Role of adipocytes and their derived extracellular vesicles in the progression, diagnosis and treatment of liver diseases (Review)

KANGRONG LI[1,2], MUHAMMAD ZUBAIR[1], YONGMIN YAN[1,3] and JIAHAO XU[1]

[1]Department of Laboratory Medicine, Wujin Hospital Affiliated with Jiangsu University, Jiangsu University, Changzhou, Jiangsu 213017, P.R. China; [2]Department of Laboratory Medicine, School of Medicine, Jiangsu University, Zhenjiang, Jiangsu 212013, P.R. China; [3]Changzhou Key Laboratory of Exosome Foundation and Transformation Application, Wujin Hospital Affiliated with Jiangsu University (Wujin Clinical College of Xuzhou Medical University), Changzhou, Jiangsu 213017, P.R. China

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Abstract. The growing burden of liver diseases underscores the urgent need to elucidate the adipose-liver axis. Although adipocyte dysfunction, dysregulated adipokine secretion and adipocyte-derived extracellular vesicles (Ad-EVs) have been implicated in hepatic steatosis, inflammation and fibrogenesis, their precise pathogenic roles and translational potential remain incompletely defined. The present review uniquely centers on adipocytes as a specific cellular source, systematically examining their biological functions and those of Ad-EVs, delineating their differential roles across the stages of liver disease, and evaluating adipocyte-targeted therapeutic strategies together with their clinical prospects. However, the clinical translation of adipocyte-targeted interventions and Ad-EV-based applications is constrained by several limitations: Current mechanistic evidence derives largely from preclinical models and awaits validation in human adipose tissue and liver biopsy specimens; moreover, methods for the isolation and characterization of Ad-EVs have yet to be standardized. The present review aimed to identify the translational connections and unresolved challenges within the adipose-liver axis, thereby informing basic research and the clinical diagnosis and treatment of liver diseases.

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Correspondence to: Mr. Jiahao Xu, Department of Laboratory Medicine, Wujin Hospital Affiliated with Jiangsu University, Jiangsu University, 2 Yongning North Road, Tianning, Changzhou, Jiangsu 213017, P.R. China
E-mail: xujiahao@wjrmyy.cn

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1. Introduction

Liver diseases encompass a broad spectrum of conditions, including viral hepatitis, alcoholic liver disease (ALD), drug-induced liver injury, metabolic dysfunction-associated steatotic liver disease (MASLD), cirrhosis, liver failure and hepatocellular carcinoma (HCC) (1). With the rising global prevalence of obesity and type 2 diabetes (T2D), the incidence of MASLD is increasing. Currently, ~38% of adults and 7-14% of children and adolescents are affected by MASLD, and projections indicate that by the year 2040, >55% of adults may be affected (2). The global prevalence of ALD is ~3.5% in the general population, rising to 26.0% among chronic alcohol abusers and 55.1% among individuals with alcohol use disorders (3). Cirrhosis markedly contributes to illness and mortality among individuals with chronic liver conditions worldwide, accounting for 2.4% of global fatalities in 2019 (4). HCC is the third leading cause of cancer-related mortality globally, representing 80% of all primary liver cancers; GLOBOCAN 2020 reported ~866,136 new cases and 758,725 deaths due to liver cancer worldwide (5). Despite these concerning statistics, the rates of incidence and mortality linked to liver diseases continue to escalate in various regions, often resulting in poor long-term outcomes, including early mortality from liver decompensation, cirrhosis and HCC (6). Liver diseases cause two million deaths annually, accounting for 4% of all deaths, predominantly due to complications of cirrhosis and HCC (7).

Substantial unmet needs persist in the clinical management of liver diseases. For the majority of chronic liver conditions, including MASLD, ALD and early-stage fibrosis, no pharmacological therapies have been approved by regulatory agencies, and management relies largely on lifestyle modifications and risk factor control. For end-stage liver disease, liver transplantation remains the only curative

option and represents the second-largest group of solid organ transplants (8). Nevertheless, the limited availability of donor livers poses a major barrier to the progress of liver transplantation (9). From a diagnostic perspective, liver biopsy remains the gold standard for assessing fibrosis, while there is a lack of non-invasive biomarkers that possess adequate sensitivity and specificity for early detection and ongoing monitoring of treatment efficacy. These shortcomings underscore the urgent need for a more in-depth understanding of liver disease mechanisms and the development of novel diagnostic and therapeutic strategies.

Adipose tissue (AT) releases adipokines that play a crucial role in regulating hepatic metabolism and inflammation. Among these, leptin and adiponectin are the two most widely studied hormones. In the progression of disease, leptin mainly exerts a pro-inflammatory effect, while adiponectin exerts an anti-inflammatory effect. These adipokines establish a complex bidirectional communication system with the liver, modulating hepatic metabolism, inflammation and fibrosis (10). In obesity, adipocytes may undergo hypertrophy or develop insulin resistance, resulting in dysregulated adipokine secretion. This disruption not only hinders the normal function of AT, but also significantly affects liver metabolism (11).

Adipocyte-derived extracellular vesicles (EVs; Ad-EVs) play a critical role in the transport of various bioactive molecules, such as proteins, lipids, mRNAs and microRNAs (miRNAs/miRs) (12). These vesicles mediate communication via the bloodstream and surrounding tissues, thereby influencing metabolic functions and inflammatory responses in target cells (13). Under conditions such as obesity and metabolic disorders, the characteristics of Ad-EVs, including their number, size and cargo composition, are altered, which can exacerbate pathological processes such as inflammation, insulin resistance and fatty liver disease (14,15). Additionally, there is a complex association between Ad-EVs and the liver, mediated by the adipose-liver axis. When the liver is overloaded with lipids, it can modulate lipogenesis, lipolysis and the remodeling of AT through liver-derived extracellular vesicles. In turn, Ad-EVs can affect hepatocyte function and contribute to the development of MASLD (16,17). Although Ad-EVs are essential for maintaining energy homeostasis under physiological conditions, they can also drive disease progression in pathological states, serving as a critical link between adipose tissue, the liver, and other metabolic organs. However, the precise molecular mechanisms by which Ad-EVs mediate hepatic injury or protection, as well as their potential as non-invasive biomarkers or therapeutic vehicles, remain poorly defined, representing a major gap in the field.

From both diagnostic and therapeutic perspectives, targeting adipocyte-hepatic interactions has emerged as a promising strategy for the management of liver disease. Research indicates that adipocyte-secreted factors are altered as liver disease progresses. The communication pathways between adipocytes and the liver involve multiple metabolic routes and signaling molecules, including proteins that regulate lipid metabolism, adipokines and non-coding RNAs, collectively forming a sophisticated regulatory framework (18,19). Furthermore, Ad-EVs hold considerable promise for both diagnosis and treatment. While EVs derived from mature adipocytes typically exert detrimental effects, those released by adipose-derived stem cells (ADSCs) may provide therapeutic benefits (20,21). These findings not only deepen the understanding of the mechanisms through which adipocytes influence liver diseases, but also lay the groundwork for the development of novel targeted therapies.

The present review provides a comprehensive and forward-looking synthesis of adipocyte-liver interactions, with a particular focus on the roles of Ad-EVs in disease and their therapeutic potential. The present review systematically delineates the mechanistic contributions of Ad-EVs to MASLD, ALD, cirrhosis and HCC, analyzing their molecular cargo-including miRNAs, proteins and lipids-in the context of hepatic steatosis, inflammation, and fibrosis. In addition, the pathogenic role of EVs from mature adipocytes is compared with the protective function of ADSC-derived EVs (ADSC-EVs). Furthermore, the present review discuss translational hurdles, such as standardization, good manufacturing practice (GMP)-compliant manufacturing and multicenter validation, and proposes a feasible roadmap for clinical application. By integrating mechanistic insights with diagnostic and therapeutic innovation, the present review aimed to inform ongoing efforts to address the pressing clinical needs in hepatology.

2. Biological characteristics and functions of adipocytes

Biological characteristics of adipocytes. AT is mainly composed of adipocytes, which serve the key purpose of energy storage as lipids and also have endocrine functions. Adipocytes are classified into three main types: White, brown and beige adipocytes, with white and brown being the most common (22). The identification of beige adipocytes as a unique thermogenic cell type, separate from both white and traditional brown adipocytes, was first established in 2012 (23).

Adipocyte formation initiates with the directed differentiation of mesenchymal stem cells (MSCs) into various cell types (24). The majority of white adipocytes are derived primarily from Myf5-negative precursor cells, whereas the majority of brown adipocytes arise from Myf5-positive progenitors of the dermomyotome (25). The origin of beige adipocytes is more intricate; they can develop from the direct differentiation of certain precursors, such as platelet-derived growth factor (PDGF) receptor α^+ or smooth-muscle-like cells, or may emerge from existing white adipocytes through transdifferentiation in response to stimuli such as exposure to cold or β-adrenergic agonists, depending on the specific fat depot and the nature of the stimulus (26-28).

When substantial numbers of adipocytes aggregate and incorporate mesenchymal tissue, AT is formed. This tissue is divided into two main types: White AT (WAT) and brown AT (BAT) (29). In both adolescents and adults, WAT is the most prevalent type, found primarily in the omentum, mesentery and subcutaneous depots (30). In humans, functional BAT is mainly located in the neck, supraclavicular region, mediastinum, paravertebral region and around the adrenal glands (31) (Fig. 1).

