Journal of Clinical and Translational Hepatology **2023** vol. 11(2) | 441–451
DOI: 10.14218/JCTH.2022.00326

Review Article

Unraveling the Emerging Niche Role of Hepatic Stellate Cell-derived Exosomes in Liver Diseases

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Received: 13 July 2022 | **Revised:** 16 September 2022 | **Accepted:** 23 September 2022 | **Published:** 18 October 2022

Abstract

Hepatic stellate cells (HSCs) play an essential role in various liver diseases, and exosomes are critical mediators of intercellular communication in local and distant microenvironments. Cellular crosstalk between HSCs and surrounding multiple tissue-resident cells promotes or inhibits the activation of HSCs. Substantial evidence has revealed that HSC-derived exosomes are involved in the occurrence and development of liver diseases through the regulation of retinoid metabolism, lipid metabolism, glucose metabolism, protein metabolism, and mitochondrial metabolism. HSC-derived exosomes are underpinned by vehicle molecules, such as mRNAs and microRNAs, that function in, and significantly affect, the processes of various liver diseases, such as acute liver injury, alcoholic liver disease, nonalcoholic fatty liver disease, viral hepatitis, fibrosis, and cancer. As such, numerous exosomes derived from HSCs or HSC-associated exosomes have attracted attention because of their biological roles and translational applications as potential targets for therapeutic targets. Herein, we review the pathophysiological and metabolic processes associated with HSC-derived exosomes, their roles in various liver diseases and their potential clinical application.

Keywords: Myofibroblast; Extracellular vesicle; Hepatic fibrosis; Cancer; Metabolic reprogramming; Biomarker.

Abbreviations: α-SMA, alpha-smooth muscle actin; aHSCs, activated hepatic stellate cells; ALD, alcohol-related liver disease; ASC, adipose mesenchymal stem cell; ECM, extracellular matrix; EVs, extracellular vesicles; GLUT, glucose transporter; HSCs, Hepatic stellate cells; IL, interleukin; MFBs, myofibroblasts; NAFLD, nonalcoholic fatty liver disease; PDGF, platelet-derived growth factor; qHSCs, quiescent hepatic stellate cells; TGF-β, transforming growth factor beta; TNF-α, tumor necrosis factor-alpha; VEGF, vascular endothelial growth factor; YAP, Yes-associated protein.

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Citation of this article: Yin KL, Li M, Song PP, Duan YX, Ye WT, Tang W, *et al*. Unraveling the Emerging Niche Role of Hepatic Stellate Cell-derived Exosomes in Liver Diseases. J Clin Transl Hepatol 2023;11(2):441–451. doi: 10.14218/JCTH.2022.00326.

Introduction

Hepatic stellate cells (HSCs) account for approximately 15% of resident cells in normal liver and 30% of nonparenchymal cells.[1,2] HSCs exist in the space of Disse with multiple lipid droplets rich in vitamin A present in the cytoplasm, representing the primary storage site of retinaldehyde derivatives.[3] In additional, HSCs are the main cells synthesizing the extracellular matrix (ECM) and collagen in the liver. HSCs are normally quiescent (qHSCs) and do not express alpha-smooth muscle actin (α-SMA), which is a marker of activated HSCs (aHSCs).[2] Numerous studies have confirmed that HSCs exhibit great heterogeneity and plasticity and facilitate fine regulatory responses to liver injury through paracrine and autocrine signals according to changes in the extracellular microenvironment.[4–6]

Exosomes are membranous vesicles that fuse with the cell membrane by multiple vesicles and are then released to the extracellular space. Exosomes have a diameter of 40–160 nm and they are released by all types of cells.[7,8] Exosomes can be found in almost all body fluids, such as plasma,[9] urine,[10] cerebrospinal fluid,[11] saliva,[12] breast milk,[13] joint fluid,[14] amniotic fluid,[15] and semen.[16] Of note, some special proteins are found on the surface of exosome vesicles, such as HSP70, CD9, CD63, CD62, and CD81. The proteins are involved in cell adhesion and targeting and can be used as biomarkers to indirectly reflect the presence of exosomes.[6] Exosomes, as heterogeneous intraluminal vesicles (ILVs), are secreted into the extracellular space by endosomal sorting complex required for transport mechanisms.[8] In these complex processes, exosomes are filled with lipids, proteins, DNA, coding RNA and noncoding (nc)RNAs such as micro (mi)RNA, long noncoding (lnc)RNA, and circular (circ)RNA.[17] Transfer of these active substances from tissue

