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Review Article

Non-coding RNA networks in metabolic dysfunction-associated steatotic liver disease: Mechanisms and therapeutic perspectives

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ABSTRACT

Metabolic dysfunction-associated steatotic liver disease (MASLD) has emerged as the most prevalent chronic liver disorder worldwide, characterized by complex molecular regulatory networks driving its pathogenesis. Non-coding RNAs (ncRNAs), including microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), serve as critical regulators of gene expression and have been increasingly recognized for their pivotal roles in MASLD development. Rather than functioning in isolation, these ncRNAs form intricate regulatory networks that integrate and amplify disease signals across multiple cellular compartments and pathological stages. This review provides a comprehensive overview of how these ncRNA networks orchestrate MASLD progression, focusing on their roles in metabolic dysregulation, inflammation, and fibrosis. We further evaluate the diagnostic potential of circulating ncRNAs as stable, non-invasive biomarkers for disease stratification and monitoring, and discuss emerging therapeutic strategies targeting ncRNAs, including antisense oligonucleotides, synthetic mimics, and advanced delivery platforms such as lipid nanoparticles and engineered exosomes. Despite significant progress, challenges related to delivery efficiency, tissue specificity, and safety remain barriers to clinical translation. By synthesizing current knowledge of ncRNA networks in MASLD and highlighting opportunities for therapeutic intervention, this review provides a roadmap for translating ncRNAs into clinical applications for this increasingly prevalent metabolic liver disease.
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1. Introduction

As the metabolic nexus of the body, the liver coordinates a broad range of physiological processes ranging from nutrient metabolism to immune surveillance through its specialized cellular composition: hepatocytes maintaining metabolic homeostasis, Kupffer cells orchestrating innate immunity, and hepatic stellate cells (HSCs) serving as vitamin A reservoirs within cytoplasmic lipid droplets.[1] This functional versatility is complemented by a remarkable regenerative capacity, enabling prompt tissue recovery following injury.[2] However, in the modern era, this inherent resilience is increasingly compromised by shifts in lifestyle and dietary patterns, which contribute to the growing global incidence of liver diseases.[3] Among these, metabolic dysfunction-associated steatotic liver disease (MASLD) has emerged as one of the most prevalent forms of chronic liver disease (CLD), affecting approximately 30%–40% of the global adult population and 7%–14% of children and adolescents.[4,5]

The concept of MASLD has undergone substantial refinement over the past decades. The nomenclature transition from NAFLD (non-alcoholic fatty liver disease) to MASLD reflects a paradigm shift in understanding this condition as a hepatic manifestation of systemic metabolic dysregulation, independent of alcohol intake.[6] MASLD is defined by the presence of hepatic steatosis (involving ≥5% of hepatocytes) along with at least one feature of cardiometabolic dysfunction, such as obesity, type 2 diabetes, or hypertension. Moreover, MASLD exhibits a bidirectional relationship with cardiovascular disease, linked by shared mechanisms such as chronic inflammation and endothelial dysfunction, underscoring

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its multisystemic nature.[7] Given its high prevalence and strong association with metabolic comorbidities, elucidating the molecular mechanisms that drive MASLD pathogenesis has become a critical research priority.

In this context, the discovery of functional non-coding RNAs (ncRNAs) has reshaped our understanding of liver pathophysiological processes, uncovering their essential contributions to the pathogenesis of MASLD. Three principal classes of ncRNAs—microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs)—cooperatively regulate key aspects of hepatic pathology, including inflammation, fibrosis, and metabolic dysregulation, via intricate molecular networks. Among them, miRNAs are the most extensively studied; their high degree of evolutionary conservation across vertebrates highlights their fundamental role in liver development and metabolic zonation.[8] LncRNAs, in contrast, exert regulatory influence through epigenetic and post-transcriptional mechanisms. Although they exhibit lower sequence conservation, their pronounced tissue specificity renders them attractive candidates for liver-directed therapeutics.[9] Characterized by covalently closed loops, circRNAs dominate the hepatic RNA landscape owing to their exceptional stability, exhibiting a half-life exceeding 48 h compared to less than 10 h for linear RNAs.[10] Collectively, the interconnected regulatory circuits, disease-stage-specific expression patterns, and detectability in biofluids position ncRNAs as promising biomarkers and therapeutic targets in MASLD, justifying a systematic investigation into their clinical applicability.

Despite considerable progress in delineating the roles of ncRNAs in MASLD, a persistent translational gap remains between mechanistic understanding and clinical implementation. This review summarizes the stage-specific functions of different ncRNA classes, including their dysregulation in steatosis, inflammation, and fibrosis, while critically assessing their diagnostic and therapeutic potential. Special emphasis is placed on overcoming delivery challenges, which currently constitute the primary bottleneck in translating ncRNA discoveries into viable treatments. Finally, we propose a translational roadmap that identifies targeted delivery systems as pivotal to realizing the clinical potential of ncRNA-based interventions for MASLD.

2. Pathogenesis and clinical aspects of MASLD

2.1. Mechanistic insights into MASLD pathogenesis

The pathogenesis of MASLD is complex and multifactorial, involving intricate interactions among metabolic, inflammatory, and fibrotic pathways that collectively drive disease initiation and progression.[11] MASLD follows a well-characterized pathological continuum, advancing from simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH) and ultimately to fibrosis, driven by a self-reinforcing cycle of metabolic dysregulation and cellular damage.[12] The disease typically originates as isolated fat accumulation within hepatocytes, in the absence of significant inflammation or fibrosis. However, approximately one-third of MASLD patients develop MASH within 4–5 years, a stage marked by persistent lipid deposition accompanied by inflammation, hepatocyte injury, and cell death.[13] MASH may then progress further to fibrosis and cirrhosis, characterized by progressive scarring and stiffening of the liver architecture, and can eventually lead to liver failure or hepatocellular carcinoma (HCC).[14]

At the core of MASLD pathogenesis lies a self-sustaining cycle of metabolic dysfunction rooted in hepatocellular lipid overload. This overload results from an imbalance among fatty acid uptake mediated by CD36 and FATP5, *de novo lipogenesis* controlled by sterol regulatory element-binding protein-1c (SREBP-1c), and very low density lipoprotein (VLDL) export, initiating a cascade of lipotoxic injury.[15] This manifests through mitochondrial β-oxidation overload generating reactive oxygen species (ROS) that exceed antioxidant defenses, endoplasmic reticulum (ER) stress triggering unfolded protein responses, and insulin receptor substrate phosphorylation impairments that exacerbate peripheral lipolysis.[16] The ensuing flux of free fatty acids not only perpetuates hepatic steatosis but also activates Kupffer cells to release pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). These signals, together with lipid-stimulated HSCs, establish a pro-fibrogenic niche that accelerates the transition from simple steatosis to inflammatory MASH.[17] Critically, this vicious cycle is driven by key cytokines (TGF-β, PDGF) and oxidative stress-induced mitochondrial dysfunction, forming a feed-forward loop that propels the disease from metabolic disturbance to end-stage fibrosis.[18] This fibrogenic cascade is further amplified by extracellular matrix (ECM) remodeling, which generates a stiffened microenvironment that in turn promotes HSC activation, culminating in architectural distortion and cirrhosis.[19]

Superimposed upon these core metabolic and inflammatory disturbances, additional layers of regulation, including genetic predisposition, epigenetic modifications, and gut-liver axis dysregulation, further amplify disease progression. Risk alleles in genes such as patatin-like phospholipase domain-containing protein 3 (*PNPLA3*), transmembrane 6 superfamily member 2 (*TM6SF2*), and membrane-bound O-acyltransferase domain containing 7 (*MBOAT7*), together with dynamic epigenetic mechanisms, including DNA methylation patterns, foster a permissive metabolic environment.[20] Concurrently, disruptions of the gut-liver axis contribute to hepatic inflammation, wherein microbiota-derived signals such as lipopolysaccharide (LPS) compromise intestinal barrier integrity and trigger Toll-like receptor (TLR) signaling, while microbial metabolites like short-chain fatty acids influence hepatic lipid metabolism.[21] Together, these multilayered interactions among host genetics, environmental triggers, and gut-derived metabolites account for the clinical heterogeneity of MASLD.

Within this already complex landscape, ncRNAs add an additional dimension of regulatory control, orchestrating disease progression through interconnected networks that operate across multiple pathological processes including lipid metabolism, inflammatory signaling, oxidative stress, mitochondrial homeostasis, and fibrogenesis, while also mediating critical crosstalk along the gut-liver axis.[22,23] By functioning as both downstream effectors and upstream regulators within these pathways, ncRNAs form a sophisticated regulatory network that not only governs the intensity and duration of pathogenic insults but also contributes to the disease-stage-specific phenotypic transitions that characterize MASLD progression.

2.2. Diagnostic approaches and therapeutic interventions

Given the complex and multifactorial nature of MASLD pathogenesis, accurate diagnosis and effective therapeutic intervention remain central challenges in clinical management. The diagnosis of MASLD requires the concurrent presence of hepatic steatosis and at least one cardiometabolic risk factor (obesity, type 2 diabetes, hypertension, or dyslipidemia), highlighting the disease's fundamental association with metabolic syndrome. Definitive confirmation of hepatic steatosis relies on liver biopsy, defined histologically by macrovesicular fat in $\geq$5% of hepatocytes.[24] Despite its diagnostic authority, the dependence on liver biopsy entails several limitations, including sampling variability,

procedural risks, and cost considerations, which collectively restrict its utility for repeated monitoring.[25] These constraints have motivated the development of non-invasive alternatives. Emerging biomarker panels (*e.g.*, NIS4, which incorporates miR-34a and adipokine signals) and multiparametric magnetic resonance imaging (MRI) techniques (including proton density fat fraction (PDFF) and magnetic resonance elastography (MRE)) have demonstrated >85% concordance with biopsy for steatosis and fibrosis staging in prospective validation studies.[26] Importantly, the early detection capability of these modalities may allow intervention at reversible disease stages, potentially preventing progression to decompensated cirrhosis and related mortality. This underscores the translational importance of non-invasive tools, even as liver biopsy remains valuable in clinical trials and mechanistic research.

Lifestyle interventions constitute the cornerstone of MASLD management, where a 7%–10% reduction in body weight through caloric restriction and aerobic exercise has been histologically proven to ameliorate hepatic steatosis and attenuate fibrosis.[27] In morbidly obese individuals with MASLD, metabolic surgery has been shown to significantly improve both liver histology and metabolic parameters, providing a viable therapeutic option for this patient subgroup.[28] In recent years, pharmacologic approaches have advanced considerably. In March 2024, the United States Food and Drug Administration (FDA) approved resmetirom, a thyroid hormone receptor-beta (THR-β) agonist, as the first pharmacologic therapy for the treatment of MASH with moderate to advanced liver fibrosis, marking a pivotal milestone in the field.[29] Vitamin E (as an antioxidant) and pioglitazone (a PPAR-γ agonist) have demonstrated efficacy in reducing inflammation and fibrosis in patients with MASH.[30] Furthermore, glucagon-like peptide-1 (GLP-1) receptor agonists (*e.g.*, liraglutide) and sodium glucose cotransporter 2 (SGLT2) inhibitors (*e.g.*, empagliflozin and dapagliflozin), which target underlying metabolic dysregulation and have demonstrated beneficial effects on hepatic steatosis and comorbid type 2 diabetes, represent promising therapeutic avenues.[31]

Despite the progress made in non-invasive diagnostics and pharmacotherapy, significant gaps remain. Current diagnostic tools, while improving, still lack the sensitivity and specificity to reliably distinguish between simple steatosis and high-risk MASH without the use of invasive biopsy.[32] Similarly, available pharmacologic options remain limited, with only one FDA-approved therapy and a paucity of agents that directly target fibrotic progression. In this context, ncRNAs, particularly those that are stably detectable in circulation, hold substantial promise. Their disease-stage-specific expression patterns, tissue origins, and presence in biofluids position them as ideal candidates for non-invasive liquid biopsy biomarkers. Moreover, the growing understanding of ncRNA regulatory networks in MASLD pathogenesis opens new avenues for mechanism-based therapeutics. As research continues to elucidate the complex roles of ncRNAs in this disease, their integration into diagnostic algorithms and therapeutic platforms represents a promising frontier for precision medicine in MASLD.

3. NcRNA networks in MASLD pathogenesis

3.1. Classification and function of ncRNAs

NcRNAs comprise a diverse array of RNA molecules that, despite lacking protein-coding potential, exert profound regulatory functions across virtually all biological processes. Based on their size, structure, and biogenesis, ncRNAs are broadly classified into several categories, including miRNAs, lncRNAs, circRNAs, small nucleolar RNAs (snoRNAs), PIWI-interacting RNAs (piRNAs), and tRNA-derived small RNAs (tsRNAs). Together, these ncRNA species constitute an intricate regulatory network that governs gene expression at multiple levels.

MiRNAs are small non-coding RNAs of approximately 22 nucleotides that function as key post-transcriptional regulators of gene expression. More than 2600 mature miRNAs are now annotated in humans, and thousands more identified across species, underscoring their evolutionary conservation and wide-ranging functional significance.[33] It is estimated that miRNAs regulate the expression of nearly 30% of the human genes, frequently through combinatorial mechanisms: individual miRNAs can target multiple mRNAs, and single genes are often influenced by multiple miRNAs.[34,35] These small non-coding RNAs are commonly located within the introns of host genes and share promoters to enable coordinated expression, although some are encoded within exons or governed by independent regulatory elements.[36] Functionally, miRNAs fine-tune gene expression through two principal mechanisms: mRNA degradation or translational repression, allowing for precise modulation of diverse biological processes.[37] Recognized as critical regulators in development, metabolism, and disease pathogenesis, miRNAs integrate into complex regulatory networks to maintain cellular homeostasis.[38,39]

LncRNAs are defined as transcripts longer than 200 nucleotides that lack protein-coding capacity. They display characteristic features such as tissue-specific expression patterns, generally low abundance, predominant nuclear localization, and limited evolutionary sequence conservation across species.[9] Despite their divergent primary sequences, lncRNAs play essential roles in gene regulation and diverse cellular processes, indicating that their functional significance likely derives from conserved secondary structures or protein interaction networks, rather than specific linear sequence motifs.[40] Mechanistically, lncRNAs function through a variety of regulatory paradigms. One well-established mechanism involves their role as modular scaffolds, where they recruit epigenetic modifiers to specific genomic loci to modulate histone modifications and DNA methylation, thereby facilitating gene activation or silencing.[41] The lncRNA HOTAIR classically directs the polycomb repressive complex 2 (PRC2) to target genes, leading to transcriptional repression.[42] LncRNAs can also bind directly to transcription factors to fine-tune transcriptional activity, or act as molecular sponges for RNA-binding proteins (RBPs), sequestering them and altering their regulatory functions.[43] A subset of lncRNAs contains open reading frames (ORFs) and can be translated into functional micropeptides, further expanding their functional repertoire.[44] Notably, the biological functions of lncRNAs are closely tied to subcellular localization: nuclear lncRNAs predominantly regulate chromatin architecture and transcription, whereas cytoplasmic lncRNAs more commonly influence mRNA stability and signal transduction pathways.[45] This functional versatility establishes lncRNAs as dynamic and multifaceted regulators of cellular homeostasis.

