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Extracellular vesicle-mediated bidirectional communication between the liver and other organs: mechanistic exploration and prospects for clinical applications

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Abstract

The liver, functioning as an endocrine organ, secretes a variety of substances that influence the activities of other body organs. Conversely, molecules generated by organs such as bone, the gut, and adipose tissue can also impact liver function. Accumulating evidence suggests bidirectional communication between the liver and other organs. However, research on how extracellular vesicles (EVs), which transport active molecular mediators, contribute to this interorgan communication is still in its nascent stages. EVs are capable of transporting functional molecules, including lipids, nucleic acids, and proteins, thereby affecting recipient cells across different organs at the biological level. This review examines the role of EVs in facilitating bidirectional communication between the liver and other organs such as bone, the cardiovascular system, the gut, the pancreas, the brain, the lungs, the kidneys, and adipose tissue. It explores their potential in disease treatment and highlights the challenges in understanding EV-mediated interorgan interactions. The contribution of mediator-carrying EVs to two-way communication between the liver and other organs remains an area of ongoing investigation. Future research will provide a more comprehensive theoretical foundation to clarify the precise mechanisms governing communication between the liver and other organs, pinpoint medical targets, and expand the application of EVs within the realm of precision medicine.

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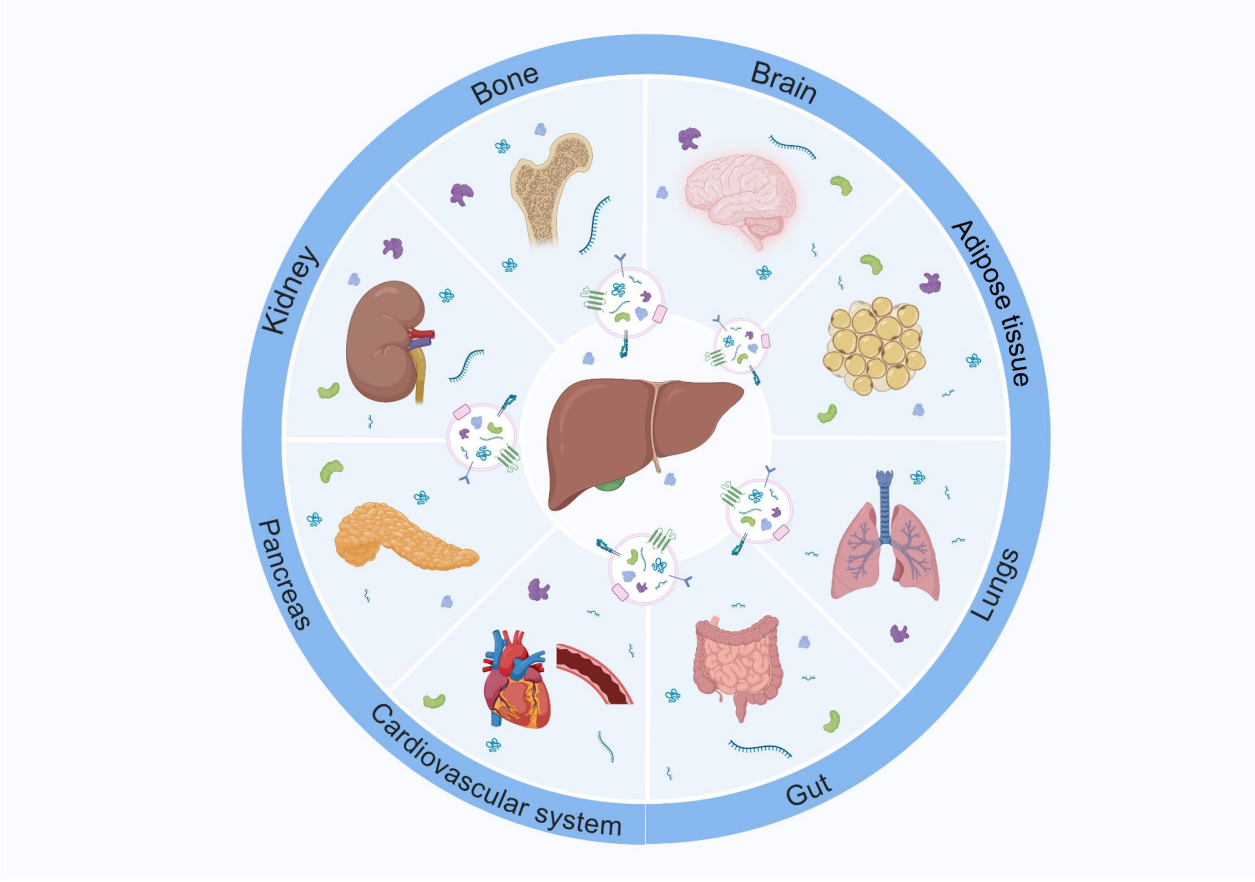
Graphical Abstract



Keywords Extracellular vesicles, Exosome, Liver, Bidirectional communication, Targeted therapy

Introduction

Through the secretion of substances including hormones, cytokines, and extracellular vesicles (EVs), inter-organs often create a complex regulatory network that maintains physiological homeostasis and enhances adaptability to disease [1]. Increasing attention has been drawn to the growing body of evidence indicating that EVs play a critical function in the interorgan communication network [2, 3]. EVs are highly heterogeneous lipid bilayer vesicles derived from the plasma membrane, which encapsulate cargo including lipids, nucleic acids, and proteins. They transmit signals from donor cells to recipient cells, thereby influencing the function and state of distant organs [4].

As the largest solid organ, the liver is essential for maintaining homeostasis since it is involved in many physiological functions, such as immunological control, synthesis of proteins, metabolism, and detoxifying [5]. Moreover, the liver sustains systemic homeostasis through bidirectional communication with other organs. For example, *Akkermansia muciniphila* and its EVs have been shown to mitigate liver injury [6, 7], while liver-derived EVs can interact with adipose tissue [8] and the pancreas [9] to regulate glucose homeostasis. Conversely, under pathological conditions, EVs secreted by ischemia-reperfused kidneys can cause liver injury [10],and EVs originating from fatty liver can drive the progression of atherosclerosis [11, 12]. Therefore, exploring EV-mediated communication between the liver and other organs is essential for a deeper understanding of organismal health and disease.

The function of EVs in facilitating communication between the liver and the bone, cardiovascular system, gut, pancreas, brain, lungs, kidneys, and adipose tissue is the main emphasis of this review, which also provides perspectives on the therapeutic potential of EVs for extrahepatic and liver-related disorders. Furthermore, a brief discussion is given of the difficulties and restrictions related to EVs in interorgan communication. It is essential to comprehend these intricate relationships in order

to guide future research paths as well as to uncover possible treatment methods for systemic and liver-related disorders.

Biological characteristics of EVs

Overview of EVs

In both healthy and pathological processes, EVs—lipid bilayer-enclosed vesicles—are produced by cells of various types and function as messengers to mediate and control intercellular communication [13]. The International Society for Extracellular Vesicles characterizes EVs as particles secreted by cells, enveloped in a lipid bilayer, and devoid of functional nuclei [14]. Based on the origin, EVs are often divided into three types: exosomes, microvesicles, and apoptotic bodies [15]. After fusing with the plasma membrane, intraluminal vesicles (ILVs) stored in multivesicular bodies (MVBs) within cells release to produce exosomes, which are around 40 to 160 nm in size [16]. Direct secretion of microvesicles (50–1000 nm) occurs when the plasma membrane buds outward [13]. Usually ranging from 1 to 5 μm in size, apoptotic bodies are created during programmed cell death [17]. EVs contribute to numerous biological processes. Acting as natural carriers of antigens, EVs are involved in antigen presentation and immune response regulation [18]. They also promote cell proliferation [19, 20], induce the differentiation of neural stem progenitor cells [21], and facilitate neurogenesis and neurite remodeling [22]. Moreover, EVs are crucial for the processes of cell motility [23, 24] and cellular reprogramming [25, 26].

Biology of EVs

Various types of cells release exosomes. The formation of early sorting endosomes (ESEs) begins with the inward budding of the plasma membrane. Later, these ESEs develop into late sorting endosomes, which in turn produce MVBs that contain ILVs [16]. The generation of ILVs is mediated by the endosomal sorting complex required for transport (ESCRT), which consists of four distinct protein complexes: ESCRT-0 through ESCRT-III [27]. ESCRT-0 identifies ubiquitinated proteins through its subunits, hepatocyte growth factor-regulated tyrosine kinase substrate and signal transducing adaptor molecule 1/2 [28, 29]. The sorting domain that ESCRT-0, ESCRT-I, and ESCRT-II create has a high affinity for ubiquitinated cargo [30]. The protein complex ESCRT-III, on the other hand, promotes budding processes [27] and facilitates the formation of ILVs through membrane scission [31]. Finally, the class I AAA ATPase Vps4 supplies the energy required for the ESCRT-III complex to dissociate from the MVB membrane [29]. In addition to being produced via the ESCRT-dependent pathway, exosomes can also be produced via an ESCRT-independent pathway. This alternative pathway may involve raft-like microdomains enriched in sphingomyelin within the endosomal membrane, where ceramide is generated by the hydrolytic removal of phosphocholine moiety [32]. The conical shape of ceramide is believed to cause the endosomal membrane to spontaneously curve negatively, which facilitates domain-induced budding [27]. Moreover, a pathway that is not dependent on ceramide or ESCRT complexes can induce melanogenesis through the tetraspanin family protein CD63 [33]. Ultimately, MVBs can either merge with the plasma membrane to release ILVs, which turn into exosomes, or they can fuse with lysosomes for destruction [16].

Microvesicles (MVs), in contrast to exosomes, are created by molecular rearrangements brought on by changes in the composition of protein and lipid in the plasma membrane, which results in membrane budding [34]. Changes in Ca^{2+} levels recruit and activate calcium-dependent enzymes, altering the lipid composition of the plasma membrane and inducing asymmetric phospholipid rearrangement [35], which leads to the externalization of phosphatidylserine [36]. Plasma membrane lipids are key to MV formation. The depletion of cholesterol can significantly reduce MV production [37]. The conical structure of ceramide also promotes membrane curvature, thereby regulating MV formation [38]. Additionally, actin dynamics are essential in MV formation [34]. Members of the small GTPase family, including RhoA and its downstream targets Rho-associated protein kinase (ROCK) and LIM domain kinase (LIMK), regulate actin cytoskeletal remodeling during MV formation [39]. ADP-ribosylation factor 6, a member of the ARF family that belongs to the Ras superfamily of small GTPases, also regulates actin dynamics [40]. Its downstream effectors, extracellular signal-regulated kinase (ERK) and myosin light chain kinase, are essential for regulating actin polymerization and myosin activity, thus playing significant roles in MV release [41]. Additionally, the core ESCRT component, tumor susceptibility gene 101 (TSG101), interacts with arrestin domain-containing protein 1 to facilitate MV release [42].

Apoptosis is characterized by the development of apoptotic bodies [43]. The first step in apoptosis is chromatin condensation in the nucleus, which is followed by membrane blebbing. Eventually, the cellular contents are fragmented and enclosed within independent membrane-bound vesicles, forming characteristic apoptotic bodies [44]. Apoptosis is usually accompanied by the externalization of phosphatidylserine, which acts as an "eat me" signal to aid phagocyte detection and absorption [45]. Additionally, calreticulin, another "eat me" ligand, is expressed on apoptotic cells when the "don't eat me" signal CD47 is downregulated [46]. Actin and myosin play roles in membrane blebbing [47], which is regulated by many kinases, including the ROCK1 and LIMK1 [48].

Table 1 Characteristics of EV subtypes

Characteristic	Exosomes	Microvesicles	Apoptotic Bodies	References
Size	40–160 nm	50–1000 nm	1–5 μm	[13, 16, 17]
Biogenesis	Release of ILVs by fusion of MVB with the plasma membrane	Budding from the plasma membrane	Membrane blebbing, protrusions, and nuclear fragmentation	[13, 16, 59]
Composition	Nucleic acids, lipids, proteins	Nucleic acids, lipids, proteins	Organelles, nucleic acids, lipids, proteins	[60]
Function	Intercellular communication, cell maintenance, tumor progression, antigen presentation, neuroprotection	Intercellular communication, cell maintenance, tumor progression	Removal of dying cells, antigen presentation, regulation of immune cell responses	[60, 61]

ROCK1 is an important modulator of membrane blebbing during apoptosis [49]. Caspase-3 cleaves ROCK1, removing its inhibitory C-terminal domain to generate an active fragment that induces myosin light chain phosphorylation, leading to membrane blebbing [50]. LIMK1 supports apoptotic membrane blebbing by phosphorylating cofilin and promoting actin polymerization [51, 52]. Additionally linked to membrane blebbing, the apoptotic volume reduction (AVD) is essential for the production of apoptotic bodies [53]. Early AVD typically occurs within 0.5 to 2 h of apoptosis induction and is unrelated to mitochondrial dysfunction or initial caspase activation [54]. After membrane blebbing, apoptotic membrane protrusions form [55]. According to research, pannexin 1 (PANX1) is a crucial negative regulator of T cell and thymocyte apoptopodia production. PANX1 suppression encourages the development of apoptopodia and apoptotic bodies [56]. The "find me" signal is released into the extracellular space when the PANX1 C-terminus is cleaved by caspase, which attracts phagocytes and promotes apoptosis [57]. Finally, nuclear fragments condense and compact into half-moon shapes, resulting in apoptotic bodies that are subsequently engulfed by macrophages [58].(Table 1).

When EVs are released, they can be internalized by the recipient cells through several types of endocytosis, including phagocytosis, macropinocytosis, clathrin-mediated endocytosis, caveolin-dependent pathways, and lipid raft-mediated endocytosis. Direct fusing of the EV membrane with the plasma membrane is an additional potential entry pathway [62]. They can also trigger intracellular signaling in target cells via direct receptor–ligand interactions [15]. EVs may either fuse with preexisting ESEs or be broken down in lysosomes after being internalized by recipient cells, releasing their cargo into the cytoplasm [16] (Fig. 1).

It is important to note that the classification and definition of EVs based on biogenesis pathways are not entirely accurate. The biogenesis of EVs can be influenced by various factors, while current isolation techniques lack the specificity to enrich EVs generated by different mechanisms. Additionally, there are no universal markers for distinguishing subtypes of EVs, leading to uncertainty in accurately categorizing isolated EVs into specific biogenesis pathways. Therefore, caution should be exercised when using terms based on biogenesis pathways [14]. In light of this, we will consistently use the generic term "EV" in subsequent descriptions to avoid confusion.

Bidirectional communication of EVs in the liver and other organs

Interorgan communication depends on the exchange of information between cells across different organs [1]. EVs released into the circulatory system mediate crosstalk between organs by facilitating cell-cell interactions through the delivery of cargo [63]. The liver, characterized by its complex and diverse hemodynamic properties [64], secretes EVs from hepatocytes that are transported via the bloodstream to various distant organs or tissues, where they exert their biological effects. Conversely, other organs transmit their physiological or pathological information to the liver in the form of EVs through systemic circulation [63]. Cellular environmental conditions, such as temperature, pH, and oxidative/hypoxic states, influence EV-cell interactions to varying degrees. Additionally, the composition of the EV membrane, including proteins, lipids, and glycans, affects the binding of EVs to target cells [15]. Moreover, the cargo carried by EVs is influenced by the type of donor cell, metabolic state, and disease context [65]. Overall, EVs serve as key mediators of intercellular communication, playing an indispensable role in facilitating information transfer between the liver and other organs. By carrying diverse substances, EVs finely regulate physiological processes and pathological progression [63]. A comprehensive understanding of the effects of specific substances carried by EVs from different sources has the potential to offer novel insights for diagnosing and treating a wide range of diseases, with significant implications for clinical practice and research. (Fig. 2).