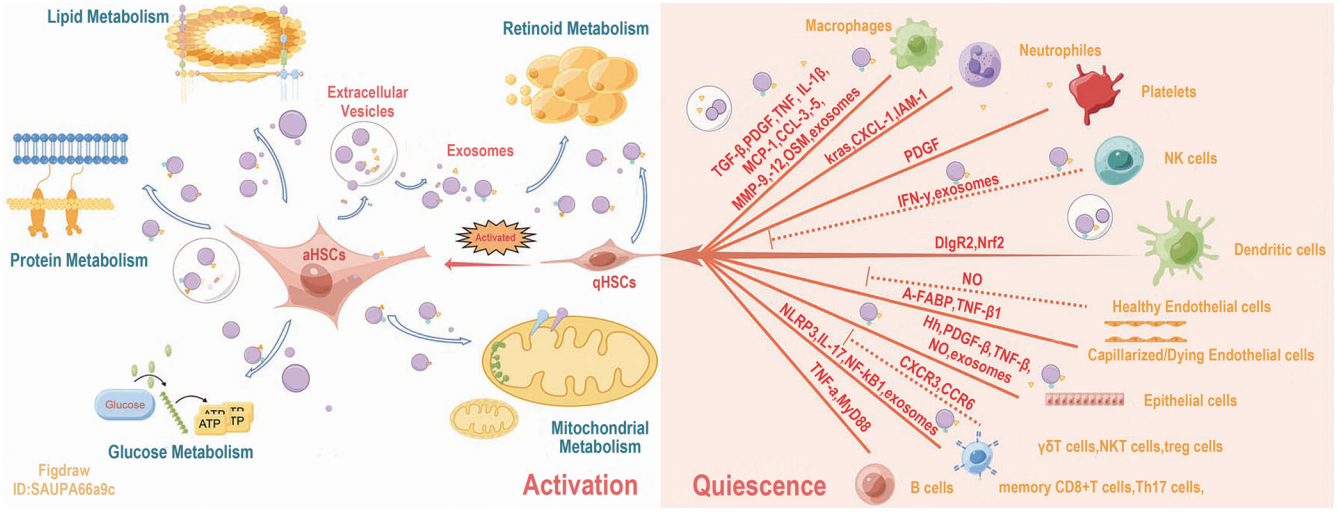

Fig. 1. Activation of HSCs and pathophysiological role of HSC-derived exosomes. Cellular crosstalk between HSCs and surrounding multiple tissue-resident cells promotes or inhibits the activation of HSCs. HSC-derived exosomes are involved in the occurrence and development of liver diseases through the regulation of retinoid metabolism, lipid metabolism, glucose metabolism, protein metabolism, and mitochondrial metabolism. HSC, hepatic stellate cell.

to body fluids in intercellular cargo contributes to the transmission of information via exosomes and subsequently affects the occurrence and development of various diseases.[18]

The roles of exosomes in intercellular information exchange have attracted more attention to dissect the mechanisms leading to the activation of HSCs.[19,20] As a part of the liver environment, HSC-derived exosomes play an important role in the development of liver diseases.[21–23] In this review, we summarize the pathophysiological and metabolic processes associated with HSC-derived exosomes, their roles in various liver diseases and their potential clinical application.

Mechanism of HSC activation

When the liver is damaged by inflammation or mechanical stimulation, fibrogenic factors, such as transforming growth factor beta (TGF-β), vascular endothelial growth factor (VEGF), insulin-like growth factor, and interleukin (IL)-6, seek HSCs as the final target cells (Fig. 1). The phenotype of HSCs then changes from quiescent to activated, and these cells transform into myofibroblasts (MFBs).[24–26] The concepts of "initiation" and "perpetuation" are widely used to interpret the activation process.[27] Briefly, initiation is characterized by event that vitamin A-rich quiescent HSCs, stimulated by inflammatory factors, downregulate vitamin A, glial fibrillary acidic protein, and peroxisome proliferator-activated receptor (PPAR)-γ.[28] Perpetuation refers to lately event that a continual increase in inflammatory factors, growth factors and cytokines, and surrounding profibrotic cells rapidly inducing HSCs to enter the activated state.[29,30] The mechanistic link between loss of lipids in HSCs and cell activation is not well understood, but is thought to involve remarkable influence of the molecular and cellular pathways in hepatic inflammatory microenvironment.[30–32] Cellular crosstalk between HSCs and surrounding multiple tissue-resident cells,[33,34] including macrophages,[35,36] neutrophils,[37,38] platelets,[33,39] dendritic cells,[40] sinusoidal endothelial cells,[41,42] epithelial cells,[43] natural killer cells,[44,45] various T lymphocytes,[46,47] and B cells,[48,49] promotes or inhibits the activation of HSCs. For example, inflammation induced by liver injury triggers the recruitment of macrophages to the liver, where they produce cytokines and chemokines, such as TGF-β, platelet-derived growth factor (PDGF), tumor necrosis factor-alpha (TNF-α), IL-1β, oncostatin M (OSM), chemokine ligand 3/5 (CCL3/5), directly inducing HSC activation, and subsequently forming a definitely complex activation network.[50–53] The notch signaling pathway also transmits activation signals to HSCs through ligand receptor interaction and communication with neighboring cells to increase the degree of fibrosis.[54] On one hand, Hedgehog signaling involves in the activation of HSCs by inducing transdifferentiation into MFBs responsible for matrix deposition.[55,56] On the other hand, the Hedgehog pathway can inhibit apoptotic signals and enhance the viability and proliferation of MFBs, which leads to endogenous Hedgehog ligand generation in an autocrine or paracrine manner, followed by a positive feedback loop of Hedgehog signaling.[55,57] Notably, some classical signaling pathways and emerging pathways synergistically promote HSC activation, hepatic fibrosis and even cross,[58–60] like Hedgehog-Yes-associated protein (YAP), YAP-transcriptional coactivator with PDZ-binding motif (TAZ), YAP1-p38. The ECM, mainly composed of laminin, collagen, and proteoglycan, is required for HSC activation.[61,62] After HSC activation, type IV collagen, heparan sulfate proteoglycan, and laminin are converted into type I and type III fibrous collagen by integrin, forming a positive feedback loop.[63,64] During the transformation process, integrins bridge the connection between qHSCs and aHSCs.[65,66] Type I collagen is one of the most abundant structural proteins in the fibrotic liver. It is regulated by RNA binding proteins at the post transcriptional level involved with mRNA processing, transport, stabilization, and translation.[67,68] HSC activation is established as the main facilitator of liver fibrosis and carcinogenesis, but much remains to be clarified about its contribution to hepatic homeostasis, fibrosis resolution, and cancer initiation.