CircRNAs are covalently closed RNA molecules generated through back-splicing of pre-mRNA. This unique circular architecture endows them with exceptional resistance to exonuclease-mediated degradation and allows them to exhibit distinct tissue- and cell type-specific expression profiles, positioning them as promising biomarkers and therapeutic targets.[46] Based on genomic origin and subcellular localization, circRNAs are categorized into three major subtypes: exonic circRNAs (ecircRNAs), which are predominantly cytoplasmic; intronic circRNAs (ciRNAs); and exon–intron circRNAs (EIciRNAs), both of which are retained in the nucleus and modulate parental gene expression through interactions with RNA polymerase II.[47] Recent advances have established circRNAs as versatile regulators functioning through miRNA sequestration, protein scaffolding, transcriptional

modulation, and even peptide encoding, thereby influencing cellular processes such as proliferation, differentiation, and apoptosis.[48]

In addition to these well-characterized classes, emerging ncRNA species have recently garnered attention for their potential roles in metabolic regulation. snoRNAs are small ncRNAs of 60–300 nucleotides that primarily guide chemical modifications of ribosomal RNA.[49] piRNAs, typically 24–31 nucleotides in length, function in transposon silencing within germline cells; however, emerging evidence implicates them in somatic tissues and metabolic processes.[50] tsRNAs are derived from mature or precursor tRNAs and have been linked to disease progression.[51] Although their roles in MASLD remain largely unexplored, preliminary studies suggest that they may contribute to hepatic lipid metabolism and insulin sensitivity, representing an exciting frontier for future investigation.[52–54]

Rather than functioning in isolation, these diverse ncRNA classes engage in extensive crosstalk through the competitive endogenous RNA (ceRNA) network.[55] The ceRNA hypothesis posits that various RNA species—including mRNAs, lncRNAs, circRNAs, and pseudogenes—communicate with one another by competing for shared miRNA binding sites. By acting as miRNA sponges, these ceRNAs modulate miRNA availability, thereby establishing a complex post-transcriptional regulatory network.[56] This interplay adds an additional layer of complexity to gene expression control and has been increasingly recognized as a key mechanism underlying the pathogenesis of various diseases, including MASLD.[57] Deciphering these ceRNA networks is therefore essential for understanding how ncRNAs collectively orchestrate disease progression and for identifying critical regulatory hubs that may serve as therapeutic targets.

3.2. NcRNA networks regulating metabolic dysregulation in MASLD

Metabolic dysregulation represents a fundamental aspect of MASLD pathophysiology, driving disease progression via interconnected pathological processes such as aberrant hepatic lipogenesis and insulin resistance. This dysfunctional metabolic state results from the coordinated dysregulation of key metabolic regulators, particularly the lipogenic transcription factors carbohydrate responsive element binding protein (ChREBP) and SREBP-1.[58] Growing evidence now identifies ncRNAs as critical modulators of these pathogenic cascades, revealing additional layers of molecular regulation with considerable diagnostic and therapeutic potential (Fig. 1A).

Among the most extensively studied hepatic miRNAs, miR-122 stands out as a master regulator of lipid homeostasis. Comprising over 50% of the liver's miRNA content, miR-122 coordinately suppresses key lipogenic targets including fatty acid synthase (FASN), 3-hydroxy-3-methylglutaryl CoA reductase (HMGCR), and SREBP isoforms.[59] Genetic ablation studies indicate its essential role in MASLD pathogenesis: miR-122-deficient mice develop severe hepatic steatosis due to enhanced triglyceride synthesis (via SREBP-1c activation) and impaired VLDL secretion. The spontaneous progression to steatohepatitis and HCC in these models, coupled with phenotypic rescue upon miR-122 restoration, establishes this miRNA as both a guardian of metabolic health and an inhibitor of hepatocarcinogenesis in CLD.[60] Beyond its cell-autonomous regulatory functions, miR-122 is actively released into the circulation during MASLD progression. Serum levels closely correlate with histological disease severity, supporting its dual role as a pathogenic mediator and a clinically relevant biomarker.[61]

Another key player is the miR-33 family (miR-33a/b), which is genomically linked to SREBP transcriptional regulators and coordinates lipid and cholesterol homeostasis.[62] Elevated miR-33 expression in MASLD promotes hepatic steatosis by concurrently suppressing cholesterol efflux transporters (ABCA1/ABCG1) and mitochondrial fatty acid oxidation (via CPT1α/PGC1α inhibition), while also impairing energy sensing through downregulation of AMP-activated protein kinase alpha (AMPKα). This multi-targeted action establishes a self-reinforcing metabolic imbalance marked by lipid accumulation and insulin resistance.[63] The conservation of miR-33's regulatory network across cardiometabolic diseases, from atherosclerosis to obesity, highlights its potential as a unique therapeutic target capable of addressing both hepatic and systemic manifestations of metabolic dysfunction.[64]

LncRNAs also contribute significantly to metabolic regulation, as exemplified by steroid receptor RNA activator (SRA). Initially identified as a steroid receptor coactivator, SRA modulates metabolism in both adipocytes and hepatocytes. In adipocytes, lncRNA SRA enhances PPARγ-mediated transcriptional activation to promote glucose uptake and differentiation, while simultaneously strengthening insulin signaling via dual mechanisms: suppression of p38/JNK phosphorylation and upregulation of insulin receptor expression.[65] In the liver, SRA promotes steatotic progression by driving lipid accumulation and repressing adipose triglyceride lipase (ATGL) expression through forkhead box protein O1 (FoxO1)-mediated transcriptional interference, underscoring its role as a cross-tissue metabolic regulator.[66] These findings establish SRA as a prototypical multifunctional lncRNA that integrates nuclear receptor signaling, insulin action, and lipid homeostasis in MASLD development.

In addition to linear ncRNAs, circRNAs have emerged as important regulators of lipid metabolism through both non-coding and coding mechanisms. For instance, circRNA RRM2 (circRRM2) is significantly downregulated in MASLD models and functions as a molecular sponge for miR-142-5p. By sequestering miR-142-5p, circRRM2 relieves the inhibition of its target neuregulin 1 (NRG1), thereby upregulating NRG1 expression. The consequent activation of NRG1 signaling suppresses key lipogenic genes (*e.g.*, *SREBP1* and *FASN*), ultimately attenuating triglyceride accumulation and steatosis in both cellular and mouse models of MASLD.[67] This study shows a novel circRNA-miRNA-mRNA network in hepatic lipid metabolism, positioning modulation of this axis as a potential therapeutic strategy for MASLD.

Another intriguing circRNA is circ-SLC9A6, which encodes a functional peptide, SLC9A6-126aa, that acts as an epigenetic regulator. Under lipid overload conditions, SLC9A6-126aa translocates to the nucleus and directly binds to the promoter of the fatty acid transporter gene *CD36*. This interaction recruits the acetyltransferase MOF to catalyze histone H4 lysine 16 acetylation (H4K16ac) at the promoter, thereby epigenetically activating CD36 transcription. Upregulated CD36 subsequently triggers phosphorylation of p38 and ERK-MAPK signaling cascades, driving hepatic lipid dyshomeostasis characterized by increased lipid uptake and storage. The clinical relevance of this axis is underscored by the positive correlation between SLC9A6-126aa levels and both CD36 expression and activated MAPK signaling in livers of MASLD patients.[68] Thus, this circRNA-derived peptide exacerbates MASLD progression through H4K16ac-mediated transcriptional reprogramming, highlighting its potential as a therapeutic target.

Overall, the emerging ncRNA regulatory network constitutes metabolic control in MASLD pathogenesis, orchestrating processes from hepatic lipogenesis to systemic insulin resistance. A more comprehensive list of ncRNAs associated with metabolic dysregulation in MASLD is provided in Table 1.[57,59,63,65–91] The simultaneous targeting of these ncRNA networks could pave the way for precision medicine approaches aimed at the multifaceted metabolic dysfunction in MASLD.

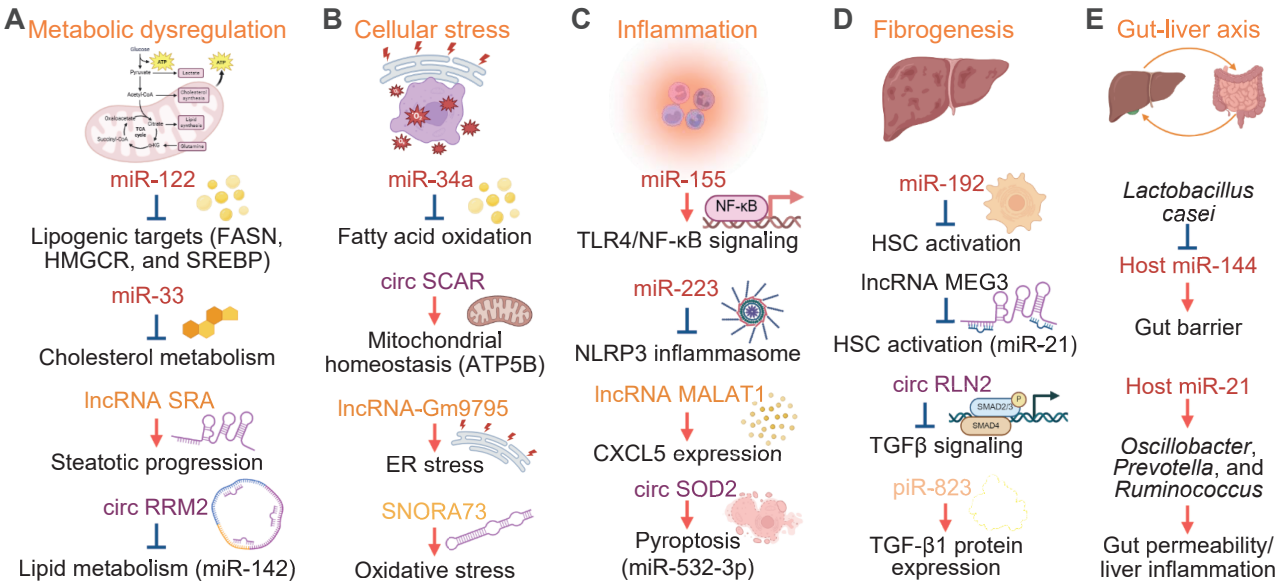

Fig. 1. Role of ncRNAs in MASLD pathogenesis. **(A)** ncRNAs involved in regulating metabolic dysregulation. **(B)** ncRNAs involved in regulating cellular stress, including oxidative stress, mitochondrial dysfunction, and ER stress. **(C)** ncRNAs involved in modulating inflammation. **(D)** ncRNAs involved in driving fibrogenesis. **(E)** ncRNAs involved in mediating the gut-liver axis. Representative ncRNAs are listed in the Figure. Figure was created with BioRender. Abbreviations: CXCL5, C-X-C motif chemokine 5; ER, endoplasmic reticulum; FASN, fatty acid synthase; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; HSC, hepatic stellate cell; lncRNA, long non-coding RNA; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; MASLD, metabolic dysfunction-associated steatotic liver disease; NF-κB, nuclear factor-kappa B; SRA, steroid receptor RNA activator; SREBP, sterol regulatory element-binding protein; TGFβ, transforming growth factor beta; TLR4, Toll-like receptor 4.

3.3. NcRNA networks regulating oxidative stress, mitochondrial dysfunction, and ER stress in MASLD

Oxidative stress and mitochondrial dysfunction represent core pathological drivers in MASLD progression, characterized by excessive ROS generation resulting from impaired β-oxidation and defective electron transport chain (ETC) complexes, which collectively promote lipid peroxidation and hepatocyte injury.[92] In parallel, ER stress has emerged as an additional cellular stress pathway that amplifies inflammation and metabolic disturbances. Within this complex stress landscape, ncRNAs function as key regulators at multiple levels (Fig. 1B).

Among the most extensively studied stress-related ncRNAs is miR-34a, which has emerged as a central regulator by concurrently modulating lipid metabolism and cellular stress responses.[59] Its hepatic overexpression directly suppresses Sirtuin 1 (SIRT1)-mediated deacetylation of lipogenic regulators and represses PPARα-driven fatty acid oxidation, resulting in impaired mitochondrial biogenesis and incomplete β-oxidation.[93] Clinically, circulating miR-34a levels correlate strongly with histological disease severity, reflecting its pathophysiological contribution to hepatocyte apoptosis. Therapeutic inhibition of miR-34a consistently alleviates steatohepatitis and fibrosis in preclinical models, supporting its inclusion in the NIS4 diagnostic algorithm for identifying at-risk MASH patients.[94–96] Together, these findings place miR-34a at the intersection of metabolic dysregulation and hepatic injury, underscoring its dual utility as a biomarker and therapeutic target in MASLD management.

