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Review

Role of Circular RNAs in Liver Diseases

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Abstract

Circular RNAs (circRNAs) are a subclass of noncoding RNAs characterized by their closed-loop structure without terminal 3′ or 5′ ends. Studies have shown that circRNAs play pivotal roles in the regulation of various cellular processes. These molecules function as microRNA (miRNA) sponges, interact with RNA-binding proteins, and modulate gene transcription. CircRNAs are vital for regulating liver homeostasis, and dysregulation of their expression is correlated with liver diseases such as hepatic fibrosis, steatosis, inflammation, and liver cancer. Elucidating the functional significance of circRNAs in liver diseases is crucial, as this knowledge may facilitate the identification of novel diagnostic biomarkers and therapeutic targets for conditions that contribute significantly to global morbidity and mortality. This review aimed to highlight current research underscoring the functional roles of circRNAs in the molecular pathogenesis and progression of liver diseases, including hepatocellular carcinoma, nonalcoholic fatty liver disease, and liver fibrosis. To provide an updated and comprehensive overview, a literature search was conducted across major scientific databases. This review reveals that circRNAs perform multifaceted functions in liver homeostasis and disease by regulating gene expression through miRNA sponging, interacting with signaling pathways, and influencing cellular processes, including vascularization, metastasis, the cell cycle, apoptosis, cellular stress, metabolic activity, inflammatory responses, and cellular senescence. Despite their pivotal involvement in liver diseases, translating circRNA-based research into clinical practice remains challenging. In conclusion, circRNAs represent an emerging frontier in liver disease research, offering considerable promise for future clinical applications.

Keywords: circular RNA; liver; NAFLD; liver fibrosis; HCC

Introduction

Circular RNAs (circRNAs) represent a distinct subclass of noncoding RNAs that exist in a covalently closed-loop form. Their closed-loop structure, devoid of enzyme recognition elements, confers resistance to exonuclease degradation; thus, circRNAs exhibit greater stability and longer half-lives than linear RNAs [1]. Although predominantly located in the cytoplasm, circRNAs are also present in the nucleus; however, the mechanisms governing their export from the nucleus remain poorly understood. CircRNAs were first discovered in plant viroids in 1976 and later in the hepatitis delta virus. Two principal models have been proposed to explain circRNA biogenesis: exon skipping (lariat) and back splicing [2]. Based on their biogenesis, several types of circRNAs have been identified, including sense overlapping, antisense, intronic, exonic, and intergenic circRNAs [3].

CircRNAs affect the expression of many mammalian genes both transcriptionally and post-transcriptionally through transcriptional regulation, collaboration with microRNAs (miRNAs), and splicing interference. During transcription, nuclear circRNAs interact with RNA polymerase II and the U1 small nuclear ribonucleoprotein particle complex [4]. A subset of circRNAs is produced through the back-splicing of pre-mRNAs to generate circular transcripts. CircRNAs serve as binding sites for miRNAs and RNA-binding proteins, facilitating their role in post-transcriptional gene regulation. In addition, circRNAs can inhibit linear RNA splicing and regulate their expression. For example, *Drosophila*

muscle-blind circRNAs drive their expression through the alternative splicing of precursor RNA [2].

Although circRNAs are considered non-coding RNAs, they can also encode proteins. For example, the groundbreaking research by van Heesch et al. on 80 human heart translatomes identified at least 40 circRNAs that encode proteins [5]. Another example is the hepatitis delta virus circRNA, which translates into a 122-amino acid protein within infected cells. In protein-coding circRNAs, cap-independent translation occurs via internal ribosome entry sites, N6-methyladenosine, or rolling circle amplification [6].

Under physiological conditions, circRNAs are involved in tissue and organ growth and development, and they regulate numerous cellular processes, including the cell cycle, cell stress, cellular senescence, metabolic activity, apoptosis, and inflammatory responses. Since circRNAs are resistant to standard RNA degradation pathways, cells eliminate them primarily via exocytosis. CircRNAs or their complexes are packaged into vesicles that are secreted into the extracellular space for removal from the cytoplasm [7]. Furthermore, the endoribonuclease RNase L degrades circRNAs [8].

CircRNAs accumulate primarily in slowly proliferating cells. Their expression varies across developmental stages and is altered in many diseases. Their low expression has hampered their characterization; however, because of their distinctive tissue-specific expression, they are useful as diagnostic biomarkers and novel therapeutic agents [3]. Next-generation sequencing and genome mapping tools have positioned circRNAs as a key focus of RNA research.

Understanding the functions of circRNAs in liver diseases is essential, as it may facilitate the discovery and validation of novel diagnostic biomarkers and therapeutic agents for disorders with substantial global health burdens. This review aimed to critically examine the evolving functions of circRNAs in the progression and pathogenesis of liver diseases.

CircRNA in the Liver

The liver is comprised of various cells that work together to regulate essential functions. Hepatic cells mediate lipid homeostasis, glucose metabolism, energy balance, immune responses, and detoxification. Globally, liver diseases are major causes of morbidity and impose a substantial economic burden on healthcare systems. They contribute to over two million deaths each year: one million due to complications from fibrosis and cirrhosis, and one million attributed to hepatocellular carcinoma (HCC) and viral hepatitis [9]. The mechanisms driving liver disease development are not fully understood, and treatment options for end-stage liver conditions remain limited, highlighting the need for early interventions and novel therapeutic strategies.

CircRNAs are important regulators of liver homeostasis and disease. One study demonstrated that 668 circRNAs are expressed exclusively in liver tissues [10]. In addition, the RAISE pipeline detected circRNAs in RNA-seq data from 61 human liver samples after rRNA depletion. In total, 59,128 circRNA candidates were observed in both adjacent non-tumor and HCC tissues [11].

CircRNAs in Liver Diseases

HCC

In 2020, HCC ranked sixth in global cancer incidence and third in cancer-related mortality. It accounts for 75–85% of all primary liver cancer cases. Primary contributors to the risk of developing HCC include metabolic syndrome, viral infection, prolonged alcohol consumption, and conditions related to obesity and diabetes. Despite advances in treatments, including surgery and systemic drug therapies, the overall survival rate for patients with HCC remains poor, largely due to late diagnosis and the high degree of tumor heterogeneity in this cancer type [12].