Pathophysiological role of HSC-derived exosomes

Retinoid metabolism

Of note, 50–95% of the body's vitamin A, including retinol and its metabolites, is stored in HSCs and acts as an important regulator of retinoic acid homeostasis. Under physiological conditions, retinoids in HSCs are associated with

several perilipins, which reduce HSC activation through increased expression. The mechanism is potentially involved in retinoid droplet stabilization and decreased catabolism.[69] HSC activation and transdifferentiation into MFBs appears to require retinol release and loss of lipid droplets, which may be essential to fuel this metabolically required cellular response.[70] Although the exact mechanistic relationship between exosomes and retinoid metabolism in HSCs has not been defined, partial answers have been revealed in several studies. In a mouse model of acute liver injury induced by CCl_4, combining vitamin A with adipose mesenchymal stem cell (ASC)-derived exosomes promoted the liver targeting of exosomes, and vitamin A-loaded ASC exosomes reduced the rapid senescence-like response.[71] We hypothesized that HSCs received vitamin A-loaded ASC exosomes to alleviate liver injury based on the characteristics of retinoid metabolism in HSCs. More relevant in-depth research needs to be performed. Moreover, autophagy plays a crucial role in the deprivation of retinyl ester-containing lipid droplets and adipogenic factors in HSCs by a selective autophagy process known as lipophagy, thus determining the activated phenotype of HSCs.[72,73] Emerging evidence indicates reciprocal regulation of autophagy and exosome biogenesis by intertwined molecular machinery. Therefore, HSC-derived exosomes involved in retinoid metabolism are inhibited by autophagy that prevents the extracellular release of exosomes. Although the exact mechanistic relationship between exosomes and retinoid metabolism in HSCs has not yet been precisely examined, further investigation is necessary to gain insight into the complete mechanism.

Lipid metabolism

A growing number of studies have found that several LD-related proteins present during HSC activation regulate the activation of HSCs by regulating lipid metabolism, such as decreased expression of external perilipin 5 (Plin5)[74] and liver fatty acid-binding protein (L-Fabp).[75] Moreover, emerging evidence indicates that exosomes play a central role in lipid metabolism of HSCs through cell-to-cell communication. A study on lipogenic enzymes in HSCs found that cancer cell-derived exosomes have a significant and positive association with lipogenesis given that the levels of lipid contents, such as ATP citrate lyase (ACLY), fatty acid synthase (FASN) and ubiquitin-specific protease 2a (USP2a), were increased in exosome-challenged HSCs.[76] In addition, HSPC111 was identified as a leading upregulated gene in HSCs incubated with colorectal cancer (CRC) cell-derived exosomes. HSPC111 altered the lipid metabolism of LX-2 by phosphorylating ACLY, revealing its promoting role in premetastatic niche formation and colorectal cancer liver metastases by reprogramming lipid metabolism in HSCs.[77] Therefore, the available evidence suggests that exogenous exosomes greatly affect the activation of lipid metabolism in HSCs.

Glucose metabolism

Glucose metabolism plays an important role in the activation of HSCs, and aHSCs correspondingly upregulate glycolysis to meet the energy requirements for the phenotypic transformation of MFBs. Importantly, modulation of glucose metabolism is not only a marker of the MFB phenotype but also contributes to activation.[1,78] aHSCs in primary culture significantly enhance glucose transportation and glycolysis activity.[79] Intriguingly, glucose transporters, including pyruvate dehydrogenase kinase 3 (PDK3),[79] glucose transporter (GLUT) 1,[79] GLUT2,[80] and GLUT4[81] are expressed in primary mouse HSCs and human LX-2 cells. High extracellular glucose or purinergic signaling conditions modulate the expression of these glucose transported. Hypoxia inducible factor-1 alpha (HIF-1α) signaling enhances exosome secretion from aHSCs and further stimulates HSC activation under hypoxic and inflammatory conditions.[82] After information transfer via exosomes, even under the condition of sufficient oxygen, HSCs still preferentially perform glycolysis rather than oxidative phosphorylation to produce ATP, and this characteristic is called the Warburg effect. On the other hand, the increased glycolysis of cultured HSCs is accompanied by the diversion of central carbon metabolites from the citric acid cycle.[83,84] Exosomes provide a mechanism for the rapid induction of glycolysis to support metabolic reprogramming from qHSCs to aHSCs to synchronize the stromal-cell injury response.

