inhibit LOXL2 as the downstream target gene of YAP, thereby achieving the purpose of anti-fibrosis [63].The signal transducer and activator of transcription 3 (STAT3) drive the activation of fibroblasts and HSCs and transforms them into a myofibroblast-like phenotype, which is closely related to the progression of liver fibrosis [85]. By transforming pro-inflammatory macrophages into an anti-inflammatory phenotype, MSC-EXOs improved liver fibrosis. Additionally, it was shown that miR-148a directly targeted KLF6 to control the STAT3 signaling pathway, preventing the advancement of liver fibrosis [64]. The degree of liver injury and fibrosis raises the expression of the Hedgehog (Hh) signaling pathway, and Hh signaling induces fibrosis through EMT. [86] Transplanted chorionic plate-derived mesenchymal stem cells (CP-MSCs) have been found to reduce liver fibrosis in a mouse model [87]. Further studies showed that miR-125b from CP-MSCs contributed to the reduction of liver fibrosis by inhibiting Smoothened (Smo) expression and Hh signaling activation [65]. The accumulation and activation of B cells in the liver can lead to inflammation and fibrosis. It is an important measure to treat liver fibrosis by regulating the immune microenvironment of the liver [77, 88]. Liver fibrosis has been reported to enhance the expression of pro-inflammatory genes in B cells. By controlling the MAPK and NF-κB signaling pathways, MSC-EXOs can mediate the inhibitory action of MSCs on B cells. Significant inhibition was observed in the activation, proliferation, and pro-inflammatory activity of B cells [89].

Additionally, engineered exosomes may be able to treat liver fibrosis. The most prevalent and liver-specific miRNA, miR-122, makes up 72% of all the miRNA in the adult liver. Studies have demonstrated the significant impact that miR-122-modified adipose tissue-derived MSCs (AD-MSCs) exosomes play in controlling liver damage [90, 91]. miR-122 is involved in regulating

collagen maturation by targeting prolyl 4-hydroxylase subunit alpha-1 (P4HA1), as well as regulating the proliferation of HSCs. Overexpression of miR-122 significantly attenuated P4HA1 expression and inhibited type I collagen maturation in HSCs by targeting the binding site located in the 3 '-UTR of P4HA1 mRNA. Research has shown that activated hematopoietic stem cells have a lower level of miR-122 expression, which could potentially accelerate the development of liver fibrosis by upregulating the expression of prolyl 4-hydroxylase and causing an excess of cross-linked collagen to be produced. [66] Hepatocytes received miR-181-5p specifically from exosomes produced from adipose-derived mesenchymal stem cells (AMSCs) treated with miR-181-5p. The STAT3/Bcl-2/ Beclin-1 pathway may be inhibited by exosomes carrying miR-181-5p in HSCs and CCl_4-induced liver fibrosis mice models. It lessens liver fibrosis brought on by TGF-β1 and raises HSC autophagy [67]. Analyzing human bone marrow mesenchymal stem cells (BM MSC) in both 2D and 3D cultures showed increased paracrine activity during wound healing and regeneration [92].Circular RNA (circRNA) is a single-stranded, covalently closed RNA molecule. Compared with other types of RNA, it has stronger stability and higher specificity. [93] Some research has found that the use of exosomes as in vivo delivery vectors to load therapeutic circRNA can be used for the treatment of liver diseases. circDIDO1 overexpression resulted in decreased levels of α-SMA and type I collagen in LX2 cells as shown by western blot. circDIDO1 increased the PTEN protein level of LX2 cells and decreased the p-AKT/AKT ratio, thereby inhibiting the activation of HSCs. [94] siRNA or antisense oligonucleotide (ASO) targeting STAT3 can be loaded into engineered MSC-EXOs. Compared with siRNA control, siRNA-STAT3 or ASO-STAT3, MSC-EXOs significantly inhibited STAT3 levels and ECM deposition in mice with liver fibrosis. The treatment of liver fibrosis was effective and the liver function was significantly improved [95]. Specific modifications of exosome membrane proteins may enable accurate treatment of liver fibrosis and enhance the therapeutic effect of exosomes. The peptide HSTP1 was evaluated to have a good targeting ability to activate hepatic stellate cells in liver fibrosis. Furthermore, engineered exosomes (HSTP1-EXOs) were formed by fusing HSTP1 with exosome-enriched membrane protein Lamp2b (Lamp2b). HSTP1-EXOs can be effectively internalized by HSC-T6 cells and enhance the ability to inhibit the activation of hepatic stellate cells [96]. Obeticholic acid (OCA), a bile acid analog, has been found to have an inhibitory effect on metabolic dysfunction-associated steatohepatitis (MASH) fibrosis in the liver, but it cannot be accurately targeted to the liver [97, 98]. Research has found that exosome-mediated delivery of OCA can effectively alleviate liver fibrosis in vivo and in vitro compared with either exosomes or OCA monotherapy. It also mediates the progression of liver fibrosis by inhibiting the activation of HSCs and enhancing the remodeling of ECM. [99]