Beyond miRNAs, circRNAs also play important roles in modulating stress responses. Notably, circ_0046366 and circ_0046367 function as endogenous modulators of MASLD by acting as molecular sponges for miR-34a. Through this competitive binding, they derepress PPARα expression, thereby activating its downstream transcriptional network of lipid metabolic genes and restoring hepatic metabolic homeostasis. Both circRNAs are significantly downregulated in steatotic liver tissue, and experimental restoration of their expression mitigates multiple MASLD pathological features, including oxidative stress, programmed cell death, and mitochondrial impairment.[3]

Another mitochondria-enriched circRNA, circRNA SCAR (steatohepatitis-associated circRNA ATP5B regulator), has been identified as a key regulator of mitochondrial homeostasis. Its expression progressively decreases from steatosis to cirrhosis in patient-derived HSCs. Mechanistically, circRNA SCAR binds directly to ATP5B, competitively inhibiting cyclophilin D (CypD)-mediated mitochondrial permeability transition pore (mPTP) opening and thereby reducing ETC leakage and mitochondrial ROS overproduction. This mitochondrial stabilization is transcriptionally regulated by the PGC-1α/CHOP axis, which becomes suppressed under lipid-induced ER stress conditions typical of MASH. Clinically, circRNA SCAR expression exhibits a strong inverse correlation with the severity of hepatic fibrosis and insulin resistance in patients with MASLD, supporting its role as both a sensitive progression biomarker and a promising candidate for mitochondrial-targeted therapies.[97]

LncRNAs also contribute to cellular stress responses, as exemplified by lncRNA-Gm9795. This lncRNA is significantly upregulated in both *in vivo* and *in vitro* models of MASH. Functional studies reveal that while it does not directly affect hepatic lipid accumulation, its overexpression potently promotes the expression of key inflammatory cytokines, including TNF-α, IL-6, and IL-1β. Mechanistically, Gm9795 exerts its pro-inflammatory effect by activating ER stress, as evidenced by its upregulation of critical ER stress markers inositol-requiring enzyme 1 alpha (IRE1α) and binding immunoglobulin protein (BIP). This ER stress activation subsequently triggers the nuclear factor-kappaB (NF-κB) and JNK signaling pathways. The causal link is demonstrated by the fact that the pro-inflammatory activation of NF-κB/JNK by Gm9795 can be rescued by the ER stress inhibitor tauroursodeoxycholic acid (TUDCA), while ER stress agonists can reverse the effects of Gm9795 knockdown.[98] These findings position Gm9795 as a key molecular link between ER stress and inflammation in MASH,

Table 1
Summary of ncRNAs involved in metabolic dysregulation of MASLD.

ncRNA category	Name	Expression	Target genes	Reference
miRNA	miR-122	Upregulated in simple steatosis but downregulated under other conditions	SREBP-1c, SREBP-2, HMGCR, and FASN	59
	miR-33a/b	Upregulated	ABCA1, ABCG1, CPT1α, and PGC1α	63
	miR-132	Upregulated	FoxO3, Pten, Sirt1, P300, and Cyp2e1	69
	miR-125b	Upregulated	ESRRA	70
	miR-192-5p	Upregulated	Yy1	71
	miR-29a	Downregulated	CD36	72
	miR-363	Upregulated	INSIG1	73
	miR-93	Upregulated	SIRT1	74
lncRNA	SRA	Upregulated	PPARγ and FOXO1/ATGL	65,66
	AC012668	Downregulated	miR-380-5p/LRP2	75
	AK142643	Upregulated	IGF2BP2/CD36	76
	CCAT1	Upregulated	miR-613/LXRα	77
	GAS5	Upregulated	miR-26a-5p/PDE4B and miR-29a-3p/NOTCH2	78,79
	Gm10804	Upregulated	PEPCK, G6Pase, SREBP-1c, and FASN	80
	Gm15622	Upregulated	miR-742-3p/SREBP-1c	81
	Gm16551	Downregulated	ACC1 and SCD1	82
	H19	Upregulated	MLXIPL, mTORC1, SREBP-1c, and miR-130a/PPARγ	83–85
	HOTAIR	Upregulated	miR-130b-3p/ROCK1	86
	LncARSR	Upregulated	YAP1/IRS2/AKT	87
	NEAT1	Upregulated	miR-146-5p/ROCK1/AMPK/SREBP	88
	SNHG4	Downregulated	miR-34b-5p/XIAP	89
circRNA	circRRM2	Downregulated	miR-142-5p/NRG1	67
	Circ-SLC9A6	Upregulated	CD36	68
	circ_0057558	Upregulated	miR-206/ROCK1/AMPK	90
	hsa_circ_0048179	Downregulated	miR-188-3p/GPX4	91
	circZBTB46	Downregulated	miRNA-326/FGF1	57

Abbreviations: ABCA1, ATP-binding cassette subfamily A member 1; ABCG1, ATP-binding cassette subfamily G member 1; ACC1, acetyl-CoA carboxylase 1; AKT, protein kinase B; AMPK, AMP-activated protein kinase; CCAT1, colon cancer-associated transcript 1; CD36, cluster of differentiation 36; circRNA, circular RNA; CPT1α, carnitine palmitoyl transferase 1-alpha; Cyp2e1, cytochrome P450 2E1; ESRRA, estrogen-related receptor alpha; FASN, fatty acid synthase; FGF1, fibroblast growth factor 1; FOXO1, forkhead box O1; G6Pase, glucose-6-phosphatase; GAS5, growth arrest-specific 5; GPX4, glutathione peroxidase 4; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; HOTAIR, HOX transcript antisense RNA; IGF2BP2, insulin-like growth factor 2 mRNA-binding protein 2; INSIG1, insulin-induced gene 1; IRS2, insulin receptor substrate 2; lncRNA, long non-coding RNA; LncARSR, lncRNA activated in renal cell carcinoma with sunitinib resistance; LRP2, low-density lipoprotein receptor-related protein 2; LXRα, liver X receptor alpha; MASLD, metabolic dysfunction-associated steatotic liver disease; miRNA, microRNA; MLXIPL, MLX-interacting protein-like; mTORC1, mechanistic target of rapamycin complex 1; ncRNA, non-coding RNA; NEAT1, nuclear enriched abundant transcript 1; NOTCH2, Notch homolog 2; P300, E1A-associated protein p300; PDE4B, phosphodiesterase 4B; PEPCK, phosphoenolpyruvate carboxykinase; PGC1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PPARγ, peroxisome proliferator-activated receptor gamma; Pten, phosphatase and tensin homolog; ROCK1, Rho-associated coiled-coil-containing protein kinase 1; SCD1, stearoyl-CoA desaturase 1; SIRT1, Sirtuin 1; SNHG4, small nucleolar RNA host gene 4; SRA, steroid receptor RNA activator; SREBP, sterol regulatory element-binding protein; XIAP, X-linked inhibitor of apoptosis protein; YAP1, Yes-associated protein 1; Yy1, Yin Yang 1.

suggesting its potential as a therapeutic target for intervening in disease progression.

Additionally, emerging evidence highlights the role of snoRNAs in metabolic stress regulation. The snoRNA SNORA73, encoded within the small nucleolar RNA hosting gene 3 (*Snhg3*) locus, is a critical regulator of cellular metabolism and the response to lipotoxic stress. In the context of MASLD, loss of SNORA73 function reprograms cellular metabolism, leading to enhanced mitochondrial oxidative function and increased glutathione (GSH) production, which protects against lipid-induced oxidative stress and cell death. *In vivo*, knockdown of SNORA73 in mouse models protects against hepatic steatosis and attenuates diet-induced inflammation and oxidative stress. Specifically, in a methionine- and choline-deficient (MCD) diet model, SNORA73 deficiency reduces hepatic lipid accumulation, inflammatory infiltrates, and the expression of pro-fibrotic markers.[54] These findings establish SNORA73 as a key modulator of metabolic stress responses and hepatic inflammation, positioning it as a potential therapeutic target for steatohepatitis.

Taken together, these findings establish ncRNAs as master regulators of oxidative stress, mitochondrial dysfunction, and ER stress in MASLD, forming a multi-layered regulatory network that governs cellular stress responses. A more comprehensive list of ncRNAs associated with stress pathways in MASLD is provided in Table 2.[3,54,93,97–102] This network opens new avenues for diagnostic and therapeutic strategies aimed at targeting metabolic liver disease at its mechanistic origins.

3.4. NcRNA networks modulating inflammation in MASLD

Inflammation serves as a critical driver of MASLD progression, primarily mediated through sustained Kupffer cell activation and the subsequent release of pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6) via pattern recognition receptor signaling pathways, notably the TLR4/MyD88/NF-κB cascade and nucleotide-binding oligomerization domain-like receptor pyrin domain-containing protein 3 (NLRP3) inflammasome activation.[17] Importantly, emerging evidence indicates that ncRNAs act as key modulators of these inflammatory networks, fine-tuning the intensity and duration of immune responses through precise regulation of cytokine production and inflammasome activity in MASLD (Fig. 1C).

Among the most well-characterized inflammatory miRNAs is miR-155, whose pleiotropic functions in MASLD pathogenesis display remarkable cell type-specificity, exerting divergent but synergistically pathogenic effects across different hepatic cell populations. In hepatocytes, downregulation of miR-155 promotes LXRα/SREBP-1c-mediated lipogenic programming by directly targeting negative regulators, thereby exacerbating hepatic steatosis.[103] In contrast, within the hepatic immune microenvironment, elevated miR-155 expression in Kupffer cells drives a potent pro-inflammatory response through several mechanisms: (i) enhancing TLR4/NF-κB signaling via suppression of the negative regulators, suppressor of cytokine signaling 1 (SOCS1) and inositol polyphosphate-5-phosphatase (SHIP1); (ii)

Table 2
Summary of ncRNAs involved in cellular stress of MASLD.

ncRNA category	Name	Expression	Target genes	Reference
miRNA	miR-34a	Upregulated	PPARα and SIRT1	93
	miR-26a	Downregulated	eIF2α	99
	miR-27a/miR-142-5p	Upregulated	Nrf2	100
	miR-96	Downregulated	p66shc	101
lncRNA	Gm9795	Upregulated	IRE1α and BIP	98
	FLRL2	Downregulated	Arnt1/Sirt1	102
circRNA	circ_0046366/_0046367	Downregulated	miR-34a/PPARα axis	3
	circ_SCAR	Downregulated	PGC1α/mROS	97
snoRNA	SNORA73	Downregulated	mTOR pathway	54

Abbreviations: Arnt1, aryl hydrocarbon receptor nuclear translocator 1; BIP, binding immunoglobulin protein; circRNA, circular RNA; eIF2α, eukaryotic initiation factor 2 alpha; FLRL2, fatty liver-related lncRNA 2; IRE1α, inositol-requiring enzyme 1 alpha; lncRNA, long non-coding RNA; MASLD, metabolic dysfunction-associated steatotic liver disease; miRNA, microRNA; mROS, mitochondrial reactive oxygen species; mTOR, mechanistic target of rapamycin; ncRNA, non-coding RNA; Nrf2, nuclear factor erythroid 2-related factor 2; p66shc, 66 kDa proto-oncogene Src homologous-collagen homolog (Shc) adaptor protein; PGC1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PPARα, peroxisome proliferator-activated receptor alpha; SIRT1, Sirtuin 1; snoRNA, small nucleolar RNA.

promoting NLRP3 inflammasome activation; and (iii) modulating the Keap1/Nrf2 pathway.[104,105] The central role of miR-155 in linking metabolic dysregulation with inflammatory cascades establishes it as both a key pathophysiological mediator and a promising therapeutic target in advanced MASLD.

In contrast to the pro-inflammatory role of miR-155, miR-223 functions as a potent anti-inflammatory regulator in MASLD pathogenesis, operating through a distinctive intercellular communication network. Whereas miR-155 amplifies inflammation via Kupffer cell activation, miR-223 is transported via neutrophil-derived extracellular vesicles (EVs) and selectively internalized by hepatocytes through an LDLR/APOE-dependent uptake mechanism—a discovery that unveils a novel mode of cellular crosstalk in steatohepatitis.[106] Within hepatocytes, miR-223 exerts multifaceted immunosuppressive effects by directly targeting the NLRP3 inflammasome pathway. Clinical investigations reveal a strong inverse correlation between circulating miR-223 levels and histological disease severity. Furthermore, gain- and loss-of-function studies in preclinical models confirm its hepatoprotective role in attenuating both inflammatory infiltration and fibrotic progression.[107]

LncRNAs also play critical roles in inflammation regulation, as exemplified by metastasis-associated lung adenocarcinoma transcript 1 (MALAT1). This nuclear-enriched lncRNA serves as a critical upstream regulator of both metabolic and inflammatory cascades in MASLD. MALAT1 enhances the stability of SREBP-1c, thereby promoting hepatic steatosis, lipid accumulation, and insulin resistance.[108] In contrast to the cytoplasmic miRNA-mediated mechanisms described earlier, MALAT1 coordinates inflammatory responses through nuclear-specific actions: it drives pro-inflammatory signaling by enhancing chemokine CXCL5 expression via NF-κB-dependent transcriptional activation, thereby facilitating neutrophil recruitment and Kupffer cell activation. Preclinical intervention study shows that MALAT1 silencing not only reduces steatosis but also significantly attenuates key features of metabolic inflammation and pro-fibrotic signaling, supporting its potential as a therapeutic target for the inflammatory axis of advanced MASLD.[109]

CircRNAs have also emerged as key players in inflammation, as demonstrated by circRNA SOD2 (circSOD2). Upregulated in the livers of both animal models and MASLD patients, circSOD2 functions as a ceRNA by sponging miR-532-3p, which is downregulated in the MASLD. This sequestration prevents miR-532-3p from binding to its target, thioredoxin-interacting protein (TXNIP) mRNA, leading to TXNIP upregulation and subsequent NLRP3 inflammasome activation, which triggers hepatocyte pyroptosis. Notably, circSOD2 knockdown attenuates this cascade, reducing the expression of pyroptosis effectors (GSDMD and cleaved caspase-1) and pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6), thereby alleviating hepatic inflammation.[110] Thus, the circSOD2/miR-532-3p/TXNIP axis represents a critical regulatory circuit that exacerbates MASLD progression by potentiating NLRP3 inflammasome-driven inflammatory responses and pyroptosis.

Collectively, these findings establish ncRNAs as master regulators of immune-metabolic crosstalk in MASLD, forming an intricate regulatory network that governs inflammatory disease progression and opens new avenues for targeted therapeutic intervention. A more comprehensive list of ncRNAs associated with inflammation in MASLD is provided in Table 3.[98,104–107,109–119]

3.5. NcRNA networks driving liver fibrogenesis in MASLD

Liver fibrogenesis marks a critical transition in MASLD pathogenesis, promoting irreversible liver damage through sustained activation of HSCs and ECM deposition. This process is orchestrated by key signaling pathways, including TGF-β, PDGF, and VEGF, that drive HSC activation and proliferation. The resulting architectural distortion and portal hypertension not only accelerate hepatic dysfunction but also elevate the risk of HCC, establishing fibrosis stage as the strongest predictor of MASLD-related mortality.[120]

Among the miRNAs implicated in fibrogenesis, miR-192 has emerged as a crucial regulator, exhibiting dual tissue-specific and circulating biomarker functions. Predominantly expressed in quiescent HSCs, miR-192 exerts potent anti-fibrotic effects by suppressing HSC activation, proliferation, and migration through inhibition of key fibrogenic pathways such as TGF-β/Smad and PDGF signaling. Paradoxically, although intrahepatic miR-192 expression declines during fibrosis progression in preclinical models, its serum levels are markedly elevated in MASLD patients and show a strong positive correlation with disease severity.[121] This inverse relationship between tissue and circulating miR-192 may reflect compensatory secretion by stressed hepatocytes or selective release from activated HSCs, supporting its inclusion among the top-tier diagnostic miRNAs (with miR-34a and miR-122) for non-invasive MASLD staging.[93]

Another pivotal miRNA is miR-21, which serves as a master orchestrator of MASLD pathogenesis by integrating metabolic dysregulation, inflammatory signaling, and fibrosis progression into a coordinated regulatory network.[93] Its expression displays a striking stage-specific upregulation in MASH patients compared to those with simple steatosis. Mechanistically, miR-21 promotes HSC activation through several synergistic pathways: (i) PTEN suppression leading to hyperactive PI3K/AKT signaling; (ii)

Table 3
Summary of ncRNAs involved in inflammation of MASLD.