Function of adipocytes. White adipocytes function primarily in energy storage and endocrine secretion, whereas brown and beige adipocytes are specialized for thermogenesis. Unlike

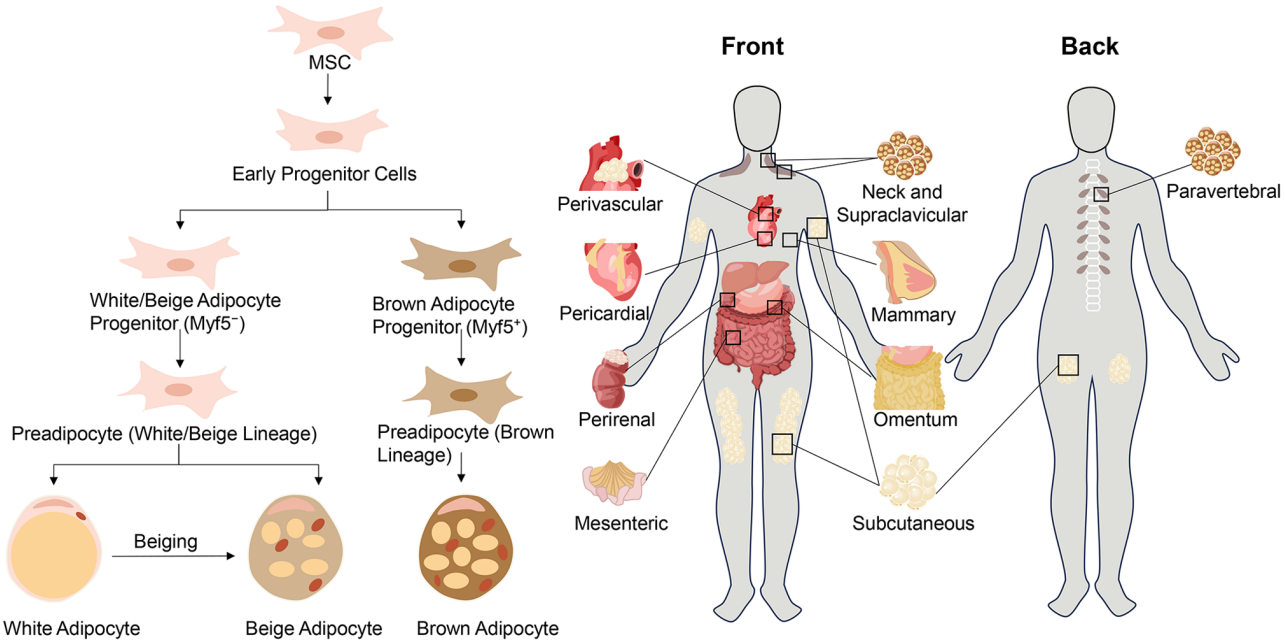

Figure 1. Differentiation and distribution of adipocytes. Adipocyte differentiation begins with MSCs that commit to either the white or brown lineage. White adipocytes arise from Myf5-negative progenitor cells, whereas brown adipocytes originate from Myf5-positive progenitors. Beige adipocytes are derived from white adipocytes through a process termed 'browning', typically induced by stimuli, such as cold exposure or β-adrenergic activation. White adipose tissue is predominantly located in the omentum, mesentery and subcutaneous depots, while brown adipose tissue is found in the neck, supraclavicular region, mediastinum, paravertebral region, and adrenal areas. Arrows indicate differentiation or conversion pathways. MSCs, mesenchymal stem cells.

constitutively active brown adipocytes, beige adipocytes acquire thermogenic capacity only in response to appropriate stimulation (e.g., exposure to cold or β-adrenergic activation) (32).

Recent research has suggested that depot-specific regulatory mechanisms are critical for the temporal activation of adipose thermogenesis (33). The loss of folliculin (FLCN)-interacting protein 1 (FNIP1) elevates intracellular calcium, thereby activating calcium-dependent thermogenic pathways and establishing FNIP1 as a negative regulator of beige adipocyte thermogenesis (34). FNIP1 is an adaptor protein known to interact with FLCN and AMP-activated protein kinase (AMPK), and regulates AMPK and mechanistic target of rapamycin complex 1 (mTORC1) signaling in various cell types (35). In adipocytes, however, FNIP1 attenuates calcium-dependent thermogenic programs by enhancing SERCA-mediated Ca^{2+} reuptake into the endoplasmic reticulum, leading to the suppression of uncoupling protein 1 (UCP1) expression and mitochondrial biogenesis. The adipocyte-specific ablation of FNIP1 alleviates this inhibitory effect, resulting in elevated cytosolic Ca^{2+} levels, the significant thermogenic remodeling of WAT, improved insulin sensitivity and reduced hepatic steatosis. These findings establish the FNIP1-SERCA-Ca^{2+} axis as a critical component in maintaining systemic metabolic homeostasis and liver function (34). UCP1 is exclusively expressed in brown and beige adipocytes and has been extensively studied for its capacity to enhance thermogenesis and mitigate obesity (36). At the molecular level, UCP1 functions as a proton transporter in the inner mitochondrial membrane, dissipating the proton gradient generated by the electron transport chain and converting energy into heat rather than ATP (37) The transcriptional activation of UCP1 is primarily regulated by the sympathetic nervous system through the β3-adrenergic receptor (β3-AR) and the cAMP-protein kinase A (PKA) pathway: Norepinephrine released in response to cold binds to β3-AR, increasing intracellular cAMP levels and activating PKA, which phosphorylates hormone-sensitive lipase (HSL) to release free fatty acids that serve as allosteric activators of UCP1 and fuel for thermogenesis (38,39). Additionally, PKA signaling activates p38 MAPK and the transcription factors, peroxisome proliferator-activated receptor (PPAR)γ and PGC-1α, which cooperatively bind the UCP1 distal enhancer element, promoting sustained UCP1 transcription (40).

Adipose-derived adipokines are crucial metabolic regulators that function as key modulators of metabolic inflammation, influencing immune and metabolic responses both locally and systemically (41). AT functions as an active endocrine organ, interacting with other organs including the liver, gut, heart and skeletal muscle through the secretion of various adipokines.

Adiponectin and leptin are two extensively studied adipokines whose biological effects are highly context-dependent and are governed by receptor-mediated signaling, systemic metabolic status and the stage of liver disease. Adiponectin is generally regarded as a beneficial adipokine in the setting of metabolic inflammation. This protein is primarily synthesized in various AT, but is also present in other cell types, such as hepatic stellate cells (42). Moreover, adiponectin exhibits cytoprotective and anti-fibrotic properties across multiple tissues (43). For instance, its circulating levels tend to decline as MASLD progresses (44). In various acute and chronic liver diseases induced by excessive alcohol consumption or a high-fat diet, adiponectin exerts anti-inflammatory, anti-apoptotic and anti-fibrotic effects (45,46). However, these beneficial actions are not absolute; they depend on the availability and sensitivity

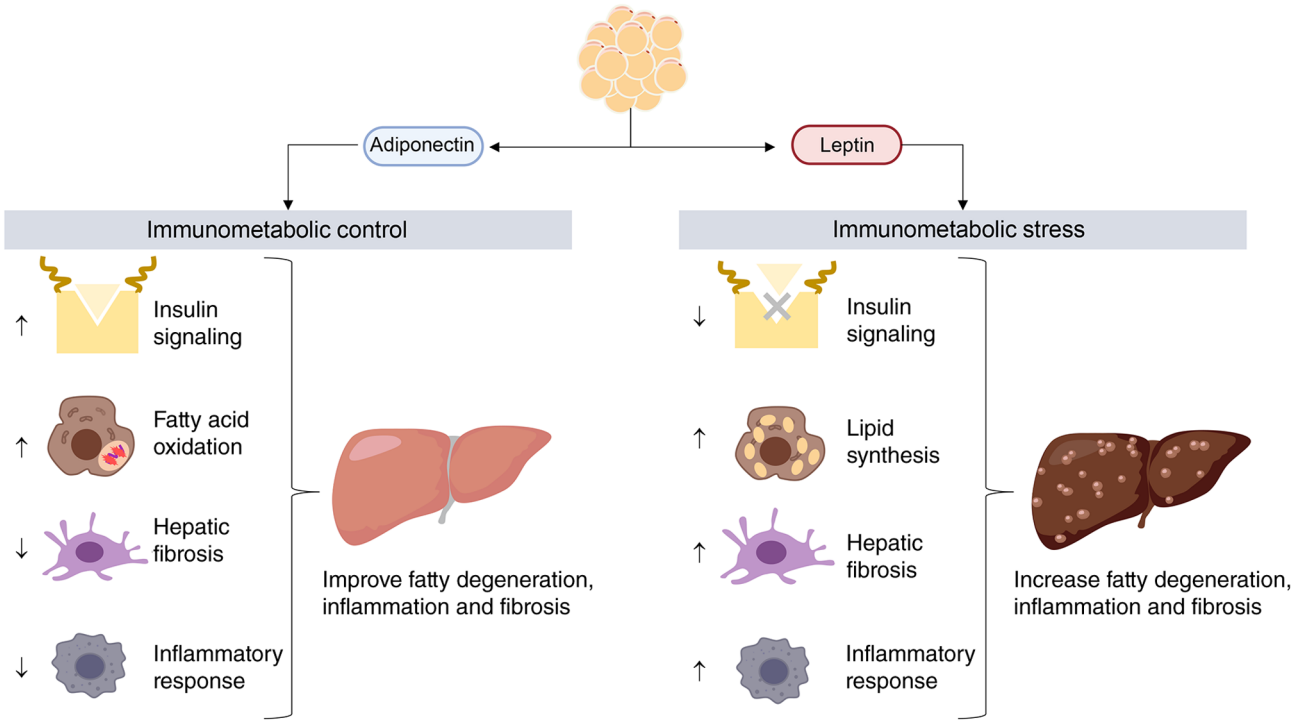

Figure 2. Role of adipokines in the liver. Adiponectin typically ameliorates hepatic steatosis, suppresses inflammation and attenuates fibrosis, whereas leptin commonly promotes lipid accumulation, pro-inflammatory cytokine production (e.g., TNF-α and IL-6), and fibrogenesis in the setting of obesity and metabolic dysfunction. Both adipokines exhibit context-dependent actions, and their effects may vary with disease stage and microenvironment.

of its receptors (AdipoR1/R2), tissue-specific responses and the prevailing metabolic microenvironment (47,48).

Leptin is frequently associated with pro-inflammatory and pro-fibrotic effects in the context of metabolic liver disease. Serum leptin levels are elevated in patients with biopsy-confirmed MASLD (49). Furthermore, research using rat models has demonstrated that leptin accelerates the development of MASLD, a process that is closely linked to cytokine-induced hepatocyte necroptosis (50). Leptin also contributes to hepatic fibrogenesis. Evidence indicates that multidrug resistance protein 2-deficient mice exhibit elevated plasma leptin levels, and the administration of exogenous leptin aggravates inflammation and fibrosis (51). However, leptin also fulfills essential physiological functions, including the central regulation of appetite, energy expenditure, and immune and reproductive homeostasis (52). In leptin-deficient states, leptin supplementation confers metabolic benefits and is critical for survival (53). Therefore, adiponectin and leptin may exert distinct roles under physiological and pathological conditions (Fig. 2).

Some inflammatory cytokines also function as adipokines, such as tumor necrosis factor (TNF), interleukin (IL)-1 and IL-6. IL-18, identified as a brown adipokine, improves insulin sensitivity in WAT through its receptor (IL18r) and stimulates thermogenesis in BAT via the sodium-chloride cotransporter. Obesity-induced adipocyte enlargement interferes with IL-18 signaling and contributes to metabolic dysfunction (54).

An imbalance in adipokines plays a crucial role in the progression of liver diseases. Reduced levels of adiponectin, together with elevated levels of leptin, resistin and TNF-α, contribute to disruptions in hepatic lipid metabolism, insulin resistance, persistent inflammation and the initiation of fibrosis. This cascade propels disease progression from MASLD to metabolic dysfunction-associated steatohepatitis (MASH), liver fibrosis and potentially, HCC.

In summary, white, brown and beige adipocytes differ in their developmental origins, anatomical distribution and specific functions. Their coordinated contributions to energy storage, heat production and adipokine release are essential for maintaining metabolic balance, which in turn plays a crucial role in the development of liver diseases.