Oncogenic circRNAs in HCC

circRNAs are crucial for regulating the initiation and progression of HCC [13]. For example, hsa_circ_0005075 interacts with miR-93-3p, miR-23b-5p, miR-23a-5p, and miR-581 to regulate cell adhesion during HCC development [14]. In hepatitis B-related HCC, upregulation of circRNA_100338, which targets miR-141-3p, is associated with poor survival and metastatic progression [15]. Additional circRNAs implicated in liver cancer include circFUT8, circZFR, and circIOP11. Specifically, circFUT8 competitively binds to miR-17–3p, miR-570–3p, and miR-552–3p; circZFR potentially interacts with miR-130b-5p, miR-511–5p, miR-642a-5p, miR-329–5p, and miR-532–3p; and circIPO11 targets miR-659–3p, miR-106a-3p, and miR-424–5p [16]. Circ-HOMER1, which is upregulated in HCC cells and tissues, stimulates HCC growth by targeting the miR-1322/CXCL6 axis [17]. RhoA and circ_000839 levels are elevated in HCC, and miR-200b expression is negatively correlated with circ_000839 levels [18]. Circβ-catenin is upregulated in liver cancer tissues, and its downregulation reduces β-catenin protein concentrations without affecting its mRNA

concentration. Circβ-catenin also plays a role in stabilizing full-length β-catenin by counteracting GSK3β-mediated phosphorylation and subsequent β-catenin degradation, thereby contributing to Wnt pathway activation [19]. Elevated levels of circACVR2A have been detected in HCC cell lines. CircACVR2A interacts with miR-511-5p to regulate the signaling axis [20]. Both HCC tissues and cells exhibit high levels of circPIAS1, and suppression of circPIAS1 reduces cell proliferation and migration. Overexpression of circPIAS, which binds to miR-455-3p, inhibits ferroptosis and upregulates nuclear protein 1, which subsequently activates FTH1 transcription, promoting iron storage [21]. In HCC, circESYT2 is upregulated and promotes tumor growth and metastasis by interacting with the miR-665/enolase 2 axis [22]. Elevated levels of circ_0067934 in HCC tissues, which correlate with increased tumor metastasis and growth, are associated with the miR-1324 and Wnt/β-catenin pathway [23]. In HCC, SCD-circRNA2 expression, which is regulated by RNA-binding protein 3 (RBM3), is upregulated. Modulation of SCD-circRNA2 and RBM3 levels increases HCC cell proliferation. Furthermore, RBM3-SCD-circRNA2 regulates p-ERK activation [24]. Hsa_circ_0000092, which targets miRNA-338-3p, is upregulated in HCC, and its downregulation correlates with reduced cell invasion, proliferation, and angiogenesis by decreasing HN1 expression [25]. Circ-PRMT5 overexpression potentially plays a critical role in HCC cell glycolysis, migration, and proliferation by targeting miR-188-5p/HK2 [26]. Mechanistically, circMAT2B stimulates the expression of the glycolytic enzyme PKM2 by interacting with miR-338-3p [27]. Glycolysis plays a pivotal role in HCC owing to its role in metabolic reprogramming, which is a hallmark of cancer. In the presence of sufficient oxygen, HCC cells preferentially utilize aerobic glycolysis rather than mitochondrial oxidative phosphorylation to generate ATP and biosynthetic macromolecules essential for rapid proliferation. Accelerated HCC growth usually exceeds angiogenesis, resulting in hypoxic conditions that further reinforce glycolytic flux to sustain anabolic demands [26, 27]. CircASAP1, which regulates miR-532-5p- and miR-326-mediated signaling, increases in HCC tissues. CircASAP1 stimulates HCC cell invasion and proliferation, and regulates macrophage infiltration into tumor tissues [28]. CircUHRF1, secreted by HCC cells, suppresses the immune response by inhibiting natural killer cell function via upregulation of TIM-3 expression [29]. CircRHOT1, which modulates TIP60 recruitment to the *NR2F6* promoter, contributes to the activation of *NR2F6* transcription and is upregulated in HCC [30]. Circ_0000105 is overexpressed in liver cancer and enhances phosphoinositide-3-kinase regulatory subunit 1 expression by targeting miR-498; its overexpression correlates with increased HCC proliferation and reduced apoptosis [31]. Circ_0091579, which targets miRNA-490-3p, is upregulated in HCC. Its downregulation strongly inhibits cell proliferation and metastasis [32]. High levels of circPRKCI in HCC suppress apoptosis and promote invasion by interacting with miRNA-545 to regulate E2F7 and reduce AKT3 protein expression [33]. HCC migration, proliferation, and invasion increase via the upregulation of hsa_circRNA_100084, which may stimulate insulin-like growth factor 2 (IGF2) by sequestering miR-23a-5p [34]. CircSOD2 overexpression correlates with cell migration, cell growth, and the cell cycle. CircSOD2 inhibits miR-502-5p, thereby suppressing SOCS3 expression and activating the Janus kinase 2 (JAK2)/STAT3 pathway [35]. MUC1, which is elevated in tumor cells, is repressed by miRNA-485-5p. Downregulation of MUC1 in cells is correlated with decreased cell viability, invasion, and migration but increased apoptosis. Upregulation of circHECTD1, which interacts with miRNA-485-5p, increases MUC1 expression and promotes HCC progression [36]. In HCC, circ_0016788 is also elevated [37,38]. Loss of circ_0016788 inhibits tumor growth *in vivo*; *in vitro*, HCC cell proliferation, invasion, colony formation, cell vitality, and glycolysis are suppressed, whereas apoptosis is enhanced. Circ_0016788 mediates its effects through themiR-506-3p/ poly(ADP-ribose) polymerase family member 14 (PARP14) and miR-486/CDK4 pathways [37,38]. CircZNF566 is implicated in HCC metastasis and tumorigenesis; *in vitro*, it targets the tryptophan 2,3-dioxygenase axis via miR-4738-3p to promote cell invasion, proliferation, and migration [39]. CircTMEM45A, which acts via the miR-665/IGF2 axis, is upregulated in HCC and correlates with tumorigenesis and the progression of cell mobility [40]. Tumor stage, size, and vascular invasion are correlated with elevated circ-0046600 expression, and suppression of circ-0046600 inhibits cell migration. Most hsa-circ-0046600 is located in the cell cytoplasm, where it stimulates HIF-1α expression through binding miR-640 [41]. The knockdown of circMAN2B2, which is markedly elevated in HCC, suppresses cell proliferation by sponging the miR-217 and regulating the mitogen-activated protein kinase 1 pathway [42]. Increased circPTGR1 expression, which has three isoforms, in serum exosomes of patients with HCC is indicative of advanced tumor stage and worse prognosis. Loss of circPTGR1 is correlated with reduced migration and invasion of