Protein metabolism

Our previous gene microarray analysis of tumor-activated HSCs showed a response to the stimulation of inflammation and tumors, and the considerable changes in genetic regulation and protein metabolism in aHSCs were associated with biological processes, molecular functions, and signaling pathways involved in the microenvironments of fibrogenesis, inflammation, and cancer.[85] A comparative study of metabolic genes differentially expressed between qHSCs and aHSCs showed that only 6% of such genes were involved in carbohydrate metabolism, whereas 38% were involved in protein metabolism.[59] Interestingly, the transformation of glutamine decomposition is particularly important in the process of protein metabolism. Recently, proteomic analysis of extracellular vesicles (EVs) from mouse HSCs found that the dynamic changes in the function and proteome composition of HSC-derived EVs during cell activation likely contributed to the regulation of HSC function and fine-tuning of fibrogenic pathways in the liver.[86] In fact, exosomes have an important role in crosstalk between HSCs and hepatocytes, hepatic macrophages, or other types of cells, as they transfer their cargo, such as proteins and genes to recipient cells, and the exosomal miRNA profile is also altered.[87] Numerous reports have demonstrated that HSC-derived exosomes actively participate in the pathological changes of various liver diseases, all of which are achieved by changes in the protein levels of key signaling pathway molecules.[88–91]

Mitochondrial metabolism

Compared to qHSCs with limited mitochondria, aHSCs have abundant mitochondria. During mitochondrial metabolism in aHSCs, the distinctive increase in mitochondrial membrane potential could sensitize the "bioenergetic signature" of fibrogenic HSCs for selective inhibition by mitotropic doxorubicin.[92] To date, related research on the effects of exosomes from HSCs on mitochondrial metabolism is limited. However, several reports have provided evidence that paracrine exosomes, especially from hepatocytes, influence mitochondrial metabolism in HSCs through cell-to-cell communication in pathological conditions. Dong *et al*.[93] noted that exosomes from hepatocytes (L-02 cells) treated with citreoviridin, a mycotoxin and ectopic ATP synthase inhibitor, induced mitochondrial calcium accumulation in aHSCs. In turn, pharmacological inhibition of mitochondrial calcium uptake alleviated the exosome-activated fibrogenic response in aHSCs, shedding light on a potential new mechanism underlying liver fibrosis. Another finding confirmed that liver injury (CCl_4 or acetaminophen) resulted in mitochondrial dysfunction and the subsequent release of mitochondrial DNA from injured hepatocytes to normal hepatocytes and

aHSCs through EVs, finally mediating fibrogenic responses in aHSCs.[94] Notably, mesenchymal stem cell (MSC)-exosomes alleviated liver fibrosis by triggering HSC ferroptosis mechanistically by promoting ferroptosis-like cell death, mitochondrial dysfunction, and lipid peroxidation in aHSCs.[95] In the future, the direct effect of HSC-derived exosomes on mitochondrial metabolism in HSCs should not be underestimated. The pathophysiological role of HSC-derived exosomes is summarized in Figure 1 and Table 1.

Roles of HSC-derived exosomes in liver diseases

Nonalcoholic fatty liver disease

Pathogenetic metabolic mechanisms, including hepatic glucose and lipid metabolism, macrophage dysfunction, bile acid toxicity, and HSC activation, are responsible for the development of nonalcoholic fatty liver disease (NAFLD).[96] The presence of exosomes in hepatocytes, adipocytes, and HSCs in the hepatic environment accelerates the progression of NAFLD. To date, there is no direct research evidence of the role of HSC-derived exosomes in NAFLD; however, several studies indirectly reveal the functional characteristics of those exosomes. For example, adipocyte exosomes cause dysregulation of the TGF-β pathway after integration into hepatocytes and HSCs, offering insight into the possible pathogenesis of NAFLD.[97] High levels of miR-1297 in exosomes derived from lipotoxic hepatocytes promote HSC activation and proliferation through the PTEN/PI3K/Akt signaling pathway, accelerating the progression of NAFLD and leading to fibrosis.[98] In NAFLD patients and mouse models, exosomal miR-27a damage the mitochondria in aHSCs and stimulate the activation and proliferation of HSC-derived fibroblasts, which could be further aggravated by lipotoxic fatty acids.[20] Whether NAFLD aggravation results from excess production and direction induction of exosomes in HSCs remains debated.

Chronic viral hepatitis

Exosomes contribute to the life cycle of hepatitis viruses, including replication, transition, and pathogenesis.[99] Hepatitis viruses (HBV[100,101] and HCV[102,103]) efficiently transfer bioactive components utilizing the exosome pathway from infected cells to naïve cells. Additionally, hepatitis B virus e antigen was demonstrated to induce the activation of HSCs.[104,105] HSC activation is closely related to liver fibrosis in chronic hepatitis virus infection by some classic fibrogenic signals, such as α-SMA,[106] collagen I,[107] TGF-β,[108] and platelet-derived growth factor-B (PDGF-B).[109] Once those signaling molecules in HSCs are activated, the corresponding expression pattern in HSC-derived exosomes is destined to change, thereby enhancing the crosstalk between hepatocytes and the stromal environment, facilitating viral transmission and aggravating hepatocyte damage.[110] The exosome-associated tetraspanin CD63, including secretions from HSCs, contributes to the efficient assembly and release of HBV. Ninomiya *et al*.[101] found that the HBV particles from CD63-depleted cells markedly induce the loss of large hepatitis B surface antigens and downregulate infectivity of the HBV. Extracellular factors that interfere with HSCs, especially infected hepatocyte-derived exosomes, also have critical roles in chronic viral hepatitis-related liver diseases. Related studies have demonstrated that exosomes from viral hepatitis-replicating hepatocytes transfer various miRNAs (e.g., miR-19a,[102] miR-192,[111] and miR-222[112]) into HSCs to upregulate fibrogenic molecules, resulting in activation, and transdifferentiation into MBFs. A detailed understanding of the mechanisms associated with HSC-derived exosomes at the molecular level may contribute to the development of a new therapy direction to prevent hepatitis virus infection.