3. Biological characteristics and functions of Ad-EVs

Classification and formation mechanisms of EVs. EVs are nanoscale membrane vesicles with a lipid bilayer, secreted by cells and widely distributed in body fluids, where they mediate intercellular communication and the transfer of molecular cargo. EVs are generally classified into three categories: Exosomes, microvesicles and apoptotic bodies (55). Exosomes (30-150 nm in diameter) are derived from intraluminal vesicles within multivesicular bodies (MVBs) and are released when MVB membranes fuse with the plasma membrane. Microvesicles (100-1,000 nm in diameter) are produced by direct budding from the cell membrane. Apoptotic bodies (500-2,000 nm in diameter) are membrane-enclosed fragments formed during apoptosis that often contain cellular components such as nuclei and organelles (56).

Adipocytes can release EVs. This secretion occurs through the formation of multivesicular bodies within the adipocytes, which subsequently fuse with the cell membrane to discharge EVs into the extracellular space. The secretion of Ad-EVs is regulated by multiple factors. Under pathological conditions, such as energy excess and inflammatory stimuli, the release

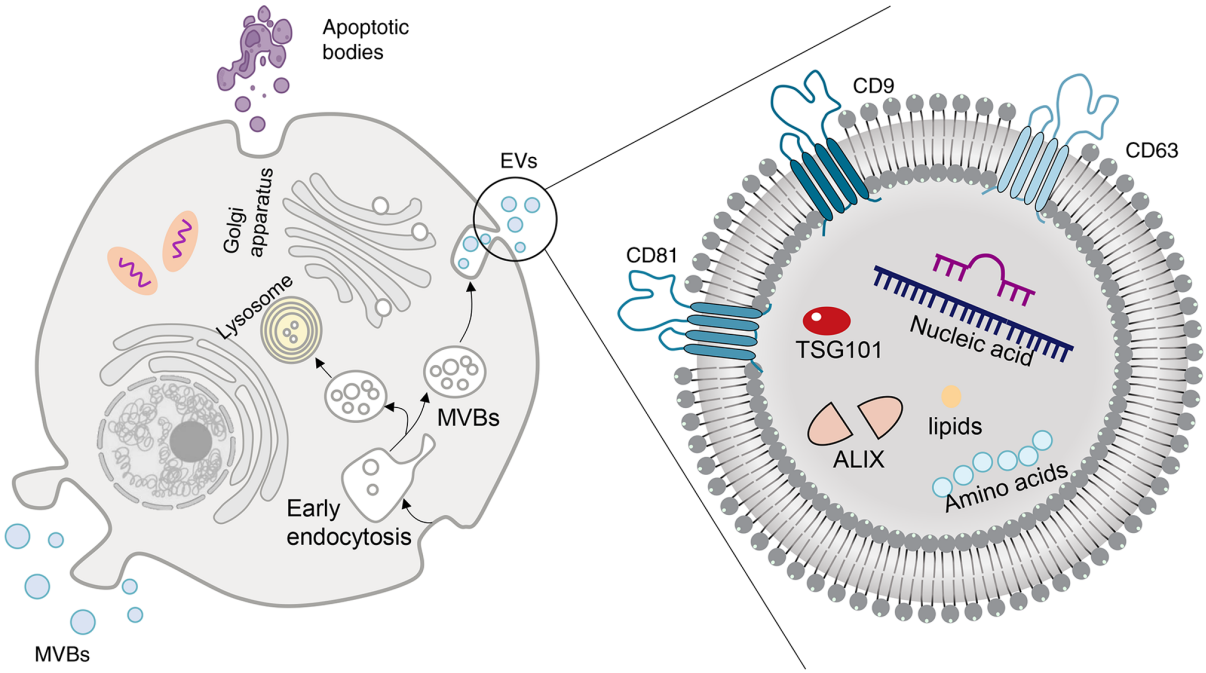

Figure 3. Structure and composition of Ad-EVs. EVs are classified into three main types based on biogenesis and size: exosomes (30-150 nm, derived from multivesicular bodies), microvesicles (100-1,000 nm, released from the plasma membrane), and apoptotic bodies (500-2,000 nm, generated during cellular apoptosis). Adipocytes secrete EVs through the formation of MVBs that fuse with the plasma membrane, releasing their contents into the extracellular space. Ad-EVs carry a complex cargo including canonical EV marker proteins (CD9, CD63, CD81, TSG101), lipids, and nucleic acids (such as miRNAs, lncRNAs, and mRNAs). EVs, extracellular vesicles; MVBs, multivesicular bodies; Ad-EVs, adipocyte-derived extracellular vesicles.

of Ad-EVs from mature adipocytes is significantly increased, accompanied by alterations in their cargo composition (57,58). In obesity and metabolic disorders, Ad-EV generation depends on both the metabolic state of the tissue and intracellular signaling pathways such as mTOR and the Rab protein family (16,56). Inflammatory cytokines (e.g., TNF-α), hypoxia and other factors can also enhance EV release by activating relevant signaling pathways within adipocytes (59).

Ad-EVs contain various bioactive molecules, including proteins, lipids and nucleic acids (60). Proteomics research has shown that they are enriched in marker proteins, such as TSG101 and Caveolin, and also carry enzymes and signaling molecules involved in lipid metabolism (61). The membrane and signaling lipids within EVs are crucial for maintaining EV membrane integrity and facilitating signal transduction (62). The nucleic acid cargo is mainly miRNAs, mRNAs and other non-coding RNAs that can alter gene expression in target cells and modulate metabolism and inflammation (62,63). Serving as a multi-faceted carrier, Ad-EVs mirror the physiological and pathological conditions of adipocytes and facilitate the functional regulation of remote cells by transporting specific biomolecules (Fig. 3).

Biological functions of Ad-EVs. Ad-EVs are involved in metabolism, inflammation, angiogenesis and tissue remodeling (55). Functioning as crucial mediators of intercellular communication, Ad-EVs deliver a range of biomolecules, including proteins, lipids and RNAs to neighboring and remote target cells via membrane fusion or receptor-mediated endocytosis, thereby facilitating signal transduction and regulatory activities (12,13).

Ad-EVs affect metabolic balance through their actions on the liver, muscle and immune system. In the healthy state, these vesicles support pancreatic β-cell viability and enhance insulin secretion, helping to keep blood glucose stable (64). When obesity and inflammation set in, Ad-EVs transport miRNAs and proteins that activate inflammatory pathways in target cells. This aggravates inflammation and contributes to insulin resistance (14,65).

Furthermore, Ad-EVs regulate immune responses. They influence the polarization of macrophages in adipose tissue, encouraging the development of the M1 pro-inflammatory type, which worsens chronic low-grade inflammation (65). In the vasculature, Ad-EVs induce the endothelial expression of the adhesion molecule VCAM-1 under inflammatory conditions, thereby enhancing leukocyte adhesion and promoting vascular inflammation and the progression of atherosclerosis (59).

Ad-EVs act on hepatocytes, Kupffer cells and hepatic stellate cells (HSCs) in the liver. They carry miRNAs and proteins that influence lipid metabolism, inflammation and fibrosis. In hepatocytes, Ad-EVs alter lipid storage and insulin signaling, shifting the hepatic lipid balance (14). They also activate Kupffer cells and HSCs, triggering inflammatory responses and contributing to liver fibrosis (57) (Table I).

In summary, Ad-EVs are intricate vesicles comprised of multiple components, and their makeup and release are influenced by the metabolic condition of adipocytes. By facilitating the transfer of miRNAs, proteins and lipids between cells, they play a crucial role in connecting issues within AT to metabolic diseases, immune system imbalances and liver-related conditions.

4. Role and mechanisms of adipocytes and Ad-EVs in the progression of liver disease

The adipose-liver axis refers to the two-way communication between AT and the liver, carried out through various signaling

Table I. Biological functions, mechanisms and target cells/tissues of Ad-EVs.

Functional category	Mechanism	Target cell/tissue
Metabolic regulation and insulin resistance	Transmit miRNAs and lipids, proteins, and interfere with the insulin signaling pathway	Liver, skeletal muscle
Inflammation and immune regulation	Carry multiple miRNAs, proteins and lipids that participate in regulating inflammation	Macrophages and other immune cells
Angiogenesis	Load angiogenic factors; miRNAs (such as miR-126) regulating endothelial function	Vascular endothelial cells
Regulation of tumor growth and migration	Transported into adjacent tumor cells and improve the proliferation, migration, and chemoresistance of tumor cells	Tumor cells
Self-regulation of AT	Transmit signal molecules to affect the proliferation and differentiation of preadipocytes	Fat precursor cells, adjacent fat cells
Disease biomarkers	As a target for disease prediction and treatment	Liver, vascular endothelial cells

Ad-EVs, adipocyte-derived extracellular vesicles; miRNAs, microRNAs; AT, adipose tissue.

Table II. Function of adipose cells and the extracellular vesicles they produce in different liver disorders, along with their primary target cells.

Hepatopathy	Main function	Target cell
ALD	The breakdown of fat increases, leading to the accumulation of lipids	Hepatocytes
MASLD	Adipocyte hypertrophy and dysfunction of adipocytes promote lipid deposition, leading to fat accumulation in liver cells	Hepatocytes
MASH	Stimulate inflammation and fibrosis	Kupffer cells, hepatic stellate cells
Liver fibrosis, liver cirrhosis	Adipocytes secrete pro-fibrotic cytokines; Activate hepatic stellate cells and accelerate the process of fibrosis	Hepatic stellate cells
HCC	Promote tumor angiogenesis; directly deliver oncogenic molecules; create oncogenic environment	Liver cancer cells, endothelial cells, tumor-associated macrophages

ALD, alcoholic liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis; HCC, hepatocellular carcinoma.

molecules and metabolic processes (66). Adipocytes regulate glycolipid metabolism by releasing adipokines, such as leptin and adiponectin. The liver also shapes AT function through bile acids and factors, such as FGF21. This ongoing interplay is essential for maintaining energy balance across the body.

In obesity, insulin resistance in AT increases basal lipolysis. This worsens adipocyte dysfunction and leads to excess free fatty acids (FFAs) in the liver. The levels of IL-6 and TNF-α then increase, and the adipokine profile shifts toward higher leptin and lower adiponectin, creating a pro-inflammatory state (67). These changes also promote triglyceride (TG) resynthesis, fostering lipid accumulation in the liver and furthering insulin resistance (68). Through endocrine signaling, adipokines released by adipocytes influence target organs such as the liver and muscle and help regulate glucose and lipid metabolism (69,70).

Research has indicated an association between the increased secretion of Ad-EVs and the inflammation of AT, as well as excessive lipid mobilization in human obesity (71). This association is crucial, as it ties AT dysfunction to broader metabolic issues, particularly ALD and MASLD, potentially resulting in the aggravation of liver fat accumulation, inflammation and fibrosis (Table II).