ncRNA category	Name	Expression	Target genes	Reference
miRNA	miR-155	Upregulated	SOCS1, SHIP1, Keap1/Nrf2, and NLRP3	104,105
	miR-223	Upregulated	LDLR/APOE and NLRP3	106,107
	miR-125b	Upregulated	TNFAIP3	111
	miR-192	Downregulated	Rictor/Akt/FoxO1	112
	miR-378	Upregulated	NF-κB/TNF-α	113
	miR-421	Upregulated	SIRT3	114
	miR-451	Downregulated	Cab39	115
lncRNA	MALAT1	Upregulated	NF-κB/CXCL5	109
	GAS5	Upregulated	miR-28a-5p/MARCH7/NLRP3	116
	Gm9795	Upregulated	NF-κB and JNK	98
	HOTAIR	Upregulated	SRSF1	117
	LncTNF	Upregulated	NF-κB	118
	Platr4	Upregulated	NF-κB/NLRP3	119
circRNA	circSOD2	Upregulated	miR-532-3p/TXNIP/NLRP3	110

Abbreviations: Akt, protein kinase B; APOE, apolipoprotein E; Cab39, calcium-binding protein 39; circRNA, circular RNA; CXCL5, C-X-C motif chemokine ligand 5; FoxO1, forkhead box O1; HOTAIR, HOX transcript antisense RNA; JNK, c-Jun N-terminal kinase; Keap1, Kelch-like ECH-associated protein 1; LDLR, low-density lipoprotein receptor; lncRNA, long non-coding RNA; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; MARCH7, membrane associated ring-CH-type finger 7; MASLD, metabolic dysfunction-associated steatotic liver disease; miRNA, microRNA; ncRNA, non-coding RNA; NF-κB, nuclear factor-kappaB; NLRP3, NOD-like receptor family pyrin domain containing 3; Rictor, rapamycin-insensitive companion of mTOR; SHIP1, SH2-containing inositol 5-phosphatase 1; SIRT3, Sirtuin 3; SRSF1, serine and arginine rich splicing factor 1; TNF-α, tumor necrosis factor-alpha; TNFAIP3, tumor necrosis factor alpha-induced protein 3; TXNIP, thioredoxin-interacting protein.

inhibition of Sprouty2 (SPRY2) and hepatocyte nuclear factor (HNF)-4α sustaining ERK1/2 activation; (iii) SMAD7 silencing enhancing TGF-β signaling; and (iv) lipoprotein receptor-related protein 6 (LRP6) downregulation promoting Wnt/β-catenin-driven fibrotic responses.[122–124] Clinically, circulating miR-21 levels correlate strongly with liver damage and predict disease progression independent of conventional risk factors, underscoring its dual role as a mechanistic mediator and a promising theranostic target in advanced MASLD.[121] Notably, the lncRNA MEG3 participates in MASLD regulation largely through sequestration of hepatic miR-21.[125]

LncRNAs also play prominent roles in fibrogenesis, as exemplified by NEAT1. This lncRNA functions as a pleiotropic effector by acting as a multi-target miRNA sponge, forming an extensive regulatory network. Among its various miRNA targets, NEAT1 promotes fibrogenic progression via sponging of miR-506, while concurrently binding miR-139-5p to activate the c-Jun/SREBP-1c axis and modulate lipid metabolism.[126,127] Hepatic NEAT1 expression is significantly upregulated in both high-fat diet-induced MASLD models and in patients with advanced MASH fibrosis, underscoring its potential role in disease progression.[9] The breadth of NEAT1's miRNA interactions, spanning from metabolic to fibrotic pathways, establishes it as a master regulator capable of coordinating multiple pathological processes in advanced MASLD.

Another lncRNA, LFAR1, promotes hepatic fibrogenesis through a dual mechanistic cascade: it serves as a scaffold enhancing TGFβR1-mediated Smad2/3 phosphorylation, and acts as a transcriptional coactivator that directly binds Smad2/3 to potentiate TGF-β/Notch signaling networks.[128] Although these findings reveal conserved pro-fibrotic pathways in murine models, the translational potential of LFAR1 remains limited due to the unresolved existence of a functional human ortholog, highlighting a critical gap in cross-species lncRNA biology.[9]

Beyond endogenous ncRNAs, engineered circRNAs have been developed as therapeutic platforms for liver fibrosis. For instance, the circRNA encoding human relaxin-2 (cRLN2) was developed as a novel circRNA therapeutic platform for liver fibrosis. In mouse models of CCl_4-induced liver fibrosis, the nanoparticle-delivered cRLN2 exerted multi-targeted anti-fibrotic effects primarily by interfering with the TGF-β1/Smad2 signaling pathway. cRLN2 significantly suppressed HSC activation and downregulated pro-fibrogenic factors (TGF-β, FGF2, and PDGFs), while simultaneously promoting ECM degradation through the upregulation of matrix metalloproteinases (MMPs) and downregulation of their inhibitors (TIMPs). Transcriptomic analyses further indicated that cRLN2 treatment partially restored global gene expression profiles and metabolic functions in fibrotic livers. Notably, cRLN2 demonstrated superior efficacy to relaxin protein treatment and exhibited excellent safety and tolerability *in vivo*, highlighting its promise as a platform for treating chronic fibrotic diseases.[129]

Emerging evidence also implicates piRNAs in fibrogenesis, as shown by piR-823. Upregulated during hepatic fibrogenesis, piR-823 plays a critical role in activating HSCs. Functionally, piR-823 promotes HSC proliferation and the production of fibrotic markers such as alpha-smooth muscle actin (α-SMA) and collagen type I (COL1A) via direct binding to the eukaryotic initiation factor 3B (EIF3B). This piR-823-EIF3B complex subsequently recruits TGF-β1 mRNA and enhances its translation, leading to increased TGF-β1 protein expression without affecting its transcription. Given that TGF-β1 is a master regulator of both inflammatory and fibrogenic responses, the piR-823/EIF3B axis represents a novel pathway regulating a core pro-inflammatory mediator in liver disease. This establishes a vicious cycle where activated HSCs further produce piR-823, driving fibrosis progression.[53] Therefore, targeting the piR-823-EIF3B interaction presents a potential therapeutic strategy to disrupt the inflammatory and fibrogenic cascade in MASLD.

Taken together, these findings delineate a sophisticated ncRNA regulatory hierarchy governing fibrosis progression in MASLD (Fig. 1D). This ncRNA interactome not only provides novel pathophysiological insights but also establishes a framework for developing combinatorial diagnostic and targeted therapeutic strategies to disrupt fibrosis at multiple nodal points in advanced disease. A more comprehensive list of ncRNAs associated with fibrogenesis in MASLD is provided in Table 4.[53,116,121–126,129–133]

3.6. NcRNA-mediated gut-liver axis crosstalk in MASLD

The gut-liver axis represents a bidirectional communication network that integrates signals from the intestinal microbiota, intestinal epithelium, and hepatic immune-metabolic systems. Disruption of this axis—manifested as increased intestinal permeability, microbial dysbiosis, and translocation of bacterial products—is increasingly recognized as a key driver of MASLD pathogenesis.[134] Within this complex interplay, ncRNAs have emerged as critical molecular mediators that orchestrate host-microbiota crosstalk and influence disease progression (Fig. 1E).[135]

Table 4
Summary of ncRNAs involved in fibrogenesis of MASLD.

ncRNA category	Name	Expression	Target genes	Reference
miRNA	miR-192	Downregulated	TGF-β/Smad and PDGF	121
	miR-21	Upregulated	PTEN, SPRY2, HNF4α, SMAD7, and LRP6	122–124
	miR-130a	Downregulated	TGFBR1 and TGFBR2	130
	miR-221	Upregulated	Timp3, Gnai2, Socs1, and PTEN	131
	miR-223	Upregulated	TAZ	132
lncRNA	NEAT1	Upregulated	miR-506	116
	LFAR1	Upregulated	Smad2/3 and TGF-β/Notch	126
	MEG3	Downregulated	miR-21	125
	HULC	Upregulated	MAPK	133
Others	cRLN2	–	TGF-β, FGF2, and PDGFs	129
	piR-823	Upregulated	EIF3B	53

Abbreviations: cRLN2, circRNA encoding human relaxin-2; EIF3B, eukaryotic translation initiation factor 3 subunit B; FGF2, fibroblast growth factor 2; Gnai2, G-protein alpha inhibiting activity polypeptide 2; HNF4α, hepatocyte nuclear factor 4 alpha; HULC, highly upregulated in liver cancer; LFAR1, liver fibrosis-associated lncRNA 1; lncRNA, long non-coding RNA; LRP6, low-density lipoprotein receptor-related protein 6; MAPK, mitogen-activated protein kinase; MASLD, metabolic dysfunction-associated steatotic liver disease; MEG3, maternally expressed gene 3; miRNA, microRNA; ncRNA, non-coding RNA; PDGF, platelet-derived growth factor; SMAD, small mothers against decapentaplegic; SPRY2, sprouty homolog 2; TAZ, transcriptional coactivator with PDZ-binding motif; TGF-β, transforming growth factor-beta; TGFBR1, transforming growth factor beta receptor 1; Timp3, tissue inhibitor of metalloproteinases 3.

Emerging evidence reveals a sophisticated bidirectional crosstalk between the gut microbiota and the host in MASLD, mediated by miRNAs via EVs. Host-derived miRNAs, packaged into exosomes, can influence microbial composition, while bacterial miRNAs within outer membrane vesicles may modulate host gene expression.[136] A study involves the probiotic *Lactobacillus casei*, whose supplementation is associated with the downregulation of host miR-144. This reduction enhances the expression of intestinal tight junction proteins (ZO-1 and OCLN), thereby improving gut barrier integrity and attenuating a critical pathological factor in MASLD.[137] Conversely, the host miR-21, which is upregulated in disease progression and promotes hepatic inflammation and fibrosis, is implicated in modulating specific gut bacteria such as *Oscillobacter*, *Prevotella*, and *Ruminococcus*.[138] This creates a vicious cycle where dysbiosis and increased gut permeability promote liver inflammation, which in turn alters miRNA expression to further disrupt microbial homeostasis, collectively driving MASLD pathogenesis.

Besides these endogenous ncRNA-mediated regulatory circuits, emerging evidence demonstrates the therapeutic potential of dietary ncRNAs acting through the gut-liver axis. Plant-derived exosome-like nanoparticles have gained attention as natural carriers of functional ncRNAs. A recent study showed that oral administration of broccoli-derived exosome-like nanoparticles (BDENs) ameliorates high-fat diet-induced MASLD in mice. BDENs encapsulate 1659 miRNAs predicted to target pathways central to MASLD pathogenesis, including immune regulation, antioxidant defense, and fatty acid biosynthesis. Mechanistically, BDENs restored intestinal barrier integrity, normalized cecal bile acid profiles, and reshaped gut microbiota composition. These effects were accompanied by reduced serum LPS levels and suppressed hepatic inflammation, as evidenced by decreased F4/80, IL-6, and IL-1β expression.[139] Overall, these findings suggest that BDENs and their miRNA cargos mitigate MASLD progression through coordinated modulation of the gut-liver axis, highlighting plant-derived exosome-like nanoparticles as both a source of bioactive ncRNAs and a novel therapeutic strategy for MASLD.

Despite these advances, the current understanding of ncRNA-mediated gut-liver crosstalk in MASLD remains preliminary. Mechanistic studies are often limited by reliance on correlative analyses, and the causal relationships between specific ncRNAs, microbial taxa, and disease phenotypes remain incompletely defined. Moreover, substantial heterogeneity in study findings—stemming from differences in experimental models, intervention protocols, and the inherent dynamism of the gut microbiota—poses significant challenges for translating these discoveries into clinical applications. Future investigations utilizing gnotobiotic models, single-cell resolution technologies, and multi-omics approaches will be essential to dissect the causal architecture of this regulatory network and to establish a foundation for ncRNA-based diagnostics and therapeutics targeting the gut-liver axis in MASLD.

4. Diagnostic and therapeutic potential of ncRNAs in MASLD

4.1. Circulating ncRNAs as non-invasive biomarkers

Although ncRNAs predominantly operate within cells, they are also selectively packaged into various circulating carriers, including EVs, high-density lipoprotein (HDL) complexes, and ribonucleoprotein complexes (*e.g.*, AGO2-bound), which protect them from degradation by ubiquitous RNases.[140] Rather than being passive by-products of cellular turnover, these circulating ncRNAs exhibit hormone-like characteristics, mediating intercellular communication via cell-specific uptake mechanisms. This shift highlights their dual roles as functional signaling molecules and stable biomarkers, with distinct EV-derived ncRNA signatures reflecting tissue-specific pathological states. Such features establish circulating ncRNAs as promising non-invasive tools for disease stratification and therapy monitoring (Fig. 2A).[141]

Virtually all cell types actively secrete ncRNAs, and among circulating species, extracellular miRNAs remain the best characterized to date.[141] Of these, exosomal miRNAs (exomiRs) have arisen as pivotal mediators of systemic metabolic crosstalk in MASLD, using small EVs to deliver bioactive cargo across distant organs.[142] ExomiRs originating from the liver or adipose tissue enter the circulation and influence the function of other organs, thereby contributing to systemic metabolic dysregulation and disease progression.[143] For example, exomiR-155 secreted by adipose tissue macrophages (ATMs) can be internalized by adipocytes, myocytes, and hepatocytes *in vitro*, where its overexpression disrupts cellular insulin signaling.[144] Similarly, exomiR-122, a well-studied liver-derived exomiR, is released by hepatocytes and can modulate energy metabolism in peripheral tissues such as skeletal muscle, underscoring its role in liver-extrahepatic communication during MASLD progression.[145] Elucidating the mechanisms of such exomiR trafficking not only supports their utility as biomarkers of MASLD progression but also identifies them as promising targets for RNA-based therapeutics designed to intercept pathological inter-organ signaling.

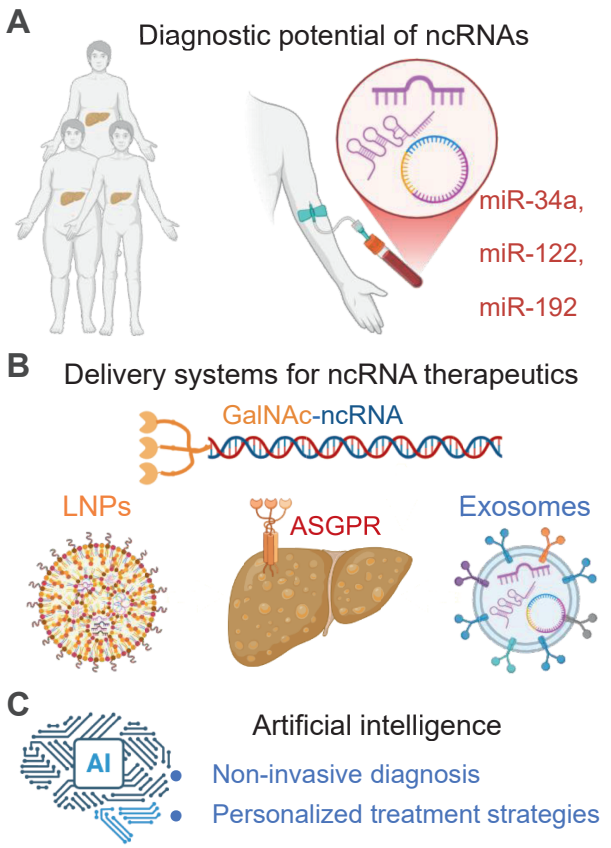

Fig. 2. Diagnostic applications and therapeutic potentials of ncRNAs in MASLD. (A) Circulating ncRNA profiles are presented as superior, non-invasive biomarkers with high sensitivity and specificity for staging, monitoring, and early diagnosis of MASLD. **(B)** The development of advanced delivery platforms represents a promising strategy to fulfill the therapeutic potential of ncRNAs for MASLD. **(C)** AI is a potential strategy to realize ncRNAs in the diagnosis and treatment of MASLD. Figure was created with BioRender. Abbreviations: AI, artificial intelligence; ASGPR, asialoglycoprotein receptor; GalNAc, N-acetylgalactosamine; LNPs, lipid-based nanoparticles; MASLD, metabolic dysfunction-associated steatotic liver disease; ncRNA, non-coding RNA.