Acute liver injury

Considerable evidence has suggested that exosomes have important roles not only in the pathogenic progression of chronic liver disease but also in the initial onset of acute liver injury.[113–115] HSC-derived exosomes are considered to be one of the most prominent indicators of the degree of liver damage,[21] which is supported by a series of experimental studies. To date, most investigations of HSC-derived exosomes on liver damage have focused on chronic liver injury and persisting consequences that result in acute liver injury. Wan *et al*.[116] provided clues regarding the involvement of HSCs in which inhibition of HIF-1 in exosomes released from HSCs suppressed the increased expression of pyruvate kinase M2 (PKM2) and GLUT1, markers of glycolysis, thus quickly reducing hepatocyte damage in the glycolysis pathway. Conversely, HSC-derived EVs protect hepatocytes from toxic-induced acute damage. Of note, HSC-MVs dose-dependently improved the viability of hepatocytes, inhibited hepatocyte apoptosis, increased the expression levels of lactate dehydrogenase, alanine aminotransaminase, and aspartate aminotransferase induced by n-acetyl-p-aminophenol n-(APAP) or H_2O_2, and activated caspase-3 expression.[117] Following acute liver injury, damaged hepatocyte-derived exosome-treated HSCs inversely stimulated γδ T cells to produce IL17A by increasing the expression of RORγt and combining with unknown self-TLR3 ligands. The finding suggests a regulatory response of HSCs recruited from exosomes of hepatocytes containing unknown mediators, such as miRNAs, at early stages of liver injury.[118] Therefore, with the exception of HSCs, exosomes from a variety of cell types participate in the process of acute liver injury through intercellular information transmission.

Alcoholic liver disease

Recent studies suggest that HSCs regulates parenchymal cell injury and inflammation that drive fibrogenesis in alcohol-related liver disease (ALD), but the mechanism remains incompletely defined.[119,120] Accordingly, the pathophysiological role of exosomes associated with HSCs in ALD is increasingly recognized based on their properties of cell-to-cell communication. First, in ALD liver injury, serum/plasma miR-122 and miR-155 levels were predominantly associated with the exosome-rich fraction,[121] and the number of exosomes was significantly increased in serum,[122] indicating that microRNAs (miRNAs) and exosomes may be biomarkers of liver damage and inflammation during the process of ALD. Consistently, exposure to alcohol and its metabolites can enhance the expression of profibrotic markers in HSCs, concomitant with significantly increased miR19b and miR92 in HSC-derived exosomes.[123] Furthermore, as a principal target of hepatocyte-derived exosomes, HSCs could receive the delivery of exosomal RNA payload in hepatocytes at intrinsic levels through the release of exosomes by donor hepatocytes, which occurs downstream of heparin- or integrin-dependent binding interactions.[124] The studies provide insight into endogenous and exogenous exosomes in aHSCs as therapeutic targets for ALD liver injury.

Liver fibrosis

Liver fibrosis results from the dynamic net accumulation of

Table 1. Summary of the mechanisms of HSC-derived and HSC-associated exosomes in various liver diseases

Disease	Cellular origin of exosomes	Content	Mechanism	Reference
NAFLD	Adipocytes	TGF-β pathway	Adipocyte-derived exosomes could cause dysregulation of the TGF-β pathway after integration into hepatocytes and HSCs in NAFLD	97
	Lipotoxic hepatocytes	miR-1297-PTEN/PI3K/Akt	miR-1297 secreted from lipotoxic hepatocytes could promote the activation and proliferation of HSCs through PTEN/PI3K/Akt signaling pathway, accelerating the progress of MAFLD and fibrosis	98
	Hepatocytes	miR-27a	Exosomal miR-27a overexpression could damage mitochondria in a-HSCs, and promote the production of ROS, and stimulate the activation and proliferation of HSC-derived fibroblasts, finally, lipotoxic fatty acids further aggravated this phenomenon	20
Chronic viral hepatitis	HSCs	Classic fibrogenic signal	α-SMA, collagen I, TGF-β and PDGF-B in HSCs were activated, and then the corresponding expression pattern in HSCs-derived exosomes was destined to change and facilitate viral transmission and hepatocyte damage	106–109
	HSCs	Tetraspanin CD63	The exosome-associated tetraspanin CD63, including secretions from HSCs, contributes to the efficient assembly and release of HBV. The HBV particles from CD63-depleted cells markedly induce a loss of large hepatitis B surface antigens, then downregulate infectivity of the HBV	101
	HCV-infected hepatocytes	miR-19a	Exosomes from hepatocytes infected with HCV could regulate the SOCS-STAT3 axis and activate HSC via miR-19a	102
	HCV-infected hepatocytes	miR-192	Exosomes derived from hepatocytes infected with HCV also transferred miR-192 to HSCs and then promoted fibrosis	111
	HBV-infected hepatocytes	miR-222	Expression level of miR-222 was significantly increased in the exosomes from HBV infected hepatocytes, and significantly enhanced the activation of HSCs by inhibiting TFRC and TFRC induced ferroptosis	112
Acute liver injury	HSCs	HIF-PKM2/GLUT1	HIF-1 in exosomes of HSCs inhibited the increased expression of PKM2 and GLUT1, and then, reduced hepatocyte damage in the glycolysis pathway	116
	HSCs	n-APAP /H2O2	HSC-MVs dose-dependently increased the viability of hepatocytes and increased expression levels of LDH, ALT, and AST, and suppressed the hepatocytes apoptosis induced by n-APAP or H_2O_2 and activated caspase-3 expression	117
	Damaged hepatocytes	RORγt-IL-17A	Hepatocyte-derived exosome-affected HSCs inversely promoted γδT cells to produce IL-17A via increasing the expression of RORγt and combine with unknown self-TLR3 ligands	118
ALD	Serum/plasma	miR-122, miR-155	miR-122 and miR-155 were predominantly associated with the exosome-rich fraction after liver damage and inflammation stimulation during the process of ALD	121
	HSCs	miR19b, miR92	Expression levels of miR19b and miR92 in HSC-derived exosomes were increased after alcohol exposure	123
	Hepatocytes	Heparin/integrin	HSCs received the delivery of exosomal RNA payload in donor hepatocytes via downstream of heparin- or integrin-dependent binding interactions	123
Liver fibrosis	HSCs	CCN2	HSC exosomal CCN2 in conjunction with other exosome constituents may amplify or fine tune fibrogenic signaling	127
	PMFs	VEGF-VEGFR2	PMFs release particles containing VEGF and activate VEGF receptor 2 in endothelial cells, thus greatly promoting angiogenesis	128