Liver and bone

The anatomical separation between the liver and bone prohibits the direct interaction. Instead, the liver influences bone metabolism by secreting proteins, enzymes, and cytokines, whereas bone secretes osteokines that regulate liver metabolism. The liver–bone axis maintains

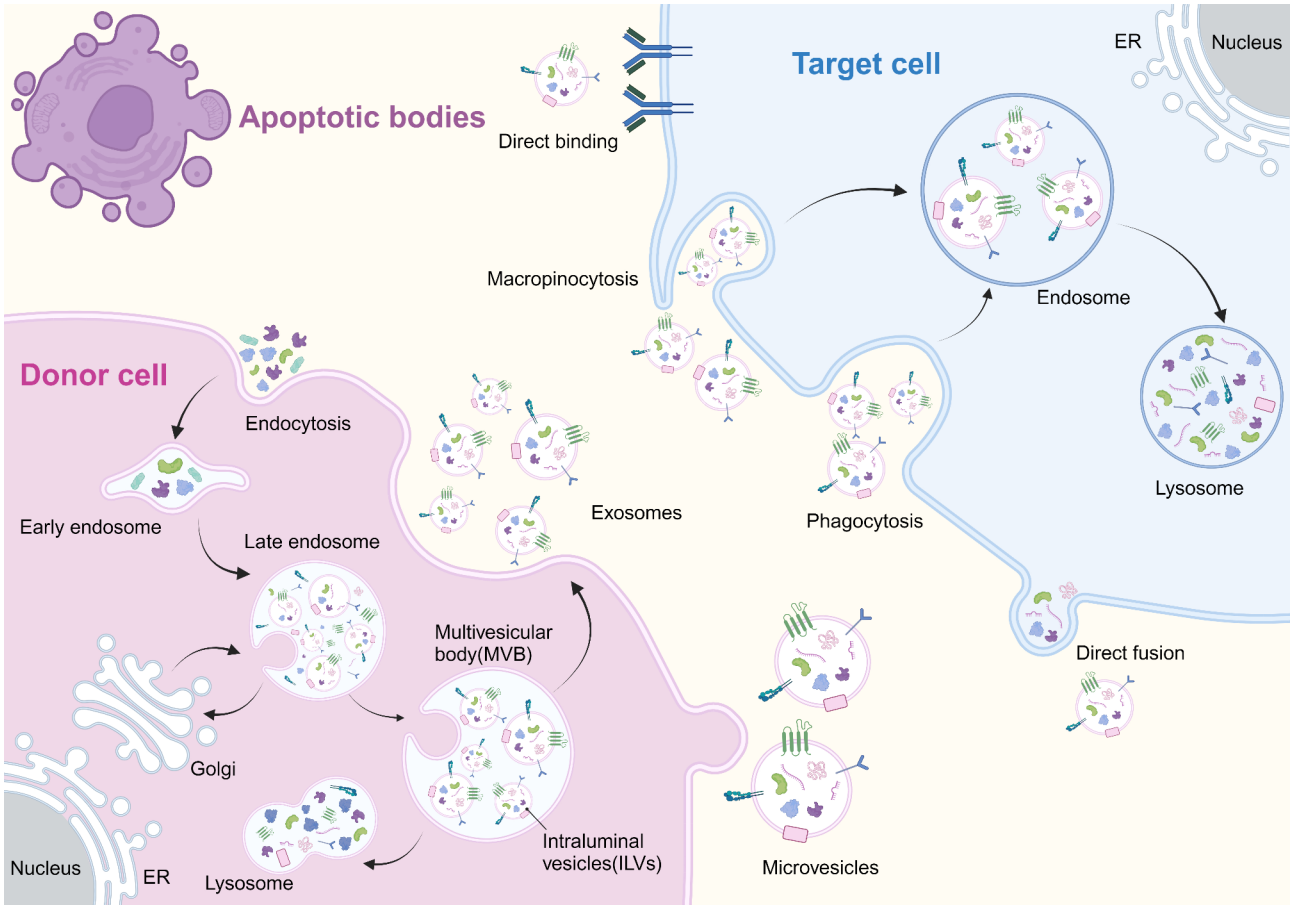


Fig. 1 Classification, biogenesis, and uptake of EVs. EVs exist in several forms, including exosomes, microvesicles, and apoptotic bodies. Early endosomes generated through endocytosis can mature into late endosomes and ultimately form MVBs containing multiple ILVs, which serve as precursors to exosomes. Exosomes are released when MVBs fuse with the plasma membrane. Apoptotic bodies are produced by the outward budding of apoptotic cell membranes, while microvesicles are directly released via the outward budding of the plasma membrane. A wide range of cargo, such as proteins, lipids, and nucleic acids, can be transported by EVs. EVs can be internalized by the target cells through mechanisms such as membrane fusion, phagocytosis, macropinocytosis, and direct binding. Abbreviation: ER: endoplasmic reticulum

homeostasis through hepatokines, osteokines, and biochemical signaling [66].

In recent years, there has been a growing focus on the role of EVs in liver-bone communication [67–71]. Maintaining liver–bone axis homeostasis is crucial for understanding osteoporosis progression [66]. Leucine-rich α-2-glycoprotein 1 (LRG1)-enriched small extracellular vesicles (sEVs) from SIRT2-deficient hepatocytes can prevent osteoclast differentiation by lowering the nuclear translocation of nuclear factor κB (NF-κB) p65. Additionally, a positive association has been observed between the plasma level of sEV-LRG1 and bone mineral density. These results indicate the potential therapeutic value of LRG1-containing sEVs in osteoporosis treatment [67]. Moreover, EVs from patients' liver tissue with type 2 diabetes can carry fatty acid synthase (Fasn) to periodontal inflammation sites, which causes ectopic fatty acid synthesis in periodontal ligament cells (PDLCs), activating the NOD-like receptor pyrin domain-containing protein 3 (NLRP3) inflammasome and the cleavage of gasdermin D (GSDMD). The activation of pyroptosis in PDLCs, driven by these factors, contributes to bone loss observed in individuals with diabetes [68]. In addition, it has been demonstrated that EVs produced from liver tissue increase osteogenic gene expression in mandibular mesenchymal stem cells, which improves the repair of mandibular defects [69].

EVs originating in the bone can also affect liver function. The balance between Tregs and Th17 cells is also modulated by the EVs generated by bone marrow-derived dendritic cells, which transport heat shock protein 70 (HSP70) to naïve T cells. This stimulates the PI3K/mTOR axis, favoring regulatory T-cell (Treg) maturation and suppressing T helper 17 cell (Th17) differentiation. The results of the study showed that hepatic ischemia-reperfusion (I/R)-injured (HIRI) mice injected with these EVs had higher amounts of anti-inflammatory factors and lower levels of inflammatory factors, aspartate

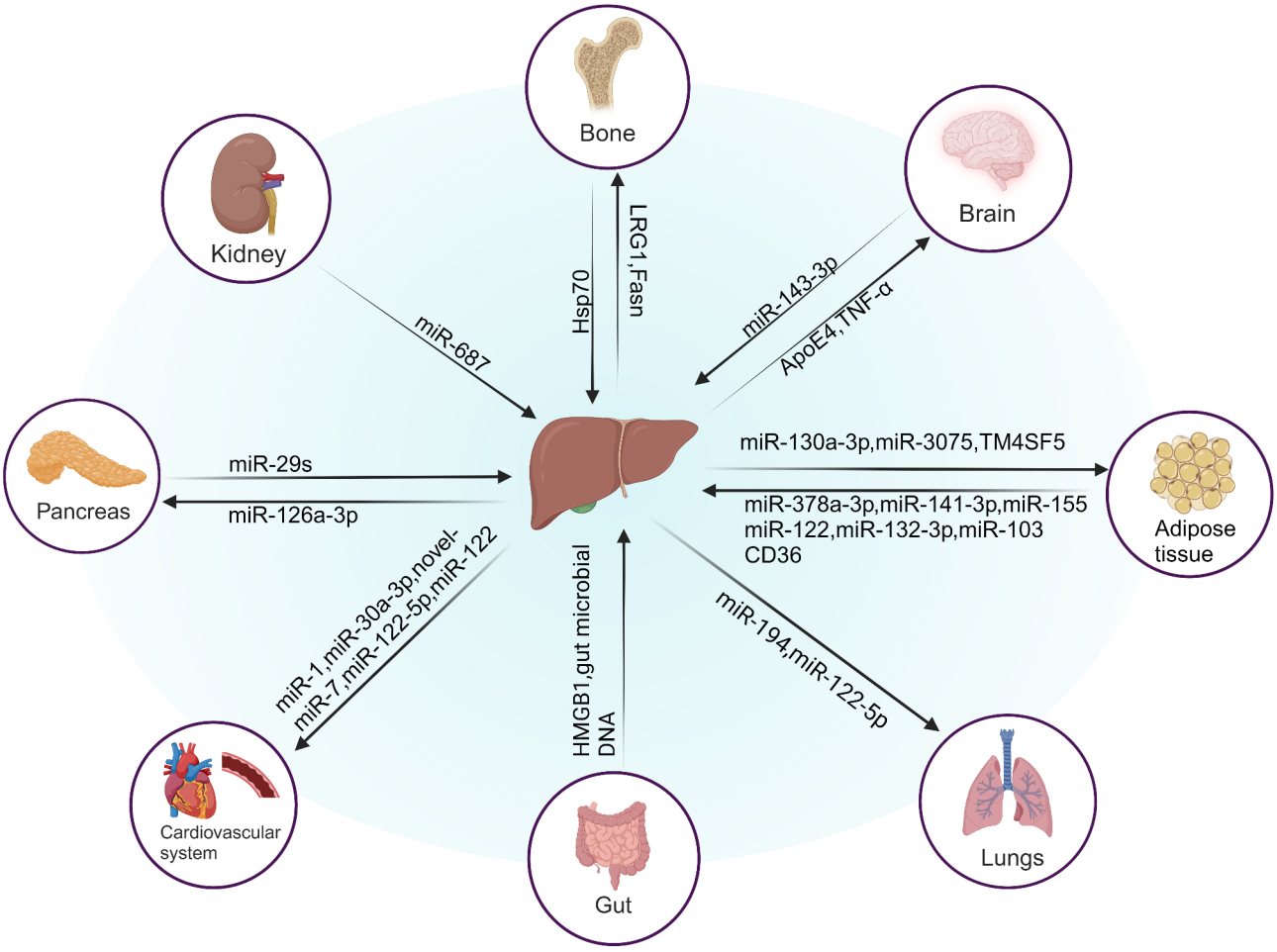


Fig. 2 Liver–organ axis: bidirectional crosstalk. EVs carry different cargo that facilitate communication between the liver and other organs, which are essential for the physiological or pathological state of the organism. Abbreviation: LRG1: leucine-rich alpha-2-glycoprotein 1; HSP70: heat shock protein 70; Fasn: fatty acid synthase; HMGB1: high-mobility group box protein 1; ApoE4: apolipoprotein E4

aminotransferase (AST), and alanine aminotransferase (ALT) in their blood, which attenuated liver injury [70]. Notably, EVs derived from human periodontal ligament fibroblasts promote hepatic lipogenesis by increasing SCD-1 expression and inhibiting the AMPK pathway, suggesting that managing periodontal disease could help prevent fatty liver [71].

In conclusion, EVs have a significant impact on bone health and contribute to the etiology of liver illnesses, which regulate liver-bone axis homeostasis. Research on exploring the operational mechanisms of EVs along the complex axis should be conducted in the future.

Liver and cardiovascular system

The liver and cardiovascular system have a complex relationship [72]. Emerging evidence underscores the role of liver-secreted EVs in modulating cardiovascular health [73].

EVs derived from fatty hepatocytes deliver miR-1, which inhibits Kruppel-like factor 4 (KLF4) and activates NF-κB, promoting endothelial inflammation and thus contributing to atherosclerosis [11]. Another study revealed that sEVs from fatty hepatocytes inhibit ATP-binding cassette transporter A1 (ABCA1)-mediated cholesterol efflux via miR-30a-3p, promoting foam cell formation and accelerating atherosclerosis [12]. Furthermore, lysosome-associated membrane protein 1 (LAMP1) is specifically targeted by novel-miR-7 in liver-derived EVs from non-alcoholic fatty liver disease(NAFLD) patients, which increases lysosomal permeability and aids in cathepsin B leakage. These lead to NLRP3 inflammasome activation, which causes microvascular endothelial cells to become hyperpermeable [74]. These findings reveal novel mechanisms underlying cardiovascular disease in NAFLD patients, suggesting that inhibiting EVs secreted by fatty liver or targeting their miRNAs could serve as potential therapeutic strategies for atherosclerosis.

ADP-ribosylation factor-like protein 2 (Arl2) is a key regulator of mitochondrial ATP production, and

silencing Arl2 reduces mitochondrial activity in cardiomyocytes [75]. One study reported that EVs from the livers of high-fat diet (HFD)-fed mice contain miR-122, which impairs cardiac mitochondrial function by inhibiting Arl2, promoting the development of obesity-related cardiomyopathy. In both primary cardiomyocytes and obese mouse models, blocking liver-derived miR-122 has been demonstrated to enhance cardiac remodeling and metabolic profiles, suggesting that miR-122 and Arl2 are potential therapeutic targets for obesity-related cardiomyopathy [76].

Physical exercise is well-established as a preventive and therapeutic intervention for multiple diseases [77]. Exercise has been shown to increase levels of miR-122-5p in the bloodstream, which is transported by liver-derived EVs. These EVs enhance fatty acid oxidation in endothelial cells by downregulating 1-acyl-sn-glycerol-3-phosphate acyltransferase(AGPAT1), leading to increased capillary density in perilesional skin tissue and promoting wound healing. This highlights a mechanism by which exercise improves cardiovascular health [78].

Although EVs produced by the liver exhibit important functions in the cardiovascular system, relatively little is known about how cardiovascular-derived EVs influence liver function. Therefore, further investigation is warranted to thoroughly elucidate the bidirectional roles of EVs within the liver-cardiovascular system axis.

Liver and gut

The gut and liver are connected by the portal vein system, and the maintenance of general physiological balance depends heavily on the reciprocal communication [79]. The liver's produced bile acids are crucial signaling molecules that influence the gut microbiota's makeup and preserve intestinal integrity to regulate liver metabolism while liver functions are regulated by the gut microbiota, its metabolites, and gut hormones [80].

Growing interest has been shown in the function of gut-derived EVs in the gut-liver axis [81]. *Akkermansia muciniphila* and its EVs can inhibit hepatic stellate cells(HSCs) activation and suppress fibrosis marker gene expression [6]. These EVs also exhibit anti-inflammatory effects by inhibiting Toll-like receptor (TLR) expression and upregulating peroxisome proliferator-activated receptor (PPAR) expression [7], thereby preventing HFD/CCL4-induced liver injury.

However, under pathological conditions, gut-derived EVs may exert adverse effects on the liver. EVs derived from the gut of mice subjected to intestinal I/R promote Kupffer cell polarization toward the M1 phenotype and increase proinflammatory cytokine expression, thereby inducing liver injury following intestinal I/R [82]. Additionally, a study revealed that gut microbial DNA-containing EVs from obese hosts impair insulin sensitivity and activate the cGAS/STING pathway in hepatocytes, enhancing inflammatory reactions [83]. It has also been demonstrated that fecal-derived EVs from nonalcoholic steatohepatitis(NASH) patients activate HSCs and disrupt hepatocyte integrity, exacerbating liver damage [84]. Furthermore, diet-induced obese (DIO) mice's portal venous blood was discovered to include higher levels of bacterial-derived EVs, which accumulated in the liver and may have a role in promoting liver inflammation through TLR4-mediated signaling [85]. High-mobility group box protein 1 (HMGB1) is expressed in HFD-induced NAFLD models [86]. Research indicates that the upregulation and release of HMGB1 are linked to hepatic steatosis and that EVs produced from the dysbiotic gut microbiota of HFD-fed mice carry HMGB1 from the gut to the liver, contributing to the development of hepatic steatosis [87]. Understanding the communication between the liver and gut through EVs provides novel insights into disease risk prediction and potential therapy strategies (Fig. 3).

Liver and pancreas

The liver and pancreas are integral to the body's energy metabolism, together forming a crucial regulatory network for maintaining energy balance. In addition to secreting insulin, which is essential for glucose homeostasis, pancreatic β-cells also release EVs to communicate with other organs, fulfilling their biological functions [88].

EVs from pancreatic β-cells deliver members of the miR-29 family (miR-29s), which have been shown to enter the liver and decrease insulin-stimulated AKT phosphorylation. The elevated level of miR-29s in the liver indicates that this miRNA primarily acts in the liver, ultimately inducing systemic insulin resistance [89].

Pancreatic β-cells can also take up liver-derived EVs. Under insulin-resistant conditions, liver-derived EVs increase the expression of insulin-related genes in pancreatic β-cells and increase the phosphorylation of the AKT downstream target FoxO1. These results point to elevated AKT phosphorylation, suggesting that some factors governing glucose homeostasis may be present in liver-derived EVs [9].

However, EVs produced from the liver may potentially negatively impact the pancreas. For example, miR-126a-3p is upregulated in EVs from fatty hepatocytes, and overexpression of miR-126a-3p may exacerbate the diabetic process by promoting β-cell apoptosis through inhibition of insulin receptor substrate-2 (IRS2) expression [90]. Insulin resistance is strongly linked to NAFLD, and the liver and pancreas play a crucial role in maintaining metabolic balance. Clarifying these illnesses and improving preventative and treatment methods require