Circulating miRNAs (particularly miR-122, miR-34a, miR-21, miR-193, and miR-192) show robust and consistent associations with MASLD/MASH progression, with miR-34a now included in the clinically validated NIS4 diagnostic panel.[26] Their exceptional biomarker potential arises from unique physicochemical properties: high abundance in serum/plasma, nuclease resistance conferred by exosomal or protein-complex packaging, and stability throughout freeze-thaw cycles, facilitating sensitive detection via PCR or next-generation sequencing (NGS) platforms.[146] Importantly, these circulating miRNA profiles directly reflect tissue-level miRNA dysregulation, capturing real-time pathophysiological changes. This combination of analytical robustness and biological relevance has positioned extracellular miRNAs at the forefront of non-invasive diagnostic development, with growing applications in disease stratification, fibrosis staging, and treatment response monitoring in MASLD.[147]

4.2. Therapeutic potential of ncRNAs

Therapeutic targeting of miRNAs primarily follows two fundamental strategies: inhibition of pathogenic miRNAs using antagomiRs, and restoration of beneficial miRNAs via synthetic mimics. This approach aims to rebalance dysregulated molecular pathways at their source. However, the clinical translation of miRNA-based therapeutics for MASLD has encountered both encouraging advances and notable setbacks. Although preclinical studies have provided compelling proof-of-concept (such as exosome-delivered miR-199a-5p modulation significantly altering hepatic steatosis in animal models), clinical progress has faced substantial hurdles.[148] The most advanced candidate, AZD4076 (RG-125), N-acetylgalactosamine (GalNAc)-conjugated antisense oligonucleotides (ASOs) targeting the insulin resistance-associated miR-103/107 cluster, was discontinued during Phase II trials in 2017 due to safety concerns linked to related compounds in the development pipeline.[93] Notably, miR-122-targeting therapies originally developed for hepatitis C virus (HCV), such as Miravirsen and RG-101, were also halted due to cases of drug-induced jaundice, despite miR-122's hepatoprotective role in MASLD.[59] These clinical experiences highlight two major challenges: (i) the need for more advanced delivery systems that improve tissue specificity and limit off-target effects, and (ii) the complex, context-dependent functions of certain miRNAs that complicate their therapeutic targeting.

The modulation of lncRNAs and circRNAs for MASLD therapy currently focuses on two approaches: (i) knockdown using ASOs or siRNAs, and (ii) overexpression via viral vectors or plasmids, with efficacy highly dependent on subcellular localization.[149] Nuclear-retained lncRNAs (*e.g.*, MALAT1 and NEAT1) are more effectively targeted by ASOs, while cytoplasmic lncRNAs (*e.g.*, DANCR) are more amenable to siRNA-mediated silencing.[150] Similarly, circRNA targeting has shown preclinical promise: lentiviral overexpression of hsa_circ_004817 ameliorated hepatic lipid deposition, and siRNA-mediated knockdown of circRNA_002581 attenuated inflammation in MASH models.[91,151] Beyond traditional plasmid- or viral vector-based overexpression, recent advances have enabled the *in vitro* synthesis of circRNAs for direct therapeutic administration. A landmark study demonstrated that synthetic RCRIN, a read-through circRNA downregulated in MASLD livers, when directly administered, significantly suppressed MASLD pathogenesis in mouse models, highlighting the feasibility of synthetic circRNA-based therapeutics.[152] However, these strategies are constrained by limitations such as poor *in vivo* stability, off-target effects, and insufficient tissue specificity. Emerging solutions, including nanoparticle- and exosome-based delivery systems (*e.g.*, GA-RM/GZ/PL nanoparticles for circRNA_0001805), improve targeting precision and efficiency, though further validation is required before clinical translation.[153] Despite the considerable therapeutic potential of lncRNAs and circRNAs, given their ability to coordinately regulate multiple disease-relevant pathways, their successful translation from bench to bedside will require advances in delivery technologies, rigorous safety evaluation, and deeper mechanistic understanding of their roles in MASLD progression.

4.3. Advances in delivery systems for ncRNA therapeutics

The development of effective delivery platforms has become crucial for realizing the therapeutic potential of ncRNAs in MASLD, with recent innovations addressing key challenges in hepatic targeting, nucleic acid stability, and clinical translation (Fig. 2B). Lipid-based nanoparticles (LNPs) and GalNAc-conjugated oligonucleotides have shown exceptional promise for liver-directed delivery.[154] LNPs employ optimized cationic lipid formulations

(*e.g.*, DLin-MC3-DMA) to efficiently encapsulate therapeutic RNAs, as demonstrated by the clinical success of FDA-approved therapies such as Patisiran for transthyretin amyloidosis.[155] Their modular design enables further functionalization with targeting ligands (*e.g.*, GalNAc for hepatocytes and anisamide for lung tumors) to enhance cell-type specificity.[156] Notably, GalNAc serves as a carbohydrate ligand that binds with high affinity to the asialoglycoprotein receptor 1 (ASGR1), which is highly expressed and continuously recycled on hepatocytes, facilitating efficient uptake of phosphorothioate-modified ASOs and siRNAs via endocytosis.[154] This strategy has facilitated clinical breakthroughs, such as Inclisiran for hypercholesterolemia, which exploits the liver's unique vascular permeability and receptor density to achieve effective cellular internalization prior to renal clearance.[157]

Therapeutic strategies for MASLD are further broadening with innovative delivery systems. Exosomes have gained attention as promising nanotherapeutic vehicles due to their innate biocompatibility and ability to be surface-engineered for tissue-specific targeting.[158] Dual-functionalized exosomes engineered with both a 5-HT1D antibody and CD47 protein successfully deliver miR-29b to activated HSCs, bypassing ECM barriers while avoiding immune clearance, leading to significant attenuation of liver fibrosis.[159] Similarly, Liu *et al.*[160] engineered EVs with a hyaluronic acid (HA) ligand for CD44-targeted delivery and loaded them with therapeutic miR-181a-5p, generating a targeted nanovesicle (DPH-EVs@miR). This strategy effectively suppresses HSC activation and ECM deposition by blocking the TGF-β/Smad signaling pathway, thereby improving liver function and mitigating fibrosis progression.

As these technologies continue to advance, the vision of clinically feasible ncRNA-based therapies for MASLD is increasingly achievable. By enabling precise delivery of ncRNAs to hepatic cell types, these next-generation systems offer considerable potential to address the multifactorial pathology of MASLD and may ultimately transform clinical management of this increasingly common metabolic disorder. The integration of novel delivery platforms with emerging ncRNA targets could finally achieve the long-standing promise of precision medicine in hepatology.

5. Challenges and proposed strategies of ncRNAs in MASLD

Despite remarkable progress in elucidating the regulatory roles of ncRNAs in MASLD, translating these mechanistic insights into clinical applications faces substantial challenges ranging from basic biology to clinical implementation.

One major bottleneck lies in the technical and biological hurdles associated with ncRNA-based therapeutics. The inherent instability of ncRNAs in biological fluids, coupled with their susceptibility to nuclease degradation, necessitates advanced delivery platforms to achieve sustained and controlled release at target sites. Although EVs and LNPs have emerged as promising carriers that protect ncRNAs from degradation and facilitate tissue-specific delivery, ensuring precise targeting while minimizing off-target effects remains a formidable challenge. ncRNAs operate within complex regulatory networks, and their regulation can inadvertently affect unintended targets, leading to unpredictable biological consequences.[161] Consequently, thorough assessment of ncRNA specificity and optimization of delivery systems are essential requirements for safe and effective therapeutic translation.

Beyond these technical challenges, the path to clinical implementation is hindered by a lack of large-scale, well-designed clinical trials. Despite encouraging preclinical data demonstrating the efficacy of ncRNA modulation in MASLD models, robust clinical evidence remains limited. Current studies are restricted in scale and often lack longitudinal follow-up to assess long-term safety and potential adverse effects, including immunogenicity, unintended immune modulation, and off-target gene silencing. The intrinsic heterogeneity of MASLD, shaped by diverse genetic backgrounds, metabolic comorbidities, and environmental exposures, further complicates trial design and outcome interpretation. Addressing these gaps will require multicenter, randomized controlled trials with standardized protocols, well-defined patient stratification, and rigorous safety monitoring to establish the therapeutic window and clinical utility of ncRNA-based interventions.

MASLD encompasses a broad spectrum of clinical phenotypes, ranging from simple steatosis to advanced fibrosis and cirrhosis, with distinct underlying metabolic drivers and genetic susceptibilities.[162] Notably, ncRNA expression profiles also exhibit marked heterogeneity across the disease stages, reflecting the dynamic nature of the regulatory networks they constitute.[93] This dual heterogeneity underscores the need for precision medicine approaches that move beyond one-size-fits-all strategies. At the systems biology level, integrated multi-omics approaches offer a powerful framework for dissecting the complex ncRNA networks that regulate MASLD pathogenesis. Furthermore, the convergence of multi-omics profiling with artificial intelligence (AI) may offer a transformative path forward (Fig. 2C).[163] Machine learning algorithms can integrate large-scale transcriptomic, epigenomic, and clinical datasets to identify patient-specific ncRNA signatures, predict treatment responses, and stratify individuals for targeted interventions. AI-driven approaches can also simulate the complex, non-linear interactions within ncRNA regulatory networks, enabling the identification of core network hubs that may serve as optimal therapeutic targets for specific patient subsets.[164]

Taken together, addressing the technical, clinical, and biological heterogeneity challenges will require concerted interdisciplinary efforts and continued innovation in delivery systems, multi-omics integration, and AI-driven analytics. Nevertheless, these collective advances hold great promise for translating ncRNA-based diagnostics and therapeutics into precision medicine strategies for MASLD.

6. Conclusions and future perspectives

MASLD has become the most prevalent CLD worldwide, driven by a complex interplay of metabolic, inflammatory, and fibrotic pathways. Over the past decade, ncRNAs, particularly miRNAs, lncRNAs, and circRNAs, have emerged as one of the central regulators of these pathological processes. Rather than functioning in isolation, these ncRNAs form intricate regulatory networks that integrate and amplify disease signals across multiple cellular compartments and pathological stages. This review has examined the stage-specific roles of ncRNAs in MASLD pathogenesis, evaluated their diagnostic and therapeutic potential, and discussed the major challenges that must be overcome to translate these discoveries into clinical practice.

A key message emerging from this synthesis is that ncRNAs function as master coordinators across the core pathological axes of MASLD. In metabolic dysregulation, molecules such as miR-122, miR-33, lncRNA SRA, circRRM2, and the circ-SLC9A6-encoded peptide orchestrate hepatic lipogenesis, cholesterol balance, and insulin sensitivity. In the domain of cellular stress, miR-34a, circSCAR, Gm9795, and SNORA73 modulate oxidative damage, mitochondrial integrity, and ER stress. Inflammatory responses are regulated by ncRNAs such as miR-155, miR-223, MALAT1, and circSOD2, which govern Kupffer cell activation, cytokine release, and inflammasome-driven pyroptosis. During fibrogenic progression, miR-192, miR-21, lncRNAs NEAT1 and LFAR1, engineered

circRNA cRLN2, and piR-823 regulate HSC activation and ECM deposition. Furthermore, ncRNAs mediate bidirectional gut-liver crosstalk, linking microbial dysbiosis to hepatic inflammation and metabolism, with plant-derived exosome-like nanoparticles (*e.g.*, BDENs) emerging as natural sources of bioactive miRNAs for therapeutic intervention.

From a diagnostic perspective, circulating ncRNAs, particularly those packaged into EVs, offer several advantages as non-invasive biomarkers. Their high stability in biofluids, tissue- and disease-stage-specific expression patterns, and detectability by standard PCR or sequencing platforms make them ideal candidates for liquid biopsy. Notably, miR-34a has already been incorporated into the clinically validated NIS4 panel for identifying at-risk MASH patients. However, broader clinical adoption requires standardized protocols for sample collection, normalization, and data analysis, as well as large-scale prospective validation studies.

Therapeutically, ncRNAs present both opportunities and challenges. Preclinical studies have demonstrated that modulating pathogenic ncRNAs using ASOs, synthetic mimics, or CRISPR-based approaches can ameliorate steatosis, inflammation, and fibrosis in MASLD models. The FDA approval of resmetirom for MASH with fibrosis marks a milestone, but ncRNA-based therapies remain in early stages. Key hurdles include the inherent instability of ncRNAs in circulation, off-target effects due to their pleiotropic regulatory networks, and the need for efficient and tissue-specific delivery systems. Advances in lipid nanoparticles, GalNAc conjugates, and engineered exosomes have improved liver-targeted delivery, but further optimization is required to achieve cell-type specificity and minimize toxicity.

ncRNAs have fundamentally reshaped our understanding of MASLD as a network-driven disease. Their dual role as both mechanistic drivers and accessible biomarkers positions them at the forefront of precision medicine efforts. While significant challenges remain, the rapid pace of discovery in ncRNA biology, coupled with advances in delivery technologies and computational analytics, offers a realistic path toward clinical translation.

Looking ahead, several research priorities could guide the field. First, the field should transition from reductionist studies of individual ncRNAs toward comprehensive mapping of the interconnected ncRNA regulatory networks underlying MASLD pathogenesis. Second, using multi-omics approaches will be essential to elucidate the dynamic interactions among ncRNAs, host genetics, and environmental factors. Third, integrating AI with multi-omics data holds promise for identifying patient-specific ncRNA signatures, predicting treatment responses, and stratifying patients for personalized interventions. Finally, continued innovation in delivery platforms and rigorous clinical trials will be critical to establish the safety, efficacy, and therapeutic windows of ncRNA-based therapies.