It is widely recognized that the secretion of Ad-EVs is heightened in the AT of individuals with obesity. However, the question of whether this increase is a direct cause of liver disease or simply an indicator of stress in adipocytes remains a matter of debate (60,71). Studies on rodents have demonstrated that Ad-EVs can drive lipid accumulation and inflammation in the liver (72,73). By contrast, human studies have largely demonstrated correlations, and it remains unclear whether the composition of Ad-EVs, particularly their lipids

and miRNAs, differs sufficiently across distinct metabolic states to give rise to divergent pathological outcomes (74). It remains unclear whether Ad-EVs primarily influence the liver through direct uptake or by altering systemic inflammation, a distinction that could have critical implications for treatment strategies (14,60,75).

Role of adipocytes and Ad-EVs in ALD. ALD is one of the main causes of chronic liver disease, and its risk is closely linked to the amount of alcohol consumed (76). Alcohol-induced AT lipolysis increases the release of FFAs, which accumulate in the liver and contribute to hepatic steatosis (77). The disruption of the protective adiponectin-FGF15/19 axis has also been implicated in disease severity (78).

However, direct evidence regarding the role of Ad-EVs in ALD remains very limited. Emerging studies suggest that Ad-EVs may modulate hepatic immunity and inflammation, hepatocyte metabolism and HSC activation (75,79). Further investigations are likely to clarify the key pathogenic molecules at play, including certain miRNAs and proteins, and assess their viability as diagnostic markers or therapeutic targets.

Role of adipocytes and Ad-EVs in MASLD. MASLD is a type of liver disease characterized by hepatic steatosis, in the presence of at least one cardiometabolic risk factor, and following the exclusion of other identifiable causes of hepatic steatosis, such as excessive alcohol consumption or viral hepatitis (80).

The association between fat cells and the liver is vital in the development of MASLD, primarily evident through alterations in adipocyte size and functionality. When energy intake is excessive, fat buildup triggers adaptive responses. Ideally, adipocytes should multiply so that cell numbers increase, while size and function stay normal, supporting metabolic health (81). However, under disease conditions, adipocytes expand excessively, entering a hypertrophic state that leads to issues such as relative hypoxia, stress on the endoplasmic reticulum, mitochondrial impairment, and increased mechanical strain, ultimately causing dysfunction in adipocytes (82,83).

Adipocyte hypertrophy is closely associated with the severity of MASLD. These enlarged adipocytes undergo structural and functional alterations within AT, driving the excessive release of lipids and inflammatory mediators into the liver. This, in turn, induces hepatic lipid accumulation and exacerbates inflammatory responses, ultimately propelling the progression from MASLD to MASH and hepatic fibrosis (84,85).

Adipocyte dysfunction is recognized as a core pathophysiological process underlying the onset and progression of MASLD (86). In obesity, adipocytes undergo hypertrophy and acquire pro-inflammatory characteristics. This changes their secretory profile: The release of pro-inflammatory factors increases and adiponectin levels decrease. Enlarged adipocytes discharge substantial amounts of FFAs, which travel directly to the liver via the portal vein and promote TG accumulation in hepatocytes (87). In insulin resistance, AT releases excessive FFAs and pro-inflammatory cytokines, such as IL-6, aggravating hepatic lipid accumulation and systemic metabolic dysfunction through a vicious liver-adipose axis (88,89). *In vitro* experiments have demonstrated that conditioned media from both mature and hypertrophic adipocytes can induce lipid accumulation in hepatocytes, with the latter exhibiting a more pronounced effect. This suggests that, in addition to FFAs, adipocytes may regulate hepatic metabolism through other soluble mediators, such as cytokines (90). Furthermore, the absence of monoglyceride lipase can alleviate diet-induced liver steatosis by suppressing the expression of key lipogenic enzymes, such as sterol regulatory element-binding protein 1c and PPARγ2, while promoting fatty acid oxidation (91).

miRNAs carried by Ad-EVs have emerged as crucial paracrine regulators of hepatic lipid metabolism, with miR-122 being the most well-validated candidate molecule. In adipocyte-derived exosomes from obese individuals, miR-122 is consistently enriched and promotes MASLD development by silencing Sirtuin 1, thereby enhancing lipogenesis, apoptosis and hepatic inflammation (92,93). Several other miRNAs, including miR-34a, miR-148a-3p and miR-27a, have also been implicated in modulating lipogenesis and insulin signaling in hepatocytes (63,94,95). Furthermore, Ad-EVs may contribute to the pathogenesis and progression of MASLD, including advanced MASH, by delivering lipids, proteins and non-coding RNAs to hepatocytes, thereby modulating lipid metabolism and inflammatory responses (96,97) (Fig. 4). However, the direction and magnitude of miRNA alterations vary considerably across existing studies, likely stemming primarily from differences in obesity models, EV isolation methods, and target cell systems. This inconsistency precludes a clear consensus on the molecular signatures of the most pathogenic Ad-EV miRNAs. Future studies are warranted to adopt standardized methodologies and perform *in vivo* validation in relevant animal models to determine whether a defined set of Ad-EV-derived miRNAs can serve as reliable biomarkers or therapeutic targets for MASLD.

In summary, alterations in adipocyte size and their dysfunction play a crucial role in aggravating liver fat buildup and inflammation. This occurs through the enhancement of insulin resistance, increased fatty acid release, the production of pro-inflammatory substances and irregular lipid metabolism within adipose tissue. These processes are central to the onset and progression of MASLD. Targeting adipocyte enlargement and associated signaling pathways may offer a novel approach for treating MASLD.

Role of adipocytes and Ad-EVs in liver fibrosis and cirrhosis. Liver fibrosis is a common pathological characteristic linked to numerous long-term liver disorders. This condition primarily arises from the stimulation of HSCs and the overproduction of extracellular matrix (ECM) proteins (98).

Adipocytes regulate HSC activity by releasing various factors and signaling molecules, influencing liver fibrosis progression (99). Research has demonstrated that adipocytes can secrete a variety of pro-fibrotic cytokines, such as transforming growth factor-β1 (TGF-β1), PDGF and connective tissue growth factor, with TGF-β1 being identified as the most potent pro-fibrotic factor (100). These cytokines activate HSCs and promote ECM deposition (101). Additionally, leptin secreted by adipocytes enhances collagen synthesis through the activation of HSCs (102). Pro-inflammatory factors derived from adipocytes, including TNF-α and IL-6, also play a critical role in the development and progression of fibrosis (103,104).

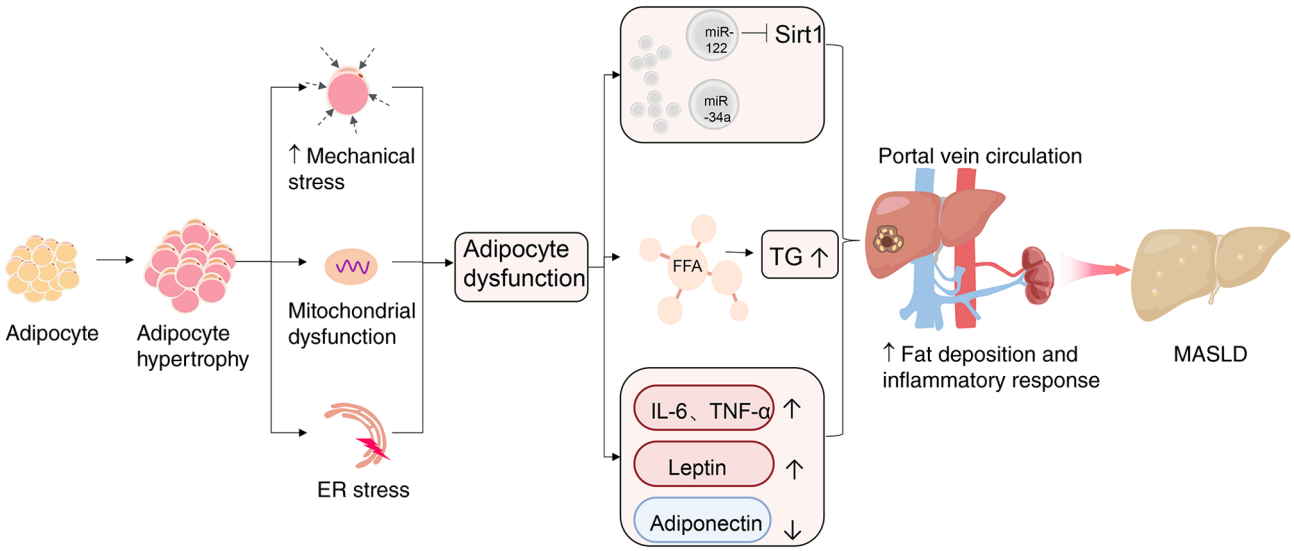

Figure 4. Role of adipocytes and Ad-EVs in MASLD. Adipocyte hypertrophy in obesity leads to mechanical stress, mitochondrial dysfunction and ER stress, collectively resulting in adipocyte dysfunction. Dysfunctional adipocytes secrete increased amounts of FFAs, adipokines and Ad-EVs. These factors reach the liver and promote hepatic lipid accumulation and inflammatory responses, primarily via activation of the NF-κB pathway in hepatocytes and Kupffer cells, ultimately inducing MASLD. MASLD, metabolic dysfunction-associated steatotic liver disease; ER stress, endoplasmic reticulum stress; Ad-EVs, adipocyte-derived extracellular vesicles; FFA, free fatty acid; TG, triglyceride.

Collectively, these factors constitute the molecular basis by which adipocytes promote hepatic fibrosis. Conversely, adiponectin from adipocytes opposes hepatic fibrosis by reducing inflammation, suppressing HSC proliferation and migration, and relieving endoplasmic reticulum stress (105,106).

Adipocytes may directly promote HSC activation. *In vitro*, it has been demonstrated that conditioned medium from mature 3T3-L1 adipocytes induces LX-2 cell activation, as evidenced by the upregulated expression of α-smooth muscle actin and type I collagen, and the activation of the TGF-β/Smad2/3 signaling pathway. The process begins when TGF-β1 binds to the always-active type II receptor (TβRII), which then recruits and phosphorylates the type I receptor (TβRI/ALK5), activating its kinase function (107,108). Once activated, TβRI phosphorylates the receptor-regulated Smad proteins, Smad2 and Smad3 (R-Smads), at specific C-terminal SSXS motifs (109). This Smad-dependent pathway is regulated by the inhibitory Smad7, which competes with R-Smads for TβRI binding, thus inhibiting R-Smad phosphorylation and reducing the intensity and duration of fibrogenic signaling (110). Alongside this canonical pathway, TGF-β1 also activates several non-canonical, Smad-independent pathways, such as the MAPK cascades (JNK, p38, ERK1/2) and NF-κB signaling, which either support or counteract Smad-mediated effects to influence HSC proliferation, survival and ECM remodeling (111,112). The intricate interactions among these pathways enhance the fibrotic response; notably, JNK activation induced by TGF-β1 facilitates the autophagic breakdown of lipid droplets in HSCs, supplying the metabolic energy necessary for their transformation into a proliferative, myofibroblast-like state (113). This process is also linked to reduced insulin sensitivity, increased endoplasmic reticulum stress, and heightened autophagy, all of which promote liver fibrosis (114). Specifically, endoplasmic reticulum stress triggers the unfolded protein response (UPR) through IRE1α, which activates the downstream ASK1/JNK axis and further amplifies TGF-β-driven fibrogenic gene expression, creating a feedforward loop between ER stress and Smad2/3 activation in HSCs (115). Furthermore, BAT can inhibit HSC activation by secreting various factors, thereby obstructing the progression of fibrosis. Conversely, BAT dysfunction intensifies fibrosis (99). This highlights the different effects of adipocyte types on hepatic fibrosis.