97L and HepG2 cells. The circPTGR1 isoforms and MET compete to specifically bind miR449a [43]. Elevated circPVT1 expression in HCC is associated with reduced miR-377 levels. Knockdown of circPVT1 impairs HCC tumor growth, suppresses glycolysis and proliferation, and enhances apoptosis. CircPVT1 in HCC is regulated by binding to miR-377 [44]. Circ_0008450 overexpression has been detected in HCC [45,46]. Downregulation of hsa_circ_0008450 results in reduced migration, proliferation, and invasion, while enhancing apoptosis. Hsa_circ_0008450 upregulates zeste homolog 2 by sponging miR-214-3p and miR-548p [45,46]. CircRNA-104718, which is overexpressed in HCC, binds to miR-218-5p, thereby increasing the expression of thioredoxin domain-containing protein 5. Thus, higher circRNA-104718 levels accelerate invasion, proliferation, and migration, while downregulating apoptosis in HCC cells. In a mouse model, upregulation of circRNA-104718 increased tumor size and promoted HCC metastasis [47]. Circ-ZNF652 is elevated in both the serum and tumor cells of patients with HCC. Circ-ZNF652 influences cell glycolysis, invasion, proliferation, and migration by interacting with miR-29a-3p, thereby modulating guanylyl cyclase domain-containing 1 [48]. Increased circ_0000267 expression correlates with poor prognosis and increased severity of HCC, and its upregulation stimulates cell growth by binding to miR-646 [49]. Circ-FOXP1 is significantly upregulated in the serum and tissues of patients with HCC. Circ-FOXP1 overexpression upregulates the oncogenic transcription factor sex-determining region Y-box 9 through miR-875-3p and miR-421. Its overexpression leads to accelerated tumor growth and reduced apoptosis in HCC cells [50]. Upregulation of hsa_circ_101280 in HCC, which is associated with enhanced tumor cell proliferation and decreased apoptosis, is mediated by miR-375 sponging and JAK2 activation [51]. In HCC cells, knockdown of circFBLIM1 levels inhibits invasion and proliferation while enhancing apoptosis. CircFBLIM1 sponges miR-346 to regulate FBLIM1 expression [52]. In HCC cells, knocking down high circABCC2 levels reduces invasion and proliferation while enhancing apoptosis. CircABCC2 upregulates ABCC2 expression by interacting with miR-665 [53].

Tumor-suppressor circRNAs in HCC

Lower hsa_circ_0001649 expression in HCC is associated with the presence of a tumor embolus and larger tumor size [54,55]. Both *in vitro* and *in vivo* studies have demonstrated that the upregulation of circ-0001649 reduces HCC migration and proliferation. Hsa_circ_0001649 mediates its effects through activation of SNF2 histone linker PHD RING helicase by sponging miR-4688, miR-127-5p, and miR-612 [54]. Circ-ITCH expression is markedly reduced in cancerous tissues compared to controls [56]. Downregulation of hsa_circ_0005986 accelerates HCC cell proliferation, and higher levels of hsa_circ_0005986 correlate with better survival outcomes in patients with cancer. Circ_0005986 downregulation results in increased miR-129-5p expression, which reduces Notch1 mRNA levels [57]. Hsa_circ_0004018, which is suppressed in HCC relative to adjacent non-tumorous tissues, is involved in HCC metastasis and carcinogenesis via the miR-626/miR-30e-5p-MYC pathway [58]. Patients with HCC and reduced circMTO1 expression (hsa_circRNA_104135/ hsa_circRNA_0007874) have shorter survival times. CircMTO1 is associated with miR-9, and its silencing in HCC decreases p21 levels, which promotes tumor growth and invasion [59]. Decreased hsa-circ-0000221 expression correlates with reduced PTPN11 mRNA expression in the serum of patients with HCC. PTPN11 inhibits proliferation in various human cancers, while these patients exhibit higher miR-661 expression. Overexpression of hsa-circ-0000221 reduces cell viability and increases apoptosis, correlating with the accumulation of G1 and upregulation of CCDN1 in HCC. Hsa-circ-0000221 regulates PTPN11 expression by inhibiting miR-661 [60]. The zinc-finger family gene *ZKSCAN1* and its circRNA, circZKSCAN, are downregulated in HCC. Inhibition of circZKSCAN1 induces cell proliferation, invasion, and migration. CircZKSCAN1 modulates cancer-associated pathways, including integrin β4, transforming growth factor-β1 (TGF-β1), and chemokine receptor 4 [61]. Hsa_circ_0067531, which is critical for HCC development via phosphoinositide 3-kinase, is reduced in human HCC tissues *in vitro* [62]. In HCC, circTRIM33–12 expression is reduced and correlates with increased invasion, migration, proliferation, and immune evasion. CircTRIM33–12 promotes Ten-eleven translocation methylcytosine dioxygenase 1 expression and reduces 5-hydroxymethylcytosine levels through miR-191 [63]. CircHIAT1 suppresses tumor growth by acting as a sponge for miR-3171, thereby upregulating PTEN, and is downregulated in patients with HCC [64]. CircLARP4 is also downregulated in HCC. CircLARP, which mediates cell cycle arrest *in vitro*, reduces HCC proliferation and promotes senescence. HCC progression is inhibited by circLARP through miR-761, thereby activating the RUNX3 and p53/p21 pathway [65]. The altered expression of circRNAs and their implicated roles in HCC are summarized in **Table 1.**

Table 1. Expression and roles of dysregulated circular RNAs in hepatocellular carcinoma