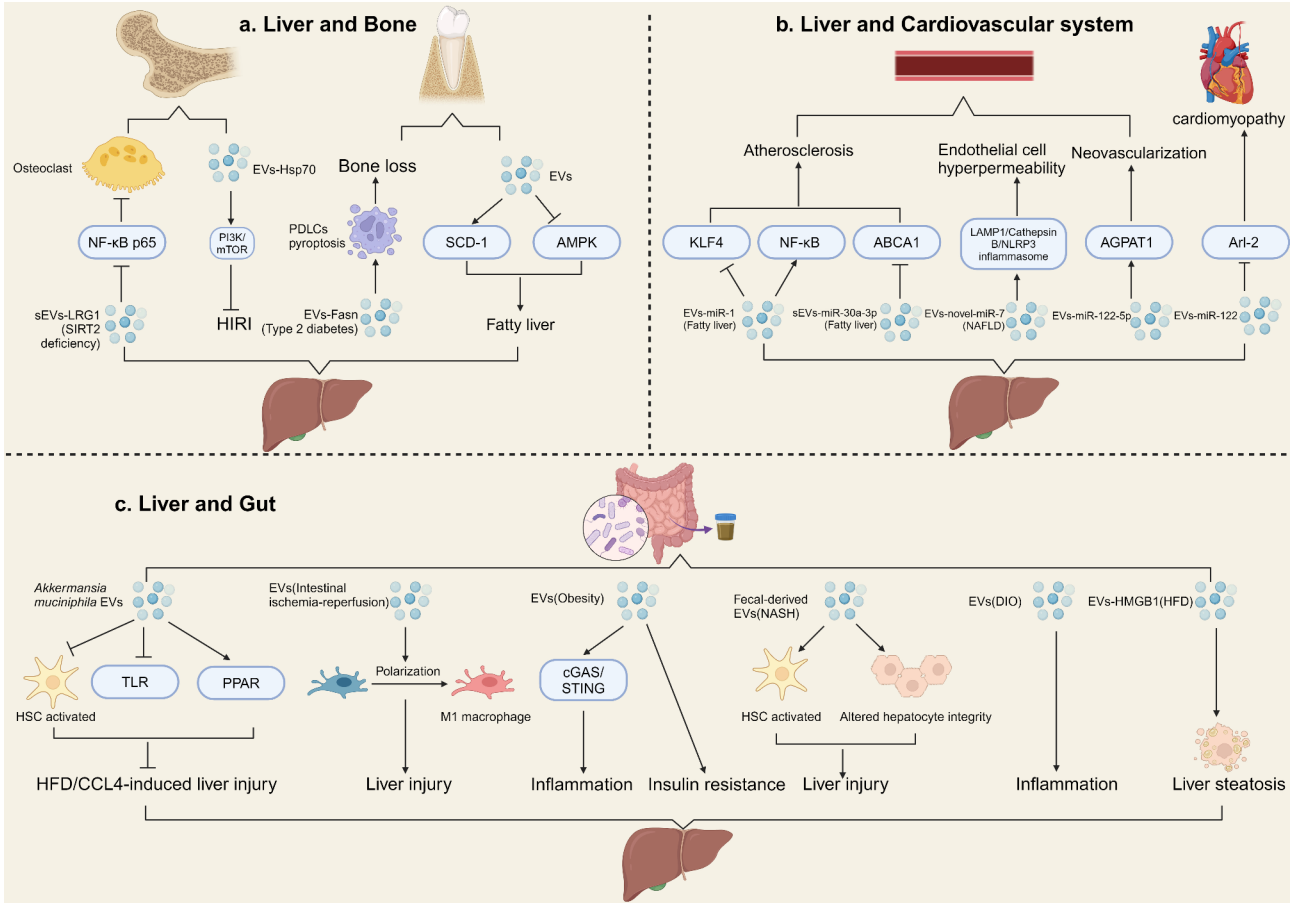


Fig. 3 Overview of the communication network between the liver, bone, cardiovascular system, and gut mediated by EVs. (**a**) Within the liver-bone axis, EVs carry different substances to maintain bone health and influence hepatic metabolism. (**b**) The liver-cardiovascular axis focuses on revealing the effects of liver-derived EVs on the vascular endothelium and the heart, ranging from atherosclerosis and neovascularisation to cardiomyopathy. (**c**) The liver-gut axis unravels the role that gut microbiota-derived EVs play in the regulation of hepatic injury. Each axis represents a distinct spectrum of organ-liver interactions and provides a thorough understanding of the liver's pivotal function in systemic physiology and pathology. Abbreviation: SIRT2: sirtuin 2; NF-κB: nuclear factor κB; LRG1: leucine-rich alpha-2-glycoprotein 1; HSP70: heat shock protein 70; HIRI: hepatic ischemia–reperfusion injury; PI3K: phosphoinositide 3-kinase; mTOR: mammalian target of rapamycin; PDLCs: periodontal ligament cells; Fasn: fatty acid synthase; SCD-1: stearoyl-CoA desaturase 1; AMPK: adenosine monophosphate (AMP)-activated protein kinase; KLF4: kruppel-like factor 4; ABCA1: ATP-binding cassette transporter A1; LAMP1: lysosomal-associated membrane protein 1; NLRP3: NOD-like receptor pyrin domain-containing protein 3; AGPAT1: 1-acyl-sn-glycerol-3-phosphate acyltransferase; Arl2: ADP-ribosylation factor-like protein 2; TLR: toll-like receptor; PPAR: peroxisome proliferator-activated receptor; HSC: hepatic stellate cell; HFD: high-fat diet; cGAS: cyclic GMP–AMP synthase; STING: stimulator of interferon genes; NASH: nonalcoholic steatohepatitis; DIO: diet-induced obese; HMGB1: high-mobility group box protein 1

a better grasp of the dynamic interactions between these two organs [91].

Liver and brain

Complex communication exists between the liver and the brain through various hormones, hepatokines, metabolites, and other substances [92], and the role of EV in the liver-brain axis is gradually being discovered [93–96].

Hepatic encephalopathy is a serious brain function disorder, frequently observed in patients with acute liver failure or chronic liver disease, and is commonly associated with hyperammonemia [97]. In hyperammonemic mice, elevated levels of tumor necrosis factor-alpha (TNF-α) in plasma EVs reach the cerebellum, where they activate microglia and astrocytes and engage the TNFR1/CCL2/BDNF/TrkB/KCC2 and TNFR1/NF-κB/glutaminase/GAT3 pathways. These increase cerebellar GABAergic neurotransmission and cause motor incoordination [93]. In addition, age-related thyroid deficiency promotes the accumulation of apolipoprotein E4 (ApoE4)-laden EVs from the liver to the brain, leading to neuronal cholesterol accumulation and triggering elevated reactive oxygen species (ROS), which activate the NLRP3 inflammasome and trigger neuronal pyroptosis, ultimately resulting in cognitive, motor, and emotional impairments [94].

Conversely, brain-derived EVs can also impact liver function. In the case of traumatic brain injury, EVs

released from the brain induce liver damage, resulting in elevated serum AST and ALT levels, excessive inflammatory exudation, sinusoidal congestion, hepatocyte swelling and degeneration, and disordered cellular structures, ultimately leading to hepatocyte apoptosis [95]. Furthermore, insulin-like growth factor-binding protein 5 (IGFBP5) is downregulated by pituitary-derived sEVs containing miR-143-3p, which therefore increases the production of insulin-like growth factor 1 (IGF-1), ultimately triggers the Wnt/β-catenin pathway to encourage hepatocyte proliferation [96].

In conclusion, the liver and brain exhibit a variety of complex interactions in both healthy and diseased states, encompassing metabolism, neuronal control, and disease initiation. A deeper understanding of the mechanisms underlying liver-brain interactions will enhance our comprehensive view of physiological processes and pathological alterations. This knowledge will also provide new insights and potential therapeutic targets for the identification, management, and prevention of associated diseases.

Liver and lungs

The pathological manifestations of hepatopulmonary syndrome (HPS) underscore the intimate connection between the liver and lungs [98]. The most markedly elevated miRNA in a mouse model of HPS was found to be miR-194. Hepatocyte-derived EVs transport miR-194 to pulmonary microvascular endothelial cells (PMVECs), where it directly suppresses the expression of THBS1, STAT1, and LIF. This suppression may enhance PMVEC migration, proliferation, and angiogenesis, thereby exacerbating the progression of HPS [99]. By lowering p65 expression, suppressor of cytokine signaling 1 (SOCS-1) is known to limit NF-κB activation [100]. According to prior research, HIRI-derived EVs deliver miR-122-5p to alveolar macrophages, where it targets and inhibits SOCS-1. This activates the NF-κB signaling pathway, which in turn promotes inflammation and M1 macrophage polarization, eventually resulting in acute lung injury [101]. Furthermore, a rise in the quantity of EVs in circulation during acute pancreatitis, mostly from the liver, dramatically raises the expression of proinflammatory proteins, causing pulmonary inflammation and a contributing cause to the lung inflammation linked to acute pancreatitis [102]. The bidirectional connection between the liver and lungs is still a relatively new area of study. Future research is necessary to comprehensively elucidate the physiological and pathological mechanisms underlying the critical role of EVs in the lung-liver axis.

Liver and kidneys

The precise communication pathways between the liver and kidneys are still not fully understood, even under normal physiological conditions. In disease states, such as hepatorenal syndrome, a fatal complication arising from acute liver failure (ALF), cirrhosis, and other severe liver conditions, rapid renal failure can occur, posing a significant threat to life [103]. Additionally, liver diseases like viral hepatitis and autoimmune hepatitis (AIH) can lead to kidney injury [104], indicating a close interaction between these two organs. EVs carrying miR-687 are secreted by ischemic renal cells during renal I/R and are deposited in the liver, which leads to elevated ALT and AST values, along with increased caspase-3 and inflammatory markers such as vascular cell adhesion molecule-1, myeloperoxidase, monocyte chemotactic protein-1 (MCP-1), and NF-κB in liver tissue. These changes, which are associated with liver inflammation and apoptosis, may contribute to distal liver injury following acute renal I/R [10]. Currently, a comprehensive understanding of the detailed communication network between the liver and kidneys requires substantial in-depth research that fully elucidates the complex interplay between the organs (Fig. 4).

Liver and adipose tissue

As a complex and extremely dynamic component of the organism, adipose tissue plays a critical role in physiological functions like insulin sensitivity, energy balance, and metabolism [105]. Recent studies show that EVs are crucial for the adipose tissue-liver axis, which together controls the balance of energy metabolism [79].

Brown adipose tissue (BAT) is of great importance in gluconeogenesis. During cold exposure, activated BAT secretes EVs containing miR-378a-3p, which reduces the protein level of p110α, a key regulator of glucose metabolism, thereby diminishing insulin-induced AKT phosphorylation, increasing hepatic gluconeogenic gene expression, and regulating gluconeogenesis [106]. Furthermore, EV miR-132-3p produced from BAT suppresses the expression of hepatic Srebf1 and lowers the expression of lipogenic genes that control hepatic lipogenesis during cold adaptation [107]. These findings demonstrate the endocrine function of BAT in mitigating cold stress.

Adipose tissue is essential for energy homeostasis. For example, miR-141-3p reduces the expression of phosphatase and tensin homolog deleted on chromosome ten (PTEN), enhancing AKT phosphorylation and insulin signaling. However, miR-141-3p of EVs is secreted at lower levels from adipose tissue in obese individuals than in healthy individuals. Consequently, when hepatocytes take up EVs with low miR-141-3p levels, insulin sensitivity and glucose uptake capacity are significantly impaired [108]. Moreover, compared with those in obese individuals with a normal intrahepatic triglyceride content, EVs derived from subcutaneous abdominal adipose tissue in

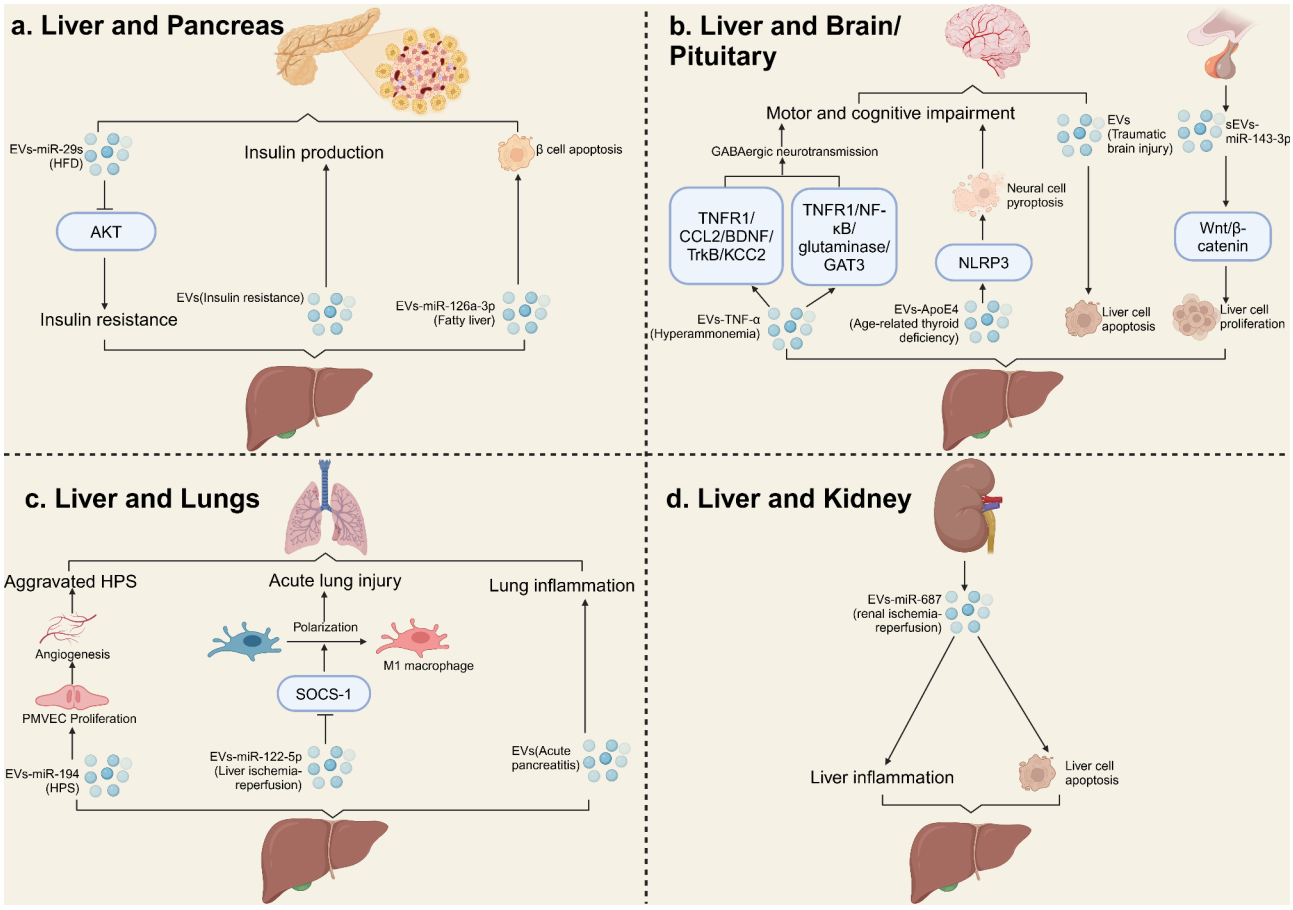


Fig. 4 Overview of the communication network between the liver, brain, lungs, and kidneys mediated by EVs. (**a**) The liver-pancreas axis mainly reflects the effects of EVs on insulin function, which is essential for regulating energy metabolism. (**b**) The liver-brain/pituitary axis reveals that EVs carrying different substances shuttle between the liver and brain/pituitary, supporting motor and cognitive functions as well as liver health. (**c**) The liver-lung axis reveals the pathological effects of liver-derived EVs on the lungs, contributing to the understanding of lung disease progression. (**d**) The liver-kidney axis research focuses on the impact of kidney disease on hepatic function, and this axis of interaction has yet to be studied in depth. Overall, these axes reflect the impact of interactions between the liver and other organs on physiological or disease states. They are important in maintaining overall homeostasis. Abbreviation: AKT: protein kinase B; TNFR1: tumor necrosis factor receptor-1; CCL2: C-C motif chemokine 2; BDNF: brain-derived neurotrophic factor; TrkB: tropomyosin-related kinase B; KCC2: K-Cl cotransporter 2; GAT3: GABA transporter type 3; ApoE4: apolipoprotein E 4; sEVs: small extracellular vesicles; Wnt: wingless-related integration site; HPS: hepatopulmonary syndrome; PMVEC: pulmonary microvascular endothelial cell

obese individuals with NAFLD downregulate AKT phosphorylation in hepatocytes, leading to impaired insulin signaling and insulin resistance [109]. miR-155 affects adipocyte metabolism by inhibiting PPARγ [110]. Adipose tissue macrophages (ATMs) secrete EVs (ATM-EVs) loaded with miR-155, and in obese mice, the miR-155 content in ATM-EVs is increased, which reduces PPARγ expression and contributes to insulin resistance [111]. Additionally, under HFD conditions, AMPK activity in white adipose tissue (WAT) decreases, leading to increased TSG101 expression [112]. An essential part of the ESCRT pathway, TSG101, is involved in the biogenesis of MVBs [113]. TSG101 facilitates CD36 sorting into WAT-derived EVs, which exacerbate NAFLD by causing lipid buildup and inflammation following hepatocyte endocytosis [112]. Besides, adipocyte-derived EVs deliver miR-122, which targets Sirt1 and suppresses its expression, thus increasing blood lipid levels, causing hepatocyte injury, and accelerating the progression of NAFLD [114]. Moreover, EVs derived from adipose tissue carry miR-103, which interacts with PTEN to inhibit hepatocyte autophagy, exacerbating liver injury, thereby promoting the development of NASH [115].

Notably, EVs released from ex vivo human subcutaneous and omental adipose tissue explants contain varying levels of MCP-1, interleukin-6, and macrophage migration inhibitory factor, which correlate with inconsistencies in AKT phosphorylation levels in hepatocytes, indicating that the impact of adipose-derived EVs on insulin signaling depends on their adipokine content [116]. The duration of HFD exposure may also influence the role of EVs. According to a study, hepatocytes are unaffected by adipose tissue-derived EVs from HFD-fed mice after 4 weeks, but lipid synthesis, insulin resistance,

inflammation, and ER stress are shown after 8 and 12 weeks, indicating that the severity of obesity affects the impact of EVs on hepatocytes [117].

Liver-derived EVs can also regulate energy metabolism in adipose tissue. Evidence shows that liver-derived EV-encapsulated miR-130a-3p can activate the AKT-AS160-GLUT4 signaling pathway in adipocytes through the inhibition of PHLPP2, thereby increasing glucose uptake and improving glucose intolerance [8]. In early-onset obese mice, hepatocyte-derived EVs enriched with miR-3075 downregulate fatty acid 2-hydroxylase (FA2H) expression, increasing insulin-stimulated AKT phosphorylation and improving insulin sensitivity and glucose uptake in adipocytes. In individuals with chronic obesity, however, this compensatory effect is lost [118]. Furthermore, transmembrane 4 L six family member 5 (TM4SF5) can bind to glucose transporter 1 to promote glucose uptake and glycolysis, and liver-derived sEVs containing TM4SF5 can target BAT for homeostatic glucose clearance [119].

In addition to regulating glucose homeostasis, liver-derived EVs may also have pathological effects on adipose tissue. Under conditions of lipid overload, the expression of geranylgeranyl diphosphate synthase in the liver is upregulated, modulating the secretion of miRNAs-containing hepatic EVs to promote lipid accumulation in adipocytes [120]. High-energy diet-induced obesity increases the triglyceride content in liver-derived EVs, promoting lipid accumulation and inflammatory gene expression in adipocytes, thereby exacerbating lipogenesis and adipocyte inflammation [121]. Numerous studies have demonstrated that EVs play significant roles in the adipose tissue-liver axis and are profoundly involved in the regulation of both the physiological and pathological states of the liver and adipose tissue (Fig. 5).