Therapeutic potential of MSC-EXOs in treating acute liver failure

The clinical state known as acute liver failure (ALF) is marked by a sharp decline in liver function that is quickly followed by ascites, coagulopathy, hepatic encephalopathy, and multi-organ failure. [100] ALF is frequently brought on by hepatotropic virus invasion, severe drug-induced liver injury, liver ischemia, and a strong immunological reaction. [101] Artificial liver and liver transplantation are often used to maintain liver function in clinical practice. However, the treatment of artificial liver is relatively limited, and liver transplantation is often accompanied by severe immune rejection [102, 103]. Therefore, there is an urgent need for immunosuppressive agents and hepatoprotective drugs to be utilized in the treatment of acute liver failure. MSC-EXOs are highly promising in the management of acute liver failure due to their physiological characteristics, which help mitigate the risk of immune rejection and enhance their distribution within the liver.

The activation of NLRP3 inflammasome plays an important role in ALF, leading to hepatocyte injury as well as the activation and expansion of immune cells in fulminant hepatitis. [104] AMSC-Exo administration was found to significantly ameliorate Lipopolysaccharide and D-galactosamine (LPS/GalN)-induced fulminant hepatitis and reduce the secretion of inflammatory factors and inflammasome activation in macrophages. Research has found that MSC-Exo is rich in miR-17 and plays a therapeutic role in acute liver failure by inhibiting TXNIP-mediated activation of NLRP3 inflammasomes and regulating the activation of liver macrophage inflammasomes [105].hucMSCs produce a large number of exosomes enriched with miR-455-3p under IL-6 stimulation. Macrophages challenged with lipopolysaccharide (LPS) release IL-6 and other inflammatory factors. These exosomes suppress inflammatory responses by targeting PIK3r1. Research has shown that hucMSC-EXOs enriched for miR-455-3p can inhibit monocyte/macrophage activation, and alleviate acute liver injury by inhibiting IL-6-related signaling pathway, reducing liver macrophage infiltration, and reducing serum inflammatory factor levels, thereby improving liver injury [68].

Autophagy is a major intracellular catabolic mechanism that removes long-living proteins or damaged organelles mainly through the lysosomal pathway and plays a role in the regular renewal of intracellular components

and organelles. Research has shown that autophagy is essential for protection after acute liver failure [106, 107]. It was discovered that bone marrow mesenchymal stem cell-derived exosomes (BMSC-EXOs) have the ability to lessen hepatocyte death following acute liver failure in the model of hepatocyte injury and apoptosis generated by D-GalN/LPS. BMSC-EXOs could increase the expression of autophagy marker proteins LC3 and Beclin-1, and promote the formation of autophagosome. BMSC-EXOs mediate autophagy to protect hepatocytes from damage caused by various stresses and inhibit the development of acute liver failure [108]. The therapeutic use of MSCs is restricted due to various cell sources, low stability, cell senescence, and other issues. As a result, it is critical to set up a system for MSC-EXO mass manufacture and application. Research reveals that the human telomerase reverse transcriptase (hTERT) gene has been widely employed for ectopic expression in cell immortalization, which can enhance stem cell characteristics and decrease BMSC spontaneous differentiation. Umbilical cord mesenchymal stem cells (UCMSC) were successfully used in this research to create the immortalized cell line hTERT-UCMSC, which maintained its primary properties even after long-term passage. Exosomes made from hTERT-UCMSC can treat ALF animals, while more research is still needed to determine the exact mechanism [109, 110].