Adipocytes can also communicate with the liver by secreting EVs, thereby influencing the metabolism and inflammatory state. These Ad-EVs carry pro-inflammatory molecules and miRNAs that activate Kupffer cells and HSCs, triggering inflammatory pathways that promote liver fibrosis (14,57). Pro-inflammatory cargo within these EVs, such as TNF-α and miR-27a, promote the conversion of stellate cells into a fibroblast-like state by triggering endoplasmic reticulum stress and TGF-β signaling, leading to increased collagen accumulation and liver cirrhosis (116,117). Ad-EVs may also transport various bioactive agents that act on hepatocytes and liver macrophages, fostering insulin resistance and hepatic fat accumulation and thereby further accelerating fibrotic progression (118,119) (Fig. 5).

To conclude, adipocytes contribute to the initiation and progression of liver fibrosis through multiple pathways, including metabolic dysregulation, secretion of adipokines and pro-fibrotic cytokines, and release of extracellular vesicles. A more in-depth understanding of these multifaceted roles will facilitate the development of stage-specific therapeutic strategies.

Role of adipocytes and Ad-EVs in HCC. HCC is a malignant liver tumor, and its development is closely tied to adipocytes. Adipocytes promote chronic liver injury and cancer development by releasing inflammatory mediators and causing hormonal dysregulation (120,121). In obesity, elevated leptin binds to the long-form leptin receptor (LEPRb/Ob-Rb) on HCC cells, inducing receptor dimerization and Janus-activated

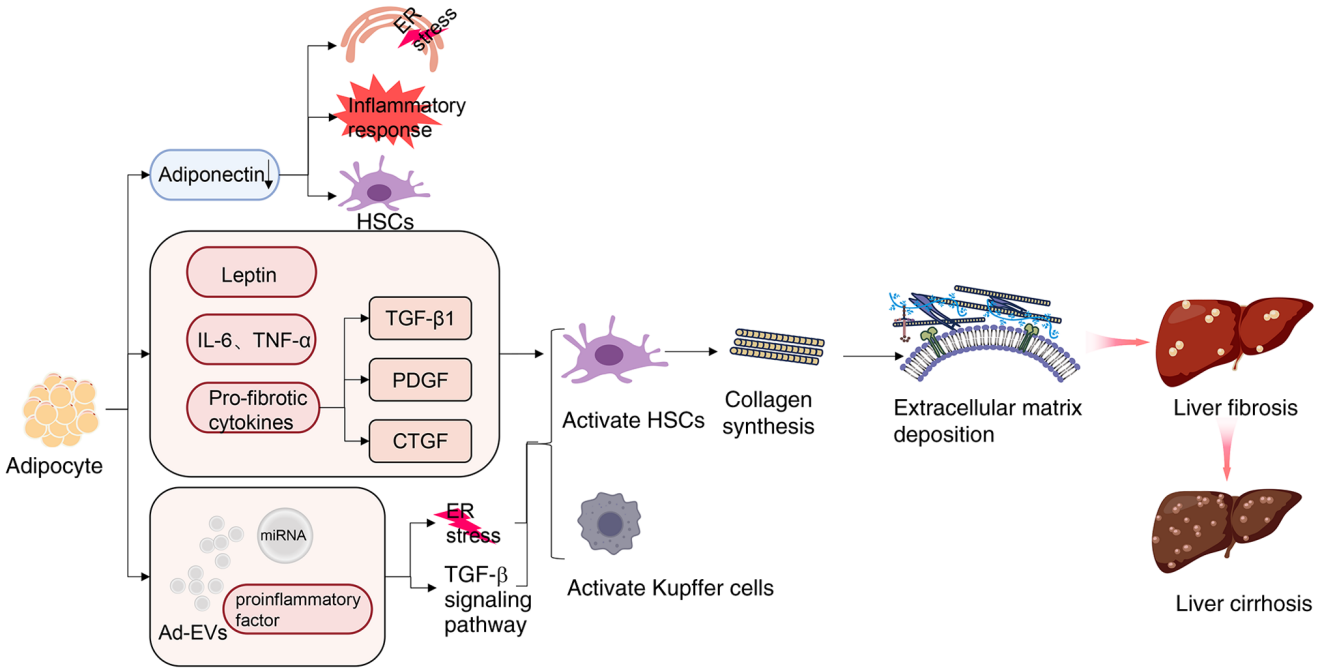

Figure 5. Role of adipocytes and Ad-EVs in liver fibrosis and cirrhosis. Activated by adipocyte-derived adipokines (e.g., leptin) and Ad-EVs, hepatic stellate cells (HSCs) transdifferentiate into myofibroblasts, while Kupffer cells become pro-inflammatory. This leads to increased synthesis of collagen types I and III, deposition of extracellular matrix, and progressive liver fibrosis, which may advance to cirrhosis. The TGF-β signaling pathway is a key mediator of HSC activation. Arrows indicate activation and progression. Ad-EVs, adipocyte-derived extracellular vesicles; HSCs, hepatic stellate cells; ER stress, endoplasmic reticulum stress; PDGF, platelet-derived growth factor; CTGF, connective tissue growth factor.

kinase (JAK2) autophosphorylation (122). Activated JAK2 phosphorylates transcription factors, such as signal transducer and activator of transcription 3 (STAT3), which upregulates pro-proliferative genes, including cyclin D1, c-Myc and Bcl-2 (123). Leptin also enhances the cyclin D1 promoter, facilitating G1/S cell cycle transition, and counteracts TGF-β1-induced apoptosis by downregulating Bax and sustaining Bcl-2 levels (124). Beyond JAK2/STAT3, leptin activates the phosphatidylinositol 3-kinase (PI3K)/AKT and ERK pathways. The blockade of JAK/STAT signaling effectively inhibits leptin-induced invasion, while the co-inhibition of ERK and PI3K further attenuates leptin-stimulated cell migration (125). In the PI3K/AKT/mTOR cascade, activated receptor tyrosine kinases recruit PI3K to the plasma membrane, triggering AKT and mTOR phosphorylation and thereby orchestrating oncogenic processes, such as cell cycle progression, apoptosis inhibition, and metabolic reprogramming (126). mTOR activation leads to the hyperphosphorylation of 4EBP-1, releasing eIF4E to form the eIF4F complex and promote cap-dependent translation of tumor-promoting proteins (127). Furthermore, the PI3K/AKT pathway promotes angiogenesis via mTOR/p70S6K1 and the suppression of FOXO and GSK-3β, resulting in increased HIF-1α and VEGF expression. It also enhances tumor invasiveness by downregulating E-cadherin and activating MMPs for extracellular matrix remodeling (128). Notably, crosstalk exists between these pathways: Leptin-induced MAPK signaling engages NF-κB through ERK1/2, p38, and JNK, upregulating pro-inflammatory and pro-angiogenic factors and establishing a self-perpetuating oncogenic cycle (129).

Antitumor adipokines, such as adiponectin exert protective effects against HCC. Adiponectin binds to AdipoR1 and AdipoR2: AdipoR1 primarily activates AMPK, whereas AdipoR2 regulates PPARα activity (130). Mechanistically, adiponectin promotes phosphorylation of AMPK and the tumor suppressor TSC2, leading to mTOR inhibition in HCC cells and consequent suppression of tumor-promoting translation (131). Additionally, adiponectin activates JNK while inhibiting STAT3, thereby counteracting the oncogenic JAK2/STAT3 axis driven by leptin (132). The adiponectin-AMPK pathway functionally opposes the PI3K/AKT/mTOR signaling cascade; consequently, obesity-associated hypoadiponectinemia disrupts this protective interaction and may signal an elevated risk of hepatocellular carcinoma (133). Sex hormones also modulate this pathway: Testosterone stimulates JNK in adipocytes, reducing adiponectin secretion and enhancing liver cancer cell proliferation. In contrast, androgen blockade in male mice elevates circulating adiponectin and activates AMPK and p38α signaling in tumor tissues, thereby decelerating tumor progression (134).

Neuregulin-4 (NRG4) is an adipose-derived endocrine factor, the loss of which exacerbates the formation of a pro-tumorigenic immune microenvironment and the development of HCC, whereas its overexpression confers protection (135). These findings position NRG4 as an immune checkpoint mediator that remodels the hepatic immune landscape to counteract HCC progression. Research further demonstrates that during fasting, adipocytes assume the uridine-producing role of the liver to sustain blood glucose homeostasis and thermoregulation, and that uridine deficiency may exacerbate metabolic disorders, correlating with increased diabetes and cancer risk (136).

The role of Ad-EVs in the HCC microenvironment is multifaceted. In obesity, these vesicles promote tumor cell

proliferation, invasion and metastasis by delivering pro-tumorigenic miRNAs and inflammatory mediators. Conversely, certain Ad-EV cargos can elicit anti-tumor immune responses that restrain tumor progression (137,138). miRNAs and long non-coding RNAs (lncRNAs) contained in Ad-EVs contribute to shaping the tumor microenvironment by fostering an immunosuppressive milieu, regulating angiogenesis, and modulating tumor cell heterogeneity (139). Thus, Ad-EVs markedly contribute to microenvironmental remodeling and the progression of HCC (Fig. 6).

The interaction between adipocytes and tumor cells is of paramount in colorectal cancer and can serve as a biomarker for subsequent research (140). However, research in the field of HCC remains limited, with studies primarily focusing on vesicles secreted by hepatocytes under fatty liver conditions. These vesicles secreted by fatty liver cells serve as pivotal mediators linking metabolic abnormalities to HCC initiation and metastasis. Their core function involves delivering miRNAs that suppress the large tumor suppressor kinase 2 gene, thereby activating the YAP signaling pathway. This reprograms the liver microenvironment, directly promoting carcinogenesis and establishing immune suppression, thereby accelerating HCC progression (141).

Adipocytes contribute to the development of HCC by releasing pro-cancerous adipokines like leptin, which function through the JAK2/STAT3 and PI3K/AKT/mTOR signaling pathways. By contrast, protective agents, such as adiponectin and NRG4 help inhibit tumor growth. Additionally, Ad-EVs influence the liver tumor microenvironment in a context-sensitive and reciprocal way, highlighting the intricate interactions between AT and HCC as a potential avenue for treatment strategies.