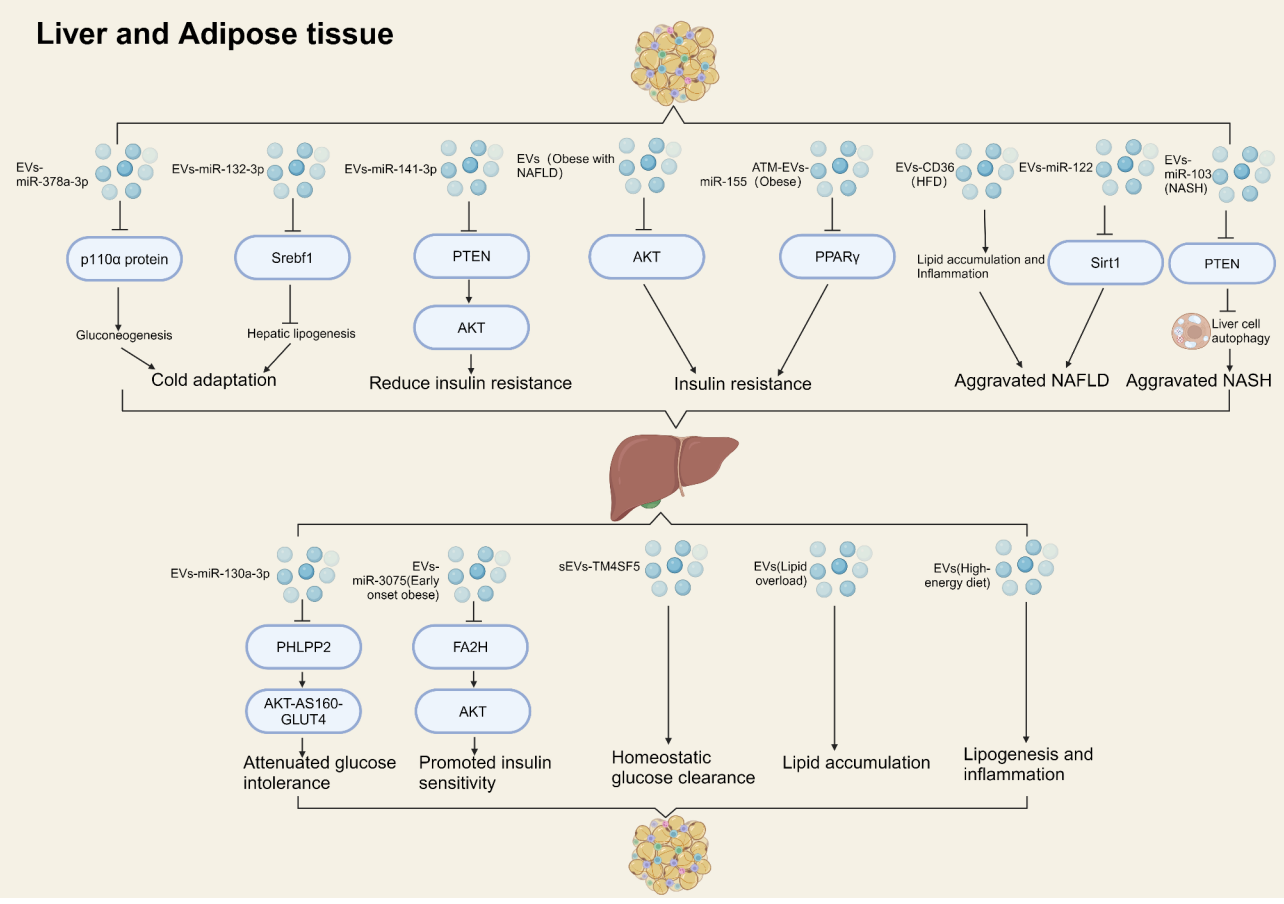


Fig. 5 Overview of the communication network between the liver and adipose tissue mediated by EVs.Adipose tissue secretes EVs that have an impact on insulin function, liver disorders, and cold acclimatization. EVs produced from the liver, in turn, have a role in controlling adipose tissue remodeling and glucose homeostasis. The relationship between EVs and metabolic balance as well as liver disorders is shown in the liver-adipose axis. Abbreviation: Srebf1: sterol regulatory element binding transcription factor 1; PTEN: phosphatase and tensin homolog deleted on chromosome 10; ATM: adipose tissue macrophage; PPARγ: peroxisome proliferator-activated receptor gamma; Sirt1: silent information regulator 1; NAFLD: nonalcoholic fatty liver disease; PHLPP2; PH domain and leucine rich repeat protein phosphatase 2; AS160: Akt substrate of 160 kDa; GLUT4: glucose transporter 4; TM4SF5: transmembrane 4 L six family member 5

Potential of EVs in disease treatment

EVs have garnered significant attention in therapeutic applications because of the favorable properties, such as stability, biocompatibility, and low immunogenicity [122]. Because of these qualities, EVs are attractive options for medication delivery systems [17]. Among the diverse types of EVs, those derived from mesenchymal stem cells (MSCs) have demonstrated significant potential in the treatment of a wide array of diseases [123]. Furthermore, potential strategies for EV-based therapies include targeting EV cargo for drug development, regulating EV secretion, and modifying their cargo and functions.

MSC-derived EVs

MSCs have demonstrated significant promise for tissue regeneration and repair, which are widely used in cell therapy. However, the limitations, such as therapeutic risks, reduced viability when stored at low temperatures, and high processing costs, have led researchers to focus on MSC-derived paracrine products, such as EVs [124]. MSC-derived EVs serve as a noninvasive, nontoxic, and low-immunogenic alternative for treating liver diseases [123]. Previously, we have found that MSC-EVs induced metabolic reprogramming of $CD4^+$ T cells by transferring mitochondrial components, thereby reducing T-cell overactivation and hepatic inflammatory injury, offering new ideas for the treatment of AIH [125]. Next, we will focus on the use of bone marrow mesenchymal stem cell-derived EVs (BMSC-EVs) and adipose mesenchymal stem cell-derived EVs (ADSC-EVs) in liver disease therapy.

BMSC- EVs

Liver fibrosis, a common complication of liver disease, has been a key target for novel therapies. BMSC-EVs enriched with miR-148a-5p have been shown to significantly alleviate liver fibrosis by inhibiting Smad4, resulting in downregulation of the mRNA and protein levels of transforming growth factor β(TGF-β)1, tissue inhibitor of metalloproteinase-1, collagen I, and α-smooth muscle actin [126]. In addition, BMSC-EVs mitigate fibrosis by preventing hepatocyte pyroptosis and promoting hepatocyte proliferation [127]. Notably, BMSC-EVs also suppress the Wnt/β-catenin signaling pathway, which lowers inflammatory cytokine levels in liver fibrosis models and prevents HSC activation, resulting in antifibrotic effects [128]. Furthermore, BMSC-EVs carrying miR-192-5p can inhibit PPP2R3A expression, which effectively prevents HSC activation and fibrosis progression [129].

In addition to the antifibrotic effects, BMSC-EVs have demonstrated therapeutic efficacy in various liver diseases. In ALF, BMSC-EVs reduce hepatocyte apoptosis by activating autophagy, decreasing the proapoptotic protein Bax, and increasing the antiapoptotic protein Bcl-2 [130]. BMSC-EVs carrying miR-136-5p alleviate chronic liver damage by promoting M2 macrophage polarization via the suppression of the GNAS-mediated PI3K/ERK/STAT3 axis [131]. Additionally, BMSC-EVs that include miR-146a-5p can activate intrinsic hepatocytic progenitor cells (HPCs) to aid in liver regeneration [132]. In AIH, BMSC-EVs containing miR-223 reduce NLRP3 and caspase-1 expression, decrease serum inflammatory cytokine levels, and ultimately ameliorate liver injury [133]. BMSC-EVs enriched with miR-25-3p inhibit PTEN expression, reduce p53 and cleaved caspase-3 levels, and lower serum ALT and AST levels, ultimately reducing apoptosis and alleviating HIRI [134].

In summary, BMSC-EVs exhibit multifunctional therapeutic potential for liver diseases, including alleviating fibrosis, improving chronic liver injury, promoting liver regeneration, and treating AIH. These findings provide new perspectives and possibilities for clinical practice.

ADSC-EVs

ADSC-EVs also exhibit promising potential in treating liver diseases. Research has demonstrated that ADSC-EVs can alleviate the process of hepatic fibrosis by inhibiting the PI3K/AKT/mTOR signaling pathway, decreasing the expression of fibrosis-related genes, and regulating choline metabolism [135]. Moreover, ADSC-EVs carrying miR-20a-5p downregulate transforming growth factor beta receptor 2 expression and suppress p38MAPK/NF−κB pathway activation, significantly reducing fibrosis markers and effectively controlling fibrosis progression. It leads to a significant reduction in fibrosis markers and effectively curbs the progression of fibrosis [136]. Notably, fibrotic tissues are characterized by decreased miR-150-5p and elevated CXC chemokine ligand-1 (CXCL1) levels. ADSC-EVs enriched with miR-150-5p can effectively inhibit CXCL1 expression, reduce TGF-β-induced HSC activation, and ultimately alleviate fibrosis [137].

ADSC-EVs also exhibit remarkable potential in alleviating HIRI. The mechanism of action involves multiple regulatory factors, including the stimulation of the Wnt/β-catenin pathway to promote hepatocyte proliferation and inhibition of the NF-κB pathway to reduce inflammation, thus alleviating HIRI-induced liver injury [138]. ADSC-EVs can also reduce hepatic endoplasmic reticulum stress (ERS) and alleviate histopathological damage and ultrastructural alterations in the ER by downregulating ERS-related factors [139]. Additionally, ADSC-EVs significantly increase the expression of the mitochondrial fusion proteins, promoting mitochondrial function recovery, increasing ATP content, and improving the hepatocyte mitochondrial ultrastructure [140]. ADSC-EVs can provide protection against HIRI-induced apoptosis by reducing caspase activity and regulating apoptosis-related factors [141], which may be a promising approach for HIRI treatment.

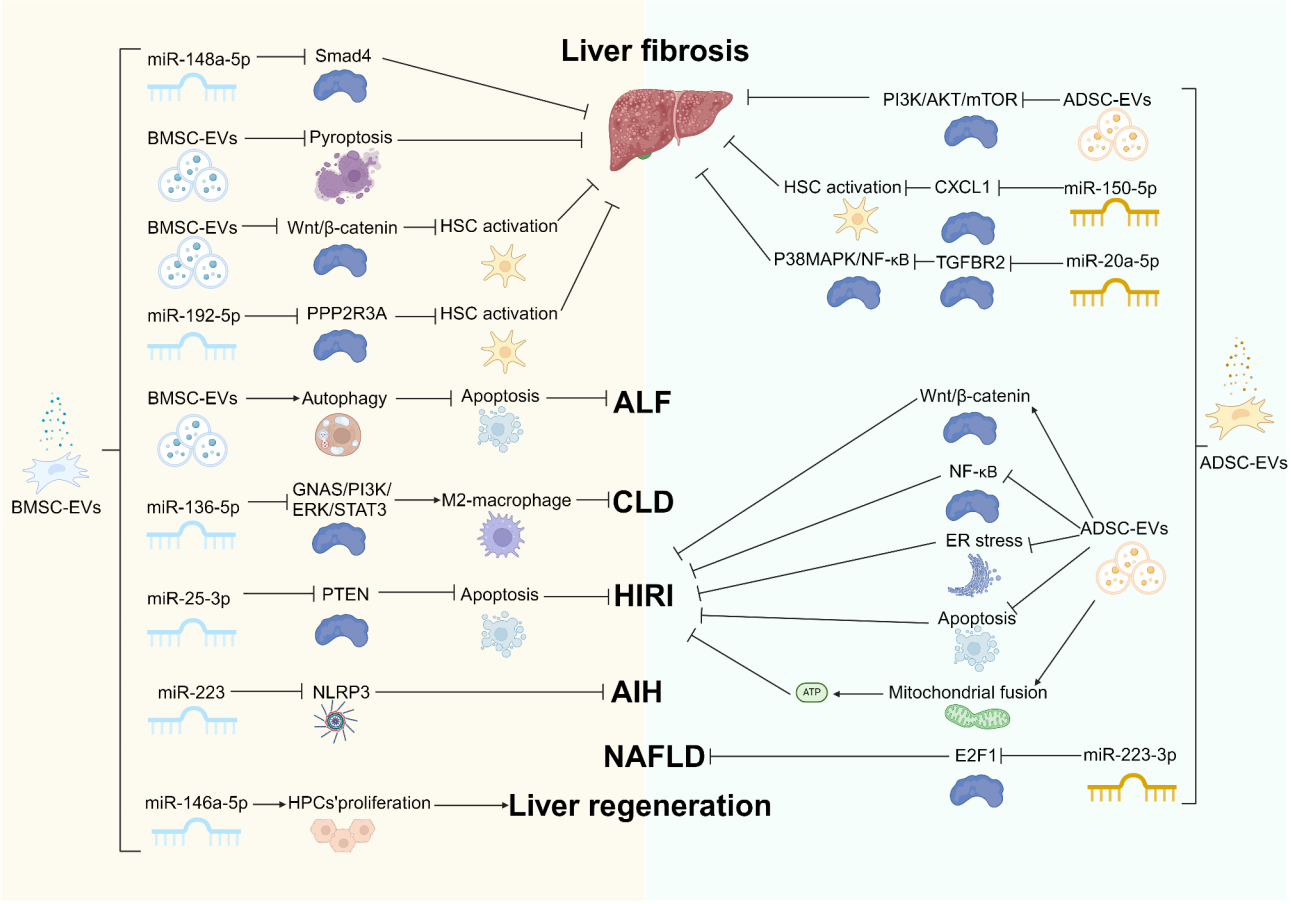


Fig. 6 Therapeutic effects of MSC-EVs on liver diseases. MSC-EVs carry a variety of bioactive molecules that target different molecular mechanisms to mitigate liver injury by inhibiting fibrosis, inflammatory responses, oxidative stress, and other pathological changes in the liver. Abbreviation: Smad4: smad family member 4; PPP2R3A: protein phosphatase 2 regulatory subunit B"alpha; GNAS: guanine nucleotide-binding protein, alpha stimulating; ERK: extracellular regulated protein kinases; STAT3: signal transducer and activator of transcription 3; VCAM-1: vascular cell adhesion molecule-1; CXCL1: CXC chemokine ligand-1; TGFBR2: transforming growth factor beta receptor 2; p38MAPK: p38 mitogen-activated protein kinase; E2F1:E2F transcription factor 1; ALF: acute liver failure; CLD: chronic liver damage; HIRI: hepatic ischemia–reperfusion injury; AIH: autoimmune hepatitis; NAFLD: nonalcoholic fatty liver disease; HPCs: hepatocytic progenitor cells

In addition, ADSC-EVs enriched with miR-223-3p inhibited E2F transcription factor 1 expression and reduced lipid buildup and fibrosis to delay the advancement of NAFLD [142]. Research has demonstrated that ADSC-EVs is a novel therapy for fibrosis with marked effects by signaling pathway regulation, gene expression modulation, and inflammation suppression. Moreover, ADSC-EVs show significant therapeutic efficacy in HIRI and hold some potential for treating other liver diseases, such as NAFLD, which may be new strategies for clinical applications (Fig. 6).

Development of targeted drugs against EVs

EVs are intriguing therapeutic targets for disease intervention in addition to being essential for interorgan communication. For example, infliximab targets TNF-α-enriched EVs derived from hyperammonemic rats, representing an innovative approach for alleviating neuromotor coordination disorders associated with hepatic encephalopathy [93]. Targeting factors such as LRG1 [67] and Fasn [68], which influence bone metabolism, may be effective therapeutic interventions for bone loss. Antagonists of miR-1 [11] and inhibitors of miR-30a-3p [12] have shown efficacy in preventing the progression of atherosclerosis, whereas inhibitors of novel-miR-7 have significantly improved endothelial barrier integrity [74]. Notably, miR-122 sponge therapy has been demonstrated to enhance cardiac mitochondrial function, paving the way for novel treatments for obesity-related cardiomyopathy [76]. Additionally, applications utilizing miR-122-5p have shown promise in tissue repair [78]. Moreover, miR-155 [111], miR-29s [89], and miR-126a-3p [90] are identified as "harmful factors", negatively impacting insulin function, whereas the delivery of miR-141-3p [108], miR-130a-3p [8], miR-3075 [118], and TM4SF5 [119] may present novel opportunities for

treating obesity or diabetes. Therefore, EVs show promising potential in therapeutic applications for various extrahepatic disorders, including bone metabolism, cardiovascular health, and energy metabolism (the remaining detailed targets are illustrated in Figs. 3, 4 and 5 and the corresponding sections). Future research into EV-targeted therapies is still in its nascent stages. The design of antagonist strategies that either load therapeutic agents or inhibit EV-mediated pathological effects on target organs will undoubtedly expand the applications of EVs in precision medicine, bringing new vitality and potential to the field.

Manipulating EV secretion, function, and cargo

Through their diverse and complex functions, EVs released by various cell types in both healthy and pathological settings have a substantial impact on the host. Research on controlling the mechanics of EV release has shown promise [143]. Environmental factors such as pH fluctuations and hypoxia can considerably impact EV formation and release [144]. Additionally, changes in nutrient composition can influence EV biogenesis and functional properties [145]. For example, pretreatment with quercetin has been found to promote miR-136-5p expression in BMSC-EVs, thereby activating the GNAS/PI3K/ERK/STAT3 signaling axis, reducing M1 macrophage polarization, alleviating liver inflammation, and ultimately improving liver function [146]. Similarly, BMSC-EVs triggered by lipopolysaccharide significantly attenuate septic liver injury by inhibiting macrophage STING signaling, which possibly was related to upregulated autophagy-related protein 2 homolog B in BMSC-EVs [147]. Engineered EVs, which are designed to enhance therapeutic outcomes through surface modifications and the loading of endogenous or exogenous substances, have emerged as an innovative strategy for improving treatment efficacy [148]. Current approaches to engineering EVs include cargo loading, surface modification, and genetic engineering [149]. For example, MSCs transduced with lentivirus-mediated hepatocyte growth factor produce EVs that exert hepatoprotective effects by alleviating liver fibrosis and restoring liver function [150]. Additionally, loading quercetin and vitamin A onto ADSC-EVs has been shown to increase their therapeutic efficacy and liver-targeting ability, mitigating the rapid senescence-like response induced by acute liver injury [151].