Therapeutic potential of MSC-EXOs in treating hepatocellular carcinoma

Liver cancer is a common malignant tumor, and Hepatocellular carcinoma (HCC) accounts for 85%-90% of primary liver cancer [111]. The treatment effect is not ideal, and new treatment methods are urgently needed. MSC-EXOs play a therapeutic role in most liver injuries. However, they play a double-edged sword role in the regulation of cancer. [112] As a kind of tumor stromal cells, MSCs participate in the construction of a tumor microenvironment. [113] Some research has shown that there is the transfer of tumor-related factors in MSC-EXOs, which is related to the promotion of cancer cell proliferation [114]. BMSCs-EXOs can promote the growth of cancer-related cells by activating the Hedgehog signaling pathway. [115]MSCs-EXOs can activate the ERK1/2 pathway to enhance the expression of VEGF in tumor tissues and promote their growth, which can also be found in liver cancer and liver fibrosis. [116] However, MSCs-EXOs have also shown therapeutic potential, with exosome-treated animals being found to have significantly smaller tumor sizes and volume ratios. Compared with the control group, the percentage of circulating NKT cells was higher in exosome-treated rats on days 5 and 15 after treatment. AMSCs-EXOs could promote HCC suppression and low-grade tumor differentiation by promoting the anti-tumor response of rat NKT cells. [117] BMSCs-EXOs could promote apoptosis and inhibit the cell cycle progression of HepG2 cells [118]. By injecting BMSCs-EXOs into HCC rats, it was found that BMSCs-EXOs could significantly inhibit tumor angiogenesis activity, tumor metastasis and invasion in vivo [119].

Due to the double-edged sword effect of MSCs-EXOs in tumor progression, the use of artificially modified exosomes has more advantages in the treatment of HCC. [120]The use of miR-199a-3p-modified AMSC-EXOs can effectively mediate the direct delivery of miR-199a-3p to AMSCs and HCC cells, thereby enhancing the chemosensitivity of HCC cells by targeting the mTOR pathway. Moreover, overexpression of mTOR reversed the reduced phosphorylation of 4EBP1 and 70S6K by AMSC-EXO-199a in HCC cells and the reduced chemoresistance of HCC cells treated with AMSC-EXO-199a. [69]MiR-451a-modified hucMSC-EXOs treatment can promote cell apoptosis, inhibit paclitaxel resistance, and regulate HCC cell cycle progression. Research has shown that hucMSC-derived exosomal miR-451a can delay the progression of EMT by inhibiting a disintegrin and metalloprotease 10 (ADAM10), thereby acting as an inhibitory factor in HCC. [70] Spalt like transcription factor 4 (SALL4) is linked to increased carcinogenesis and tumor progression and is overexpressed in a number of illnesses, including lung and cervical cancer. [121, 122] By down-regulating SALL4 expression, miR-15a-modified MSC-EXOs inhibited HCC cell growth, migration and invasion after being introduced into HCC cells [71].

MSC-EXOs can serve as effective drug delivery carriers for packaging the anticancer drug norcantharidin (NCTD), thereby realizing their potential in the treatment of hepatocellular carcinoma HCC. In vitro, drug release studies found that BMSCs-EXOs-NCTD can release drugs continuously and slowly. Pharmacodynamic analysis both in vitro and in vivo demonstrated the efficacy of the BMSC-EXOs-NCTD delivery system in increasing cell death, inducing cell cycle arrest, decreasing tumor cell proliferation, and promoting cell uptake. Compared with NCTD treatment alone, BMSCs-EXOs-NCTD has a significant anti-tumor effect in vivo [123]. In addition, BMSC-EXOs modified with siGRP78 showed therapeutic potential by combining with targeted drugs for liver cancer. In vivo, sorafenib-resistant cells' growth was markedly suppressed by SIGRP78-modified exosomes when paired with sorafenib. And sorafenib-sensitive cells showed no tumor formation. Furthermore, the potential of tumor invasion may be inhibited by combining sorafenib with exosomes modified by SIGRP78. Research has demonstrated that sorafenib in combination with exosomes modified with SIGRP78 can