In summary, adipocytes and their extracellular vesicles play a crucial role in the onset and progression of various liver conditions, such as ALD, MASLD, fibrosis, cirrhosis and HCC. This occurs through overlapping pathways involving lipotoxic effects, adipokine dysregulation, and intercellular communication facilitated by EVs, underscoring the importance of the adipose-liver axis as a key area for both diagnostic and therapeutic opportunities.

5. Role of adipocytes and Ad-EVs in the diagnosis and treatment of liver disease

Diagnostic value of Ad-EVs in liver disease. Ad-EVs hold considerable promise for the early detection of liver disorders, attributed to their unique miRNA content and protein expression characteristics. Variations in the quantity and source of these vesicles carry diagnostic value for MASLD. As the condition advances, there is an increase in both the overall number and specific types of vesicles originating from hepatocytes, macrophages, and neutrophils found in the bloodstream. This implies that assessing the ratio of vesicles from distinct cellular sources could provide valuable diagnostic insights (142). Ad-EVs contain high levels of certain miRNAs, including miR-148a-3p, miR-98-5p and miR-365-3p. These miRNAs are tied to how adipocytes handle metabolism and affect cell growth, insulin signaling, immune responses, thermogenesis and lipid metabolism (63). Moreover, the protein composition of Ad-EVs includes specific biomarkers that mirror the physiological and pathological conditions of their originating cells (143). In liver diseases, the miRNA and protein profiles of Ad-EVs shift markedly. These changes track with hepatic steatosis, inflammation, and fibrosis (13,144). As a non-invasive liquid biopsy tool, EVs can be isolated from blood, thereby avoiding the risks associated with invasive procedures such as liver biopsy, while improving patient compliance and monitoring feasibility (145,146).

Recent clinical studies have validated the diagnostic potential of circulating EVs in MASLD. Liver-derived $ASGR1^+$ and $CD36^+$ EV subpopulations are elevated in patients with MASLD, decline markedly after weight loss, and are associated with hepatic fat content and fibrosis markers, establishing them as dynamic, disease-responsive biomarkers (147). $CD63^+$ $ASGR1^+$ EVs are more abundant in steatohepatitis and promote TGF-β/TIMP-1 secretion in macrophages, implicating these EV phenotypes in fibrogenic signaling pathways (148).

Machine learning combined with multi-omics has improved the EV-based diagnosis of MASLD. Previously, researchers used explainable artificial intelligence to evaluate plasma EV size and concentration (149). This model achieved an AUC of 0.86 for telling steatosis from non-steatosis. When combined with clinical and body measurement data, it achieved an exceptional AUC of 1.00 for detecting severe steatosis (149). Serum EV-derived miRNA panels, including miR-574-3p, miR-542-3p and miR-200a-3p, have been confirmed as diagnostic markers through purification-free methods, with higher levels of miR-542-3p and miR-200a-3p linked to advanced fibrosis, suggesting their potential for disease staging (150).

Beyond MASLD, EV-encapsulated miRNAs have surfaced as valuable analytes for liquid biopsies in HCC. In a previous study, an analysis of plasma EV miRNAs in individuals with HCC not associated with hepatitis B or C revealed that EV-miR-19-3p stands out as the most effective diagnostic marker, exhibiting significant sensitivity for cases that are AFP-negative and in the early stages of the disease (151). Furthermore, multivariate analysis indicated that higher levels of EV-miR-19-3p were independently linked to a poorer overall survival, highlighting its potential as both a diagnostic and prognostic biomarker (151).

The successful clinical translation of EV-based diagnostics is critically dependent on the rigorous standardization of both isolation and characterization methods. In accordance with the Minimal Information for Studies of Extracellular Vesicles 2018 (MISEV2018) guidelines, standard EV characterization typically employs nanoparticle tracking analysis to determine size distribution and concentration, transmission electron microscopy to examine morphology and flow cytometry or immunoblotting to profile surface markers, including CD9, CD63, CD81 and TSG101, all of which are recognized as canonical EV identity markers (152). The updated MISEV2023 guidelines provide a comprehensive framework for essential reporting standards, emphasizing quantitative assessment of EV yield, purity and cargo composition to improve cross-study comparability and support regulatory evaluation (152). Adherence to these guidelines is essential not only for ensuring reproducibility in individual studies, but also for enabling meaningful comparisons of EV-based biomarker data across diverse cohorts, a prerequisite for future regulatory approval and clinical implementation.

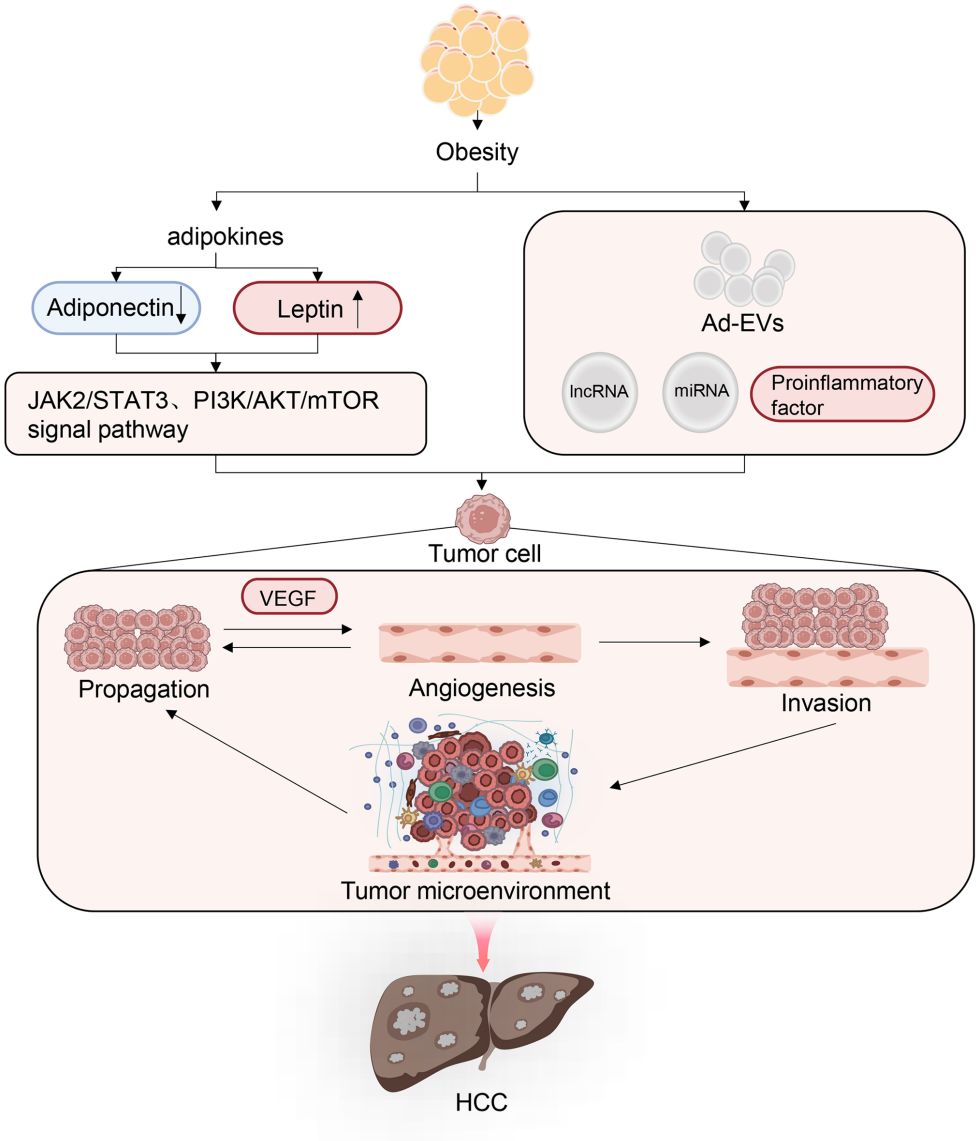

Figure 6. Role of adipocytes and Ad-EVs in HCC. In the obese state, adipocyte-secreted adipokines (e.g., leptin) and Ad-EVs promote HCC progression through multiple mechanisms. Adipokines activate oncogenic signaling pathways, such as JAK2/STAT3 and PI3K/AKT/mTOR in liver cancer cells. Ad-EVs carry pathogenic lncRNAs, miRNAs and pro-inflammatory factors that enhance cancer cell proliferation, invasion, and vascular metastasis, and remodel the tumor microenvironment. Ad-EVs, adipocyte-derived extracellular vesicles; HCC, hepatocellular carcinoma; lncRNAs, long non-coding RNAs; miRNAs, microRNAs.

An evaluation of candidate EV biomarkers based on their diagnostic efficacy and validation status reveals a layered landscape. For the assessment of advanced fibrosis (≥F3), protein-based indicators currently yield the most reliable results: Complement component C7 effectively differentiates between advanced and mild fibrosis, achieving an AUC of 0.83 (153). Fibulin-3 has also been shown to serve as an independent predictor of liver-related clinical outcomes, such as HCC and hepatic decompensation, in biopsy-confirmed groups of >500 patients (149). EV-derived miRNA panels provide specific mechanistic insight and can indicate dynamic pathological alterations. Nonetheless, they face marked methodological variability across different studies, particularly concerning EV isolation techniques, RNA extraction processes and normalization methods. The lack of direct comparative evaluations remains a key barrier to their clinical implementation. Consequently, to facilitate the integration of these promising biomarkers into standard clinical workflows, there is an urgent need for extensive multicenter validation studies that utilize standardized protocols for EV isolation and analysis.

To conclude, miRNA and protein biomarkers sourced from Ad-EVs exhibit notable potential as non-invasive liquid biopsy methods for diagnosing, staging, and evaluating the prognosis of MASLD, fibrosis and HCC, particularly when combined with machine learning and multi-omics approaches. However, it is crucial to conduct extensive multicenter validation and establish standardized protocols for EV isolation and analysis before these methods can be applied clinically.

Diagnostic value of adipocyte-associated factors and proteins. Accumulating evidence indicates that various adipokines play pivotal roles in hepatic metabolism (154). However, the diagnostic performance of a single adipokine is generally insufficient to meet the demands of reliable clinical application. A prevailing consensus holds that combined testing

panels integrating multiple adipokines with other biomarkers can substantially enhance diagnostic accuracy, surpassing the performance of individual markers. For instance, in a previous study, the combination of serum adiponectin, the homeostatic model assessment of insulin resistance, and serum type IV collagen 7S domain increased the diagnostic sensitivity for early-stage MASH from 68% (with adiponectin alone) to 94%, while maintaining a specificity of 74% (155). Moreover, while the area under the receiver operating characteristic (AUROC) of IGF-1 alone for detecting advanced fibrosis was 0.67, its combination with the international normalized ratio and serum ferritin elevated the AUROC to 0.81 (156).