(continued)

Table 1. *(continued)*

Disease	Cellular origin of exosomes	Content	Mechanism	Reference
	HSCs	IL-6,TNFα	Activated human HSCs-exosomes stimulated macrophage IL-6 and TNFα synthesis and release and macrophage migration, in fibrosis	90
	HSCs	PDGF-Hh ligands	PDGF-treated HSCs released exosomal Hh ligands and induced similar Hh-dependent changes in hepatic sinusoidal endothelial cells gene expression	129
	HSCs	HNF4α	HSC-derived exosomes together with activated HNF4α partially induced the transdifferentiation of HSCs to hepatocyte-like phenotype	128
	Stem cells	miR-92a-3p, miR-302-3p, miR-146a-5p, SphK1	Human iPSCs-derived exosomal miR-92a-3p and miR-302-3p, liver stem cell-derived EVs miR-146a-5p and SECs-derived exosomal SphK1 shuttled profibrotic transcripts into HSCs, and alleviated fibrotic phenotype of HSCs	131–133
Liver cancer	HSCs	miR-148a-3p	Activated HSC exosome-depleted miR-148a-3p accelerated HCC progression through ITGA5/PI3K/Akt axis	88
	HSCs	DHFR	Activated HSC exosomal DHFR induced M1 macrophage polarization of M0 macrophage enhancement	89

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALD, alcohol-related liver disease; α-SMA, alpha-smooth muscle actin; CCN2, connective tissue growth factor; DHFR, dihydrofolate reductase; GLUT1, glucose transporter-1; HSC, hepatic stellate cell; HIF-1, hypoxia inducible factor-1; HCV, hepatitis C virus; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HNF4α, hepatocyte nuclear factor 4 alpha; iPSC, induced pluripotent stem cells; ITGA5, integrin alpha 5; LDH, lactic dehydrogenase; MV, extracellular vesicles; MAFLD, metabolic associated fatty liver disease; n-APAP, n-acetyl-p-aminophenol; NAFLD, nonalcoholic fatty liver disease; PTEN, phosphatase and tensin homolog; PDGF-B, platelet-derived growth factor-B; PMF, portal vein myofibroblasts; PI3K, phosphatidylinositol 3-kinase; RORγt, retinoic acid receptor-related orphan receptor γt; ROS, reactive oxygen species; SOCS, suppressor of cytokine signaling; STAT3, signal transducer and activator of transcription 3; SEC, sinusoidal endothelial cells; SphK1, sphingosine kinase 1; TLR3, toll-like receptor 3; TGF-β, transforming growth factor beta; TFRC, transferrin receptor; TNFα, tumor necrosis factor alpha; VEGF, vascular endothelial growth factor.

ECM due to chronic liver injury based on the abovementioned etiology. The process mainly involves intercellular communication between HSCs and inflammation-damaged hepatocytes.[29,125,126] In hepatic fibrosis, diverse intracellular signaling cascades maintain the activated phenotype and control the fibrogenic and proliferative state of HSCs. Exosomes represent an emerging means of intercellular signaling in the inflammation-irritated liver microenvironment undergoing coordinated immune responses to liver repair. HSC exosomal CCN2 in conjunction with other exosome constituents induces shifts between qHSCs or aHSCs and may amplify or fine tune fibrogenic signaling.[127] In the study of hepatic fibrosis caused by portal vein dilation, portal vein myofibroblasts (PMFs), which are transdifferentiated from aHSCs, act the key cells of hepatic vascular remodeling. PMFs release microvesicles containing VEGF and activate VEGF receptor 2 in SECs, thus greatly promoting angiogenesis and providing a larger fibrotic skeleton for liver cirrhosis.[128] Benbow *et al*.[90] found that activated human HSC exosomes stimulated macrophage IL6 and TNF-α synthesis and release as well as macrophage migration, which was innately linked to the hepatic immune response to fibrosis. In addition, PDGF-treated HSCs released exosomes containing biologically active Hh ligands and induced similar Hh-dependent changes in hepatic sinusoidal endothelial cell (SEC) gene expression, suggesting a novel mechanism for vascular remodeling during cirrhosis.[129] Based on the signal transduction and biological effects exerted by exosomes, mouse liver AML12 cell exosomes encapsulating the CRISPR/dCas9-VP64 system were delivered to HSCs. In turn, the engineered HSC-derived exosomes together with activated hepatocyte nuclear factor 4 alpha (HNF4α) partially induced the transdifferentiation of HSCs to a hepatocyte-like phenotype.[130] Similarly, human induced pluripotent stem cell (iPSC)-derived exosomal miR-92a-3p and miR-302-3p,[131] liver stem cell-derived EV miR-146a-5p,[132] and SEC-derived exosomal SphK1[133] shuttled profibrotic transcripts into HSCs and alleviated the fibrotic phenotype of HSCs. Together, the fibrogenesis mechanisms involved are not yet completely understood, but the findings suggest that imbalance of diverse extra- and intra-HSC-exosomal profibrotic or antifibrotic factors may determine the development of liver fibrosis.