target GRP78 in hepatocellular carcinoma cells and prevent cancer cells from growing and invading in vitro. In drug-resistant HCC cells, exosomal transfer of siGRP78 increased chemosensitivity to sorafenib [124]. In addition to showing its therapeutic potential in liver fibrosis, exosomes modified by miR-122 have been shown to be involved in regulating the chemosensitivity of HCC cells [125]. AMSCs can be used as an ideal vector for miR-122 to mediate miR-122 communication between AMSCs and HCC cells. Research has shown that miR-122 can enhance the chemosensitivity of HCC cells by modifying AMSCs [72].

Therapeutic potential of MSC-EXOs in treating liver oxidative stress

Ischemia–reperfusion injury is often caused by vascular clamping after liver resection and liver transplantation, and the most important injury is caused by oxidative stress. Oxidative stress is mainly caused by the imbalance of oxidants and antioxidants. [126] Exosome therapy has shown potential in the treatment of oxidative stress in a variety of organs, and there is increasing evidence that MSC-EXOs play a unique therapeutic effect in the treatment of oxidative stress in the liver. Treatment of mice with CCl_4-induced acute liver injury with hucMSC-EXOs showed that the production of 8-OHdG and the expression of apoptosis-related genes were decreased in the injured liver. Bifendate (DDB) has minimal side effects in the treatment of hepatitis. With the increase in dose, DDB shows the potential for anti-oxidation and anti-apoptosis, but it is still unable to achieve the therapeutic effect of hucMSC-EXOs, and the hepatoprotective effect of hucMSC-EXOs is more obvious than that of DDB. [127] After CCl_4 and H_2O_2 generated injury, it was discovered that MDA, reactive oxygen species (ROS), and oxidative stress-induced apoptosis increased; however, following hucMSC-EXOs therapy, MDA, ROS, and oxidative stress-induced apoptosis decreased. In L02 cells harmed by CCl_4 and H_2O_2, hucMSC-EXOs have a strong antioxidant effect. This effect may be attributed to the action of glutathione peroxidase 1 (GPX1), which reduces hepatic ROS and prevents oxidative stress-induced apoptosis by up-regulating ERK1/2 and Bcl-2 and down-regulating the IKKB/NFkB/casp-9/3 pathway. [128] Human-induced pluripotent stem cells(hiPSCs) were effectively induced into hiPSC-MSCs with typical MSC characteristics. Following the injection of hiPSC-MSC-EXOs, the treatment group's levels of inflammatory markers like tumor necrosis factor (TNF)-α, interleukin (IL)-6, and high mobility group box 1 (HMGB1) were significantly lower than those of the control group, as were the hepatocyte injury markers aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Furthermore, the experimental group's liver tissue exhibited significantly lower levels of apoptotic markers, caspase-3 and bax, and significantly greater levels of oxidative markers, such as glutathione (GSH) and superoxide dismutase (SOD), in comparison to the control group. These findings imply that by reducing inflammation, hiPSC-MSC-EXOs may lessen the reaction and decrease oxidative stress cell death. [129] MALAT1 is a long non-coding RNA that is highly present in hepatocytes and the liver under sepsis and inhibits the antioxidant system. [130] MSC-EXOs inhibit MALAT1 through miR-26a-5p, thereby inhibiting the oxidative stress process [73].