Park JH outlined the directions and challenges of EVs as nanomedicines, covering the three dimensions of improving the targeting of therapeutic EVs, controlling pathological EVs by inhibiting EV biogenesis in disease-associated cells, removing circulating EVs, and preventing the uptake of EVs by target cells [152]. Whether they focus on the targeting strategies and effectiveness of therapeutic EVs or control them by targeting the biogenesis and action pathways of pathological EVs, the realization of these optimization measures is highly valuable for promoting the applied research of EVs in the field of disease treatment (Fig. 7).

Challenges and prospects EV-Mediated interorganism communication networks

Nearly all bodily fluids include EVs, which are crucial for facilitating interorgan communication through fluid transfer [63]. However, the EV-mediated complete communication network between the liver and other organs remains unclear. CX3C-chemokine ligand 1 and CX3C-chemokine receptor 1(CX3CR1) are critical for regulating liver inflammation and fibrosis [153]. HAN C et al. found that CX3CR1 monocytes with a classical phenotype moved to the fibrotic liver from the spleen. They worsen liver fibrosis through the release of cytokines and alter the migratory patterns of hepatic endogenous $CX3CR1^{GFP}$ cells [154]. Furthermore, $CD11b^{+}CD43^{hi}Ly6C^{lo}$ splenic monocytes migrate to the liver and acquire macrophage phenotype, which accelerates fibrosis progression [155]. These findings highlight the close interrelationship between the liver and spleen.

Research has also suggested a link between liver function and ocular health. According to reports, retinitis pigmentosa-induced retinal stress may interfere with the melanosystem or the exit of soluble macromolecules from the retina, resulting in liver oxidative stress [156]. Patients with liver disease often experience abnormal skin conditions, including palmar erythema and spider angiomas [157]. Notably, psoriasis patients have a higher risk of developing NAFLD [158]. Moreover, AIH may be related to alopecia areata, psoriasis, and pyoderma gangrenosum [159]. The relationship between the liver and muscle has received more attention lately. A recent study has demonstrated that the expression of interferon regulatory factor 4 (IRF4) is markedly upregulated in the skeletal muscle of mice with NASH. IRF4 transcriptionally modulates follistatin-like protein 1, which could be a critical factor in the pathophysiology of NASH [160]. On the other hand, liver-derived fibroblast growth factor 21 has been shown to impair muscle regeneration by inhibiting the PI3K/AKT pathway, suggesting a new therapeutic strategy for decompensated cirrhosis-related sarcopenia [161]. In summary, it is worthwhile to investigate whether EVs, as new mediators of interorgan communication, have a significant regulatory function in the connections between the liver and other organs (such as the spleen, eye, skin, and muscle).

The role of EVs in the propagation of disease phenotypes across organ tissues and individuals is also of interest. Intravenous injection of EVs from the serum of patients with Behçet's syndrome (BS) into healthy mice

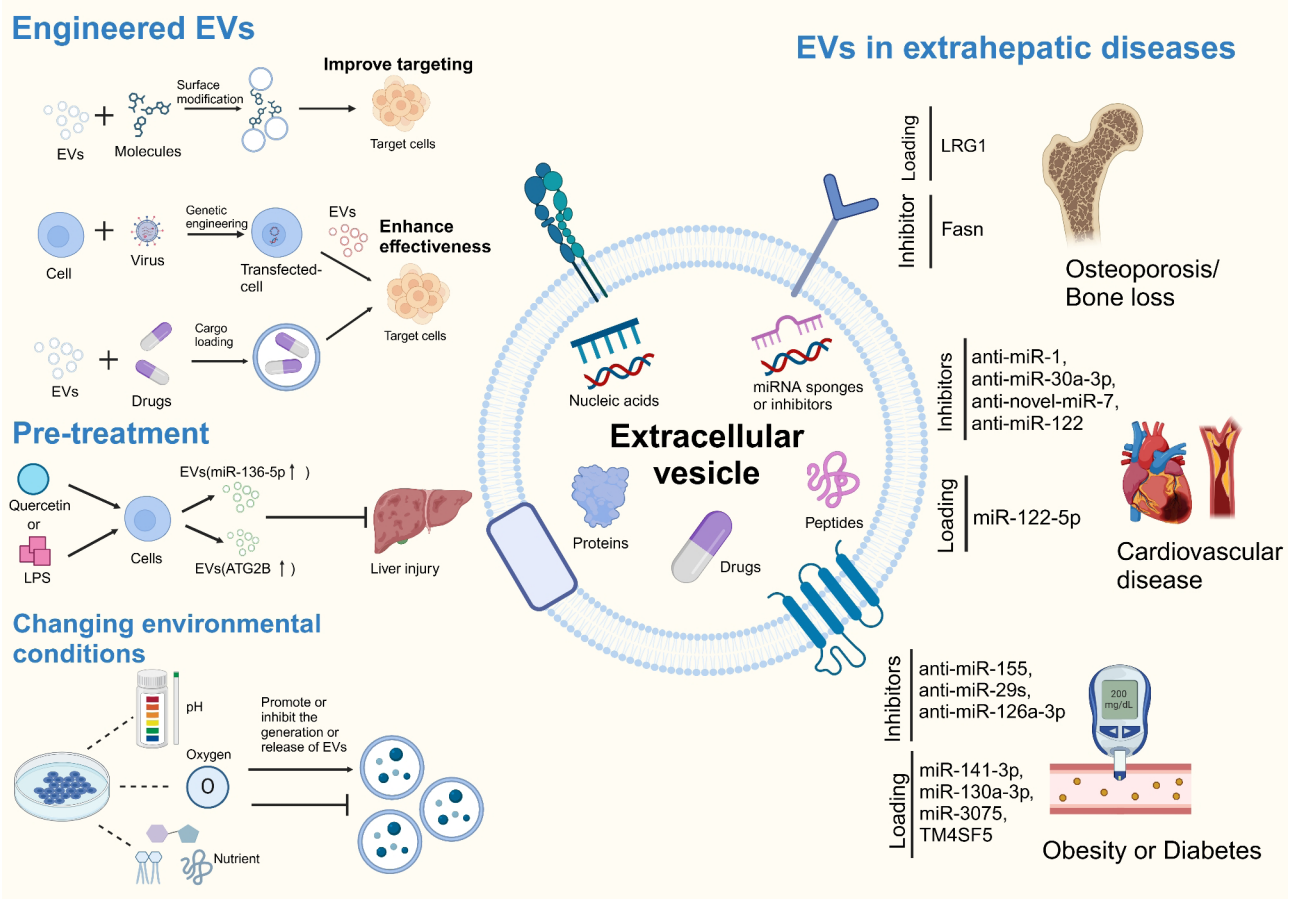


Fig. 7 Therapeutic strategies involving EVs. For EVs, we can design specific drugs or inhibitors to block the signaling of disease-causing molecules or load components with therapeutic effects. Moreover, pretreatment of EV-producing cells can also produce unexpected results. Engineered EVs, which take three main approaches: cargo loading, surface modification, and genetic engineering to improve the targeting and efficacy of EVs, are the new solutions for optimizing therapeutic treatments nowadays. In addition, different environments can regulate the biogenesis and function of EVs, which provides new ideas for enhancing the yield and quality of therapeutic EVs and inhibiting the secretion of pathological EVs. Abbreviations: ATG2B: autophagy-related protein 2 homolog B. LPS: lipopolysaccharide

caused significant inflammatory cell infiltration at the injection site, resulting in a pathological inflammatory response similar to BS symptoms. This experimental evidence strongly underscores the vital role of EVs in the propagation and exacerbation of inflammation [162]. Similarly, healthy human hepatocytes with gut microbial EVs derived from obese hosts enhance inflammatory responses [83]. EVs from individuals with insulin resistance carry phosphotyrosine 1 phosphatase and protein phosphatase 2, which impair insulin signaling in adipose tissue, liver, and systemic tissues after injection into healthy mice [163]. It is fascinating to consider whether EVs could potentially play a critical role in transmitting disease phenotypes across individuals, organs, and tissues in a broader spectrum of diseases and organ interactions.

Current research on EVs mediating interorgan communication remains deficient. Previous research has mostly concentrated on how miRNAs transported by EVs control both physiological and pathological activities in different organs. However, EVs are highly heterogeneous and served as multifunctional messengers that carry various biomolecules [17]. It is worth investigating whether EVs release a wider range of substances, not just limited to miRNAs, that work in concert with target organs to drive and facilitate disease progression. Furthermore, it is worth noting that a number of existing researches heavily rely on in vitro cell culture models or animal models. While these models serve as valuable tools for gaining preliminary understanding of underlying mechanisms, they fail to fully encompass the intricacies and complexities seen in human physiological environments. The limitation not only restricts the breadth and depth of research but also hinders the translation of findings into clinical applications. Addressing these limitations and pursuing deeper insights are essential tasks for future research in the field.

Current and future perspectives on EVs

EVs exhibit substantial potential for applications in the medical field. As drug delivery vehicles, EVs possess numerous advantages and can be loaded with therapeutic agents through various methods to treat diseases. Additionally, EVs serve as valuable biomarkers for disease diagnosis, as their contents reflect cellular states, aiding in early disease detection. Furthermore, EVs play a crucial role in targeted therapies by enabling surface modifications that enhance their targeting specificity, thereby effectively treating a wide range of diseases [164].

Preclinical studies are indispensable for advancing the clinical application of EVs. Researchers investigate the pharmacokinetics of EVs through cell and animal studies to further evaluate the efficacy and safety of EV-based products [165]. Clinical trials involving EVs are currently underway. In diagnostics, EVs are predominantly utilized for cancer-related applications; in therapeutics, most trials employ EVs derived from MSCs, with a few utilizing engineered EVs. Additionally, there are ongoing clinical trials exploring the efficacy of incorporating other therapeutic agents into EVs [166].

As a minimally invasive tool, liquid biopsy represents an emerging field currently utilized in the diagnosis and treatment of diseases. EVs present in human body fluids carry a diverse array of bioactive molecules and contain a wealth of information, making them ideal targets for liquid biopsy [167]. The application of liquid biopsy for detecting EVs holds significant value in disease diagnosis, treatment, and prognosis [165, 167].

As research on EVs advances, novel applications and capabilities are continually being demonstrated. However, the field is also encountering several challenges during its development. Addressing these challenges will be crucial for the continued advancement of the EV field.

Currently, EVs are mainly categorized into cell culture-derived EVs, fluid-derived EVs, and tissue-derived EVs (Ti-EVs). The first two categories constitute the main focus of current EV research [168]. However, Ti-EVs offer a more accurate depiction of the pathophysiological characteristics and cellular behavior, with minimal contamination, thereby providing a distinct advantage for elucidating disease progression [168]. Additionally, the development of appropriate models for real-time tracking of endogenous EVs in vivo could provide valuable insights into the long-distance communication networks mediated by EVs across organs. This would be of significant scientific value in elucidating the complex dynamics between liver and extrahepatic diseases [169].

Second, unique combinations of size, origin, and surface markers impart distinctive characteristics to EV subpopulations, contributing to their high heterogeneity [170]. The insufficient knowledge of specific EV markers hinders the ability to distinguish them from EVs already present in the body, whether derived from parental or normal cells. This limitation makes it challenging to achieve therapeutic goals by blocking the biogenesis and uptake of pathological EVs [152]. A better understanding of EV heterogeneity is becoming increasingly important for recognizing the critical role in health and disease [171]. As a high-throughput method, the proximity barcoding assay can identify the protein composition on individual EV surfaces, offering a novel technique for resolving EV heterogeneity [172]. This method facilitates comparisons of EV heterogeneity across different sources [173] and contributes to the development of disease biomarkers [174, 175]. Therefore, employing advanced technologies to identify heterogeneous EV subgroups originating from various organs and cell lineages will significantly enhance our comprehension of EV functions in disease progression.

Third, due to their distinct biological characteristics, EVs hold immense promise as novel therapeutic tools, in addition to serving as essential mediators of intercellular communication and carriers of vital signals [176]. However, the heterogeneity of EVs poses significant challenges, including the lack of standardized techniques for isolating EV subpopulations. Existing methods are often limited in terms of efficiency and purity, necessitating an ideal solution that combines simplicity, cost-effectiveness, and high efficiency to bridge this technological gap [177]. Moreover, while various modalities such as electroporation and sonication have been developed, the efficiency of drug loading into EVs remains suboptimal [178]. Furthermore, the absence of clinical-grade production capabilities constitutes a significant barrier to the translation of EV research from laboratory settings to clinical applications [179]. Consequently, researchers have explored several strategies to enhance EV secretion, including donor cell optimization and the use of bioreactors, which offer innovative approaches to scaling up EV production [180]. Addressing these issues is imperative for advancing the therapeutic application of EVs.

Summary

EV-mediated bidirectional communication between the liver and other organs is crucial for maintaining systemic homeostasis. In this review, we highlight the biological characteristics of EVs, summarize the involvement in physiological and pathological processes that mediate interactions between the liver and various organs (as detailed in Table 2), and discuss the therapeutic potential, as well as the challenges facing this field. Current research on the mechanisms of EV-mediated interactions between the liver and multiorgan systems is progressing rapidly. However, the exploration in this field is still far from exhaustive, and a deeper understanding may lie in the intricate details of EV biology.

Table 2 EV-mediated communication between the liver and other organs

EV cargo	Source	Target	(Disease) Model	Effect or Mechanism	Reference
Group 1					
HSP70	Bone	Liver	Liver ischemia-reperfusion	Treat liver damage by controlling the ratio of Th17 cells to Tregs through the PI3K/mTOR axis	[70]
Unknown	Bone	Liver	Periodontitis	Enhance SCD-1 expression and suppress AMPK signaling pathway, exacerbating fatty liver	[71]
LRG1	Liver	Bone	SIRT2 deficiency	Reduce NF-κB p65 nuclear translocation and inhibit osteoclast differentiation, which reduce bone loss	[67]
Fasn	Liver	Bone	Type 2 diabetes	Increase ectopic fatty acid synthesis in PDLCs, activate NLRP3 inflammasome, and induce GSDMD cleavage, which lead to PDLCs pyroptosis and thus exacerbate bone loss	[68]
Unknown	Liver	Bone	Mandibular defect	Increase osteogenesis-related gene expression in mandibular mesenchymal stem cells, which promote mandibular healing	[69]
Group 2					
miR-1	Liver	Cardiovascular system	ApoE$^{-/-}$ mice, HFD	Promote atherosclerosis by inhibiting KLF4 and activating NF-κB	[11]
miR-30a-3p	Liver	Cardiovascular system	High-fat, high-cholesterol diet-fed ApoE$^{-/-}$ mice	Promote foam cell formation and atherosclerosis by inhibiting ABCA1-mediated cholesterol efflux	[12]
novel-miR-7	Liver	Cardiovascular system	NAFLD	Increase endothelial permeability by targeting the LAMP1/Cathepsin B/NLRP3 inflammasome axis	[74]
miR-122-5p	Liver	Cardiovascular system	Exercise	Enhance endothelial fatty acid oxidation by downregulating AGPAT1, which promote angiogenesis and wound healing	[78]
miR-122	Liver	Cardiovascular system	Obesity	Promote obesity-related cardiomyopathy progression by inhibiting Arl-2 to impair mitochondrial function	[76]
Group 3					
Unknown	Gut	Liver	HFD/CCl4-induced liver injury	Inhibit HSCs activation and reduce fibrosis marker gene expression	[6]
Unknown	Gut	Liver	NASH	Exacerbate liver damage by activateing HSCs, which involved in fibrosis progression, and impairing hepatocyte integrity	[84]
Unknown	Gut	Liver	HFD/CCL4-induced liver injury	Inhibit TLR expression and upregulate PPAR to exert anti-inflammatory effects	[7]
Microbial DNA	Gut	Liver	HFD	Activate cGAS/STING pathway to enhance inflammation and impair insulin sensitivity	[83]
Unknown	Gut	Liver	Diet-induced obesity	May promote liver inflammation via TLR4-mediated signaling	[85]
Unknown	Gut	Liver	Gut ischemia-reperfusion	Cause liver damage by polarizing Kupffer cells toward M1 and increasing pro-inflammatory cytokine mRNA expression	[82]
HMGB1	Gut	Liver	HFD	Trigger hepatic steatosis	[87]
Group 4					
miR-29s	Pancreas	Liver	HFD	Reduce AKT phosphorylation induced by insulin, leading to systemic insulin resistance	[89]
Unknown	Liver	Pancreas	Insulin resistance	Regulate glucose homeostasis by increasing insulin gene expression and AKT phosphorylation	[9]
miR-126a-3p	Liver	Pancreas	Diet-induced obesity	Possibly exacerbate diabetes by promoting β-cell apoptosis through inhibition of IRS2 expression	[90]
Group 5					
TNF-α	Liver	Brain	Hyperammonemia	Induce motor incoordination by activating TNFR1-CCL2-BDNF-TrkB-KCC2 and TNFR1-NF-κB-glutaminase-GAT3 pathways	[93]
ApoE4	Liver	Brain	Age-related thyroid deficiency	Increase cholesterol in neurons, trigger ROS elevation, which activate NLRP3 inflammasome, leading to cognitive, motor, and emotional impairments	[94]
miR-143-3p	Pituitary	Liver	—	Promote hepatocyte proliferation by downregulating IGFBP5 to increase IGF-1 expression and activating Wnt/β-catenin pathway	[96]

Table 2 (continued)

