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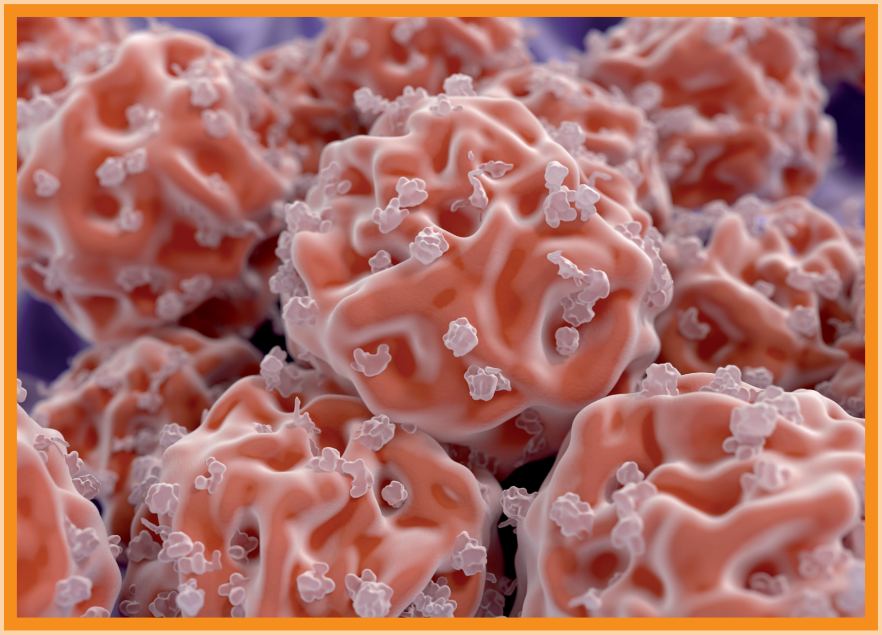

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REVIEW

STEM CELL-BASED BIOTECHNOLOGICAL ADVANCES IN REGENERATIVE MEDICINE

Stem cell-derived exosome transplantation as a new cell-free therapy for liver regeneration

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ABSTRACT

Stem cell transplantation has been used to treat some diseases with promising results. Stem cells stem cells can rescue injured tissues through various mechanisms, such as stimulation of growth factor secretion, activation of other/local stem cells, differentiation into specialized cells, and modulation of the immune system. However, stem cell transplantation also carries risks related to immune rejection as well as tumorigenesis. In recent years, more evidence has suggested that transplantation of stem cell-derived exosomes can induce effects similar to stem cell transplantation. Particularly, exosomes are less immunogenic than the parent cells due to their low content of membrane proteins. This review aims to summarize the characteristics of exosomes, including their physiological functions, and to highlight the therapeutic effects of exosome injection in hepatic regeneration.

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Key words: Exosomes - Extracellular vesicles - Stem cells - Mesenchymal stromal cells - Liver regeneration.

Stem cells are unspecialized cells that can differentiate into various functional cells under suitable conditions. They possess self-renewal potential that is long-term [1] and, therefore, have been tested and used successfully to treat diseases including liver disease. Mesenchymal stem cells (MSCs) are a type of stem cells that can attenuate liver fibrosis by suppressing T helper (Th)17 cells.[2] Adipose-derived stem cells (ADSCs) can also stimulate liver regeneration.[3] Xenografts of MSCs can induce liver regeneration; indeed, the regenerated cells are similar to hepatocytes.[4] Moreover, MSC xenografts accelerate healing of acute liver injury.[5] Given their immunomodulatory properties, MSCs can be beneficial in liver transplantation.[6]

However, whole stem cell transplantation contains some limitations. Immune rejection, ectopic tissue formation, and infusion-related toxicity are some main disadvantages of whole cell transplantation.[7] More importantly, whole stem cells are subjected to the limitations of cryopreservation and shipping. Indeed, whole stem cells need to be stored in liquid nitrogen which can limit the commercial processing of these products.