The modified MSC-EXOs also exert great therapeutic potential in the process of regulating oxidative stress. Hydrogen sulfide(H2S) has a unique therapeutic effect on oxidative stress, the release of pro-inflammatory factors (TNF-α, IL-1, and IL-6), and hepatocyte apoptosis. It can influence cellular physiological processes through both epigenetic and non-epigenetic pathways [131, 132]. H2S preconditioning-derived exosomes can protect mouse liver against I/R injury by improving total oxidative status, inflammatory cytokines, apoptosis and ROS production. [131] Pretreatment of MSC-EXOs with rupatadine (RUP) can significantly express miRNA-200a, which plays an important role in preventing oxidative stress, inflammation, necroptosis and anti-fibrosis, and plays a more obvious anti-oxidative stress effect. RUP not only enhanced the direct anti-oxidative, anti-inflammatory, anti-necrotizing and anti-fibrosis effects of MSC-EXOs pretreatment, but also exerted an indirect effect by creating a more favorable environment to mediate the effects of MSC-EXOs [74].

Therapeutic potential of MSC-EXOs in treating liver steatosis

Metabolic dysfunction-associated steatotic liver disease (MASLD) encompasses a spectrum of progressive steatotic liver disorders and is the most prevalent cause of chronic liver disease. This condition is characterized by the excessive accumulation of lipids in the liver, resulting in an inflammatory response and liver fibrosis [133]. MASLD is becoming the fastest growing factor leading to adverse liver outcomes, including cirrhosis, liver failure, and hepatocellular carcinoma, so the development of treatments for hepatic steatosis is particularly important. [134]MSC-EXOs have shown therapeutic potential for hepatic steatosis in several reserach.

It has been found that inhibition of caspase-2 can prevent high fat diet (HFD) -induced obesity and may improve systemic carbohydrate utilization. BMSCs-EXOs inhibit caspase-2 by up-regulating hepatic miR-96-5p, thereby hindering fatty acid synthesis and lipid uptake, and up-regulating fatty acid oxidation in the

experimental MASH model induced by HFD. [75]miR-627-5p can interact with obesity-related genes (FTO) to improve glucose and lipid metabolism in L02 cells by targeting FTO. Upregulation of miR-627-5p was found by treating MASLD rats and palmitic acid (PA) -treated L02 cells with hucMSC-EXOs. Additionally, the results demonstrated that exosomal miR-627-5p produced from hucMSCs enhanced lipid and glucose metabolism and decreased liver damage by blocking FTO expression, therefore promoting the advancement of MASLD. [76] Peroxisome proliferator-activated receptor α (PPARα), a member of the nuclear receptor family, regulates lipid metabolism homeostasis in the liver [135]. HucMSCs were discovered to slow the course of MASH in the mice model of MCD. By controlling the anti-inflammatory characteristics of macrophages and reversing the production of PPARα protein in hepatocytes, hucMSC-EXOs mitigated MCD-induced MASH in mice. [136] Using HFD-induced hepatic steatosis paradigm, MSC-EXOs were shown to prevent liver deposition and improve liver function. Furthermore, MSC-EXOs decreased the synthesis of fatty acid metabolites and increased the β-oxidation of fatty acids, which decreased lipid accumulation in hepatocytes. The improvements in lipid accumulation were facilitated by MSC-EXO-transferred calcium/calmodulin-dependent protein kinase 1 (CAMKK1), as shown by mass spectrometry and gene knockdown/overexpression analysis. This, in turn, prevented fatty acid synthesis mediated by sterol regulatory element-binding protein-1C (SREBP-1C) and promoted fatty acid oxidation mediated by PPARα. [137, 138]