Circular RNA	Expression Pattern	Sponge Target	Biological Function	Reference
Hsa_circ_0005075	Increased	miR-93-3p miR-23b-5p miR-23a-5p miR-581	Hsa_circ_0005075 regulates cell adhesion.	[14]
CircRNA_100338	Increased	miR-141-3p	Elevated circRNA_100338 levels are linked to decreased survival and metastatic advancement.	[15]
CircFUT8 Hsa_circ_0003028 Hsa_circ_101368	Increased	miR-570-3p miR-17-3p miR-552-3p	Not identified	[16]
CircZFR Hsa_circ_10072088 Hsa_circRNA_103809	Increased	miR-511–5p miR-532–3p miR-130b-5p miR-329–5p miR-642a-5p	Not identified.	[16]
CircIOP11 Hsa_circ_0007915 Hsa_circ_103847	Increased	miR-659-3p miR-106a-3p miR-424-5p	Not identified.	[16]
Circ-HOMER1	Increased	miR-1322	Circ-HOMER1 stimulates migration, proliferation, and invasion, while reducing apoptosis. HOMER1 targets CXCL6.	[17]
Circ_000839	Increased	Not identified	Not identified.	[18]
Circβ-catenin	Increased	Not identified	Circβ-catenin activates Wnt/β-catenin.	[19]
CircACVR2A	Increased	miR-511-5p	CircACVR2A regulates invasion, proliferation, and migration. CircACVR2A regulates PI3K-Akt.	[20]
CircPIAS1	Increased	miR-455-3p	CircPIAS1 knockdown reduces migration and proliferation. Its overexpression suppresses ferroptosis and upregulates NUPR1.	[21]
CircESYT2	Increased	miR-665	CircESYT2 mediates metastasis and growth through its interaction with ENO2.	[22]
Circ_0067934	Increased	miR-1324	Circ_0067934 overexpression promotes growth and metastasis. It regulates FZD5/Wnt/β-catenin.	[23]
SCD-circRNA2	Increased	Not identified	SCD-circRNA2 upregulation is mediated by RBM3. RBM3-SCD-circRNA2 promotes proliferation and p-ERK activation.	[24]
Hsa_circ_0000092	Increased	miR-338-3p	Hsa_circ_0000092 increases progression by upregulating HN1 expression.	[25]
Circ-PRMT5	Increased	miR-188-5p	Circ-PRMT5 mediates migration, proliferation, and glycolysis through the HK2 axis.	[26]
CircMAT2B	Increased	miR-338-3p	CircMAT2B stimulates *PKM2* gene expression, which encodes a glycolysis enzyme.	[27]
CircASAP1	Increased	miR-326 miR-532-5p	CircASAP1 stimulates invasion and proliferation and regulates the infiltration of macrophages.	[28]
CircUHRF1	Increased	Not identified	CircUHRF1 regulates immunosuppression by inhibiting natural killer cell functions through upregulation of TIM-3 expression.	[29]
CircRHOT1	Increased	Not identified	CircRHOT1 promotes HCC proliferation and metastasis. It recruits TIP60 to the promoter of *NR2F6* to initiate the transcription of *NR2F6*.	[30]
Circ_0000105	Increased	miR-498	Circ_0000105 promotes proliferation and reduces apoptosis in HCC. Circ_0000105 promotes PIK3R1 expression.	[31]
Circ_0091579	Increased	miRNA-490-3p	Circ_0091579 promotes HCC proliferation and metastasis.	[32]
Circ-PRKCI	Increased	miRNA-545	circ-PRKCI significantly inhibits HCC cell apoptosis and promotes cell invasion.	[33]
Hsa_circRNA_100084	Increased	miR-23a-5p	Hsa_circRNA_100084 stimulates IGF2.	[34]
CircSOD2	Increased	miR-502-5p	CircSOD2 promotes growth, cycle, and migration. Increased DNMT3a downregulates SOCS3 and enhances JAK2/STAT3.	[35]
CircHECTD1	Increased	miRNA-485-5p	CircHECTD1 facilitates MUC1 expression and promotes progression.	[36]
Hsa_circ_0016788	Increased	miR-506-3p miR-486	Hsa_circ_0016788 mediates CDK4 and PARP14.	[37,38]
CircZNF566	Increased	miR-4738-3p	CircZNF566 upregulation increases tumorigenesis, metastasis, invasion, migration, and proliferation. CircZNF566 regulates the TDO2 axis.	[39]
CircTMEM45A	Increased	miR-665	CircTMEM45A regulates cell mobility and tumorigenesis. Its action is mediated by the IGF2 axis.	[40]
Hsa-circ-0046600	Increased	miR-640	Hsa-circ-0046600 mediates migration.	[41]
CircMAN2B2	Increased	miR-217	CircMAN2B2 regulates proliferation via MAPK1.	[42]
CircPTGR1	Increased	miR449a	CircPTGR1 isoforms stimulate migration by targeting MET.	[43]
CircPVT1	Increased	miR-377	CircPVT1 regulates proliferation, glycolysis, and apoptosis by targeting TRIM23.	[44]
Hsa_circ_0008450	Increased	miR-548p miR-214-3p	Hsa_circ_0008450 regulates proliferation, invasion, and apoptosis by promoting EZH2.	[45,46]
CircRNA-104718	Increased	miR-218-5p	CircRNA-104718 overexpression increases tumor size, promotes metastasis, migration, invasion, and proliferation, and inhibits apoptosis.	[47]
Circ-ZNF652	Increased	miR-29a-3p	Circ-ZNF652 regulates glycolysis, proliferation, invasion, and migration through	[48]

Circular RNA	Expression Pattern	Sponge Target	Biological Function	Reference
			GUCD1.	
Circ_0000267	Increased	miR-646	Circ_0000267 upregulation promotes invasion, migration, and proliferation, and ameliorates apoptosis.	[49]
Circ-FOXP1	Increased	miR-421 miR-875-3p	Overexpression of circ-FOXP1 increases oncogenic transcription factor SOX9 expression, cell growth, and invasion, and suppresses apoptosis.	[50]
Hsa_circ_101280	Increased	miR-375	Hsa_circ_101280 mediates tumorigenesis and proliferation, while reducing apoptosis by JAK2.	[51]
CircFBLIM1	Increased	miR-346	CircFBLIM1 knockdown increases apoptosis and decreases cell proliferation and invasion.	[52]
CircABCC2	Increased	miR-665	CircABCC2 inhibition reduces proliferation and invasion and increases apoptosis by regulating ABCC2.	[53]
Hsa_circ_0001649	Decreased	miR-127-5p miR-4688 miR-612	Circ-0001649 upregulation reduces proliferation and migration. It mediates SHPRH activation.	[54,55]
Circ-ITCH	Decreased	Not identified	Polymorphisms (rs4911154 and rs10485505) in circ-ITCH increase the risk of HCC.	[56]
Hsa_circ_0005986	Decreased	miR-129-5p	Downregulation of hsa_circ_0005986 stimulates proliferation and reduces Notch1 expression.	[57]
Hsa_circ_0004018	Decreased	miR-626 miR-30e-5p	Hsa_circ_0004018 regulates metastasis and carcinogenesis by targeting MYC.	[58]
CircMTO1 Hsa_circRNA_104135 Hsa_circRNA_0007874	Decreased	miR-9	CircMTO1 silencing reduces p21 expression as well as proliferation and invasion.	[59]
Hsa-circ-0000221	Decreased	miR-661	Low hsa-circ-0000221 expression reduces PTPN11 expression. Its overexpression lowers cell viability, increases apoptosis, and upregulates G1 protein and CCDN1.	[60]
CircZKSCAN1	Decreased	Not identified	Silencing circZKSCAN1 in HCC induces proliferation, invasion, and migration. CircZKSCAN1 influences TGF-β1, ITGB4, and CXCR4 expression.	[61]
Hsa_circ_0067531	Decreased	Not identified	Hsa_circ_0067531 regulates the PI3K pathway.	[62]
CircTRIM33–12	Decreased	miR-191	CircTRIM33–12 reduction increases migration, invasion, proliferation, and immune evasion by promoting TET1 expression and reducing 5hmC expression.	[63]
CircHIAT1	Decreased	miR-3171	CircHIAT1 inhibits growth and upregulates PTEN expression.	[64]
CircLARP4	Decreased	miR-761	CircLARP4 reduces proliferation, mediates cell cycle arrest, and promotes senescence by increasing RUNX3 expression and activating p53/p21.	[65]