Liver cancer

Chronic liver disease with fibroinflammation contributes not only to fibrosis but also hepatocyte regeneration as well as replication-induced DNA damage, all of which may promote the development of liver cancer.[134–139] Extensive data have described exosomes as carriers of various cargoes conveying cellular information that enables them to serve as important players in malignant cell–nonmalignant cell communication during cancer developemnt.[88,140–142] miRNA expression profiling of HSCs cocultured with liver cancer cells showed that miR-148a-3p was significantly reduced in HSCs.[88] Subsequent studies demonstrated that aHSC exosome-depleted miR-148a-3p accelerated hepatocellular carcinoma (HCC) progression through the ITGA5/PI3K/Akt axis. To validate the effects of HSC-derived exosomes on effective intercellular transportation and information integration, Peng, *et al*.[89] provided related evidence that aHSC exosomal DHFR induced M1 macrophage polarization of M0 macrophages. Two interesting studies verified that the exosomes secreted by qHSCs do not have the ability to affect liver cancer cells, whereas senescent HSC or aHSC exosomes promote the progression of HCC.[143,144] In the tumor microenvironment, cancer cell-derived exosomes and HSC-derived exosomes mediate intercellular communication and form a positive feedback loop, thereby jointly constructing a prometastatic milieu suitable for the invasion and metastasis of tumor