MSC-EXOs promote liver regeneration

The liver has a strong ability to regenerate after various injuries, and liver regeneration after injury is a multifactor and multi-step process regulated by many molecular mechanisms. [139] Despite the liver's strong capacity for regeneration, conditions like cirrhosis or fatty liver can negatively impact a patient's ability to compensate for liver damage and regenerate their liver, particularly in those who have had a hepatectomy. [140] Therefore, understanding the mechanism and regulation of liver regeneration is significant for the repair of patients after liver injury. MSCs can differentiate and transdifferentiate into various tissue types, stimulate tissue regeneration and repair damaged tissues. MSC-based therapies have been widely studied in the field of regenerative medicine. MSC-EXO therapy has great potential in regenerative medicine due to its unique cell-free nature, which can reduce the risk of potential immune response.(Table 2) [141] IL-6 and TNF-α are important promoters of liver regeneration when initiating injury. After partial hepatectomy (PHx), TNFR I-deficient mice, which have defects in DNA synthesis, restored liver regeneration by IL-6 injection. [142] macrophage inflammatory protein 2 (MIP-2) promotes liver cell proliferation during injury recovery by up-regulating the nuclear translocation of STAT3. [143] After treatment with exosomes, the expression of the above priming factors was increased, and the cell viability was improved. Exosome treatment of injured hepatocytes significantly increased the expression of NF-κB and STAT3 transcription factors, and the above up-regulated gene and protein expression together supported the recovery of global cell viability. TNF can activate NF-κB and IL-6-dependent pathways to activate liver regeneration. These findings imply that exosome treatment, by stimulating hepatocyte liver regeneration, may modulate liver repair following acute liver injury [144].

Chronic inflammation hinders the progress of liver regeneration, while alternately activated macrophages stimulate the proliferation of hepatocytes and endothelial cells in acute liver injury. TNF-α and IL-6, two proinflammatory cytokines critical for liver regeneration during PHx, are mostly derived by macrophages. Through the exosomes they release, hypoxia-preconditioned MSCs (Hp-MSCs) stimulate liver regeneration in mice following PHx. Hypoxic MSC-EXOs (Hp-EXOs), as opposed

Table 2 Application of MSC-EXOs in liver regeneration

Source	miRNA	Model	Mechanism
hESC	Unknown	CCl_4-induced mouse model	Increased the expression of NF-κB and STAT3 transcription factors and initiated liver regeneration by activating NF-κB and IL-6 dependent pathways [144].
hypoxic MSC	miR-182-5p	PHx mouse model	Regulated the forkhead box transcription factor 1 (FOXO1)/toll-like receptor 4 (TLR4) signaling pathway to enhance macrophage polarization during liver regeneration [145].
CP-MSC	miR-125b	CCl_4-induced mouse model	Regulates the expression of the Hh signaling pathway, promotes fibrosis regression, and ultimately promotes liver regeneration [65].
hucbMSC	miR-124	PHx mouse model	Promote liver regeneration after PHx in rats by down-regulating the transcription Foxg1 [146].
PD-MSC	unknown	BDL rat model	Upregulate CRP and promote angiogenesis by activating the Wnt pathway, and play a direct role in liver regeneration of hepatocytes [149].

to normoxic MSC-EXOs (N-EXOs), improved M2 macrophage polarization in both vivo and vitro. Ultimately, it was shown that miR-182-5p in Hp-EXOs regulated the forkhead box transcription factor 1 (FOXO1) / toll-like receptor 4 (TLR4) signaling pathway to enhance macrophage polarization during liver regeneration [145]. It has been demonstrated that CP-MSCs stimulate liver regeneration. It was found that miR-125b produced by CP-MSCs regulates the expression of the Hh signaling pathway, promotes fibrosis regression, and ultimately promotes liver regeneration. [65] Human umbilical cord blood mesenchymal stem cell-derived exosomes(hucbMSC-EXOs) have been found to promote liver regeneration and ameliorate PHx-induced liver injury in rats. Additional microRNA microarray analysis revealed that exosomal miR-124 generated from hucbMSC enhanced liver regeneration and decreased hepatic damage in mice. exosomal miR-124 generated from hucbMSC was found to promote liver regeneration after PHx in rats by down-regulating the transcription factor forkhead box G1(Foxg1). [146] The liver produces and secretes C-reactive protein (CRP), which is found in blood vessels as a pentamer and aids in angiogenesis [147, 148]. By analyzing a rat model of bile duct ligation(BDL) after placenta-derived mesenchymal stem cells (PD-MSCs) transplantation, exosomes secreted by PD-MSCs upregulate CRP and promote angiogenesis by activating the Wnt pathway, and play a direct role in liver regeneration of hepatocytes. [149]