Authors' contributions

Ruizhe Ren: Writing – review & editing, Writing – original draft, Funding acquisition, Visualization, Conceptualization. **Siying Ren:** Writing – original draft. **Yihan Xu:** Writing – review & editing. **Xiao Liang:** Writing – original draft, Conceptualization, Supervision. **Xiyang Wei:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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References

1. Trefts E, Gannon M, Wasserman DH. The liver. *Curr Biol*. 2017;27:R1147–R1151. https://doi.org/10.1016/j.cub.2017.09.019.
2. Michalopoulos GK, Bhushan B. Liver regeneration: biological and pathological mechanisms and implications. *Nat Rev Gastroenterol Hepatol*. 2021;18:40–55. https://doi.org/10.1038/s41575-020-0342-4.
3. Chien Y, Tsai PH, Lai YH, et al. CircularRNA as novel biomarkers in liver diseases. *J Chin Med Assoc*. 2020;83:15–17. https://doi.org/10.1097/JCMA.0000000000000230.
4. Tilg H, Petta S, Stefan N, Targher G. Metabolic dysfunction-associated steatotic liver disease in adults: a review. *JAMA*. 2026;335:163–174. https://doi.org/10.1001/jama.2025.19615.
5. Ruan S, Huang L, Song J, et al. Global burden trends and forecasts for MAFLD in adolescents and young adults from 1990 to 2021. *Sci Rep*. 2025;15:13534. https://doi.org/10.1038/s41598-025-98489-9.
6. Eslam M, Newsome PN, Sarin SK, et al. A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement. *J Hepatol*. 2020;73:202–209. https://doi.org/10.1016/j.jhep.2020.03.039.
7. Targher G, Byrne CD, Tilg H. MASLD: a systemic metabolic disorder with cardiovascular and malignant complications. *Gut*. 2024;73:691–702. https://doi.org/10.1136/gutjnl-2023-330595.
8. Zailaie SA, Khoja BB, Siddiqui JJ, et al. Investigating the role of non-coding RNA in non-alcoholic fatty liver disease. *Noncoding RNA*. 2024;10:10. https://doi.org/10.3390/ncrna10010010.
9. DiStefano JK, Gerhard GS. Long noncoding RNAs and human liver disease. *Annu Rev Pathol*. 2022;17:1–21. https://doi.org/10.1146/annurev-pathol-042320-115255.
10. Yepmo M, Potier JB, Pinget M, Grabarz A, Bouzakri K, Dumond Bourie A. Discussing the role of circular RNA in the pathogenesis of non-alcoholic fatty liver disease and its complications. *Front Endocrinol (Lausanne)*. 2022;13:1035159. https://doi.org/10.3389/fendo.2022.1035159.
11. Palomer X, Wang JR, Tang X, et al. Peroxisome proliferator-activated receptor β/δ: a link between metabolism, inflammation, and fibrosis in metabolic dysfunction-associated steatotic liver disease. *Cells*. 2026;15:464. https://doi.org/10.3390/cells15050464.
12. De A, Chalasani N, Duseja A. Biomarkers in metabolic dysfunction-associated steatotic liver disease. *Gastroenterol Clin North Am*. 2026;55:185–202. https://doi.org/10.1016/j.gtc.2025.09.003.
13. Devasia AG, Ramasamy A, Leo CH. Current therapeutic landscape for metabolic dysfunction-associated steatohepatitis. *Int J Mol Sci*. 2025;26:1778. https://doi.org/10.3390/ijms26041778.
14. Leslie J, Krishnamurthy KA, Gopalsamy IK, et al. Metabolic dysfunction-associated steatotic liver disease and steatohepatitis-associated hepatocarcinoma preclinical models. *Nat Rev Gastroenterol Hepatol*. 2026;23:286–317. https://doi.org/10.1038/s41575-025-01162-9.
15. Friedman SL, Neuschwander-Tetri BA, Rinella M, Sanyal AJ. Mechanisms of NAFLD development and therapeutic strategies. *Nat Med*. 2018;24:908–922. https://doi.org/10.1038/s41591-018-0104-9.
16. Jin S, Zhu L, Bao R, et al. Helicobacter hepaticus promotes hepatic steatosis through CdtB-induced mitochondrial stress and lipid metabolism reprogramming. *Nat Commun*. 2025;16:7954. https://doi.org/10.1038/s41467-025-63351-z.
17. Jara M, Norlin J, Kjær MS, et al. Modulation of metabolic, inflammatory and fibrotic pathways by semaglutide in metabolic dysfunction-associated steatohepatitis. *Nat Med*. 2025;31:3128–3140. https://doi.org/10.1038/s41591-025-03799-0.
18. Horn P, Tacke F. Metabolic reprogramming in liver fibrosis. *Cell Metab*. 2024;36:1439–1455. https://doi.org/10.1016/j.cmet.2024.05.003.
19. He W, Huang C, Zhang X, et al. Identification of transcriptomic signatures and crucial pathways involved in non-alcoholic steatohepatitis. *Endocrine*. 2021;73:52–64. https://doi.org/10.1007/s12020-021-02716-y.
20. Bhattacharya I, Maity DK, Kumar A, et al. Beyond obesity: lean metabolic dysfunction-associated steatohepatitis from unveiling molecular pathogenesis to therapeutic advancement. *Naunyn-Schmiedebergs Arch Pharmacol*. 2025;398:13647–13665. https://doi.org/10.1007/s00210-025-04257-x.
21. Bauer KC, Littlejohn PT, Ayala V, Creus-Cuadros A, Finlay BB. Nonalcoholic fatty liver disease and the gut-liver axis: exploring an undernutrition perspective. *Gastroenterology*. 2022;162:1858–1875 (e2). https://doi.org/10.1053/j.gastro.2022.01.058.
22. Locatelli C, Luz K, Andrade SF, et al. MicroRNAs as key regulators in the progression of metabolic dysfunction-associated steatotic liver disease: a bioinformatics analysis. *Biomedicines*. 2026;14:120. https://doi.org/10.3390/biomedicines14010120.

23. Feng T, Liang Y, Sun L, et al. Regulation of hepatic lipid metabolism by intestine epithelium-derived exosomes. *Life Metab*. 2023;2:load044. https://doi.org/10.1093/lifemeta/load044.
24. Gofton C, Upendran Y, Zheng MH, George J. MAFLD: how is it different from NAFLD? *Clin Mol Hepatol*. 2023;29:S17–S31. https://doi.org/10.3350/cmh.2022.0367.
25. Castera L, Friedrich-Rust M, Loomba R. Noninvasive assessment of liver disease in patients with nonalcoholic fatty liver disease. *Gastroenterology*. 2019;156:1264–1281 (e4). https://doi.org/10.1053/j.gastro.2018.12.036.
26. Sanyal AJ, Shankar SS, Yates KP, et al. Diagnostic performance of circulating biomarkers for non-alcoholic steatohepatitis. *Nat Med*. 2023;29:2656–2664. https://doi.org/10.1038/s41591-023-02539-6.
27. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. *Gastroenterology*. 2015;149:367 (e5). https://doi.org/10.1053/j.gastro.2015.04.005.
28. Lassailly G, Caiazzo R, Buob D, et al. Bariatric surgery reduces features of nonalcoholic steatohepatitis in morbidly obese patients. *Gastroenterology*. 2015;149:379 (e16). https://doi.org/10.1053/j.gastro.2015.04.014.
29. Johnson-Moore T, Simmons D, Okafor A, Washington D, Baskaran P. Resmetirom and beyond: a new era in MASLD therapeutics. *Liver Res*. 2025;9:362–364. https://doi.org/10.1016/j.livres.2025.10.004.
30. Knorr JP, Reese R, Serbantez M, Lin KP. Metabolic dysfunction-associated steatotic liver disease (MASLD): integrating metabolic and hepatic management into pharmacy practice. *Am J Health Syst Pharm*. https://doi.org/10.1093/ajhp/zxag095. Published online March 25, 2026.
31. Suresh MG, Mohamed S, Geetha HS, et al. Metabolic dysfunction-associated steatotic liver disease and type 2 diabetes: pathophysiology, diagnosis, and emerging therapeutic strategies. *World J Diabetes*. 2026;17:113149. https://doi.org/10.4239/wjd.v17.i2.113149.
32. Kim Y, Rydqvist P, Ramezani T, et al. Metabolic dysfunction-associated steatohepatitis diagnosis and management in Germany: insights from an expert consensus panel. *Liver Int*. 2025;45:e70225. https://doi.org/10.1111/liv.70225.
33. Kozomara A, Birgaoanu M, Griffiths-Jones S. miRBase: from microRNA sequences to function. *Nucleic Acids Res*. 2019;47:D155–D162. https://doi.org/10.1093/nar/gky1141.
34. Friedman RC, Farh KK, Burge CB, Bartel DP. Most mammalian mRNAs are conserved targets of microRNAs. *Genome Res*. 2009;19:92–105. https://doi.org/10.1101/gr.082701.108.
35. Macvanin M, Obradovic M, Zafirovic S, Stanimirovic J, Isenovic ER. The role of miRNAs in metabolic diseases. *Curr Med Chem*. 2023;30:1922–1944. https://doi.org/10.2174/0929867329666220801161536.
36. Ozsolak F, Poling LL, Wang Z, et al. Chromatin structure analyses identify miRNA promoters. *Genes Dev*. 2008;22:3172–3183. https://doi.org/10.1101/gad.1706508.
37. Guo H, Ingolia NT, Weissman JS, Bartel DP. Mammalian microRNAs predominantly act to decrease target mRNA levels. *Nature*. 2010;466:835–840. https://doi.org/10.1038/nature09267.
38. O'Connell RM, Rao DS, Baltimore D. microRNA regulation of inflammatory responses. *Annu Rev Immunol*. 2012;30:295–312. https://doi.org/10.1146/annurev-immunol-020711-075013.
39. Leung AK, Sharp PA. MicroRNA functions in stress responses. *Mol Cell*. 2010;40:205–215. https://doi.org/10.1016/j.molcel.2010.09.027.
40. Quinn JJ, Chang HY. Unique features of long non-coding RNA biogenesis and function. *Nat Rev Genet*. 2016;17:47–62. https://doi.org/10.1038/nrg.2015.10.
41. Mattick JS, Amaral PP, Carninci P, et al. Long non-coding RNAs: definitions, functions, challenges and recommendations. *Nat Rev Mol Cell Biol*. 2023;24:430–447. https://doi.org/10.1038/s41580-022-00566-8.
42. Gupta RA, Shah N, Wang KC, et al. Long non-coding RNA HOTAIR reprograms chromatin state to promote cancer metastasis. *Nature*. 2010;464:1071–1076. https://doi.org/10.1038/nature08975.
43. Statello L, Guo CJ, Chen LL, Huarte M. Gene regulation by long non-coding RNAs and its biological functions. *Nat Rev Mol Cell Biol*. 2021;22:96–118. https://doi.org/10.1038/s41580-020-00315-9.
44. Cheng Y, He RR, Jiang J, et al. Noncanonical open reading frames from lncRNAs encode functional micropeptides that help shape agronomic traits in rice. *Dev Cell*. 2026;61:919–935 (e6). https://doi.org/10.1016/j.devcel.2026.01.010.
45. Wanowska E, Kubiak M, Makałowska I, Szcześniak MW. A chromatin-associated splicing isoform of OIP5-AS1 acts in cis to regulate the OIP5 oncogene. *RNA Biol*. 2021;18:1834–1845. https://doi.org/10.1080/15476286.2021.1871816.
46. O'Leary E, Jiang Y, Kristensen LS, Hansen TB, Kjems J. The therapeutic potential of circular RNAs. *Nat Rev Genet*. 2025;26:230–244. https://doi.org/10.1038/s41576-024-00806-x.
47. Chen LL. The expanding regulatory mechanisms and cellular functions of circular RNAs. *Nat Rev Mol Cell Biol*. 2020;21:475–490. https://doi.org/10.1038/s41580-020-0243-y.
48. Baiddou C, Knidiri M, Ghazi B, Abu Obaid A, Hamdi S, Errafii K. The circular RNA landscape: biogenesis, functions, identification pipelines, and biomedical applications. *Noncoding RNA Res*. 2026;18:39–51. https://doi.org/10.1016/j.ncrna.2025.12.005.
49. Zhang X, Wang C, Xia S, et al. The emerging role of snoRNAs in human disease. *Genes Dis*. 2022;10:2064–2081. https://doi.org/10.1016/j.gendis.2022.11.018.
50. Zhang C, Yang K, Zhao Z, Feng M, Song L, Xu Z. piRNA: molecular mechanisms from germline silencing to somatic regulation and roles in disease. *Int J Mol Sci*. 2026;27:2685. https://doi.org/10.3390/ijms27062685.
51. Wang Y, Song X, Ma G, et al. tRNA-derived small RNAs in pulmonary diseases: regulatory functions and clinical prospects. *Pharmacol Res*. 2026;226:108153. https://doi.org/10.1016/j.phrs.2026.108153.
52. Li YL, Xu Y, Guan ZW, Meng L, Qu Y, Qiu J. Biological function of tRNA-derived small RNA and its expression and clinical significance in liver diseases. *J Clin Hepatol*. 2025;41:1227–1234. https://doi.org/10.12449/jch250634.
53. Lucaciu RL, Orasan OH, Hangan AC, et al. miRNAs, lncRNAs, circRNAs and piRNAs in nonalcoholic fatty liver disease: past, present and future. *Int J Mol Sci*. 2025;26:10402. https://doi.org/10.3390/ijms262110402.
54. Sletten AC, Davidson JW, Yagabasan B, et al. Loss of SNORA73 reprograms cellular metabolism and protects against steatohepatitis. *Nat Commun*. 2021;12:5214. https://doi.org/10.1038/s41467-021-25457-y.
55. Dunkel H, Jensen LR, Sperling F, et al. Cross-organ communication based on non-coding RNA networks leads to cognitive dysfunction in mice. *Neurobiol Dis*. 2026;221:107319. https://doi.org/10.1016/j.nbd.2026.107319.
56. Yin X, Du Z, Jiang S, et al. RNA regulatory networks: key hubs in the panorama of cancer and emerging therapeutic targets. *MedComm (2020)*. 2026;7:e70586. https://doi.org/10.1002/mco2.70586.
57. Zeng QM, Hu T, Jiang W, et al. CircZBTB46 alleviates metabolic dysfunction-associated steatotic liver disease by targeting miRNA-326/FGF1 axis. *Cell Death Discov*. 2026;12:17. https://doi.org/10.1038/s41420-025-02833-x.
58. Huang DQ, Wong VWS, Rinella ME, et al. Metabolic dysfunction-associated steatotic liver disease in adults. *Nat Rev Dis Primers*. 2025;11:14. https://doi.org/10.1038/s41572-025-00599-1.
59. Su Q, Kumar V, Sud N, Mahato RI. MicroRNAs in the pathogenesis and treatment of progressive liver injury in NAFLD and liver fibrosis. *Adv Drug Deliv Rev*. 2018;129:54–63. https://doi.org/10.1016/j.addr.2018.01.009.
60. Hsu SH, Wang B, Kota J, et al. Essential metabolic, anti-inflammatory, and anti-tumorigenic functions of miR-122 in liver. *J Clin Invest*. 2012;122:2871–2883. https://doi.org/10.1172/jci63539.
61. Wang X, He Y, Mackowiak B, Gao B. MicroRNAs as regulators, biomarkers and therapeutic targets in liver diseases. *Gut*. 2021;70:784–795. https://doi.org/10.1136/gutjnl-2020-322526.
62. Zhang X, Zhao H, Sheng Q, et al. Regulation of microRNA-33, SREBP and ABCA1 genes in a mouse model of high cholesterol. *Arch Anim Breed*. 2021;64:103–108. https://doi.org/10.5194/aab-64-103-2021.
63. Horie T, Nishino T, Baba O, et al. MicroRNA-33 regulates sterol regulatory element-binding protein 1 expression in mice. *Nat Commun*. 2013;4:2883. https://doi.org/10.1038/ncomms3883.
64. Näär AM. miR-33: a metabolic conundrum. *Trends Endocrinol Metab*. 2018;29:667–668. https://doi.org/10.1016/j.tem.2018.04.004.
65. Zayed RK, Sayed NH, Shaker OG, Seleem MM, Darwish HA, Shaheen A. Role of lncRNAs H19, KCNQ1OT1 and SRA in relation to peroxisome proliferator-activated receptor gamma in the occurrence and progression of non-alcoholic fatty pancreas disease in obese and non-obese Egyptian patients. *Int J Biol Macromol*. 2025;331:148270. https://doi.org/10.1016/j.ijbiomac.2025.148270.
66. Chen G, Yu D, Nian X, et al. LncRNA SRA promotes hepatic steatosis through repressing the expression of adipose triglyceride lipase (ATGL). *Sci Rep*. 2016;6:35531. https://doi.org/10.1038/srep35531.
67. Wu LF, Zhou ZJ, Zeng YH, Yang SL, Zhang QY. Circular RNA RRM2 alleviates metabolic dysfunction-associated steatotic liver disease by targeting miR-142-5p to increase NRG1 expression. *Am J Physiol Gastrointest Liver Physiol*. 2024;327:G485–G498. https://doi.org/10.1152/ajpgi.00255.2023.
68. Wang Y, Tian X, Wang Z, et al. A novel peptide encoded by circ-SLC9A6 promotes lipid dyshomeostasis through the regulation of H4K16ac-mediated CD36 transcription in NAFLD. *Clin Transl Med*. 2024;14:e1801. https://doi.org/10.1002/ctm2.1801.
69. Hanin G, Yayon N, Tzur Y, et al. miRNA-132 induces hepatic steatosis and hyperlipidaemia by synergistic multitarget suppression. *Gut*. 2018;67:1124–1134. https://doi.org/10.1136/gutjnl-2016-312869.
70. Gao F, Ma Y, Yu C, Duan Q. miR-125b-5p regulates FFA-induced hepatic steatosis in L02 cells by targeting estrogen-related receptor alpha. *Gene*. 2025;959:149419. https://doi.org/10.1016/j.gene.2025.149419.
71. Ma L, Song H, Zhang CY, Hou D. MiR-192-5p ameliorates hepatic lipid metabolism in non-alcoholic fatty liver disease by targeting Yy1. *Biomolecules*. 2023;14:34. https://doi.org/10.3390/biom14010034.
72. Lin HY, Wang FS, Yang YL, Huang YH. MicroRNA-29a suppresses CD36 to ameliorate high fat diet-induced steatohepatitis and liver fibrosis in mice. *Cells*. 2019;8:1298. https://doi.org/10.3390/cells8101298.
73. Wang L, Jia G, Fu R, et al. Hepatic miR-363 promotes nonalcoholic fatty liver disease by suppressing INSIG1. *J Nutr Biochem*. 2024;134:109717. https://doi.org/10.1016/j.jnutbio.2024.109717.
74. Lee YH, Lee J, Jeong J, et al. Hepatic miR-93 promotes the pathogenesis of metabolic dysfunction-associated steatotic liver disease by suppressing SIRT1. *Metabolism*. 2025;169:156266. https://doi.org/10.1016/j.metabol.2025.156266.
75. Chen X, Ma H, Gao Y, et al. Long non-coding RNA AC012668 suppresses non-alcoholic fatty liver disease by competing for microRNA miR-380-5p with lipoprotein-related protein LRP2. *Bioengineered*. 2021;12:6738–6747. https://doi.org/10.1080/21655979.2021.1960463.
76. Wang P, Wang X, He D, Zhuang C. LncRNA AK142643 promotes hepatic lipid accumulation by upregulating CD36 via interacting with IGF2BP2. *Gene*. 2023;887:147747. https://doi.org/10.1016/j.gene.2023.147747.