These studies demonstrate that combined adipokine panels hold considerable promise for the non-invasive diagnosis of MASH and for identifying patients with progressive fibrosis (157). Beyond classical adipokines, hepatokines such as FGF21 have emerged as leading candidate molecules for the detection of early-stage MASH and the assessment of disease severity, with consistently observed significant elevations in the circulation of patients with MASLD/MASH (158,159). Inflammatory mediators, including TGF-β and IL-6, contribute by directly reflecting AT inflammation levels that are associated with the development of MASH and its inflammatory severity (160).

At the cellular and molecular level, adipocyte-specific proteins and morphological features are also being explored as potential diagnostic indicators. Adipocyte fatty acid-binding protein is aberrantly expressed in the livers of patients with MASLD and is associated with hepatic inflammatory responses, demonstrating high sensitivity and specificity for the diagnosis of MASLD. Serum levels of apolipoprotein F are significantly elevated in patients with MASLD and are associated with insulin resistance, further supporting its potential for clinical application (161,162). In addition, alterations in adipocyte size have been linked to the progression of liver disease, and researchers have developed MATLAB-based script tools, such as PixCell that enable precise quantification of adipocyte lipid droplet size in confocal microscopy images, thereby allowing a more reliable assessment of adipocyte functional status (163).

Although combined adipokine testing has shown promise in the diagnosis of liver diseases, its clinical translation remains constrained by several key bottlenecks. The majority of current combined testing models are derived from retrospective studies with insufficient prospective validation; the incremental value of adipocyte-specific markers over existing non-invasive scores remains to be clarified; and the optimal combination strategy for multiple marker categories has yet to be established. Future research is warranted to prioritize prospective multi-center validation, head-to-head comparisons of multiple combinations, and the integration with emerging technologies such as extracellular vesicles.

Therapeutic role of Ad-EVs in liver disease. The functional outcomes of AT-derived EVs are largely dictated by their cellular source and the physiological state of the donor cells. BAT serves as a primary source of exosomes, secreting significantly greater quantities and higher protein content than WAT; these BAT-derived exosomes have been shown to alleviate metabolic syndrome in high-fat diet-fed mice, and are thus generally considered beneficial with therapeutic potential (164). ADSC-EVs also exert protective effects. However, vesicles released from mature adipocytes under metabolic stress are predominantly pathogenic, driving disease progression rather than alleviating it (165).

Pathogenic roles of EVs derived from mature adipocytes. Unlike BAT exosomes, EVs secreted by mature adipocytes under pathological conditions (e.g., obesity) predominantly exert detrimental effects. At the molecular level, these mature Ad-EVs regulate hepatic metabolic pathways, inflammatory responses, and fibrotic progression by transporting specific miRNAs, lncRNAs and proteins. For instance, miR-410-3p inhibits adipocyte differentiation by targeting IRS-1 in cancer-associated cachexia (166). Moreover, the reduced expression of miR-29a-3p in mature Ad-EVs exhibits a close association with increased hepatic lipid deposition (167). Mature Ad-EVs modulate the expression of fibrosis-related genes in the liver, thereby promoting MASH development. A specific mechanism involves exosomes secreted by adipocytes under endoplasmic reticulum stress delivering aldo-keto reductase family 1 member B7 to hepatocytes, increasing glycerol levels and thereby triggering MASH (168). Nevertheless, these findings indicate that mature Ad-EVs play only a limited role in energy metabolism and leptin sensitization under homeostatic conditions and are therefore not currently considered suitable clinical therapeutic tools.

An alternative therapeutic paradigm involves inhibiting the secretion of pathogenic mature Ad-EVs. Pharmacological inhibition using GW4869, a neutral sphingomyelinase 2 inhibitor that blocks exosome biogenesis and release by reducing ceramide generation, has been shown in preclinical obesity models to reduce EV release and ameliorate hepatic steatosis and inflammation (96). Although the majority of studies have focused on EVs derived from hepatocytes or tumors, direct evidence in adipocytes is emerging, although it is still less extensive (79,169). However, the lack of adipocyte-specific targeting, potential interference with physiological EV functions, and unknown long-term safety profile currently preclude clinical translation.

Therapeutic potential of EVs derived from adipose-derived MSCs. In contrast to the pathogenic nature of mature Ad-EVs, ADSC-EVs provide a safe and effective therapeutic alternative for liver diseases (170). They can alleviate insulin resistance and local inflammation, and can attenuate or inhibit the progression of liver tumors. Engineered ADSCs exhibit potent anti-fibrotic properties by selectively transporting miR-181-5p to HSCs via exosomes, establishing a theoretical framework for using ADSC-EVs to deliver miRNA for the treatment of liver fibrosis (171). Notably, ADSC-EVs have demonstrated direct hepatoprotective effects in models of acute liver injury: In a previous study, intravenously administered ADSC-EVs significantly attenuated carbon tetrachloride (CCl_4)-induced hepatocyte apoptosis and oxidative stress, reduced serum ALT/AST levels, and accelerated liver regeneration, highlighting their therapeutic relevance specifically within hepatic disease contexts (172).

ADSC-EVs inherently possess excellent biocompatibility and tissue-targeting capabilities, and can be engineered to achieve effective delivery to liver-specific cells (173,174). They play a crucial role in regulating hepatic inflammation

and fibrosis by transporting miRNAs (such as miR-23a/b and miR-27b-3p) and proteins. This transport modulates signaling pathways in recipient cells, including the NF-κB pathway, which alleviates hepatic cellular stress, inflammatory responses, and fibrotic progression (143,175). Moreover, bioengineered EVs (such as those with surface modifications or fused with carrier molecules) can enhance their targeting to the liver and their capacity to deliver therapeutic agents, thereby improving therapeutic efficacy (176,177). By integrating EVs with biomaterials, such as hydrogels to create drug delivery systems, controlled release and sustained action can be achieved, which improves the hepatic microenvironment and promotes liver tissue repair (178). These strategies represent innovative approaches for the therapeutic application of ADSC-EVs in liver diseases, particularly MASH, liver fibrosis, and hepatic injury.

Recent studies have further expanded the mechanistic understanding of hepatoprotection by ADSC-EVs to encompass the gut-liver axis. In models of CCl_4/diethylnitrosamine-induced liver fibrosis, ADSC-EVs not only directly suppress hepatic stellate cell activation and reduce collagen deposition, but also restore gut barrier integrity and rebalance dysbiotic gut microbiota composition, thereby interrupting the enterohepatic cycle of inflammatory signaling and attenuating fibrogenesis through simultaneous modulation of hepatic, intestinal and microbial compartments (179).

ADSC-EVs provide a flexible and hopeful therapeutic approach for liver disorders, as their engineered surface alterations, cargo enhancements, preconditioning techniques and integration with biomaterials work together to improve their effectiveness in reducing inflammation, fibrosis, and protecting liver cells in various preclinical studies.

EVs from other sources for the treatment of liver disease. In addition to vesicles from fat cells, EVs from various origins exhibit promise in addressing liver disorders. Exosomes from human umbilical cord-derived MSCs can influence fat accumulation and obesity-related genes through the delivery of miR-627-5p, which enhances glucose and lipid metabolism in rats with MASLD and reduces liver injury, offering a new approach for MASLD treatment (180). Likewise, exosomes from MSCs contain miR-24-3p, which mitigates oxidative stress and inflammation in fatty liver disease by targeting the Keap-1 signaling pathway, thus providing liver protection (181). Non-adipose EVs serve as a valuable addition to ADSC-EV strategies, with preliminary trials indicating their potential for treating MASLD, fibrosis, liver failure and HCC.

Even with recent therapeutic advances, significant translational hurdles remain before Ad-EV-based diagnostics and therapies can be widely adopted in clinical settings. A major obstacle is the lack of standardization in EV isolation and characterization; methods such as ultracentrifugation, size-exclusion chromatography and precipitation kits yield heterogeneous EV populations with inconsistent cargo, compromising cross-study comparability and regulatory compliance (182,183). Although the latest MISEV2023 guidelines outline essential reporting criteria, uniform clinical-grade GMP protocols for therapeutic EV production are still under development (184,185). Scaling up the production of engineered EVs, particularly those from genetically altered ADSC parent cells, necessitates a shift from lab-scale to pharmaceutical-grade manufacturing, a challenge currently being tackled with microfluidic and bioreactor technologies (186). Systematically addressing these translational issues is crucial for unlocking the complete clinical potential of the adipocyte-liver EV axis in the field of hepatology.

In summary, EV-based therapeutic strategies can be broadly divided into two categories. The first involves inhibiting the release of pathogenic Ad-EVs using agents such as GW4869, which has shown preliminary efficacy in cellular and animal models; however, long-term safety and target specificity await systematic evaluation. The second harnesses ADSC-EVs, which have demonstrated robust hepatoprotective, anti-fibrotic and anti-inflammatory effects in various animal models of liver disease. At the clinical level, early-phase trials of MSC-derived EVs for chronic liver diseases have been reported (e.g., umbilical cord-derived MSC-EVs), whereas clinical trials involving ADSC-EVs have not yet been initiated, and no product has received market approval.

Therapeutic applications for targeting adipocytes in liver diseases. Adipocyte-centered therapeutic strategies have emerged as a promising direction for combatting metabolic dysfunction-associated liver diseases; however, the vast majority of targets remain at the preclinical validation stage.

The first category comprises targets whose inhibition or deletion ameliorates disease. The adipocyte-specific knockout of autophagy-related 7, glucose-dependent insulinotropic polypeptide receptor, or the inhibition of the deubiquitinase ubiquitin-specific protease 1 all attenuate hepatic lipid accumulation (187-189). Furthermore, antagonizing neuropeptide Y signaling reduces AT inflammation and ameliorates hepatic steatosis; intervening in the poly(ADP-ribose) polymerase 1 (PARP1)/Lix1 homolog like (LIX1L)/cluster of the CD36 axis (e.g., inhibiting PARP1 activity or knocking down LIX1L) suppresses hepatic lipid accumulation, inflammation, and fibrosis by downregulating CD36 expression; and inhibiting integrator complex subunit 6 markedly reduces hepatocyte steatosis through the β-catenin-peroxisome proliferator-activated receptor gamma (PPARγ) pathway (190-192). The second category encompasses targets whose loss of function exacerbates disease; accordingly, enhancing the activity of adrenomedullin 2 (ADM2) or the adenosine A2A receptor (A2AR) exerts protective effects. The AT overexpression of ADM2 or the administration of an A2A receptor agonist both ameliorate hepatic lipid deposition and inflammation (193,194). Similarly, PR domain-containing protein 16 has been demonstrated to confer hepatoprotection in models of alcoholic liver disease and diet-induced obesity, among others (195). Collectively, the hepatoprotective effects of these targets have been validated in mouse models *in vivo*; however, direct histological evidence from human liver tissue remains lacking for the majority of targets, and thorough validation in human AT is indispensable before translating these findings into therapeutic regimens for human MASLD.