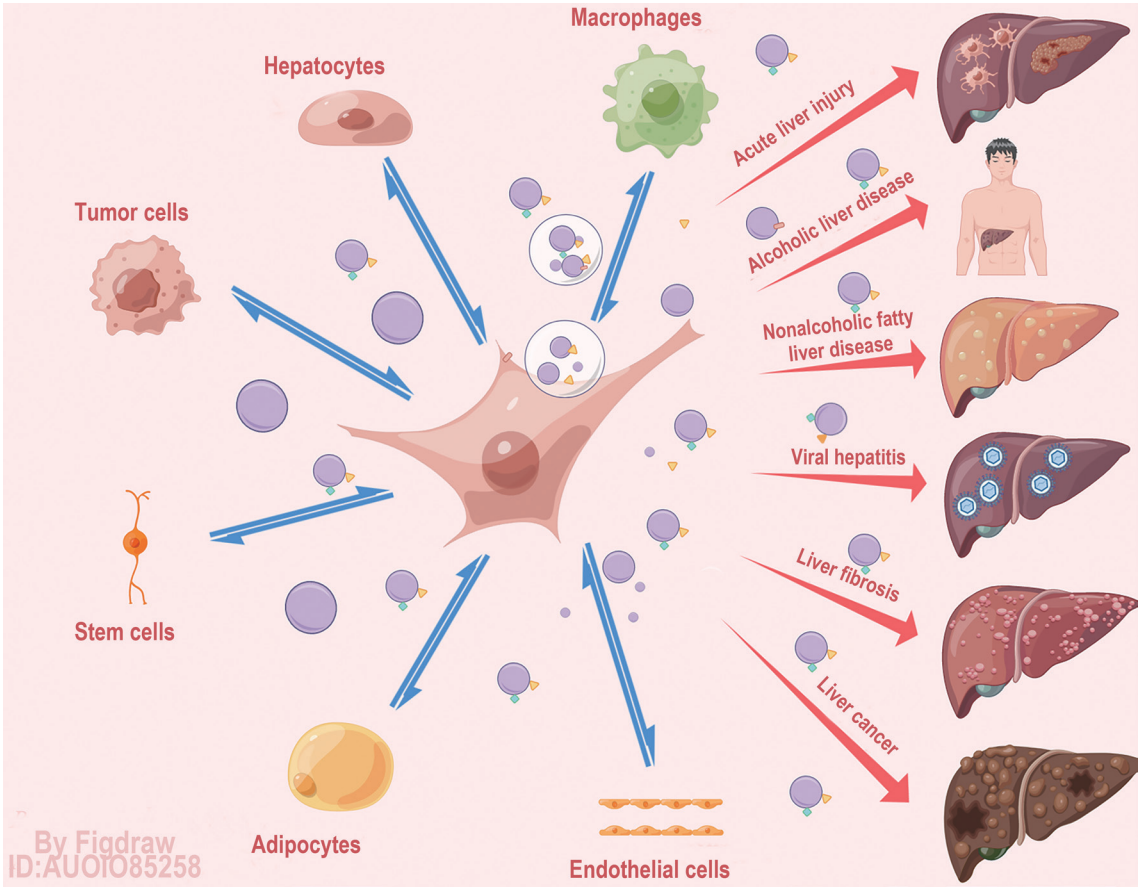

Fig. 2. Brief summary of the roles of HSC-derived exosomes in liver diseases and involved molecules and signaling pathways. Various types of cells, such as hepatocytes, macrophages, adipocytes, and endothelial cells, exhibit intercellular communication with HSCs via extracellular vesicles (EVs) and significantly affect the processes associated with various liver diseases, such as acute liver injury, alcoholic liver disease, nonalcoholic fatty liver disease, viral hepatitis, fibrosis, and cancer, through the modulation of some critical molecules and signaling pathways. HSC, hepatic stellate cell. EVs, extracellular vesicles.

cells.[145] After the education of pancreatic cancer cells[74] or colorectal cancer cells[77] by exosomes, aHSCs were identified as a component of the potential premetastatic niche that promotes liver metastasis. The detailed mechanisms of HSC-derived or HSC-associated exosomes in tumor invasion and metastasis remain incompletely characterized and more in-depth research work needs to be performed. The roles of HSC-derived exosomes in liver diseases are summarized in Figure 2.

Clinical value of HSC-derived exosomes in liver diseases

Currently, early and accurate diagnostic, therapeutic and prognostic biomarkers of various liver diseases are lacking. Additionally, there are relatively few applied and translational studies of HSC-derived exosomes in liver diseases. Most relevant studies focus on exosomes derived from hepatocytes, nonparenchymal cells and nonparenchymal immune cells or exosomal mRNAs and ncRNAs, such as lncRNAs, miRNAs, and circRNAs. Recently, as potential biomarkers assessed by liquid biopsy, the safety and reliability of methods used to evaluate exosomes in patients and the therapeutic effect of exosomes have been evaluated in various liver diseases, such as ALD,[146] NAFLD,[147] viral hepatitis,[148] fibrosis,[149] and liver cancer.[150]

HSC-associated exosomes may offer potential clinical benefits for liver diseases, mainly fibrosis and cancer. In fibrosis, as mentioned above,[116] HSC exosomal GLUT1 and PKM2 interfere with the metabolic activity of liver nonparenchymal cells around the liver through the glycolytic pathway, representing a new therapeutic target of liver fibrosis. Regarding extracellular exosomes targeted to HSCs, M2 macrophage-derived exosomal miR-411-5p inhibited HSC activation to inactivate stellate cells in an NAFLD model by directly downregulating the expression of calmodulin-regulated spectrin-associated protein 1 (CAMSAP1). Thus, an exosomal miR-411-5p inhibitor may serve as a potential therapeutic target for NAFLD and fibrosis.[35] Similarly, through targeting HSCs, several exosomal microRNAs originating from other cell types, such as liver stem cells (miR-141-3p[151] and miR-146a-5p[132]) and hepatocytes (miRNA-26b,[152] miRNA-107,[153] and miR-19a[102]) have biological effects that influence the fibrogenic phenotype of HSCs.

In the liver cancer microenvironment, on the one hand, HSC exosomal microRNAs and mRNAs (miR-148a-3p[88] and DHFR[89]) participate in the malignant behavior of tumors via intercellular information shuttling. On the other hand, exosomes from liver cancer cells stimulate multiple signaling pathways (IGF2-PI3K.[154] HSPC111-CXCL5-CXCR2,[77] IL-6-STAT3,[155] and MIRLET7BHG-miR-330-5p-SMO[156] axes) in HSCs, subsequently contribute to tumor development and consequently provide potential targets for the prevention and treatment of liver cancer. The studies suggest that exo-

somal miRNAs and mRNAs derived from HSCs or targeted to HSCs are major regulators of tumor homeostasis and have bright prospects for clinical application.

Conclusions and perspectives

As multifaceted regulators in liver diseases responding to their activated state, HSCs generate corresponding cytokines and microRNAs that interact with adjacent cells during changes in glucose metabolism, lipid metabolism, amino acid metabolism, protein metabolism, and mitochondrial metabolism, in which HSC-derived exosomes have important roles. During the activation process, the metabolic regulation of HSC-derived exosomes may provide important information regarding the prevention and treatment of various liver diseases. An increasing number of studies highlight key extra- and intracellular exosomal pathways involved in HSC activation. In the near future, more in-depth research data are urgently needed to provide references for the potential translational and clinical application of exosomes derived from or associated with HSCs for various liver diseases.

Funding

This study was supported by Japanese China Sasakawa Medical Fellowship, Science and Health Joint Research Project of Chongqing Municipality (2020GDRC013) and Program for Youth Innovation in Future Medicine, Chongqing Medical University (W0087).

Conflict of interest

RL has been an editorial board member of *Journal of Clinical and Translational Hepatology* since 2021. The other authors have no conflicts of interest related to this publication.

Author contributions

Study concept and design (KLY, ML, QG, RL), drafting of the manuscript (KLY, ML, YXD, WTY, QG, RL), critical revision of the manuscript for important intellectual content (KLY, ML, PPS, YXD, WTY, WT, NK, RL, QG). All authors have made a significant contribution to this study and have approved the final manuscript.

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