Due to its biocompatibility and biodegradability, the hydrogel is a great alternative to the natural ECM and can be utilized as a sustained-release medication carrier to deliver therapeutic medicines to the injured location [150, 151]. By modifying gelatin and alginate, and then mixing them in a certain proportion under the action of photo-crosslinker lithium phenyl-2,4,6-trimethyl benzoyl phosphinate(LAP) and ultraviolet light, the viscous gelatin matrix (GelMA)/ alginate-dopamine (Alg-DA) hydrogel composite hydrogel was prepared to sustainably release up to 50% of EXOs within 14 days. GelMA/Alg-DA-1/EXO shows significant promise for liver regeneration, when compared to EXO-free hydrogels, and may efficiently improve cell proliferation and migratory ability under the same conditions. [152]

Conclusion and prospect

MSC-EXOs target disease progression to restore liver homeostasis and enable hepatocyte recovery, repair and regeneration. MSC-EXOs can be combined with a variety of current drugs as carrier particles carrying specific components to exert therapeutic effects. When using MSC transplantation therapy, most MSCs are unable to reach the site of injury, and only one percent of MSCs are available for the therapeutic process [153]. Due to their unique cell-free properties, MSC-EXOs can not only avoid unnecessary immune rejection and tumorigenesis, but also provide more accurate delivery to target tissues to improve the efficacy of drugs. Due to its characteristics, MSC-EXOs can be taken up by different cell types, which can reduce the side effects caused by treatment. At present, a number of studies have been conducted to modify the exosome membrane to improve its targeting specificity. [154] Unlike other lipid nanoparticles, exosomes are rich in membrane proteins that mediate adhesion between recipient cells and exosomes, influencing exosome uptake. [155]

Despite their promise, MSC-EXOs have limitations. Given their similarities to MSCs, potential risks associated with exosome application in tumor treatment cannot be disregarded. [112] MSC-EXOs possess multiple functions and may carry harmful components that can affect therapeutic outcomes. Therefore, it is critical to modify exosomes to eliminate irrelevant components and ensure treatment safety. [156] Exosomes can be broadly classified into naturally occurring and engineered exosomes. Engineered exosomes offer distinct advantages. For instance, most exosomes used in liver injury treatment are modified by miRNA, enhancing efficiency in treatment. Compared to direct MSC-EXO therapy, specific miRNA-modified exosomes optimize therapeutic outcomes on liver injury and elucidate treatment pathways. Engineering exosomes with modified membrane proteins can further amplify therapeutic efficacy by enhancing targeting capabilities and cellular internalization. In liver injury treatment, engineered exosomes effectively serve as drug carriers, improving drug efficacy while reducing potential side effects through precise delivery to target organs. Exosome engineering is particularly essential for treating hepatocellular carcinoma. Unmodified exosomes play a complex role in tumor regulation due to their biological characteristics. The therapeutic potential of unmodified exosomes remains ambiguous, as they may produce adverse effects in cancer management. However, following artificial modification, exosomes can regulate diseases through diverse miRNA modifications or by acting as drug carriers, influencing cancer cell sensitivity and inhibiting drug resistance. Such modifications enable the application of exosome therapy in cancer treatment and maximize the biomaterial potential of exosomes.

Moreover, current research on MSC-EXOs is primarily confined to cell experiments. Thus, further investigations are necessary to confirm their therapeutic efficacy in humans. Although clinical trials on the use of MSCs for liver diseases such as cirrhosis, liver failure, autoimmune hepatitis, and liver transplantation have been conducted, there is limited clinical research progress

regarding MSC-EXOs. Reports on MSC-EXOs usage in treating decompensated liver cirrhosis illustrate promising results, demonstrating both safety and efficacy. (NCT05871463) Nonetheless, a significant gap remains in the clinical application of MSC-EXOs, necessitating new clinical trial initiatives. Establishing a monitoring system to assess the safety and efficacy of MSC-EXOs is imperative. Despite the large quantities of exosomes applied in addressing tissue damage, challenges persist. While MSC-EXOs may expand more easily than MSCs, they still do not meet current treatment demands and are not yet viable for mass production. Thus, there is an urgent need to develop production technologies that facilitate large-scale, stable generation of MSC-EXOs to fulfill therapeutic requirements. Furthermore, challenges in utilizing MSC-EXOs as drug delivery carriers must be addressed. Optimizing the isolation and purification methods of exosomes is crucial, and enhancing their targeting capabilities warrants immediate solutions. Although exosomes can mitigate partial immune rejection compared to MSCs, potential immunogenicity remains a concern that requires further investigation and validation. While MSC-EXOs hold significant potential for treating liver diseases, the specific mechanisms underlying their action in mediating diseases remain to be elucidated.