Abbreviations: HCC: hepatocellular carcinoma; circRNA: circular RNA; miR / miRNA: microRNA; MAPK1: mitogen-activated protein kinase 1; JAK2: Janus kinase 2; EZH2: enhancer of zeste homolog 2; TXNDC5: thioredoxin domain-containing protein 5; MET: mesenchymal-epithelial transition factor; PTPN11: protein tyrosine phosphatase non-receptor type 11; CCDN1: cyclin D1; SOX9: SRY-box 9; FZD5: frizzled class receptor 5; PKM2: pyruvate kinase M2; HKL2: hexokinase-like 2; DNMT3a: DNA methyltransferase 3 alpha; SOCS3: suppressor of cytokine signaling 3; STAT3: signal transducer and activator of transcription 3; IGF2: insulin-like growth factor 2; CDK4: cyclin-dependent kinase 4; PARP14: poly (ADP-ribose) polymerase family member 14; TDO2: tryptophan 2,3-dioxygenase; GUCD1: guanylyl cyclase domain containing 1; SHPRH: SNF2 histone linker PHD RING helicase; ITGB4: integrin beta 4; TGF-β1: transforming growth factor beta 1; CXCR4: chemokine receptor 4; PI3K: phosphoinositide 3-kinase; TET1: ten-eleven translocation methylcytosine dioxygenase 1; 5hmC: 5-hydroxymethylcytosine; PTEN: phosphatase and tensin homolog; RUNX3: runt-related transcription factor 3; p-ERK: phosphorylated extracellular signal-regulated kinase; TRIM23: tripartite motif containing 23; FBLIM1: filamin-binding LIM protein 1.

Nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH)

NAFLD, the primary cause of chronic liver disease worldwide, is characterized by abnormal fat accumulation in hepatocytes. Triglyceride accumulation, lipid peroxidation, and mitochondrial dysfunction are the hallmarks of liver steatosis [66]. With the global prevalence of NAFLD at approximately 30%, it may increase over the next two decades. Therefore, raising awareness and promoting the understanding of NAFLD remain crucial. The inadequate response of healthcare organizations places a substantial strain on healthcare systems and economies [66].

NAFLD is a multisystem condition associated with metabolic disorders. NASH, a more advanced form of NAFLD, can progress to hepatic fibrosis, cirrhosis, and eventually liver cancer. The hallmark features of NASH include hepatocyte ballooning and hepatic inflammation [66]. NAFLD affects both children and adults, with its prevalence increasing with age in males between 45 and 65 years [67]. Genetic factors, including polymorphisms in *PNPLA3* and *TM6SF2* genes, elevate the risk of NAFLD [68].

CircRNAs are increasingly recognized for their distinctive expression patterns in NAFLD. Significant differences in circRNA expression have been observed in NASH and NAFLD animal models [69]. In one NAFLD animal model, 231 circRNAs were upregulated and 165 were downregulated, as quantified using a circRNA microarray [70]. Another study revealed that the expression of 57 circRNAs was upregulated and that of 36 circRNAs was downregulated in a high-fat diet-fed mouse model. CircRNAs also regulate the expression of *DDAH1* and *VAV3* genes in NAFLD [71].

Circ_0057558 levels were elevated in NAFLD models. This circRNA acts as a sponge for miR-206 and enhances triglyceride production and lipogenesis by relieving the repression of AMP-activated protein kinase (AMPK) and Rho-kinase 1 signaling pathways [72]. CircRNA_002581 is also highly expressed in

NASH. Knockdown of circRNA_002581 reduces hepatic inflammation, oxidative stress, and lipid accumulation, whereas its overexpression alleviates the suppression of cytoplasmic polyadenylation element-binding protein by miR-122. CircRNA_002581 contributes to NASH pathogenesis by suppressing autophagy through the PTEN-AMPK-mTOR axis [73]. CircRNA-homeodomain-interacting protein kinase 3 is induced in patients with NASH compared to controls, suggesting that its interaction with miRNA-29a regulates NASH pathogenesis. miRNA-29a may contribute to NASH pathogenesis by decreasing the activity of the Wnt-β-catenin pathway [74].