Recently, the therapeutic effects of stem cells (including MSCs) were demonstrated to occur via at least 3 mechanisms, which included homing and differentiation of grafted stem cells at injured sites, immune modulation, and paracrine effects of the stem cell secretome. Exosomes are, in fact, the main component of the secretome. Indeed, exosomes act as cargos to information between cells. The information/factors inside exosomes have been shown to trigger angiogenesis, tissue regeneration and immune regulation.[8]

Due to these aforementioned mechanisms, exosome injection should exhibit some beneficial effects in ani-

mal models of liver disease. This review summarizes some effects of exosomes and their mechanisms in liver disease. Exosomes from MSCs, pluripotent stem cells, and liver stem cells will be discussed.

Exosomes and their functions

Exosomes are a type of extracellular vesicles (EVs) produced by alive cells during their lifespan. As nanoparticles they are usually about 40-150 nm in diameter. Unlike microvesicles that are produced from the plasma membrane, exosomes are produced by the secretory mechanism and regulated by endosomal sorting complex mechanisms.[8] For this reason, exosomes usually do not express cell markers on their surface but do express some tetraspanins (CD63, CD81, CD9, etc.). As products of the secretory process, exosomes carry information inside the cell to other cells.

Indeed, the components of exosomes have been carefully studied. Almost every study has suggested that exosomes contain four kinds of biological information: proteins, mRNAs, miRNAs and lipids. These information can be transferred to the target cells and induce changes in recipient cells.[8] However, most studies have suggested that the effects of exosomes come mainly from the miRNAs, which are small non-coding RNAs containing 22 nucleotides.[9] The main function of these miRNAs are to specifically target mRNA to mediate inhibition of translation.[10] Some of the main components of exosomes are presented in Figure 1.

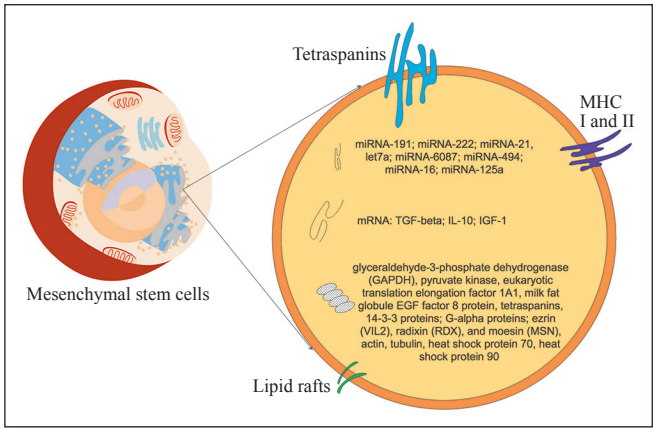

Figure 1.—Composition of exosomes. Exosomes contain various molecules from RNAs to proteins. The physiological effects of exosomes are usually achieved by miRNAs.

MSC-derived exosomes in liver regeneration

MSC-derived exosomes for liver fibrosis

Liver fibrosis results from the chronic damage to the liver which causes the upregulation of extracellular matrix (ECM) protein synthesis.[11] The disease usually results from chronic HCV infection, alcohol abuse or other factors. Upregulation of ECM protein synthesis can lead to development of nodules for regenerating hepatocytes (cirrhosis). It is the cirrhosis that produces dysfunctional hepatocytes as well as the increase in intrahepatic resistance to blood flow which lead to portal hypertension.[12]

In previous studies, liver fibrosis could be treated by MSC transplantation.[13-16] These studies suggested that MSC transplantation leads to a significant improvement of liver functions. Recently, MSC-derived exosomes have been used to treat these diseases. Almost all the preclinical trials used the carbon tetrachloride (CCl4)-induced liver fibrosis mouse model. The first study using exosomes from MSCs for liver fibrosis treatment was reported by Li *et al.* In this study, they transplanted human umbilical cord (UC)-MSCs into acutely fibrotic livers (fibrosis induced by CCl4). The results showed that transplantation of exosomes from MSCs reduced the surface fibrous capsules and reduced hepatic inflammation and collagen deposition in the liver.[17] Exosome transplantation also recovered aspartate transaminase (AST) levels, reduced collagen type I and III, and decreased transforming growth factor beta 1 (TGF-b1).[17]