EV cargo	Source	Target	(Disease) Model	Effect or Mechanism	Reference
Unknown	Brain	Liver	Traumatic brain injury	Elevate serum AST and ALT levels, cause histopathological changes in liver, and ultimately induce hepatocyte apoptosis	[95]
Group 6					
miR-194	Liver	Lung	Hepatopulmonary syndrome(HPS)	Likely promote angiogenesis by targeting THBS1, STAT1, and LIF, which worsen HPS	[99]
miR-122-5p	Liver	Lung	Liver ischemia-reperfusion	Cause acute lung injury by inhibiting SOCS-1 expression and activating NF-κB to promote inflammation and M1 macrophage polarization	[101]
Unknown	Liver	Lung	Acute pancreatitis	Increase expression of pro-inflammatory factors to promote lung inflammation	[102]
Group 7					
miR-687	Kidney	Liver	Kidney ischemia-reperfusion	Promote liver inflammation and apoptosis, which cause liver injury	[10]
Group 8					
miR-378a-3p	Adipose	Liver	Cold exposure	Promote gluconeogenesis by targeting p110α and downregulating AKT phosphorylation	[106]
miR-141-3p	Adipose	Liver	Obesity	Increase AKT phosphorylation levels by downregulating PTEN, leading to increased insulin sensitivity	[108]
Unknown	Adipose	Liver	Obesity with NAFLD	Downregulate AKT phosphorylation, which causes insulin resistance	[109]
miR-155	Adipose	Liver	Obesity	Inhibit PPARγ to reduce insulin-induced AKT phosphorylation, leading to insulin resistance	[111]
CD36	Adipose	Liver	HFD	Induction of lipid accumulation and inflammation leading to exacerbation of NAFLD	[112]
miR-122	Adipose	Liver	NAFLD	Enhance glucose and lipid metabolism by inhibiting Sirt1 expression, which worsen liver injury	[114]
miR-132-3p	Adipose	Liver	Cold exposure	Suppresse hepatic Srebf1 expression in order to reduce hepatic lipogenesis for cold adaptation	[107]
miR-103	Adipose	Liver	NASH	Interact with PTEN to inhibit hepatocyte autophagy so that involve in NASH progression	[115]
miR-130a-3p	Liver	Adipose	High-fat diet-fed miR-130a knockout or overexpression mice	Improve glucose intolerance by inhibiting PHLPP2 to activate AKT-AS160-GLUT4 pathway	[8]
miRNAs	Liver	Adipose	HFD	Increase lipid production to remodel adipose tissue	[120]
miR-3075	Liver	Adipose	Early-onset obesity	Downregulation of FA2H expression results in higher levels of insulin-stimulated AKT phosphorylation, which in turn increases glucose uptake to exert a compensatory effect	[118]
TM4SF5	Liver	Adipose	TM4SF5 knockout or overexpression	Improve glucose tolerance and maintain glucose homeostasis	[119]
Unknown	Liver	Adipose	High-energy diet	Aggravate adipocyte inflammation and lipid accumulation	[121]

With advancements in research, we anticipate revealing how EVs cross physiological barriers to establish sophisticated interorgan communication networks and how they serve as crucial mediators in the propagation of pathological phenotypes among different organs under disease conditions. The studies will provide significant insights into the multifaceted processes of understanding complex diseases, while also opening the door to a new era of precision therapeutic treatments and customized medicine.

Abbreviations

EVs	Extracellular vesicles
ILVs	Intraluminal vesicles
MVBs	Multivesicular bodies
ESEs	Early sorting endosomes
ESCRT	Endosomal sorting complex required for transport
MVs	Microvesicles
ROCK	Rho-associated protein kinase
LIMK	LIM domain kinase
ERK	Extracellular signal-regulated kinase
TSG101	Tumor susceptibility gene 101
AVD	Apoptotic volume reduction
PANX1	Pannexin 1
DC	Dendritic cell
TGF-β	Transforming growth factor β
I/R	Ischemia-reperfusion
HIRI	Hepatic ischemia-reperfusion injure
DIO	Diet-induced obese
TNF-α	Tumor necrosis factor-alpha
ApoE4	Apolipoprotein E4
HPS	Hepatopulmonary syndrome
ALF	Acute liver failure
AIH	Autoimmune hepatitis
MCP-1	Monocyte chemotactic protein-1
PMVEC	Pulmonary microvascular endothelial cell

BAT	Brown adipose tissue
HSP70	Heat shock protein 70
Th17	T helper 17 cell
Treg	Regulatory T-cell
PI3K/mTOR	Phosphoinositide 3-kinase/mammalian target of rapamycin
SCD-1	Stearoyl-CoA desaturase 1
AMPK	Adenosine monophosphate (AMP)-activated protein kinase
NF-κB	Nuclear factor κB
LRG1	Leucine-rich alpha-2-glycoprotein 1
SIRT2	Sirtuin 2
PDLCs	Periodontal ligament cells
NLRP3	NOD-like receptor pyrin domain-containing protein 3
Fasn	Fatty acid synthase
GSDMD	Gasdermin D
KLF4	Kruppel-like factor 4
HFD	High-fat diet
ABCA1	ATP-binding cassette transporter A1
LAMP1	Lysosomal-associated membrane protein 1
AGPAT1	1-acyl-sn-glycerol-3-phosphate acyltransferase
Arl2	ADP-ribosylation factor-like protein 2
HSC	Hepatic stellate cell
NASH	Nonalcoholic steatohepatitis
TLR	Toll-like receptor
PPAR	Peroxisome proliferator-activated receptor
cGAS	cyclic GMP–AMP synthase
STING	Stimulator of interferon genes
HMGB1	High-mobility group box protein 1
miR-29s	miR-29 family
AKT	Protein kinase B
IRS2	Insulin receptor substrate-2
TNFR1	Tumor necrosis factor receptor-1
CCL2	C-C motif chemokine 2
BDNF	Brain-derived neurotrophic factor
TrkB	Tropomyosin-related kinase B
KCC2	K-Cl cotransporter 2
GAT3	GABA transporter type 3
sEVs	small extracellular vesicles
ROS	Reactive oxygen species
IGFBP5	Insulin-like growth factor-binding protein 5
IGF-1	Insulin-like growth factor 1
Wnt	Wingless-related integration site
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
THBS1	Thrombospondin 1
STAT1	Signal transducerand activator of transcription 1
LIF	Leukemia inhibitory factor
SOCS-1	Suppressor of cytokine signaling 1
PTEN	Phosphatase and tensin homolog deleted on chromosome 10
ATMs	Adipose tissue macrophages
ATM-EVs	Adipose tissue macrophages-derived extracellular vesicles
WAT	White adipose tissue
PPARγ	Peroxisome proliferator-activated receptor gamma
NAFLD	Nonalcoholic fatty liver disease
Sirt1	Silent information regulator 1
Srebf1	Sterol regulatory element binding transcription factor 1
PHLPP2	PH domain and leucine rich repeat protein phosphatase 2
AS160	Akt substrate of 160 kDa
GLUT4	Glucose transporter 4
FA2H	Fatty acid 2-hydroxylase
TM4SF5	Transmembrane 4 L six family member 5
MSC	Mesenchymal stem cell
BMSC-EVs	Bone marrow mesenchymal stem cell-derived extracellular vesicles
ADSC-EVs	Adipose mesenchymal stem cell-derived extracellular vesicles
HPCs	Hepatocytic progenitor cells
Smad4	Smad family member 4
STAT3	Signal transducer and activator of transcription 3
PPP2R3A	Protein phosphatase 2 regulatory subunit B"alpha
GNAS	Guanine nucleotide-binding protein, alpha stimulating
VCAM-1	Vascular cell adhesion molecule-1
TGFBR2	Transforming growth factor beta receptor 2
p38MAPK	p38 mitogen-activated protein kinase
CXCL1	CXC chemokine ligand-1
ERS	Endoplasmic reticulum stress
CX3CR1	CX3C-chemokine receptor 1
IRF	Interferon regulatory factor
BS	Behçet's syndrome
Ti-EVs	Tissue-derived EVs

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W.M. and Y.P. contributed equally to this work. Writing—original draft: W.M. and Y.P. Conceptualization: W.M., Y.P. and Y.Z. Visualization: W.M., Y.P. and S.Z. Writing—review and editing: X.F. and L.D. All authors contributed to data interpretation and manuscript editing work.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

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Competing interests
The authors declare no competing interests.

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References

1. Castillo-Armengol J, Fajas L, Lopez-Mejia IC. Inter-organ communication: a gatekeeper for metabolic health. EMBO Rep. 2019;20:e47903.
2. Du Y, Wu L, Wang L, Reiter RJ, Lip GYH, Ren J. Extracellular vesicles in cardiovascular diseases: from pathophysiology to diagnosis and therapy. Cytokine Growth Factor Rev. 2023;74:40–55.
3. Hu S, Hu Y, Yan W. Extracellular vesicle-mediated interorgan communication in metabolic diseases. Trends Endocrinol Metab. 2023;34:571–82.
4. Takahashi Y, Takakura Y. Extracellular vesicle-based therapeutics: extracellular vesicles as therapeutic targets and agents. Pharmacol Ther. 2023;242:108352.
5. Cheng ML, Nakib D, Perciani CT, MacParland SA. The immune niche of the liver. Clin Sci (Lond). 2021;135:2445–66.
6. Keshavarz Azizi Raftar S, Ashrafian F, Yadegar A, Lari A, Moradi HR, Shahriary A, Azimirad M, Alavifard H, Mohsenifar Z, Davari M, et al. The protective effects of live and pasteurized Akkermansia muciniphila and its extracellular vesicles against HFD/CCl4-Induced liver injury. Microbiol Spectr. 2021;9:e0048421.
7. Raftar SKA, Ashrafian F, Abdollahiyan S, Yadegar A, Moradi HR, Masoumi M, Vaziri F, Moshiri A, Siadat SD, Zali MR. The anti-inflammatory effects of Akkermansia muciniphila and its derivates in HFD/CCL4-induced murine model of liver injury. Sci Rep. 2022;12:2453.

8. Wu J, Dong T, Chen T, Sun J, Luo J, He J, Wei L, Zeng B, Zhang H, Li W, et al. Hepatic exosome-derived miR-130a-3p attenuates glucose intolerance via suppressing PHLPP2 gene in adipocyte. Metabolism. 2020;103:154006.
9. Mahmoudi-Aznaveh A, Tavoosidana G, Najmabadi H, Azizi Z, Ardestani A. The liver-derived exosomes stimulate insulin gene expression in pancreatic beta cells under condition of insulin resistance. Front Endocrinol (Lausanne). 2023;14:1303930.
10. Ashour H, Rashed L, Elkordy MA, Abdelwahed OM. Remote liver injury following acute renal ischaemia-reperfusion: involvement of Circulating Exosomal miR-687 and regulation by thymoquinone. Exp Physiol. 2021;106:2262–75.
11. Jiang F, Chen Q, Wang W, Ling Y, Yan Y, Xia P. Hepatocyte-derived extracellular vesicles promote endothelial inflammation and atherogenesis via microRNA-1. J Hepatol. 2020;72:156–66.
12. Chen X, Chen S, Pang J, Huang R, You Y, Zhang H, Xiao J, Xue H, Ling W. Hepatic steatosis aggravates atherosclerosis via small extracellular vesicle-mediated Inhibition of cellular cholesterol efflux. J Hepatol. 2023;79:1491–501.
13. van Niel G, D'Angelo G, Raposo G. Shedding light on the cell biology of extracellular vesicles. Nat Rev Mol Cell Biol. 2018;19:213–28.
14. Welsh JA, Goberdhan DCI, O'Driscoll L, Buzas EI, Blenkiron C, Bussolati B, Cai H, Di Vizio D, Driedonks TAP, Erdbrügger U, et al. Minimal information for studies of extracellular vesicles (MISEV2023): from basic to advanced approaches. J Extracell Vesicles. 2024;13:e12404.
15. Liu YJ, Wang C. A review of the regulatory mechanisms of extracellular vesicles-mediated intercellular communication. Cell Commun Signal. 2023;21:77.
16. Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes. Science. 2020;367:eaau6977.
17. Gurunathan S, Kang MH, Qasim M, Khan K, Kim JH, Biogenesis. Membrane trafficking, functions, and next generation nanotherapeutics medicine of extracellular vesicles. Int J Nanomed. 2021;16:3357–83.
18. Robbins PD, Morelli AE. Regulation of immune responses by extracellular vesicles. Nat Rev Immunol. 2014;14:195–208.
19. Wei G, Li C, Jia X, Xie J, Tang Z, Jin M, Chen Q, Sun Y, He S, Li X, et al. Extracellular vesicle-derived CircWhsc1 promotes cardiomyocyte proliferation and heart repair by activating TRIM59/STAT3/Cyclin B2 pathway. J Adv Res. 2023;53:199–218.
20. Takasugi M, Okada R, Takahashi A, Virya Chen D, Watanabe S, Hara E. Small extracellular vesicles secreted from senescent cells promote cancer cell proliferation through EphA2. Nat Commun. 2017;8:15729.
21. Stronati E, Conti R, Cacci E, Cardarelli S, Biagioni S, Poiana G. Extracellular Vesicle-Induced differentiation of neural stem progenitor cells. Int J Mol Sci. 2019;20:3691.
22. Takeda YS, Xu Q. Neuronal differentiation of human mesenchymal stem cells using exosomes derived from differentiating neuronal cells. PLoS ONE. 2015;10:e0135111.
23. Ferraz M, Carothers A, Dahal R, Noonan MJ, Songsasen N. Oviductal extracellular vesicles interact with the spermatozoon's head and mid-piece and improves its motility and fertilizing ability in the domestic Cat. Sci Rep. 2019;9:9484.
24. Silva TA, Smuczek B, Valadão IC, Dzik LM, Iglesia RP, Cruz MC, Zelanis A, de Siqueira AS, Serrano SM, Goldberg GS, et al. AHNAK enables mammary carcinoma cells to produce extracellular vesicles that increase neighboring fibroblast cell motility. Oncotarget. 2016;7:49998–50016.
25. Brena D, Huang MB, Bond V. Extracellular vesicle-mediated transport: reprogramming a tumor microenvironment conducive with breast cancer progression and metastasis. Transl Oncol. 2022;15:101286.
26. Parayath NN, Padmakumar S, Amiji MM. Extracellular vesicle-mediated nucleic acid transfer and reprogramming in the tumor microenvironment. Cancer Lett. 2020;482:33–43.
27. Zhang Y, Liu Y, Liu H, Tang WH. Exosomes: biogenesis, biologic function and clinical potential. Cell Biosci. 2019;9:19.
28. Kobayashi H, Tanaka N, Asao H, Miura S, Kyuuma M, Semura K, Ishii N, Sugamura K. Hrs, a mammalian master molecule in vesicular transport and protein sorting, suppresses the degradation of ESCRT proteins signal transducing adaptor molecule 1 and 2. J Biol Chem. 2005;280:10468–77.
29. Henne WM, Buchkovich NJ, Emr SD. The ESCRT pathway. Dev Cell. 2011;21:77–91.
30. McGough IJ, Vincent JP. Exosomes in developmental signalling. Development. 2016;143:2482–93.
31. Wollert T, Wunder C, Lippincott-Schwartz J, Hurley JH. Membrane scission by the ESCRT-III complex. Nature. 2009;458:172–7.
32. Trajkovic K, Hsu C, Chiantia S, Rajendran L, Wenzel D, Wieland F, Schwille P, Brügger B, Simons M. Ceramide triggers budding of exosome vesicles into multivesicular endosomes. Science. 2008;319:1244–7.
33. van Niel G, Charrin S, Simoes S, Romao M, Rochin L, Saftig P, Marks MS, Rubinstein E, Raposo G. The tetraspanin CD63 regulates ESCRT-independent and -dependent endosomal sorting during melanogenesis. Dev Cell. 2011;21:708–21.
34. Minciacchi VR, Freeman MR, Di Vizio D. Extracellular vesicles in cancer: exosomes, microvesicles and the emerging role of large oncosomes. Semin Cell Dev Biol. 2015;40:41–51.
35. Piccin A, Murphy WG, Smith OP. Circulating microparticles: pathophysiology and clinical implications. Blood Rev. 2007;21:157–71.
36. Lima LG, Chammas R, Monteiro RQ, Moreira ME, Barcinski MA. Tumor-derived microvesicles modulate the establishment of metastatic melanoma in a phosphatidylserine-dependent manner. Cancer Lett. 2009;283:168–75.
37. Del Conde I, Shrimpton CN, Thiagarajan P, López JA. Tissue-factor-bearing microvesicles arise from lipid rafts and fuse with activated platelets to initiate coagulation. Blood. 2005;106:1604–11.
38. Budnik V, Ruiz-Cañada C, Wendler F. Extracellular vesicles round off communication in the nervous system. Nat Rev Neurosci. 2016;17:160–72.
39. Li B, Antonyak MA, Zhang J, Cerione RA. RhoA triggers a specific signaling pathway that generates transforming microvesicles in cancer cells. Oncogene. 2012;31:4740–9.
40. D'Souza-Schorey C, Chavrier P. ARF proteins: roles in membrane traffic and beyond. Nat Rev Mol Cell Biol. 2006;7:347–58.
41. Muralidharan-Chari V, Clancy J, Plou C, Romao M, Chavrier P, Raposo G. D'Souza-Schorey C. ARF6-regulated shedding of tumor cell-derived plasma membrane microvesicles. Curr Biol. 2009;19:1875–85.
42. Nabhan JF, Hu R, Oh RS, Cohen SN, Lu Q. Formation and release of arrestin domain-containing protein 1-mediated microvesicles (ARMMs) at plasma membrane by recruitment of TSG101 protein. Proc Natl Acad Sci U S A. 2012;109:4146–51.
43. Battistelli M, Falcieri E. Apoptotic bodies: particular extracellular vesicles involved in intercellular communication. Biology (Basel). 2020;9:21.
44. Akers JC, Gonda D, Kim R, Carter BS, Chen CC. Biogenesis of extracellular vesicles (EV): exosomes, microvesicles, retrovirus-like vesicles, and apoptotic bodies. J Neurooncol. 2013;113:1–11.
45. Birge RB, Boeltz S, Kumar S, Carlson J, Wanderley J, Calianese D, Barcinski M, Brekken RA, Huang X, Hutchins JT, et al. Phosphatidylserine is a global immunosuppressive signal in efferocytosis, infectious disease, and cancer. Cell Death Differ. 2016;23:962–78.
46. Gardai SJ, McPhillips KA, Frasch SC, Janssen WJ, Starefeldt A, Murphy-Ullrich JE, Bratton DL, Oldenborg PA, Michalak M, Henson PM. Cell-surface calreticulin initiates clearance of viable or apoptotic cells through trans-activation of LRP on the phagocyte. Cell. 2005;123:321–34.
47. Mills JC, Stone NL, Erhardt J, Pittman RN. Apoptotic membrane blebbing is regulated by myosin light chain phosphorylation. J Cell Biol. 1998;140:627–36.
48. Santavanond JP, Rutter SF, Atkin-Smith GK, Poon IKH. Apoptotic bodies: mechanism of formation, isolation and functional relevance. Subcell Biochem. 2021;97:61–88.
49. Tixeira R, Phan TK, Caruso S, Shi B, Atkin-Smith GK, Nedeva C, Chow JDY, Puthalakath H, Hulett MD, Herold MJ, Poon IKH. ROCK1 but not LIMK1 or PAK2 is a key regulator of apoptotic membrane blebbing and cell disassembly. Cell Death Differ. 2020;27:102–16.
50. Sebbagh M, Renvoizé C, Hamelin J, Riché N, Bertoglio J, Bréard J. Caspase-3-mediated cleavage of ROCK I induces MLC phosphorylation and apoptotic membrane blebbing. Nat Cell Biol. 2001;3:346–52.
51. Yang N, Higuchi O, Ohashi K, Nagata K, Wada A, Kangawa K, Nishida E, Mizuno K. Cofilin phosphorylation by LIM-kinase 1 and its role in Rac-mediated actin reorganization. Nature. 1998;393:809–12.
52. Arber S, Barbayannis FA, Hanser H, Schneider C, Stanyon CA, Bernard O, Caroni P. Regulation of actin dynamics through phosphorylation of Cofilin by LIM-kinase. Nature. 1998;393:805–9.
53. Núñez R, Sancho-Martínez SM, Novoa JM, López-Hernández FJ. Apoptotic volume decrease as a geometric determinant for cell dismantling into apoptotic bodies. Cell Death Differ. 2010;17:1665–71.
54. Maeno E, Tsubata T, Okada Y. Apoptotic volume decrease (AVD) is independent of mitochondrial dysfunction and initiator caspase activation. Cells. 2012;1:1156–67.
55. Caruso S, Atkin-Smith GK, Baxter AA, Tixeira R, Jiang L, Ozkocak DC, Santavanond JP, Hulett MD, Lock P, Phan TK, Poon IKH. Defining the role of