CircRNA_0046367 expression is diminished in hepatocellular steatosis models; however, its restoration interferes with miR-34a suppression of peroxisome proliferator-activated receptor α (PPARα) [75]. Restoration of PPARα activity improves hepatocellular steatosis by modulating genes involved in fatty acid oxidation, transport, and lipid metabolism [75]. CircRNA_0046366 plays a critical role in lipid metabolism, as its levels decrease in free fatty acid (FFA)-induced hepatocellular steatosis. CircRNA_0046366 counteracts the inhibitory impacts of miR-34a on PPARα. Enhanced gene expression of triglyceride-specific lipolysis, such as solute carrier family 27A, correlates with restored PPARα expression, thereby decreasing triglyceride content and alleviating hepatocellular steatosis [76]. CircScd1 expression is reduced in NAFLD tissues and regulates the degree of lipid accumulation. CircScd1 also reduces steatosis by activating the JAK2/STAT5 pathway [77]. In addition, hsa_circ_0048179 levels are suppressed in NAFLD models induced by oleate and palmitate, along with decreased glutathione peroxidase 4 (GPX4) expression, an antioxidant enzyme that protects cells by preventing peroxidation of membrane lipids. Overexpression of Hsa_circ_0048179 stimulates GPX4 expression via miR-188-3p, attenuating oleate/palmitate-induced reactive oxygen species (ROS), lipid accumulation, steatosis, and mitochondrial dysfunction in HepG2 cells [78]. In patients with NASH, the mitochondrial steatohepatitis-associated circRNA ATP5B Regulator (SCAR) limits fibroblast activation and mitochondrial ROS production. A reduction in its expression correlates with the transition from steatosis to NASH and insulin resistance. *In vivo*, modulation of circRNA SCAR attenuates insulin resistance and cirrhosis associated with a high-fat diet [79]. In rodents with NAFLD, a high-fat, high-cholesterol diet disrupts the hepatic circRNA profile, notably reducing 28 circRNAs. LNCPINT-derived circRNAs are critical regulators of circRNA, miRNA, and mRNA interactions. Deficiency of these circRNAs relieves the inhibition of miR-669c-3p and miR-466i-3p, resulting in AMPK deactivation. Downregulation of the AMPK pathway promotes lipogenic gene expression and drives hepatic steatosis [80]. CircRNA_0001805 expression is decreased in high-fat diet-fed mice, FFA-treated hepatocytes, and patients with NAFLD. Enhanced expression of circRNA_0001805 correlates with the attenuation of lipid metabolism abnormalities and inflammatory activity. CircRNA_0001805 targets miR-106a-5p and miR-320a, both of which act as upstream suppressors of ABCA1/CPT1 [81]. In hepatic steatosis, circRNA_021412 modulates the miR-1972/LPIN1 pathway, which regulates the expression of steatosis-related genes through PPARα activation [82]. **Table 2** presents the correlation between circRNAs and NAFLD.

Hepatic Fibrosis

Liver fibrosis results from excessive buildup of extracellular matrix components triggered by ongoing liver damage, which promotes wound healing. Fibrosis-related liver injuries result from various factors, including chronic hepatitis B or C infections, drug use, genetic conditions, excessive alcohol intake, metabolic disorders, autoimmune diseases, and cholestasis. The rising incidence of type 2 diabetes has led to an increase in liver fibrosis due to NASH. Liver fibrosis can be reversed at early stages if the underlying causes are addressed. However, progression of fibrosis can cause cirrhosis, liver failure, portal hypertension, and HCC [83]. Hepatic fibrosis involves various cell types and mediators. Among these, hepatic stellate cells (HSCs), which are considered the main producers of fibrous matrices, are crucial for the initiation and progression of liver fibrosis and serve as primary effector cells during fibrosis development. Following liver injury, quiescent HSCs are activated by cytokines—such as interleukin 6 (IL-6), IL-17, and IL-22—which are secreted by adjacent cells. Once activated, HSCs transdifferentiate into myofibroblasts, which are involved in fibrosis development [84]. HSC activation is also triggered by lipopolysaccharide (LPS) and TGF-β, both of which increase the production of fibrotic markers [84]. Excessive production of the extracellular matrix disrupts the liver's structure, leading to the replacement of hepatocytes with scar tissue. Examples of extracellular matrix include fibronectin, laminin, collagen I, and collagen III. Since many circRNAs are involved in advancing or suppressing hepatic fibrosis, they represent promising biological markers for tracking the progression of liver fibrosis. In addition, these

circRNAs provide critical insights into the mechanisms underlying hepatic fibrosis and highlight promising targets for diagnostic and therapeutic applications [84].

In irradiated HSCs, 179 circRNAs were highly expressed, whereas 630 circRNAs showed reduced expression relative to normal conditions. Among these altered circRNAs, hsa_circ_0072765, hsa_circ_0054345, and hsa_circ_0071410 were significantly upregulated, whereas hsa_circ_0070963, hsa_circ_0013255, and hsa_circ_0061893 were significantly downregulated. Silencing hsa_circ_0071410 elevated miR-9-5p expression, which attenuated HSC activation. Downregulation of miR-9-5p mitigates the effect of hsa_circ_0071410 inhibition, thereby reducing HSC activation [85]. CircUbe2k is upregulated in mice treated with carbon tetrachloride (CCl_4) to induce liver fibrosis, as well as in LX-2 cells stimulated with TGF-β1. CircUbe2k increases TGF-β2 activity by targeting miR-149-5p, and suppression of circUbe2k inhibits the expression of fibrotic markers such as alpha smooth muscle actin (α-SMA) and collagen, type I, alpha 1 **(**Col1α1) [86]. Circ-PWWP2A expression promotes HSC activation and proliferation after LPS and TGF-β treatment, with MiR-223 and miR-203 identified as its downstream targets [87]. CircRNA-0067835 is markedly upregulated in LX-2 cells lacking thymosin β4, and silencing of this circRNA suppresses cell proliferation and enhances apoptosis. Bioinformatic analyses predict that circRNA-0067835 interacts with miR-155, thereby modulating forkhead box O3 expression through its sponging activity [88]. In LX2 cells exposed to radiation, CircRSF1 expression is increased and predicted to bind to miR-146a-5p. The circRSF1-miR-146a-5p complex increases cell viability, fibrosis, and inflammation via RAC1 activation [89]. CircTUBD1 promotes liver fibrosis by modulating miRNA-203a-3p and Smad signaling. In a radiation-induced liver fibrosis model, reducing circTUBD1 activity suppresses hepatic fibrosis biomarkers [90]. Hsa_circ_0072765 is upregulated in HSCs exposed to TGF-β1, and its knockdown ameliorates HSC activation and migration through the transient receptor potential vanillin 3 pathway [91]. In CCl_4-treated mice and RAW264.7 cells stimulated with IFN-γ and LPS, circMcph1 expression is elevated. CircMcph1 regulates IL-1 receptor-associated kinase 2 (Irak2) activity during liver fibrosis by sponging miR-370-3p [92]. CircRNA-007371 exhibits angiogenic effects in a mouse fibrosis model induced by thioacetamide. Overexpression of circRNA-007371 promotes cell proliferation. Acting as a miRNA sponge, circRNA-007371 enhances angiogenesis [93]. CircRNA cVIM facilitates the upregulation of TGF-β receptor subtypes through miR-122-5p and miR-9-5p, resulting in the activation of the TGF-β/Smad signaling axis [94]. Circ_0008494 functions as a sponge for miR-185-3p in human fibrotic tissues, and knockdown of this interaction reduces HSC proliferation, activation, and migration while promoting apoptosis [95].