In a more recent study, Qu *et al.* used engineered ADSCs which over-expressed miRNA-181-5p to treat liver fibrosis in a mouse model. The authors also showed that exosomes from ADSCs could attenuate liver injury and significantly downregulated collagen I, vimentin, alpha-SMA and fibronectin in the liver. The authors suggested that the therapeutic effects came from the transfer of miRNA-181-5p from exosomes to the damaged liver cells (Table I).[17-22]

The therapeutic efficacy of exosomes in fibrosis liver treatment is dependent on the miRNA molecules inside the exosomes. Indeed, some previous studies have shown that exosomes from MSCs contain miR-125b and miR-122.[19, 23] The transfer of miR-125b from exosomes of MSCs to hepatocytes leads to reduced fibrosis via downregulation of hedgehog (Hh) signaling.[19] Indeed, miR-122 can negatively regulate collagen production in hepatic stem cells (Figure 2).[23]

TABLE I.—*Preclinical trials of MSC-derived exosomes for liver regeneration.*

N.	Exosomes from	Animal models	Functions	Ref
1	hUC-MSCs	CCl4-induced mice	Inhibit hepatocyte EMT and collagen production	Li *et al.*[17]
2	CP-MSCs	CCl4-induced rats	Impede Hh signaling activation in HSCs	Hyun *et al.*[19]
3	ADSCs expressing miRNA-181-5p	CCl4-induced mice	Attenuate liver injury, and regulate collagen I, vimentin, alpha-SMA and fibronectin	Qu *et al.*[18]
4	BM-MSCs	Liver failure induced by injection of d-galactosamine/TNF-alpha in mice	Increase survival rate of mice	Haga *et al.*[20]
5	ADSCs	Rat N1S1 cell-bearing orthotopic HCC rat model	Suppress HCC by promoting NKT cell anti-tumor responses	Ko *et al.*[21]
6	ADSCs	HepG2 cell xenograft in nude mice	Sensitize HCC to 5-FU or sorafenib therapy	Lou *et al.*[22]

MSC-derived exosomes for acute liver failure

Acute liver failure is a condition of severe complications of damaged liver disease (loss of function in 80-90% of liver cells). Acute liver failure is characterized by hepatic dysfunction, abnormal liver biochemical values, coagulophathy and encephalopathy; along with multi-organ failure, it can result in death.[24, 25]

MSCs have been used to treat acute liver failure with some promising results. Bone marrow (BM)-MSCs overexpressing c-Met demonstrated they could home to liver and repair acute liver failure with higher efficacy than non-c-Met BM-MSCs in a mouse model.[26] In a pig model, MSCs could also correct the hemodynamic dysfunction associated with liver injury after extended resection. In one study, MSCs were capable of supporting kidney and liver functions after extended liver resection.[27] In another study, by the same authors, MSC transplantation attenuated acute liver failure due to metabolic implications;[28] in this particular study, Tautenhahn *et al.* demonstrated the role of the paracrine effects of MSC transplantation in acute liver failure treatment.[28]

MSCs have also been used successfully to clinically treat acute-on-chronic liver failure (ACLF). Shi *et al.* proved that MSCs from umbilical cord can improve liver function in patients with end-stage liver disease. In 24 patients injected with UC-MSCs three times at 4-week intervals, the authors recorded a significant increase of survival rate in ACLF patients, without any side effects. Some parameters of hematology and chemistry also increased, including serum albumin, cholinesterase, prothrombin and platelet count. Meanwhile, serum bilirubin and alanine aminotransferase (ALT) levels significantly decreased.[29] The mechanism of MSCs in mediating recovery of liver injury is via altering the ratio of interleukin-17 producing and regulatory natural killer T cells.[30] In agreement with our study, Gazdic *et al.* also confirmed the role of MSCs in protection against acute liver injury, which was related to attenuation of hepatotoxicity of liver natural killer T cells.[31]