Abbreviations

AD	Alzheimer's disease
ADAM10	A disintegrin and metalloprotease 10
AD-MSCs	Adipose tissue-derived MSCs
ALF	Acute liver failure
Alg-DA	Alginate-dopamine
ALT	Alanine aminotransferase
AMSCs	Adipose-derived mesenchymal stem cells
ASO	Antisense oligonucleotide
AST	Aspartate aminotransferase
BDL	Bile duct ligation
BM MSC	Bone marrow mesenchymal stem cells
BMSC-EXOs	Bone marrow mesenchymal stem cell-derived exosomes
CAMKK1	Calcium/calmodulin-dependent protein kinase 1
circRNA	Circular RNA
CLD	Chronic liver disease
CP-MSCs	Chorionic plate-derived mesenchymal stem cells
CRP	C-reactive protein
DDB	Bifendate
ECM	Extracellular matrix
EMT	Epithelial-to-mesenchymal transition
Foxg1	Forkhead box G1
FOXO1	Forkhead box transcription factor 1
GelMA	Gelatin matrix
GPX1	Glutathione peroxidase 1
GSH	Glutathione
H2S	Hydrogen sulfide
hBM-MSC-EXOs	Human bone mesenchymal stem cell-derived exosomes
HCC	Hepatocellular carcinoma
HFD	High fat diet
Hh	Hedgehog
hiPSCs	Human-induced pluripotent stem cells
HMGB1	High mobility group box 1
Hp-EXOs	Hypoxic MSC-EXOs
Hp-MSCs	Hypoxia-preconditioned MSCs
HSC	Hepatic stellate cell
hTERT	Human telomerase reverse transcriptase
hucbMSC-EXOs	Human umbilical cord blood mesenchymal stem cell-derived exosomes
hucMSC-EXOs	Human mesenchymal stem cells
IL	Interleukin
ILVs	Intraluminal vesicles
LAP	Phenyl-2,4,6-trimethyl benzoyl phosphinate
LOXL2	Lysyl oxidase-like 2
LPS	Lipopolysaccharide
MASH	Metabolic dysfunction-associated steatohepatitis
MASLD	Metabolic dysfunction-associated steatotic liver disease
MCAO	Middle cerebral artery occlusion
MIP-2	Macrophage inflammatory protein 2
MSC-EXOs	Mesenchymal stem cell-derived exosomes
MSCs	Mesenchymal stem cells
MVBs	Multivesesomes
MVs	Microvesicles
NCTD	Norcantharidin
N-EXOs	Normoxic MSC-EXOs
nSMase2	Neutral sphingomyelinase 2
OCA	Obeticholic acid
P4HA1	Prolyl 4-hydroxylase subunit alpha-1
PA	Palmitic acid
PD-MSCs	Placenta-derived mesenchymal stem cells
PHx	Hepatectomy
PPARα	Peroxisome proliferator-activated receptor α
PSC	Primary sclerosing cholangitis
RBPs	RNA-binding proteins
ROS	Reactive oxygen species
RUP	Rupatadine
SALL4	Spalt like transcription factor 4
Smo	Smoothened
SOD	Superoxide dismutase
SREBP-1C	Sterol regulatory element-binding protein-1C
STAT3	Signal transducer and activator of transcription 3
TLR4	Toll-like receptor 4
TNF	Tumor necrosis factor
TSG101	Tumor susceptibility gene 101 protein
UCMS	Umbilical cord mesenchymal stem cells
YAP	Yes-associated protein

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