Table 2. Expression and roles of dysregulated circular RNAs in nonalcoholic fatty liver disease

Circular RNA	Expression Pattern	Sponge Target	Biological Function	Reference
Circ_0057558	Increased	miR-206	Circ_0057558 promotes lipogenesis and triglyceride secretion by relieving the repression of ROCK1 and AMPK.	[72]
CircRNA_002581	Increased	miR-122	CircRNA_002581 regulates CPEB1. CircRNA_002581 knockdown reduces oxidative stress, lipid accumulation, and inflammation.	[73]
CircRNA-HIPK3	Increased	miRNA-29a	CircRNA-HIPK3 overexpression downregulates Wnt/β-catenin, contributing to NASH pathogenesis.	[74]
CircRNA_0046367	Decreased	miR-34a	Normal circRNA_0046367 concentrations abolish the inhibitory effects of PPARα.	[75]
CircRNA_0046366	Decreased	miR-34a	CircRNA_0046366 reduces triglycerides and ameliorates hepatocellular steatosis. Normal circRNA_0046366 concentrations abolish the inhibition of PPARα.	[76]
CircScd1	Decreased	Not identified	CircScd1 reduces the severity of lipid accumulation by JAK2/STAT5 activation.	[77]
Hsa_circ_0048179	Decreased	miR-188-3p	Hsa_circ_0048179 accelerates GPX4 and reduces reactive oxygen species and lipid accumulation.	[78]
CircRNA SCAR	Decreased	ATP5B	CircRNA SCAR suppresses reactive oxygen species and fibroblast activation. It binds to ATP5B and suppresses mPTP activity by preventing CypD and mPTP linkage.	[79]
Circ_0001452 Circ_0001453 Circ_0001454	Decreased	miR-669c-3p miR-466i-3p	Circ_0001452 suppression inhibits AMPK and promotes lipogenic gene expression.	[80]
CircRNA_0001805	Decreased	miR-106a-5p miR-320a	CircRNA_0001805 overexpression decreases lipid accumulation and mitigates lipid metabolism disorders and inflammation. It acts as ABCA1/CPT1 suppressor	[81]
CircRNA_021412	Decreased	miR-1972	CircRNA_021412 regulates LPIN1, inducing steatosis-related genes via PPARα activation.	[82]

Abbreviations: AMPK: AMP-activated protein kinase; ROCK1: Rho-kinase 1; CPEB1: cytoplasmic polyadenylation element-binding protein 1; NASH: nonalcoholic steatohepatitis; PPARα: peroxisome proliferator-activated receptor alpha; JAK2: Janus kinase 2; STAT5: signal transducer and activator of transcription 5; GPX4: glutathione peroxidase 4; ATP5B: ATP synthase subunit beta; mPTP: mitochondrial permeability transition pore; CypD: cyclophilin D; ABCA1: ATP-binding cassette transporter A1; CPT1: carnitine palmitoyltransferase 1; miR / miRNA: microRNA.

CircPSD3, derived from the pleckstrin and Sec7 domain-containing 3 (*PSD3*) gene, is reduced in CCl_4-treated mouse livers and primary HSCs. Furthermore, overexpression of circPSD3 is associated with decreased collagen deposition, reduced liver enzyme and hydroxyproline levels, and lower expression of profibrogenic and proinflammatory cytokines. CircPSD3 acts as a miR-92b-3p sponge, enhancing Smad7 expression [96]. CircFBXW4 expression is reduced during liver fibrosis. Increased circFBXW4 suppresses HSC proliferation and activation, promotes apoptosis, mitigates hepatic fibrotic damage in mice, and exhibits anti-inflammatory properties. Mechanistically, circFBXW4 interacts with miR-18b-3p during hepatic fibrosis [97]. Hsa_circ_0004018 expression decreases during liver fibrogenesis, and its overexpression suppresses fibrosis progression. By sponging hsa-miR-660-3p, hsa_circ_0004018 may indirectly reduce TEP1 expression [98]. CircCREBBP expression is also reduced during liver fibrosis. Overexpression of circCREBBP prevents liver fibrosis progression by inhibiting HSC proliferation and activation. Mechanistically, circCREBBP enhances LEFTY2 expression by interacting with hsa-miR-1291 [99]. Hsa_circ_0070963 reduces fibrotic damage by modulating miR-223-3p, which interacts with LEMD3. This circRNA is downregulated during fibrosis; however, restoring its normal expression suppresses HSC activation and attenuates fibrotic biomarkers [100]. *In silico* analysis indicated that the regulatory role of mmu_circ_34116 in HSC activation was mediated through the miR-22-3P/BMP7 signaling pathway. Suppression of mmu_circ_34116 stimulates α-SMA expression [101]. CircDIDO1 inhibits fibrosis by acting as an miR-141-3p sponge. CircDIDO1 overexpression downregulates profibrotic markers, suppresses proliferation, and enhances apoptosis and cell cycle arrest in HSCs by suppressing the PTEN/AKT pathway [102]. Hsa_circ_0007874 (circMTO1), derived from the *MTO1* gene, is downregulated in fibrotic mouse livers and activated HSCs. Enhancing circMTO1 expression inhibits the activation of HSCs triggered by TGF-β1. CircMTO1 targets PTEN and Smad7 via miR-17-5p and miR-181b-5p [103,104]. **Table 3** summarizes the circRNAs associated with the regulation of liver fibrosis.