Initially, Xagorari *et al.* found that MSC-derived conditioned medium (CM) could reduce hepatic cell apoptosis after acute liver injury.[32] The CCl4-induced acute liver injury was used in this study. CM from MSCs could decrease the number of apoptotic hepatocytes.[32] In another study, Tan *et al.* also confirmed that exosomes from MSCs could promote hepatic regeneration in CCl4-induced liver injury models [33] by stimulating hepatocyte proliferation, inhibiting acetaminophen (APAP)- and hydrogen peroxide (H_2O_2)-induced hepatocyte apoptosis through upregulation of Bcl-xL protein expression.[33]

Recently, Haga *et al.* used EVs from BM-derived MSCs to treat lethal hepatic failure in mice.[20] The authors induced liver failure by injection of d-galactosamine and tumor necrosis factor (TNF)-alpha in mice. Then, EVs from BM-MSCs were infused into the mice. The results showed that the survival rate of mice dramatically increased compared to placebo.[20] Moreover, Y-RNA-1 is the most important factor inside EVs as it plays a critical role in recovery of liver failure. Indeed, knocking down Y-RNA-1 in MSCs caused EVs to have reduced protective effects in the liver.[20]

Although the exact mechanism of exosomes in the treatment of liver failure is unclear, a recent study suggested that exosomes can induce the conversion of hepatocytes into progenitor oval cells [34] to recover damaged hepatocytes. Indeed, CM from MSC cultures can promote the formation of small oval cell hepatocytes.

These cells showed an upregulated expression of EpCAM and OC2 – markers of oval cells. The EpCAM^{high} cells that can form colonies also increased.[34]

MSC-derived exosomes for hepatocellular carcinoma

Hepatocellular carcinoma is the most common type of liver cancer in adults. It results from chronic liver inflammation due to hepatitis infection (hepatitis B and C) or toxins (alcohol and aflatoxins).[35] The role of MSC-derived exosomes were described in different publications with some converse effects. Indeed, some studies showed that MSC-derived EVs stimulated cancer growth and metastasis,[36, 37] while in other studies they inhibited tumor growth.[21, 22]

In 2013, Bruno *et al.* tested the effects of microvesicles from BM-MSCs in various tumors, including HepG2 hepatoma, Kaposi's sarcoma, and Skov-3 ovarian tumor. The results showed that MVs from BM-MSCs could inhibit cell cycle progression and induce apoptosis of HepG2. In mouse models, MV injection could inhibit tumor growth.[38]

Although there has not been a study on the role of exosomes and EVs in liver tumor growth, some studies have shown that EVs and exosomes can stimulate breast cancer growth and metastasis,[36] multiple myeloma,[37] and renal cell carcinoma.[39] The effects of EVs on tumor growth may be mediated by upregulation of vascular endothelial growth factor (VEGF) expression through the activation of extracellular signal regulated kinase 1/2 (ERK1/2) and p38 MAPK pathway,[37] via expression of p38, p53, c-Jun N-terminal kinase, and Akt pathways,[36] via induction of hepatocyte growth factor (HGF) expression, and/or via activation of Akt and ERK1/2 signaling pathways.[39] Exosomes can also promote drug resistance to bortezomib in multiple myeloma [36] by reducing Bcl-2 expression and the cleavage of caspase-9, capase-3 and PARP.