cytoskeletal components in the formation of apoptopodia and apoptotic bodies during apoptosis. Apoptosis. 2019;24:862–77.
56. Atkin-Smith GK, Tixeira R, Paone S, Mathivanan S, Collins C, Liem M, Goodall KJ, Ravichandran KS, Hulett MD, Poon IK. A novel mechanism of generating extracellular vesicles during apoptosis via a beads-on-a-string membrane structure. Nat Commun. 2015;6:7439.
57. Poon IK, Chiu YH, Armstrong AJ, Kinchen JM, Juncadella IJ, Bayliss DA, Ravichandran KS. Unexpected link between an antibiotic, pannexin channels and apoptosis. Nature. 2014;507:329–34.
58. Ihara T, Yamamoto T, Sugamata M, Okumura H, Ueno Y. The process of ultrastructural changes from nuclei to apoptotic body. Virchows Arch. 1998;433:443–7.
59. Yu L, Zhu G, Zhang Z, Yu Y, Zeng L, Xu Z, Weng J, Xia J, Li J, Pathak JL. Apoptotic bodies: bioactive treasure left behind by the dying cells with robust diagnostic and therapeutic application potentials. J Nanobiotechnol. 2023;21:218.
60. Doyle LM, Wang MZ. Overview of extracellular vesicles, their origin, composition, purpose, and methods for exosome isolation and analysis. Cells. 2019;8:727.
61. Caruso S, Poon IKH. Apoptotic Cell-Derived extracellular vesicles: more than just debris. Front Immunol. 2018;9:1486.
62. Mulcahy LA, Pink RC, Carter DR. Routes and mechanisms of extracellular vesicle uptake. J Extracell Vesicles. 2014;3:24641.
63. Lee Y, Kim JH. The emerging roles of extracellular vesicles as intercellular messengers in liver physiology and pathology. Clin Mol Hepatol. 2022;28:706–24.
64. Zhao J, Zhang X, Li Y, Yu J, Chen Z, Niu Y, Ran S, Wang S, Ye W, Luo Z, et al. Interorgan communication with the liver: novel mechanisms and therapeutic targets. Front Immunol. 2023;14:1314123.
65. Dixson AC, Dawson TR, Di Vizio D, Weaver AM. Context-specific regulation of extracellular vesicle biogenesis and cargo selection. Nat Rev Mol Cell Biol. 2023;24:454–76.
66. Gao H, Peng X, Li N, Gou L, Xu T, Wang Y, Qin J, Liang H, Ma P, Li S, et al. Emerging role of liver-bone axis in osteoporosis. J Orthop Translat. 2024;48:217–31.
67. Lin L, Guo Z, He E, Long X, Wang D, Zhang Y, Guo W, Wei Q, He W, Wu W, et al. SIRT2 regulates extracellular vesicle-mediated liver-bone communication. Nat Metab. 2023;5:821–41.
68. Liu J, Dou G, Zhao W, Hu J, Jiang Z, Wang W, Wang H, Liu S, Jin Y, Zhao Y, et al. Exosomes derived from impaired liver aggravate alveolar bone loss via shuttle of Fasn in type 2 diabetes mellitus. Bioact Mater. 2024;33:85–99.
69. Li CH, Lei X, Zheng CX, Jin Y, Sui BD, Ying SQ. [Study on liver tissue derived-extracellular vesicles regulating the osteogenic differentiation ability of mesenchymal stem cells and promoting the healing of jaw bone defects]. Zhonghua Kou Qiang Yi Xue Za Zhi. 2024;59:435–43.
70. Zheng L, Li Z, Ling W, Zhu D, Feng Z, Kong L. Exosomes derived from dendritic cells attenuate liver injury by modulating the balance of Treg and Th17 cells after ischemia reperfusion. Cell Physiol Biochem. 2018;46:740–56.
71. Ding C, Shen Z, Xu R, Liu Y, Xu M, Fan C, Hu D, Xing T. Exosomes derived from periodontitis induce hepatic steatosis through the SCD-1/AMPK signaling pathway. Biochim Biophys Acta Mol Basis Dis. 2024;1870:167343.
72. Møller S, Bernardi M. Interactions of the heart and the liver. Eur Heart J. 2013;34:2804–11.
73. Liu X, Shao Y, Han L, Zhang R, Chen J. Emerging evidence linking the liver to the cardiovascular system: liver-derived secretory factors. J Clin Transl Hepatol. 2023;11:1246–55.
74. Zuo R, Ye LF, Huang Y, Song ZQ, Wang L, Zhi H, Zhang MY, Li JY, Zhu L, Xiao WJ, et al. Hepatic small extracellular vesicles promote microvascular endothelial hyperpermeability during NAFLD via novel-miRNA-7. J Nanobiotechnol. 2021;19:396.
75. Nishi H, Ono K, Iwanaga Y, Horie T, Nagao K, Takemura G, Kinoshita M, Kuwabara Y, Mori RT, Hasegawa K, et al. MicroRNA-15b modulates cellular ATP levels and degenerates mitochondria via Arl2 in neonatal rat cardiac myocytes. J Biol Chem. 2010;285:4920–30.
76. Wang Y, Jin P, Liu J, Xie X. Exosomal microRNA-122 mediates obesity-related cardiomyopathy through suppressing mitochondrial ADP-ribosylation factor-like 2. Clin Sci (Lond). 2019;133:1871–81.
77. Luan X, Tian X, Zhang H, Huang R, Li N, Chen P, Wang R. Exercise as a prescription for patients with various diseases. J Sport Health Sci. 2019;8:422–41.
78. Lou J, Wu J, Feng M, Dang X, Wu G, Yang H, Wang Y, Li J, Zhao Y, Shi C, et al. Exercise promotes angiogenesis by enhancing endothelial cell fatty acid utilization via liver-derived extracellular vesicle miR-122-5p. J Sport Health Sci. 2022;11:495–508.
79. Luo XY, Ying SQ, Cao Y, Jin Y, Jin F, Zheng CX, Sui BD. Liver-based inter-organ communication: A disease perspective. Life Sci. 2024;351:122824.
80. Tilg H, Adolph TE, Trauner M. Gut-liver axis: pathophysiological concepts and clinical implications. Cell Metab. 2022;34:1700–18.
81. Villard A, Boursier J, Andriantsitohaina R. Bacterial and eukaryotic extracellular vesicles and nonalcoholic fatty liver disease: new players in the gut-liver axis? Am J Physiol Gastrointest Liver Physiol. 2021;320:G485–95.
82. Zhao J, Chen XD, Yan ZZ, Huang WF, Liu KX, Li C. Gut-Derived Exosomes Induce Liver Injury After Intestinal Ischemia/Reperfusion by Promoting Hepatic Macrophage Polarization. Inflammation. 2022; 45:2325-38.
83. Luo Z, Ji Y, Gao H, Gomes Dos Reis FC, Bandyopadhyay G, Jin Z, Ly C, Chang YJ, Zhang D, Kumar D, Ying W. CRIg(+) macrophages prevent gut microbial DNA-Containing extracellular Vesicle-Induced tissue inflammation and insulin resistance. Gastroenterology. 2021;160:863–74.
84. Fizanne L, Villard A, Benabbou N, Recoquillon S, Soleti R, Delage E, Wertheimer M, Vidal-Gómez X, Oullier T, Chaffron S, et al. Faeces-derived extracellular vesicles participate in the onset of barrier dysfunction leading to liver diseases. J Extracell Vesicles. 2023;12:e12303.
85. Jain H, Kumar A, Almousa S, Mishra S, Langsten KL, Kim S, Sharma M, Su Y, Singh S, Kerr BA, Deep G. Characterisation of LPS + bacterial extracellular vesicles along the gut-hepatic portal vein-liver axis. J Extracell Vesicles. 2024;13:e12474.
86. Chen X, Ling Y, Wei Y, Tang J, Ren Y, Zhang B, Jiang F, Li H, Wang R, Wen W, et al. Dual regulation of HMGB1 by combined JNK1/2-ATF2 axis with miR-200 family in nonalcoholic steatohepatitis in mice. Faseb J. 2018;32:2722–34.
87. Chen Y, Sun H, Bai Y, Zhi F. Gut dysbiosis-derived exosomes trigger hepatic steatosis by transiting HMGB1 from intestinal to liver in mice. Biochem Biophys Res Commun. 2019;509:767–72.
88. Wei J, Wang Z, Han T, Chen J, Ou Y, Wei L, Zhu X, Wang K, Yan Z, Han YP, Zheng X. Extracellular vesicle-mediated intercellular and interorgan crosstalk of pancreatic islet in health and diabetes. Front Endocrinol (Lausanne). 2023;14:1170237.
89. Li J, Zhang Y, Ye Y, Li D, Liu Y, Lee E, Zhang M, Dai X, Zhang X, Wang S, et al. Pancreatic B cells control glucose homeostasis via the secretion of Exosomal miR-29 family. J Extracell Vesicles. 2021;10:e12055.
90. Chen Q, Jiang FJ, Gao X, Li XY, Xia P. Steatotic hepatocyte-derived extracellular vesicles promote β-cell apoptosis and diabetes via microRNA-126a-3p. Liver Int. 2023;43:2560–70.
91. López-Bermudo L, Luque-Sierra A, Maya-Miles D, Gallego-Durán R, Ampuero J, Romero-Gómez M, Bernà G, Martín F. Contribution of liver and pancreatic islet crosstalk to β-Cell function/dysfunction in the presence of fatty liver. Front Endocrinol (Lausanne). 2022;13:892672.
92. Yang X, Qiu K, Jiang Y, Huang Y, Zhang Y, Liao Y. Metabolic crosstalk between liver and brain: from diseases to mechanisms. Int J Mol Sci 2024; 25.
93. Izquierdo-Altarejos P, Martínez-García M, Felipo V. Extracellular vesicles from hyperammonemic rats induce neuroinflammation in cerebellum of normal rats: role of increased TNFα content. Front Immunol. 2022;13:921947.
94. Zhang M, Gong W, Zhang D, Ji M, Chen B, Chen B, Li X, Zhou Y, Dong C, Wen G, et al. Ageing related thyroid deficiency increases brain-targeted transport of liver-derived ApoE4-laden exosomes leading to cognitive impairment. Cell Death Dis. 2022;13:406.
95. Li F, Liu Y, Li L, Peng R, Wang C, Liu C, Shi M, Cao Y, Gao Y, Zhang H, et al. Brain-derived extracellular vesicles mediate traumatic brain injury associated multi-organ damage. Biochem Biophys Res Commun. 2023;665:141–51.
96. Xiong JL, Wang YX, Luo JY, Wang SM, Sun JJ, Xi QY, Chen T, Zhang YL. Pituitary-derived small extracellular vesicles promote liver repair by its cargo miR-143-3p. Sci Rep. 2024;14:16635.
97. Rose CF, Amodio P, Bajaj JS, Dhiman RK, Montagnese S, Taylor-Robinson SD, Vilstrup H, Jalan R. Hepatic encephalopathy: novel insights into classification, pathophysiology and therapy. J Hepatol. 2020;73:1526–47.
98. Rodríguez-Roisin R, Krowka MJ. Hepatopulmonary syndrome–a liver-induced lung vascular disorder. N Engl J Med. 2008;358:2378–87.
99. Chen L, Han Y, Li Y, Chen B, Bai X, Belguise K, Wang X, Chen Y, Yi B, Lu K. Hepatocyte-derived Exosomal MiR-194 activates PMVECs and promotes angiogenesis in hepatopulmonary syndrome. Cell Death Dis. 2019;10:853.
100. Lv LL, Feng Y, Wu M, Wang B, Li ZL, Zhong X, Wu WJ, Chen J, Ni HF, Tang TT, et al. Exosomal miRNA-19b-3p of tubular epithelial cells promotes M1 macrophage activation in kidney injury. Cell Death Differ. 2020;27:210–26.
101. Lyu J, Sheng M, Cao Y, Jia L, Zhang C, Weng Y, Yu W. Ischemia and reperfusion-injured liver-derived exosomes elicit acute lung injury through miR-122-5p regulated alveolar macrophage polarization. Int Immunopharmacol. 2024;131:111853.