Modulation of the adipokine axis also represents a current research hotspot. A preliminary study involving 37 obese individuals with hepatic steatosis demonstrated that a very low-energy ketogenic diet reduced the leptin-to-adiponectin ratio and concurrently improved parameters, including the controlled attenuation parameter and liver stiffness measurement, suggesting that modulating the adipokine axis through

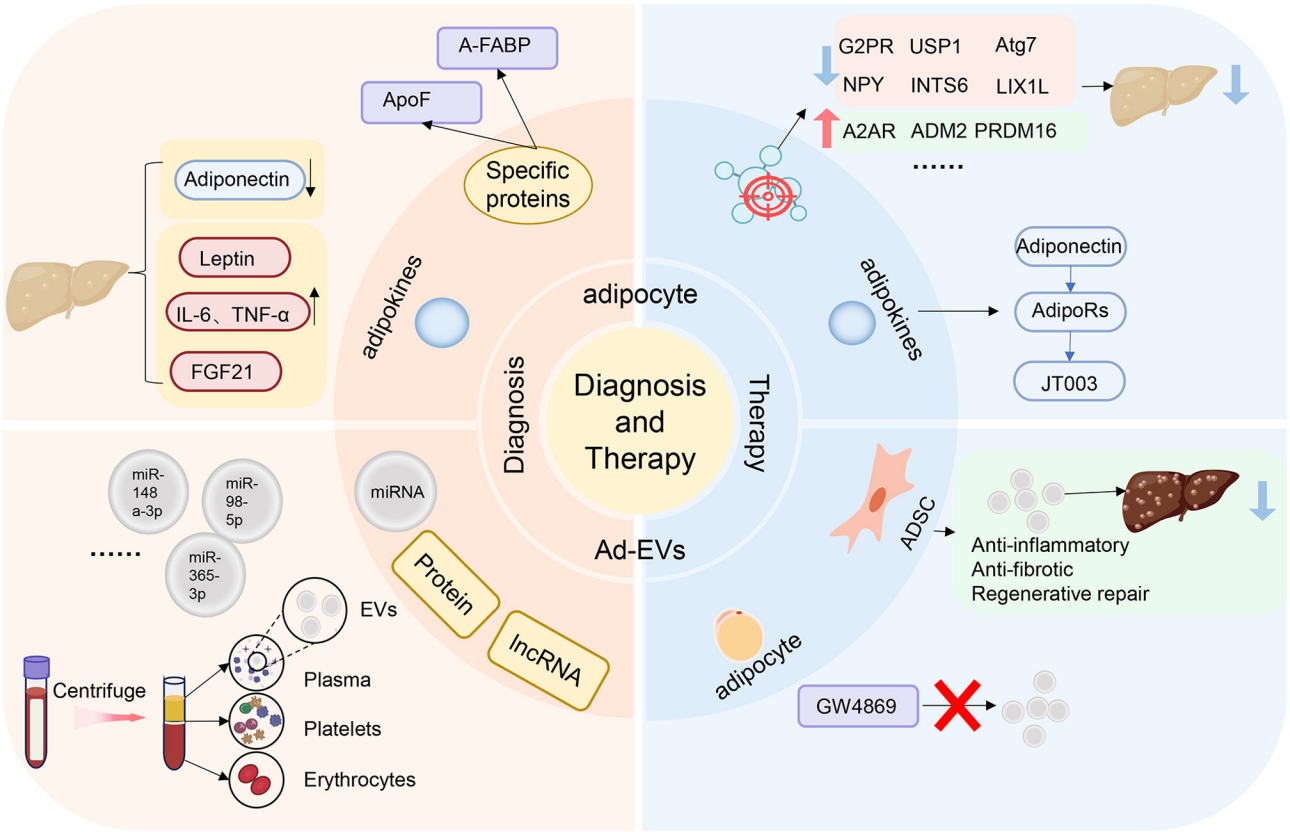

Figure 7. Adipocytes and Ad-EVs in the diagnosis and treatment of liver diseases. Adipocyte-secreted adipokines and adipocyte-specific proteins (e.g., A-FABP, ApoF) serve as circulating biomarkers that reflect hepatic inflammation and fibrosis severity, facilitating the non-invasive diagnosis of liver disease. Several adipocyte-specific molecular targets (e.g., GIPR, USP1, ATG7, NPY, INTS6, LIX1L, A2AR, ADM2 and PRDM16) are associated with the progression of liver disease. For therapy, the adiponectin-based agonist JT003 (a dual AdipoR1/R2 agonist) improves insulin resistance in high-fat-diet-induced metabolic dysfunction-associated steatohepatitis (MASH) mice and inhibits HSC activation in CCl_4-induced liver fibrosis. Ad-EVs regulate hepatic metabolic pathways, inflammatory responses, and fibrogenesis by transporting specific miRNAs, lncRNAs and proteins. By contrast, therapeutically beneficial vesicles mainly originate from ADSC-EVs, which exert hepatoprotective effects, whereas EVs secreted by mature adipocytes under pathological conditions predominantly play pathogenic roles. Ad-EVs, adipocyte-derived extracellular vesicles; A-FABP, adipocyte fatty acid binding protein; ApoF, apolipoprotein F; GIPR, glucose-dependent insulinotropic polypeptide receptor; USP1, ubiquitin-specific protease 1; ATG7, autophagy-related 7; NPY, neuropeptide Y; INTS6, integrator complex subunit 6; LIX1L, Lix1 homolog like; A2AR, adenosine A2A receptor; ADM2, adrenomedullin 2; PRDM16, PR domain-containing protein 16; ADSC-EVs, adipose-derived mesenchymal stem cells.

dietary intervention can ameliorate liver disease parameters (196). In another study, at the pharmacological level, the dual adiponectin receptor AdipoR1/R2 agonist JT003 not only ameliorated MASH and liver fibrosis, but also concurrently activated AdipoR and PI3K-Akt signaling pathways in mouse models, thereby providing a biological foundation for the development of AdipoR-targeted anti-fibrotic therapies (197). However, leptin resistance represents a major obstacle to leptin pathway intervention, whereas the clinical translation of adiponectin receptor agonists such as JT003 faces challenges including pharmacokinetic considerations (Fig. 7).

In summary, Ad-EVs and adipocyte-derived factors have emerged as highly promising non-invasive diagnostic biomarkers and therapeutic platforms in the field of liver diseases. Although MSC-derived exosomes, engineered exosomes, adiponectin agonists and adipocyte-specific molecular targets have demonstrated encouraging efficacy in preclinical and early clinical studies, translating these approaches into clinical practice will require overcoming persistent challenges in standardization, large-scale manufacturing, and multicenter validation.

6. Conclusion and future perspectives

Lifestyle and dietary changes have contributed to the increasing prevalence of liver diseases in recent years, prompting concern among public health organizations (198,199). The role of adipocytes and their extracellular vesicles in liver disorders has attracted increasing attention, providing new perspectives on the pathogenesis of the disease and therapeutic strategies (74,142).

The present review discussed the morphology and function of adipocytes, summarizing their EV-mediated crosstalk with the liver, and summarizing emerging therapeutic strategies targeting the adipose-liver axis. A comprehensive analysis of the existing literature confirms that adipocytes function not merely as lipid storage depots, but as active endocrine and immunoregulatory cells (200). Studies have established their central role in the pathogenesis of liver diseases (201,202). This insight provides a critical framework for dissecting the complex pathological processes underlying hepatic disorders. Accumulating evidence demonstrates that adipocytes regulate hepatic metabolism, inflammation, and fibrosis through the secretion of diverse bioactive factors (121).

Under normal physiological conditions, Ad-EVs help regulate energy storage and consumption in the liver, muscle and AT, whereas under pathological conditions they may promote obesity, endocrine disorders and cancer. As central mediators of inter-organ communications, Ad-EVs carry specific miRNAs, proteins and lipids that can target the liver and modulate its insulin sensitivity and lipid metabolism (203). The molecular cargo of Ad-EVs therefore represents a valuable source of diagnostic biomarkers for liver disease, with considerable potential for clinical application. Conversely, pathogenic vesicles derived from mature adipocytes have been shown to aggravate liver disease progression in preclinical models. Targeting their biogenesis, secretion and pathogenic cargo represents a promising therapeutic direction, although this strategy remains at the preclinical stage. Adipocyte-targeted strategies may provide new paradigms for treating metabolic liver diseases, with the potential to intervene at the root of the disease process and steer therapeutic models toward greater precision; however, these concepts await clinical validation.

Preclinical studies indicate that ADSC-EVs can influence multiple regulatory mechanisms and hold promise as natural drug carriers, potentially providing novel avenues for treating liver diseases (74,204). Despite this broad potential, the clinical translation of EV-based approaches continues to face substantial challenges, including the lack of standardized methods for efficient purification and characterization, the inherent heterogeneity of EV populations, and the absence of validated therapeutic dosages and safety protocols (142). Further research is thus warranted to prioritize in-depth exploration of the biological functions of ADSC-EVs, the engineering of EVs to improve targeting and therapeutic efficacy, and the conduct of rigorous clinical trials to verify their safety and effectiveness.

Given the heterogeneity of adipocytes and their diverse functions, future studies are required to more precisely dissect the specific mechanisms of action of distinct adipocyte subpopulations at different stages of liver disease. Integrating multi-omics technologies with advanced cell-tracking methods will enable a more comprehensive understanding of the role of adipocytes within the global metabolic network and their impact on liver pathology (205). Moreover, adipocytes interact with multiple organs beyond the liver, including the intestine, pancreas, and immune system (206). In the pancreas, healthy Ad-EVs preserve β-cell function, whereas obese or inflamed Ad-EVs impair β-cell viability and worsen glucose tolerance (64). In the intestine, ADSC-EVs restore gut barrier integrity and modulate microbiota to ameliorate liver fibrosis (179). Additionally, Ad-EVs carry immunomodulatory cargo that shapes macrophage polarization and T-cell responses within and beyond AT, thereby linking adipose inflammation to systemic immune dysregulation relevant to liver disease progression (207). A comprehensive investigation of these multi-organ interactions-spanning the adipose-gut-liver-pancreas-immune axis-represents a critical frontier for future research and is expected to yield more integrated therapeutic strategies for metabolic liver diseases.

A more in-depth understanding of how adipocytes and their released EVs communicate with the liver will not only clarify the mechanisms underlying liver disease, but may also provide a theoretical foundation for developing targeted therapies directed at the adipose-liver axis. Future research is warranted to further explore the impact of adipocyte diversity on liver pathology and advance the development of innovative precision therapies focused on this axis. Such advancements may open new avenues for the prevention and management of liver diseases. Staying abreast of the latest advances in this rapidly evolving field and promoting synergy between fundamental research and clinical practice will be essential for improving the long-term prevention and treatment of liver diseases.

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Availability of data and materials

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Authors' contributions

All authors (KL, MZ, YY and JX) conceptualized the study. KL performed the literature search and wrote the original draft of the manuscript. MZ polished the language of the entire text. YY and JX critically reviewed and edited the draft of the manuscript. All authors have read and approved the final version. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work AI tools (Citexs and DeepSeek) were used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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