77. Huang F, Liu H, Lei Z, et al. Long noncoding RNA CCAT1 inhibits miR-613 to promote nonalcoholic fatty liver disease via increasing LXRα transcription. *J Cell Physiol*. 2020;235:9819–9833. https://doi.org/10.1002/jcp.29795.
78. Xu S, Wang Y, Li Z, Hua Q, Jiang M, Fan X. LncRNA GAS5 knockdown mitigates hepatic lipid accumulation via regulating miR-26a-5p/PDE4B to activate cAMP/CREB pathway. *Front Endocrinol (Lausanne)*. 2022;13:889858. https://doi.org/10.3389/fendo.2022.889858.
79. Cui J, Wang Y, Xue H. Long non-coding RNA GAS5 contributes to the progression of nonalcoholic fatty liver disease by targeting the microRNA-29a-3p/NOTCH2 axis. *Bioengineered*. 2022;13:8370–8381. https://doi.org/10.1080/21655979.2022.2026858.
80. Li T, Huang X, Yue Z, Meng L, Hu Y. Knockdown of long non-coding RNA Gm10804 suppresses disorders of hepatic glucose and lipid metabolism in diabetes with non-alcoholic fatty liver disease. *Cell Biochem Funct*. 2020;38:839–846. https://doi.org/10.1002/cbf.3495.
81. Ma M, Duan R, Shen L, et al. The lncRNA Gm15622 stimulates SREBP-1c expression and hepatic lipid accumulation by sponging the miR-742-3p in mice. *J Lipid Res*. 2020;61:1052–1064. https://doi.org/10.1194/jlr.RA120000664.
82. Di Mauro S, Salomone F, Scamporrino A, et al. Coffee restores expression of lncRNAs involved in steatosis and fibrosis in a mouse model of NAFLD. *Nutrients*. 2021;13:2952. https://doi.org/10.3390/nu13092952.
83. Wang H, Cao Y, Shu L, et al. Long non-coding RNA (lncRNA) H19 induces hepatic steatosis through activating MLXIPL and mTORC1 networks in hepatocytes. *J Cell Mol Med*. 2020;24:1399–1412. https://doi.org/10.1111/jcmm.14818.
84. El Sobky SA, Aboud NK, El Assaly NM, Fawzy IO, El-Ekiaby N, Abdelaziz AI. Regulation of lipid droplet (LD) formation in hepatocytes via regulation of SREBP1c by non-coding RNAs. *Front Med (Lausanne)*. 2022;9:903856. https://doi.org/10.3389/fmed.2022.903856.
85. Liu J, Tang T, Wang GD, Liu B. LncRNA-H19 promotes hepatic lipogenesis by directly regulating miR-130a/PPARγ axis in non-alcoholic fatty liver disease. *Biosci Rep*. 2019;39:BSR20181722. https://doi.org/10.1042/BSR20181722.
86. Guo B, Cheng Y, Yao L, et al. LncRNA HOTAIR regulates the lipid accumulation in non-alcoholic fatty liver disease via miR-130b-3p/ROCK1 axis. *Cell Signal*. 2022;90:110190. https://doi.org/10.1016/j.cellsig.2021.110190.
87. Chi Y, Gong Z, Xin H, Wang Z, Liu Z. Long noncoding RNA lncARSR promotes nonalcoholic fatty liver disease and hepatocellular carcinoma by promoting YAP1 and activating the IRS2/AKT pathway. *J Transl Med*. 2020;18:126. https://doi.org/10.1186/s12967-020-02225-y.
88. Bu FT, Wang A, Zhu Y, et al. LncRNA NEAT1: shedding light on mechanisms and opportunities in liver diseases. *Liver Int*. 2020;40:2612–2626. https://doi.org/10.1111/liv.14629.
89. Ding Y, Zheng S, Fu XN, Ma C, Juan Y. LncRNA SNHG4 regulates lipid metabolism and inflammation in non-alcoholic fatty liver disease by targeting miR-34b-5p/XIAP axis. *Turk J Gastroenterol*. 2025;36:629–640. https://doi.org/10.5152/tjg.2025.24191.
90. Chen X, Tan QQ, Tan XR, Li SJ, Zhang XX. Circ_0057558 promotes nonalcoholic fatty liver disease by regulating ROCK1/AMPK signaling through targeting miR-206. *Cell Death Dis*. 2021;12:809. https://doi.org/10.1038/s41419-021-04090-z.
91. Yang W, Zhao J, Zhao Y, et al. Hsa_circ_0048179 attenuates free fatty acid-induced steatosis via hsa_circ_0048179/miR-188-3p/GPX4 signaling. *Aging (Albany NY)*. 2020;12:23996–24008. https://doi.org/10.18632/aging.104081.
92. Chen Z, Tian R, She Z, Cai J, Li H. Role of oxidative stress in the pathogenesis of nonalcoholic fatty liver disease. *Free Radic Biol Med*. 2020;152:116–141. https://doi.org/10.1016/j.freeradbiomed.2020.02.025.
93. Hochreuter MY, Dall M, Treebak JT, Barrès R. MicroRNAs in non-alcoholic fatty liver disease: progress and perspectives. *Mol Metab*. 2022;65:101581. https://doi.org/10.1016/j.molmet.2022.101581.
94. Fu T, Choi SE, Kim DH, et al. Aberrantly elevated microRNA-34a in obesity attenuates hepatic responses to FGF19 by targeting a membrane coreceptor β-Klotho. *Proc Natl Acad Sci U S A*. 2012;109:16137–16142. https://doi.org/10.1073/pnas.1205951109.
95. Feili X, Wu S, Ye W, Tu J, Lou L. MicroRNA-34a-5p inhibits liver fibrosis by regulating TGF-β1/Smad3 pathway in hepatic stellate cells. *Cell Biol Int*. 2018;42:1370–1376. https://doi.org/10.1002/cbin.11022.
96. Harrison SA, Ratziu V, Boursier J, et al. A blood-based biomarker panel (NIS4) for non-invasive diagnosis of non-alcoholic steatohepatitis and liver fibrosis: a prospective derivation and global validation study. *Lancet Gastroenterol Hepatol*. 2020;5:970–985. https://doi.org/10.1016/s2468-1253(20)30252-1.
97. Zhao Q, Liu J, Deng H, et al. Targeting mitochondria-located circRNA SCAR alleviates NASH via reducing mROS output. *Cell*. 2020;183:76–93 (e22). https://doi.org/10.1016/j.cell.2020.08.009.
98. Ye L, Zhao D, Xu Y, et al. LncRNA-Gm9795 promotes inflammation in non-alcoholic steatohepatitis via NF-κB/JNK pathway by endoplasmic reticulum stress. *J Transl Med*. 2021;19:101. https://doi.org/10.1186/s12967-021-02769-7.
99. Xu H, Tian Y, Tang D, et al. An endoplasmic reticulum stress-microRNA-26a feedback circuit in NAFLD. *Hepatology*. 2021;73:1327–1345. https://doi.org/10.1002/hep.31428.
100. Teimouri M, Hosseini H, Shabani M, Koushki M, Noorbakhsh F, Meshkani R. Inhibiting miR-27a and miR-142-5p attenuate nonalcoholic fatty liver disease by regulating Nrf2 signaling pathway. *IUBMB Life*. 2020;72:361–372. https://doi.org/10.1002/iub.2221.
101. Zhang Y, Wang C, Lu J, et al. Targeting of miR-96-5p by catalpol ameliorates oxidative stress and hepatic steatosis in LDLr-/- mice via p66shc/cytochrome C cascade. *Aging (Albany NY)*. 2020;12:2049–2069. https://doi.org/10.18632/aging.102721.
102. Chen Y, Chen X, Gao J, et al. Long noncoding RNA FLRL2 alleviated nonalcoholic fatty liver disease through Arntl-Sirt1 pathway. *FASEB J*. 2019;33:11411–11419. https://doi.org/10.1096/fj.201900643RRR.
103. Wang L, Zhang N, Wang Z, Ai DM, Cao ZY, Pan HP. Decreased MiR-155 level in the peripheral blood of non-alcoholic fatty liver disease patients may serve as a biomarker and may influence LXR activity. *Cell Physiol Biochem*. 2016;39:2239–2248. https://doi.org/10.1159/000447917.
104. Torres JL, Novo-Veleiro I, Manzanedo L, et al. Role of microRNAs in alcohol-induced liver disorders and non-alcoholic fatty liver disease. *World J Gastroenterol*. 2018;24:4104–4118. https://doi.org/10.3748/wjg.v24.i36.4104.
105. Bala S, Ganz M, Babuta M, et al. Steatosis, inflammasome upregulation, and fibrosis are attenuated in miR-155 deficient mice in a high fat-cholesterol-sugar diet-induced model of NASH. *Lab Invest*. 2021;101:1540–1549. https://doi.org/10.1038/s41374-021-00626-1.
106. He Y, Rodrigues RM, Wang X, et al. Neutrophil-to-hepatocyte communication via LDLR-dependent miR-223-enriched extracellular vesicle transfer ameliorates nonalcoholic steatohepatitis. *J Clin Invest*. 2021;131:e141513. https://doi.org/10.1172/jci141513.
107. He Y, Hwang S, Cai Y, et al. MicroRNA-223 ameliorates nonalcoholic steatohepatitis and cancer by targeting multiple inflammatory and oncogenic genes in hepatocytes. *Hepatology*. 2019;70:1150–1167. https://doi.org/10.1002/hep.30645.
108. Yan C, Chen J, Chen N. Long noncoding RNA MALAT1 promotes hepatic steatosis and insulin resistance by increasing nuclear SREBP-1c protein stability. *Sci Rep*. 2016;6:22640. https://doi.org/10.1038/srep22640.
109. Leti F, Legendre C, Still CD, et al. Altered expression of MALAT1 lncRNA in nonalcoholic steatohepatitis fibrosis regulates CXCL5 in hepatic stellate cells. *Transl Res*. 2017;190:25–39 (e21). https://doi.org/10.1016/j.trsl.2017.09.001.
110. Chen F, Xing Y, Chen Z, et al. Competitive adsorption of microRNA-532-3p by circular RNA SOD2 activates Thioredoxin Interacting Protein/NLR family pyrin domain containing 3 pathway and promotes pyroptosis of non-alcoholic fatty hepatocytes. *Eur J Med Res*. 2024;29:250. https://doi.org/10.1186/s40001-024-01817-4.
111. Zhang Q, Yu K, Cao Y, Luo Y, Liu Y, Zhao C. miR-125b promotes the NF-κB-mediated inflammatory response in NAFLD via directly targeting TNFAIP3. *Life Sci*. 2021;270:119071. https://doi.org/10.1016/j.lfs.2021.119071.
112. Liu XL, Pan Q, Cao HX, et al. Lipotoxic hepatocyte-derived exosomal microRNA 192-5p activates macrophages through Rictor/Akt/Forkhead box transcription factor O1 signaling in nonalcoholic fatty liver disease. *Hepatology*. 2020;72:454–469. https://doi.org/10.1002/hep.31050.
113. Zhang T, Hu J, Wang X, et al. MicroRNA-378 promotes hepatic inflammation and fibrosis via modulation of the NF-κB-TNFα pathway. *J Hepatol*. 2019;70:87–96. https://doi.org/10.1016/j.jhep.2018.08.026.
114. Yang L, Liu S, He Y, et al. Exosomes regulate SIRT3-related autophagy by delivering miR-421 to regulate macrophage polarization and participate in OSA-related NAFLD. *J Transl Med*. 2024;22:475. https://doi.org/10.1186/s12967-024-05283-8.
115. Hur W, Lee JH, Kim SW, et al. Downregulation of microRNA-451 in non-alcoholic steatohepatitis inhibits fatty acid-induced proinflammatory cytokine production through the AMPK/AKT pathway. *Int J Biochem Cell Biol*. 2015;64:265–276. https://doi.org/10.1016/j.biocel.2015.04.016.
116. Chen T, Meng Y, Zhou Z, et al. GAS5 protects against nonalcoholic fatty liver disease via miR-28a-5p/MARCH7/NLRP3 axis-mediated pyroptosis. *Cell Death Differ*. 2023;30:1829–1848. https://doi.org/10.1038/s41418-023-01183-4.
117. Guo B, Yan S, Zhai L, Cheng Y. LncRNA HOTAIR accelerates free fatty acid-induced inflammatory response in HepG2 cells by recruiting SRSF1 to stabilize MLXIPL mRNA. *Cytotechnology*. 2024;76:259–269. https://doi.org/10.1007/s10616-023-00614-x.
118. Atanasovska B, Rensen SS, Marsman G, et al. Long non-coding RNAs involved in progression of non-alcoholic fatty liver disease to steatohepatitis. *Cells*. 2021;10:1883. https://doi.org/10.3390/cells10081883.
119. Lin Y, Wang S, Gao L, et al. Oscillating lncRNA Platr4 regulates NLRP3 inflammasome to ameliorate nonalcoholic steatohepatitis in mice. *Theranostics*. 2021;11:426–444. https://doi.org/10.7150/thno.50281.
120. Hammerich L, Tacke F. Hepatic inflammatory responses in liver fibrosis. *Nat Rev Gastroenterol Hepatol*. 2023;20:633–646. https://doi.org/10.1038/s41575-023-00807-x.
121. Atic AI, Thiele M, Munk A, Dalgaard LT. Circulating miRNAs associated with nonalcoholic fatty liver disease. *Am J Physiol Cell Physiol*. 2023;324:C588–C602. https://doi.org/10.1152/ajpcell.00253.2022.
122. Liu CH, Ampuero J, Gil-Gómez A, et al. miRNAs in patients with non-alcoholic fatty liver disease: a systematic review and meta-analysis. *J Hepatol*. 2018;69:1335–1348. https://doi.org/10.1016/j.jhep.2018.08.008.
123. Zhang Z, Zha Y, Hu W, et al. The autoregulatory feedback loop of microRNA-21/programmed cell death protein 4/activation protein-1 (MiR-21/PDCD4/AP-1) as a driving force for hepatic fibrosis development. *J Biol Chem*. 2013;288:37082–37093. https://doi.org/10.1074/jbc.M113.517953.
124. Wang XM, Wang XY, Huang YM, et al. Role and mechanisms of action of microRNA-21 as regards the regulation of the WNT/β-catenin signaling