Table 3. Expression and roles of dysregulated circular RNAs in liver fibrosis

Circular RNA	Expression Pattern	Sponge Target	Biological Function	Reference
Hsa_circ_0071410	Increased	miR-9-5p	Hsa_circ_0071410 downregulation reduces HSCs activation.	[85]
CircUbe2k	Increased	miR-149-5p	CircUbe2k increases TGF-β2 activity, and its suppression reduces α-SMA and Col1α1.	[86]
Circ-PWWP2A	Increased	miR-223 miR-203	Circ-PWWP2A regulates HSC activation and proliferation.	[87]
CircRNA-0067835	Increased	miR-155	CircRNA-0067835 regulates fibrosis progression by modulating FOXO3a expression. Its silencing suppresses HSC proliferation and enhances apoptosis.	[88]
CircRSF1	Increased	miR-146a-5p	CircRSF1 increases cell viability, cell fibrosis, and inflammation by activating RAC1.	[89]
CircTUBD1	Increased	miR-203a-3p	CircTUBD1 induces liver fibrosis by regulating Smad3. A reduction in circTUBD1 suppresses the expression of COL1A1, COL3A1, and CTGF.	[90]
Hsa_circ_0072765	Increased	miR-197-3p	Hsa_circ_0072765 suppression inhibits activation, migration, and proliferation by targeting TRPV3.	[91]
CircMcph1	Increased	miR-370-3p	A reduction in circMcph1 decreases fibrosis and inflammation. It modulates Irak2 expression.	[92]
CircRNA-007371	Increased	Not identified	CircRNA-007371 overexpression increases angiogenesis, proliferation, and migration.	[93]
CircRNA cVIM	Increased	miR-9-5p miR-122-5p	CircRNA cVIM activates HSCs and regulates TGFBR, resulting in TGF-β/Smad activation.	[94]
Circ_0008494	Increased	miR-185-3p	Circ_0008494 downregulation decreases HSC proliferation, activation, and migration and stimulates apoptosis. Col1a1 is its target.	[95]
CircPSD3	Decreased	miR-92b-3p	CircPSD3 overexpression decreases collagen, profibrogenic and proinflammatory markers, liver enzymes, and liver hydroxyproline by enhancing Smad7.	[96]
CircFBXW4	Decreased	miR-18b-3p	CircFBXW4 suppresses hepatic inflammation, HSC proliferation, and activation, and promotes apoptosis by controlling FBXW7.	[97]
Hsa_circ_0004018	Decreased	miR-660-3p	Hsa_circ_0004018 suppresses fibrosis by inhibiting TEP1.	[98]
CircCREBBP	Decreased	miR-1291	CircCREBBP reduces the activation and proliferation of HSCs. It is involved in LEFTY2 expression.	[99]
Hsa_circ_0070963	Decreased	miR-223-3p	Hsa_circ_0070963 reduces HSC activation and α-SMA and type I collagen expression. Its antifibrotic effect is mediated by LEMD3 regulation.	[100]
Mmu_circ_34116	Decreased	miR-22-3P	Mmu_circ_34116 regulates HSC activation. Its inhibition is associated with increased α-SMA expression.	[101]
CircDIDO1	Decreased	miR-141-3p	CircDIDO1 decreases profibrotic markers and HSC proliferation and induces apoptosis by inhibiting the PTEN/AKT pathway.	[102]
CircMTO1	Decreased	miR-17-5p miR-181b-5p	CircMTO1 decreases HSC proliferation as well as the expression of α-SMA and type I collagen by PTEN and Smad7 regulation.	[103,104]

Abbreviations: HSCs: hepatic stellate cells; TGF-β1: transforming growth factor beta 1; α-SMA: alpha-smooth muscle actin; Col1α1 / COL1A1: collagen type I alpha 1 chain; COL3A1: collagen type III alpha 1 chain; CTGF: connective tissue growth factor; TRPV3: transient receptor potential vanilloid 3; Irak2: interleukin-1 receptor-associated kinase 2; TGFBR: transforming growth factor beta receptor; Smad3 / Smad7: mothers against decapentaplegic homolog 3 / 7; FBXW7: F-box and WD repeat domain

containing 7; TEP1: telomerase-associated protein 1; LEFTY2: left-right determination factor 2; LEMD3: LEM domain containing 3; PTEN: phosphatase and tensin homolog; AKT: protein kinase B; miR / miRNA: microRNA

Conclusions

This review highlights the biogenesis, function, and importance of circRNAs, emphasizing their essential roles as hallmarks of HCC, NAFLD, NASH, and liver fibrosis. However, further research is needed to elucidate the mechanisms underlying their synthesis, biological functions, and clearance. The effects of circRNAs on liver disease through their interactions with miRNAs indicate their potential as biomarkers for prognosis, diagnosis, and targeted therapy. Despite this promise, translating the mechanisms identified by basic research into clinical applications for early detection and prognosis of liver disease remains a considerable challenge. Understanding the dysregulation of circRNA expression in liver diseases may clarify their roles in regulating various molecules and signaling pathways. Nonetheless, their contributions to liver homeostasis, disease development, and the molecular mechanisms regulating circRNAs remain poorly understood. The distinct functions of various liver cell types in liver pathogenesis complicate efforts to determine the precise roles of circRNAs in liver disease. In addition, studies linking circRNAs with liver diseases have focused primarily on HCC, highlighting the need to expand investigations to other liver diseases. Finally, the regulatory effects of circRNA polymorphisms on circRNA expression and function remain to be elucidated.

Abbreviations

miRNA: microRNA; circRNAs: Circular RNAs; HCC: hepatocellular carcinoma; NAFLD: nonalcoholic fatty liver diseases; Mbl: muscle-blind; NUPR1: nuclear protein 1; ENO2: enolase 2; MAPK1: mitogen-activated protein kinase 1; EZH2: zeste homolog 2; TXNDC5: thioredoxin domain-containing protein 5; GUCD1: guanylyl cyclase domain containing 1; SOX9: SRY (sex determining region Y)-box 9; JAK2: Janus kinase 2; ITGB4: integrin β4; TGF-β1: transforming growth factor-β1; CXCR4: chemokine receptor 4; SHPRH: SNF2 histone linker PHD RING helicase; PI3K: phosphoinositide 3-kinase; TET1: ten-eleven translocation methylcytosine dioxygenase 1; 5hmC: 5-hydroxymethylcytosine; NASH: nonalcoholic steatohepatitis; ROCK1: Rho-kinase 1; AMPK: AMP-activated protein kinase; CPEB: cytoplasmic polyadenylation element-binding protein; HIPK3: homeodomain interacting protein kinase 3; PPARα: peroxisome proliferator-activated receptor α; FFA: free fatty acid; SLC27A: solute carrier family 27A; GPX4: glutathione peroxidase 4; ROS: reactive oxygen species; SCAR: circRNA ATP5B regulator; mROS: mitochondrial ROS; HSCs: hepatic stellate cells; IL: interleukin; LPS: lipopolysaccharide; α-SMA: alpha smooth muscle actin; Col1α1: collagen, type I, alpha 1; Tβ4: thymosin β4; FOXO3a: forkhead box O3; TRPV3: transient receptor potential vanillin 3; IRAK2: IL-1 receptor-associated kinase 2; TAA: thioacetamide; PSD3: pleckstrin and Sec7 domain-containing 3.

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Author contributions

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Competing Interests

The authors have declared that no competing interest exists.

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