102. Bonjoch L, Casas V, Carrascal M, Closa D. Involvement of exosomes in lung inflammation associated with experimental acute pancreatitis. J Pathol. 2016;240:235–45.
103. Ginès P, Solà E, Angeli P, Wong F, Nadim MK, Kamath PS. Hepatorenal syndrome. Nat Rev Dis Primers. 2018;4:23.
104. Noble J, Jouve T, Malvezzi P, Rostaing L. Renal complications of liver diseases. Expert Rev Gastroenterol Hepatol. 2018;12:1135–42.
105. Lopez-Yus M, Hörndler C, Borlan S, Bernal-Monterde V, Arbones-Mainar JM. Unraveling adipose tissue dysfunction: molecular mechanisms, novel biomarkers, and therapeutic targets for liver fat deposition. Cells. 2024;13:380.
106. Xu J, Cui L, Wang J, Zheng S, Zhang H, Ke S, Cao X, Shi Y, Li J, Zen K, et al. Cold-activated brown fat-derived extracellular vesicle-miR-378a-3p stimulates hepatic gluconeogenesis in male mice. Nat Commun. 2023;14:5480.
107. Kariba Y, Yoshizawa T, Sato Y, Tsuyama T, Araki E, Yamagata K. Brown adipocyte-derived Exosomal miR-132-3p suppress hepatic Srebf1 expression and thereby attenuate expression of lipogenic genes. Biochem Biophys Res Commun. 2020;530:500–7.
108. Dang SY, Leng Y, Wang ZX, Xiao X, Zhang X, Wen T, Gong HZ, Hong A, Ma Y. Exosomal transfer of obesity adipose tissue for decreased miR-141-3p mediate insulin resistance of hepatocytes. Int J Biol Sci. 2019;15:351–68.
109. Fuchs A, Samovski D, Smith GI, Cifarelli V, Farabi SS, Yoshino J, Pietka T, Chang SW, Ghosh S, Myckatyn TM, Klein S. Associations among adipose tissue immunology, inflammation, exosomes and insulin sensitivity in people with obesity and nonalcoholic fatty liver disease. Gastroenterology. 2021; 161:968– 81.e12.
110. Tryggestad JB, Teague AM, Sparling DP, Jiang S, Chernausek SD. Macrophage-Derived microRNA-155 increases in obesity and influences adipocyte metabolism by targeting peroxisome Proliferator-Activated receptor gamma. Obes (Silver Spring). 2019;27:1856–64.
111. Ying W, Riopel M, Bandyopadhyay G, Dong Y, Birmingham A, Seo JB, Ofrecio JM, Wollam J, Hernandez-Carretero A, Fu W et al. Adipose tissue Macrophage-Derived Exosomal MiRNAs can modulate in vivo and in vitro insulin sensitivity. Cell 2017; 171:372– 84.e12.
112. Yan C, Tian X, Li J, Liu D, Ye D, Xie Z, Han Y, Zou MH. A High-Fat diet attenuates AMPK A1 in adipocytes to induce exosome shedding and nonalcoholic fatty liver development in vivo. Diabetes. 2021;70:577–88.
113. Colombo M, Moita C, van Niel G, Kowal J, Vigneron J, Benaroch P, Manel N, Moita LF, Théry C, Raposo G. Analysis of ESCRT functions in exosome biogenesis, composition and secretion highlights the heterogeneity of extracellular vesicles. J Cell Sci. 2013;126:5553–65.
114. Chen K, Lin T, Yao W, Chen X, Xiong X, Huang Z. Adipocytes-derived Exosomal miR-122 promotes non-alcoholic fat liver disease progression via targeting Sirt1. Gastroenterol Hepatol. 2023;46:531–41.
115. Lu MM, Ren Y, Zhou YW, Xu LL, Zhang MM, Ding LP, Cheng WX, Jin X. Antagonizing adipose tissue-derived exosome miR-103-hepatocyte phosphatase and tensin homolog pathway alleviates autophagy in non-alcoholic steatohepatitis: A trans-cellular crosstalk. World J Gastroenterol. 2023;29:4528–41.
116. Kranendonk ME, Visseren FL, van Herwaarden JA, Nolte-'t Hoen EN, de Jager W, Wauben MH, Kalkhoven E. Effect of extracellular vesicles of human adipose tissue on insulin signaling in liver and muscle cells. Obes (Silver Spring). 2014;22:2216–23.
117. Son T, Jeong I, Park J, Jun W, Kim A, Kim OK. Adipose tissue-derived exosomes contribute to obesity-associated liver diseases in long-term high-fat diet-fed mice, but not in short-term. Front Nutr. 2023;10:1162992.
118. Ji Y, Luo Z, Gao H, Dos Reis FCG, Bandyopadhyay G, Jin Z, Manda KA, Isaac R, Yang M, Fu W, et al. Hepatocyte-derived exosomes from early onset obese mice promote insulin sensitivity through miR-3075. Nat Metab. 2021;3:1163–74.
119. Jung JW, Kim JE, Kim E, Lee H, Lee H, Shin EA, Lee JW. Liver-originated small extracellular vesicles with TM4SF5 target brown adipose tissue for homeostatic glucose clearance. J Extracell Vesicles. 2022;11:e12262.
120. Zhao Y, Zhao MF, Jiang S, Wu J, Liu J, Yuan XW, Shen D, Zhang JZ, Zhou N, He J, et al. Liver governs adipose remodelling via extracellular vesicles in response to lipid overload. Nat Commun. 2020;11:719.
121. Lee J, Jeong I, Kim OK. Liver-Derived exosomes induce inflammation and lipogenesis in mice fed High-Energy diets. Nutrients. 2022;14:5124.
122. Wu Q, Fu S, Xiao H, Du J, Cheng F, Wan S, Zhu H, Li D, Peng F, Ding X, Wang L. Advances in extracellular vesicle nanotechnology for precision theranostics. Adv Sci (Weinh). 2023;10:e2204814.
123. Psaraki A, Ntari L, Karakostas C, Korrou-Karava D, Roubelakis MG. Extracellular vesicles derived from mesenchymal stem/stromal cells: the regenerative impact in liver diseases. Hepatology. 2022;75:1590–603.
124. Wu R, Fan X, Wang Y, Shen M, Zheng Y, Zhao S, Yang L. Mesenchymal stem Cell-Derived extracellular vesicles in liver immunity and therapy. Front Immunol. 2022;13:833878.
125. Shen M, Zhou L, Fan X, Wu R, Liu S, Deng Q, Zheng Y, Liu J, Yang L. Metabolic reprogramming of CD4(+) T cells by mesenchymal stem Cell-Derived extracellular vesicles attenuates autoimmune hepatitis through mitochondrial protein transfer. Int J Nanomed. 2024;19:9799–819.
126. Xuan J, Xu H, Li H, Chen D, Qiu Y, Chen X, Shao M, Xia X. Extracellular vesicles from miR-148a-5p-Enriched bone marrow mesenchymal stem cells relieve hepatic fibrosis by targeting Smad4. Mol Biotechnol. 2022;64:535–45.
127. Zhang Y, Zhangdi H, Nie X, Wang L, Wan Z, Jin H, Pu R, Liang M, Chang Y, Gao Y et al. Exosomes Derived from BMMSCs Mitigate the Hepatic Fibrosis via Anti-Pyroptosis Pathway in a Cirrhosis Model. Cells. 2022; 11:4004.
128. Rong X, Liu J, Yao X, Jiang T, Wang Y, Xie F. Human bone marrow mesenchymal stem cells-derived exosomes alleviate liver fibrosis through the Wnt/β-catenin pathway. Stem Cell Res Ther. 2019;10:98.
129. Tan J, Chen M, Liu M, Chen A, Huang M, Chen X, Tian X, Chen W. Exosomal miR-192-5p secreted by bone marrow mesenchymal stem cells inhibits hepatic stellate cell activation and targets PPP2R3A. J Histotechnol. 2023;46:158–69.
130. Zhao S, Liu Y, Pu Z. Bone marrow mesenchymal stem cell-derived exosomes attenuate D-GaIN/LPS-induced hepatocyte apoptosis by activating autophagy in vitro. Drug Des Devel Ther. 2019;13:2887–97.
131. Jiang X, Liu Z, You H, Tang Z, Ma Y, Nie R, Yang Z, Che N, Liu W. Extracellular vesicles derived from bone marrow mesenchymal stem cells ameliorate chronic liver damage via microRNA-136-5p. Mol Cell Biochem. 2024:1–19.
132. Ichinohe N, Ishii M, Tanimizu N, Mizuguchi T, Yoshioka Y, Ochiya T, Suzuki H, Mitaka T. Extracellular vesicles containing miR-146a-5p secreted by bone marrow mesenchymal cells activate hepatocytic progenitors in regenerating rat livers. Stem Cell Res Ther. 2021;12:312.
133. Chen L, Lu FB, Chen DZ, Wu JL, Hu ED, Xu LM, Zheng MH, Li H, Huang Y, Jin XY, et al. BMSCs-derived miR-223-containing exosomes contribute to liver protection in experimental autoimmune hepatitis. Mol Immunol. 2018;93:38–46.
134. Li H, Lin W, Zhang G, Liu R, Qu M, Zhang J, Xing X. BMSC-exosomes miR-25-3p regulates the p53 signaling pathway through PTEN to inhibit cell apoptosis and ameliorate liver Ischemia–reperfusion injury. Stem Cell Rev Rep. 2023;19:2820–36.
135. Zhang Z, Shang J, Yang Q, Dai Z, Liang Y, Lai C, Feng T, Zhong D, Zou H, Sun L, et al. Exosomes derived from human adipose mesenchymal stem cells ameliorate hepatic fibrosis by inhibiting PI3K/Akt/mTOR pathway and remodeling choline metabolism. J Nanobiotechnol. 2023;21:29.
136. Gan L, Zheng L, Yao L, Lei L, Huang Y, Zeng Z, Fang N. Exosomes from adipose-derived mesenchymal stem cells improve liver fibrosis by regulating the miR-20a-5p/TGFBR2 axis to affect the p38 MAPK/NF-κB pathway. Cytokine. 2023;172:156386.
137. Du Z, Wu T, Liu L, Luo B, Wei C. Extracellular vesicles-derived miR-150-5p secreted by adipose-derived mesenchymal stem cells inhibits CXCL1 expression to attenuate hepatic fibrosis. J Cell Mol Med. 2021;25:701–15.
138. Piao C, Sang J, Kou Z, Wang Y, Liu T, Lu X, Jiao Z, Wang H. Effects of exosomes derived from Adipose-Derived mesenchymal stem cells on pyroptosis and regeneration of injured liver. Int J Mol Sci. 2022;23:12065.
139. Wang Y, Liu T, Jiao G, Lv Y, Piao C, Lu X, Ma H, Wang H. Exosomes from adipose-derived mesenchymal stem cells can attenuate liver injury caused by minimally invasive hemihepatectomy combined with ischemia-reperfusion in minipigs by modulating the Endoplasmic reticulum stress response. Life Sci. 2023;321:121618.
140. Zhang Q, Piao C, Ma H, Xu J, Wang Y, Liu T, Liu G, Wang H. Exosomes from adipose-derived mesenchymal stem cells alleviate liver ischaemia reperfusion injury subsequent to hepatectomy in rats by regulating mitochondrial dynamics and biogenesis. J Cell Mol Med. 2021;25:10152–63.
141. Jiao Z, Ma Y, Wang Y, Liu T, Zhang Q, Liu X, Piao C, Liu B, Wang H. Protective Effect of Adipose-Derived Mesenchymal Stem Cell Secretome against Hepatocyte Apoptosis Induced by Liver Ischemia-Reperfusion with Partial Hepatectomy Injury. Stem Cells Int. 2021; 2021:9969372.
142. Niu Q, Wang T, Wang Z, Wang F, Huang D, Sun H, Liu H. Adipose-derived mesenchymal stem cell-secreted extracellular vesicles alleviate non-alcoholic fatty liver disease via delivering miR-223-3p. Adipocyte. 2022;11:572–87.
143. Hao Y, Song H, Zhou Z, Chen X, Li H, Zhang Y, Wang J, Ren X, Wang X. Promotion or Inhibition of extracellular vesicle release: emerging therapeutic opportunities. J Control Release. 2021;340:136–48.

144. Debbi L, Guo S, Safina D, Levenberg S. Boosting extracellular vesicle secretion. Biotechnol Adv. 2022;59:107983.
145. Wang Y, Lou P, Xie Y, Liu S, Li L, Wang C, Du D, Chen Y, Lu Y, Cheng J, Liu J. Nutrient availability regulates the secretion and function of immune cell-derived extracellular vesicles through metabolic rewiring. Sci Adv. 2024;10:eadj1290.
146. Jiang X, Liu Z, You H, Tang Z, Ma Y, Nie R, Yang Z, Che N, Liu W. Quercetin-primed BMSC-derived extracellular vesicles ameliorate chronic liver damage through miR-136-5p and GNAS/STAT3 signaling pathways. Int Immunopharmacol. 2024;142:113162.
147. Liu J, Tang M, Li Q, Li Q, Dai Y, Zhou H. ATG2B upregulated in LPS-stimulated BMSCs-derived exosomes attenuates septic liver injury by inhibiting macrophage STING signaling. Int Immunopharmacol. 2023;117:109931.
148. Ziegler JN, Tian C. Engineered extracellular vesicles: emerging therapeutic strategies for translational applications. Int J Mol Sci. 2023;24:15206.
149. Li B, Qi C, Zhang Y, Shi L, Zhang J, Qian H, Ji C. Frontier role of extracellular vesicles in kidney disease. J Nanobiotechnol. 2024;22:583.
150. Yu L, Xue J, Wu Y, Zhou H. Therapeutic effect of exosomes derived from hepatocyte-growth-factor-overexpressing adipose mesenchymal stem cells on liver injury. Folia Histochem Cytobiol. 2023;61:160–71.
151. Fang J, Liang W. ASCs -derived exosomes loaded with vitamin A and Quercetin inhibit rapid senescence-like response after acute liver injury. Biochem Biophys Res Commun. 2021;572:125–30.
152. Park JH. Regulation of in vivo fate of exosomes for therapeutic applications: new frontier in nanomedicines. J Control Release. 2022;348:483–8.
153. Aoyama T, Inokuchi S, Brenner DA, Seki E. CX3CL1-CX3CR1 interaction prevents carbon tetrachloride-induced liver inflammation and fibrosis in mice. Hepatology. 2010;52:1390–400.
154. Han C, Zhai Y, Wang Y, Peng X, Zhang X, Dai B, Leng Y, Zhang Z, Qi S. Intravital imaging of Splenic classical monocytes modifying the hepatic CX3CR1(+) cells motility to exacerbate liver fibrosis via spleen-liver axis. Theranostics. 2024;14:2210–31.
155. Zhang S, Wan D, Zhu M, Wang G, Zhang X, Huang N, Zhang J, Zhang C, Shang Q, Zhang C, et al. CD11b + CD43 Hi Ly6C lo splenocyte-derived macrophages exacerbate liver fibrosis via spleen-liver axis. Hepatology. 2023;77:1612–29.
156. Perdices L, Fuentes-Broto L, Segura F, Ben Gdara N, Sánchez-Cano AI, Insa G, Orduna E, Pinilla I. Hepatic oxidative stress in pigmented P23H rhodopsin Transgenic rats with progressive retinal degeneration. Free Radic Biol Med. 2018;124:550–7.
157. Dogra S, Jindal R. Cutaneous manifestations of common liver diseases. J Clin Exp Hepatol. 2011;1:177–84.
158. Miele L, Vallone S, Cefalo C, La Torre G, Di Stasi C, Vecchio FM, D'Agostino M, Gabrieli ML, Vero V, Biolato M, et al. Prevalence, characteristics and severity of non-alcoholic fatty liver disease in patients with chronic plaque psoriasis. J Hepatol. 2009;51:778–86.
159. Terziroli Beretta-Piccoli B, Invernizzi P, Gershwin ME, Mainetti C. Skin manifestations associated with autoimmune liver diseases: a systematic review. Clin Rev Allergy Immunol. 2017;53:394–412.
160. Guo S, Feng Y, Zhu X, Zhang X, Wang H, Wang R, Zhang Q, Li Y, Ren Y, Gao X, et al. Metabolic crosstalk between skeletal muscle cells and liver through IRF4-FSTL1 in nonalcoholic steatohepatitis. Nat Commun. 2023;14:6047.
161. Zhou D, Shi Y, Zhang D, Zuo J, Zeng C, Mamtawla G, Huang L, Gao X, Zhang L, Wang X. Liver-secreted FGF21 induces sarcopenia by inhibiting satellite cell myogenesis via Klotho beta in decompensated cirrhosis. Redox Biol. 2024;76:103333.
162. Konaka H, Kato Y, Hirano T, Tsujimoto K, Park J, Koba T, Aoki W, Matsuzaki Y, Taki M, Koyama S, et al. Secretion of mitochondrial DNA via exosomes promotes inflammation in Behçet's syndrome. Embo J. 2023;42:e112573.
163. Ali S, Vidal-Gómez X, Piquet M, Vergori L, Simard G, Dubois S, Ducluzeau PH, Pomiès P, Kamli-Salino S, Delibégovic M et al. Circulating extracellular vesicle-carried PTP1B and PP2A phosphatases as regulators of insulin resistance. Diabetologia. 2024:1–12.
164. Zhao J, Zhu W, Mao Y, Li X, Ling G, Luo C, Zhang P. Unignored intracellular journey and biomedical applications of extracellular vesicles. Adv Drug Deliv Rev. 2024;212:115388.
165. Miceli RT, Chen TY, Nose Y, Tichkule S, Brown B, Fullard JF, Saulsbury MD, Heyliger SO, Gnjatic S, Kyprianou N, et al. Extracellular vesicles, RNA sequencing, and bioinformatic analyses: challenges, solutions, and recommendations. J Extracell Vesicles. 2024;13:e70005.
166. Mizenko RR, Feaver M, Bozkurt BT, Lowe N, Nguyen B, Huang KW, Wang A, Carney RP. A critical systematic review of extracellular vesicle clinical trials. J Extracell Vesicles. 2024;13:e12510.
167. Min L, Wang B, Bao H, Li X, Zhao L, Meng J, Wang S. Advanced nanotechnologies for extracellular Vesicle-Based liquid biopsy. Adv Sci (Weinh). 2021;8:e2102789.
168. Li SR, Man QW, Gao X, Lin H, Wang J, Su FC, Wang HQ, Bu LL, Liu B, Chen G. Tissue-derived extracellular vesicles in cancers and non-cancer diseases: present and future. J Extracell Vesicles. 2021;10:e12175.
169. Verweij FJ, Revenu C, Arras G, Dingli F, Loew D, Pegtel DM, Follain G, Allio G, Goetz JG, Zimmermann P et al. Live tracking of inter-organ communication by endogenous exosomes in vivo. Dev Cell. 2019; 48:573– 89.e4.
170. van de Wakker SI, Meijers FM, Sluijter JPG, Vader P. Extracellular vesicle heterogeneity and its impact for regenerative medicine applications. Pharmacol Rev. 2023;75:1043–61.
171. Willms E, Cabañas C, Mäger I, Wood MJA, Vader P. Extracellular vesicle heterogeneity: subpopulations, isolation techniques, and diverse functions in Cancer progression. Front Immunol. 2018;9:738.
172. Wu D, Yan J, Shen X, Sun Y, Thulin M, Cai Y, Wik L, Shen Q, Oelrich J, Qian X, et al. Profiling surface proteins on individual exosomes using a proximity barcoding assay. Nat Commun. 2019;10:3854.
173. Banijamali M, Höjer P, Nagy A, Hååg P, Gomero EP, Stiller C, Kaminskyy VO, Ekman S, Lewensohn R, Karlström AE, et al. Characterizing single extracellular vesicles by droplet barcode sequencing for protein analysis. J Extracell Vesicles. 2022;11:e12277.
174. Sun N, Zhang C, Lee YT, Tran BV, Wang J, Kim H, Lee J, Zhang RY, Wang JJ, Hu J, et al. HCC EV ECG score: an extracellular vesicle-based protein assay for detection of early-stage hepatocellular carcinoma. Hepatology. 2023;77:774–88.
175. Guo W, Cai Y, Liu X, Ji Y, Zhang C, Wang L, Liao W, Liu Y, Cui N, Xiang J et al. Single-Exosome profiling identifies ITGB3 + and ITGAM + Exosome subpopulations as promising early diagnostic biomarkers and therapeutic targets for colorectal cancer. Research (Wash D C). 2023; 6:0041.
176. Wiklander OPB, Brennan M, Lötvall J, Breakefield XO, El Andaloussi S. Advances in therapeutic applications of extracellular vesicles. Sci Transl Med. 2019;11:eaav8521.
177. Al-Madhagi H. The landscape of exosomes biogenesis to clinical applications. Int J Nanomed. 2024;19:3657–75.
178. Zeng H, Guo S, Ren X, Wu Z, Liu S, Yao X. Current strategies for exosome cargo loading and targeting delivery. Cells 2023; 12.
179. Meng W, He C, Hao Y, Wang L, Li L, Zhu G. Prospects and challenges of extracellular vesicle-based drug delivery system: considering cell source. Drug Deliv. 2020;27:585–98.
180. Wang L, Wang D, Ye Z, Xu J. Engineering extracellular vesicles as delivery systems in therapeutic applications. Adv Sci (Weinh). 2023;10:e2300552.

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