pathway in the pathogenesis of non-alcoholic fatty liver disease. *Int J Mol Med*. 2019;44:2201–2212. https://doi.org/10.3892/ijmm.2019.4375.
125. Huang P, Huang FZ, Liu HZ, Zhang TY, Yang MS, Sun CZ. LncRNA MEG3 functions as a ceRNA in regulating hepatic lipogenesis by competitively binding to miR-21 with LRP6. *Metabolism*. 2019;94:1–8. https://doi.org/10.1016/j.metabol.2019.01.018.
126. Jin SS, Lin XF, Zheng JZ, Wang Q, Guan HQ. lncRNA NEAT1 regulates fibrosis and inflammatory response induced by nonalcoholic fatty liver by regulating miR-506/GLI3. *Eur Cytokine Netw*. 2019;30:98–106. https://doi.org/10.1684/ecn.2019.0432.
127. Jin SS, Lin CJ, Lin XF, Zheng JZ, Guan HQ. Silencing lncRNA NEAT1 reduces nonalcoholic fatty liver fat deposition by regulating the miR-139-5p/c-Jun/SREBP-1c pathway. *Ann Hepatol*. 2022;27:100584. https://doi.org/10.1016/j.aohep.2021.100584.
128. Chen C, Li H, Wang X, Wang L, Zeng Q. Lnc-LFAR1 affects intrahepatic cholangiocarcinoma proliferation, invasion, and EMT by regulating the TGFβ/Smad signaling pathway. *Int J Clin Exp Pathol*. 2019;12:2455–2461.
129. Zhong J, Zhang Z, Xiao L, et al. Circular RNA encoding relaxin-2 as a potential therapy for liver fibrosis. *Mol Ther Nucleic Acids*. 2026;37:102807. https://doi.org/10.1016/j.omtn.2025.102807.
130. Wang Y, Du J, Niu X, et al. MiR-130a-3p attenuates activation and induces apoptosis of hepatic stellate cells in nonalcoholic fibrosing steatohepatitis by directly targeting TGFBR1 and TGFBR2. *Cell Death Dis*. 2017;8:e2792. https://doi.org/10.1038/cddis.2017.10.
131. Markovic J, Sharma AD, Balakrishnan A. MicroRNA-221: a fine tuner and potential biomarker of chronic liver injury. *Cells*. 2020;9:1767. https://doi.org/10.3390/cells9081767.
132. Hou X, Yin S, Ren R, et al. Myeloid-cell-specific IL-6 signaling promotes microRNA-223-enriched exosome production to attenuate NAFLD-associated fibrosis. *Hepatology*. 2021;74:116–132. https://doi.org/10.1002/hep.31658.
133. Shen X, Guo H, Xu J, Wang J. Inhibition of lncRNA HULC improves hepatic fibrosis and hepatocyte apoptosis by inhibiting the MAPK signaling pathway in rats with nonalcoholic fatty liver disease. *J Cell Physiol*. 2019;234:18169–18179. https://doi.org/10.1002/jcp.28450.
134. Rusman RD, Akil F, Parewangi ML, et al. Gut microbiota and metabolic-associated steatosis liver disease: unveiling mechanisms and opportunities for therapeutic intervention. *World J Exp Med*. 2025;15:107316. https://doi.org/10.5493/wjem.v15.i4.107316.
135. Yamin M, Alsahafi N, Abdulal RH, Asad M, Bosaeed M, Zohaib A. Non-coding RNAs in the viral host-pathogen interaction: molecular regulation and therapeutic potential. *Front Cell Infect Microbiol*. 2025;15:1734182. https://doi.org/10.3389/fcimb.2025.1734182.
136. Asero C, Franzè MS, Cacciola I, Gangemi S. MASLD under the microscope: how microRNAs and microbiota shape hepatic metabolic disease progression. *Int J Mol Sci*. 2025;26:8633. https://doi.org/10.3390/ijms26178633.
137. Hou Q, Huang Y, Wang Y, et al. Lactobacillus casei LC01 regulates intestinal epithelial permeability through miR-144 targeting of OCLN and ZO1. *J Microbiol Biotechnol*. 2020;30:1480–1487. https://doi.org/10.4014/jmb.2002.02059.
138. Behrouzi A, Ashrafian F, Mazaheri H, et al. The importance of interaction between MicroRNAs and gut microbiota in several pathways. *Microb Pathog*. 2020;144:104200. https://doi.org/10.1016/j.micpath.2020.104200.
139. Zhang F, Liu R, Xu T, Xu W, Huang K, He X. Broccoli-derived exosome-like nanoparticles alleviates metabolic dysfunction-associated steatotic liver disease through modulating the gut-liver axis. *Nutrients*. 2026;18:953. https://doi.org/10.3390/nu18060953.
140. Vickers KC, Palmisano BT, Shoucri BM, Shamburek RD, Remaley AT. MicroRNAs are transported in plasma and delivered to recipient cells by high-density lipoproteins. *Nat Cell Biol*. 2011;13:423–433. https://doi.org/10.1038/ncb2210.
141. van Zonneveld AJ, Zhao Q, Rotmans JI, Bijkerk R. Circulating non-coding RNAs in chronic kidney disease and its complications. *Nat Rev Nephrol*. 2023;19:573–586. https://doi.org/10.1038/s41581-023-00725-w.
142. Wang Z, Kim SY, Tu W, et al. Extracellular vesicles in fatty liver promote a metastatic tumor microenvironment. *Cell Metab*. 2023;35:1209–1226 (e13). https://doi.org/10.1016/j.cmet.2023.04.013.
143. Samy AM, Kandeil MA, Sabry D, Abdel-Ghany AA, Mahmoud MO. Exosomal miR-122, miR-128, miR-200, miR-298, and miR-342 as novel diagnostic biomarkers in NAFL/NASH: impact of LPS/TLR-4/FoxO3 pathway. *Arch Pharm (Weinheim)*. 2024;357:e202300631. https://doi.org/10.1002/ardp.202300631.
144. Ying W, Riopel M, Bandyopadhyay G, et al. Adipose tissue macrophage-derived exosomal miRNAs can modulate in vivo and in vitro insulin sensitivity. *Cell*. 2017;171:372–384 (e12). https://doi.org/10.1016/j.cell.2017.08.035.
145. Chai C, Rivkin M, Berkovits L, et al. Metabolic circuit involving free fatty acids, microRNA 122, and triglyceride synthesis in liver and muscle tissues. *Gastroenterology*. 2017;153:1404–1415. https://doi.org/10.1053/j.gastro.2017.08.013.
146. Ciesla M, Skrzypek K, Kozakowska M, Loboda A, Jozkowicz A, Dulak J. MicroRNAs as biomarkers of disease onset. *Anal Bioanal Chem*. 2011;401:2051–2061. https://doi.org/10.1007/s00216-011-5001-8.
147. Cortez MA, Bueso-Ramos C, Ferdin J, Lopez-Berestein G, Sood AK, Calin GA. MicroRNAs in body fluids–the mix of hormones and biomarkers. *Nat Rev Clin Oncol*. 2011;8:467–477. https://doi.org/10.1038/nrclinonc.2011.76.
148. Li Y, Luan Y, Li J, et al. Exosomal miR-199a-5p promotes hepatic lipid accumulation by modulating MST1 expression and fatty acid metabolism. *Hepatol Int*. 2020;14:1057–1074. https://doi.org/10.1007/s12072-020-10096-0.
149. Zeng Q, Liu CH, Ampuero J, et al. Circular RNAs in non-alcoholic fatty liver disease: functions and clinical significance. *RNA Biol*. 2024;21:1–15. https://doi.org/10.1080/15476286.2023.2290769.
150. Lennox KA, Behlke MA. Cellular localization of long non-coding RNAs affects silencing by RNAi more than by antisense oligonucleotides. *Nucleic Acids Res*. 2016;44:863–877. https://doi.org/10.1093/nar/gkv1206.
151. Jin X, Gao J, Zheng R, et al. Antagonizing circRNA_002581-miR-122-CPEB1 axis alleviates NASH through restoring PTEN-AMPK-mTOR pathway regulated autophagy. *Cell Death Dis*. 2020;11:123. https://doi.org/10.1038/s41419-020-2293-7.
152. Wang Y, Wang J, Zhou Z, et al. A read-through circular RNA RCRIN inhibits metabolic dysfunction-associated steatotic liver disease. *J Hepatol*. 2025;82:1068–1079. https://doi.org/10.1016/j.jhep.2024.11.052.
153. Li J, Qi J, Tang Y, et al. A nanodrug system overexpressed circRNA_0001805 alleviates nonalcoholic fatty liver disease via miR-106a-5p/miR-320a and ABCA1/CPT1 axis. *J Nanobiotechnology*. 2021;19:363. https://doi.org/10.1186/s12951-021-01108-8.
154. Roberts TC, Langer R, Wood MJA. Advances in oligonucleotide drug delivery. *Nat Rev Drug Discov*. 2020;19:673–694. https://doi.org/10.1038/s41573-020-0075-7.
155. Ferraresso F, Strilchuk AW, Juang LJ, Poole LG, Luyendyk JP, Kastrup CJ. Comparison of DLin-MC3-DMA and ALC-0315 for siRNA delivery to hepatocytes and hepatic stellate cells. *Mol Pharm*. 2022;19:2175–2182. https://doi.org/10.1021/acs.molpharmaceut.2c00033.
156. Tam YY, Chen S, Cullis PR. Advances in lipid nanoparticles for siRNA delivery. *Pharmaceutics*. 2013;5:498–507. https://doi.org/10.3390/pharmaceutics5030498.
157. Ray KK, Landmesser U, Leiter LA, et al. Inclisiran in patients at high cardiovascular risk with elevated LDL cholesterol. *N Engl J Med*. 2017;376:1430–1440. https://doi.org/10.1056/NEJMoa1615758.
158. Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes. *Science*. 2020;367:eaau6977. https://doi.org/10.1126/science.aau6977.
159. Zhang H, Xing J, Sun M, et al. Engineered exosomes for targeted microRNA delivery to reverse liver fibrosis. *Biomaterials*. 2026;324:123510. https://doi.org/10.1016/j.biomaterials.2025.123510.
160. Liu Y, Chen S, Huang H, et al. Ligand-tethered extracellular vesicles mediated RNA therapy for liver fibrosis. *Adv Healthc Mater*. 2025;14:e2403068. https://doi.org/10.1002/adhm.202403068.
161. Li Z, Ding H, Liu X, et al. miRNA regulatory networks as precision diagnostic and therapeutic targets in pulmonary arterial hypertension: from molecular cascades to clinical translation. *Am J Cardiovasc Dis*. 2025;15:335–356. https://doi.org/10.62347/rgty8619.
162. Mastoridou EM, Goussia AC, Kataki A, et al. The interplay between cellular senescence and lipid metabolism in the progression of metabolic dysfunction-associated steatotic liver disease (MASLD). *Int J Mol Sci*. 2026;27:1066. https://doi.org/10.3390/ijms27021066.
163. Huang XL, Chen WH, Ding M, Song YM, Zheng YW. The revolutionary role of machine learning in predicting, diagnosing, and treating liver disease. *Liver Res*. 2025;9:249–251. https://doi.org/10.1016/j.livres.2025.04.001.
164. Zhang H, Wang Y, Pan Z, et al. ncRNAInter: a novel strategy based on graph neural network to discover interactions between lncRNA and miRNA. *Brief Bioinform*. 2022;23:bbac411. https://doi.org/10.1093/bib/bbac411.