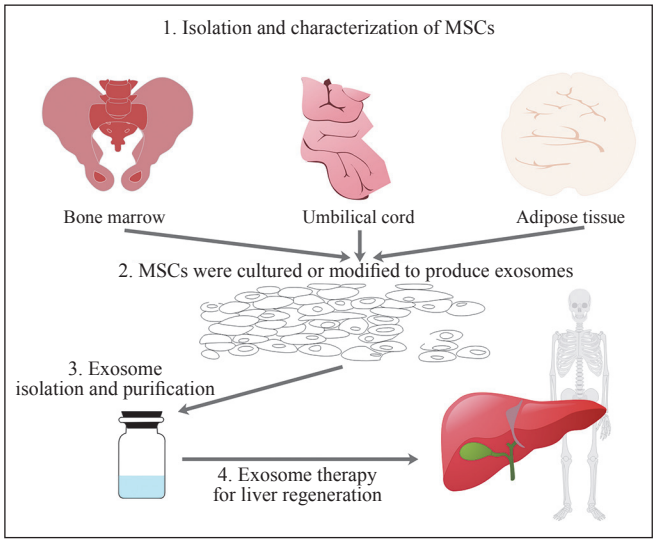

Figure 2.—Mesenchymal stem cell (MSC)-derived exosomes are a promising therapy for liver regeneration. MSCs can be obtained from various sources, including bone marrow, adipose tissue and umbilical cord tissue. Exosomes isolated from MSCs have therapeutic efficacy against liver injuries.

Induced pluripotent stem cell-derived exosomes in liver regeneration

Induced pluripotent stem cells (iPSCs) are pluripotent stem cells that are produced from the transgenesis of exogenous pluripotent factors, including Oct-3/4, Nanog, Sox2 and Klf4.[40] These cells exhibit full characteristics of embryonic stem cells. This means they can differentiate into all cell types from three embryonic layers. Indeed, iPSCs have been used preclinically to treat various liver diseases, including hereditary liver disease, liver failure and liver cirrhosis. In hereditary disease treatment, iPSCs have been applied in several animal models of metabolic disorders. For example, Yusa *et al.* engineered iPSCs with gene correction of alpha1-antitrypsin deficiency (A1ATD) [41] to treat this disorder. The results indicated that therapies based on iPSCs and gene correction might be promising. In another strategy, Isobe *et al.* differentiated iPSCs toward hepatocyte-like cells (HLCs) and then infused the HLCs into rodents to rescue the lethal drug-induced acute liver failure.[42]

Moreover, iPSCs can be differentiated into typical MSCs before they are used to produce exosomes. The exosomes derived from MSCs (differentiated from iPSCs) have been tested in a variety of liver diseases. Du *et al.* showed that these exosomes can fuse with hepatocytes, increase the activity of sphingosine kinase and synthesis of sphingosine-1-phosphate (S1P), and alleviate hepatic injury.[43] Similarly, in a study by Nong *et al.*, exosomes from MSCs that were differentiated from IPSCs were evaluated for treatment of hepatic ischemia reperfusion injury in rats. These exosomes could decrease markers of liver injury, including AST and ALT,

inflammatory factors (*e.g.* TNF-alpha, IL-6, etc.), and high mobility group box 1 (HMGB1).[44]

Liver stem cells

Liver stem cell-derived EVs have also been tested to treat liver diseases in a rat model of hepatectomized rats; Herrera *et al.* used EVs from liver stem cells and showed that these EVs could induce proliferation, reduce apoptosis of human and rat hepatocytes *in vitro*, and accelerate the morphological and functional recovery of the liver in a model of 70% hepatectomy in rats *in vivo*.[45] In a more recent study by the same group, Herrera *et al.* also successfully used EVs from human liver stem cells to restore the argininosuccinate synthase 1 (ASS1) deficiency. These EVs were co-cultured with human liver stem cells isolated from the liver of a patient with type I citrullinemia, and could restore both ASS1 activity and urea production.[46]

Conclusions

Exosomes as well as EVs from stem cells (*e.g.* MSCs, iPSCs and liver stem cells) exhibit protective/therapeutic effects on liver fibrosis, acute liver failure and other liver diseases. While to date there has not been any clinical trial using exosomes or EVs to treat liver disease in humans, the clinical trials will be performed soon. Indeed, besides the proven beneficial characteristics of exosomes and EVs in animal models, they have also been confirmed to be safe therapies in the animals, including rabbits, guinea pigs, mice and rats.[47] In normal animals, exosomes from MSCs have protective effect on weight loss, without any adverse effects on liver or renal function.[47] Thus, in the near future, exosomes from stem cells, particularly MSCs, will be promising candidates for liver regeneration.

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