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REVIEW

Long non-coding RNAs as modulators and therapeutic targets in non-alcoholic fatty liver disease (NAFLD)

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Abstract Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease in the world, with epidemiological studies indicating a 25% prevalence. NAFLD is considered to be a progressive disease that progresses from simple hepatic steatosis to non-alcoholic steatohepatitis (NASH), then to liver fibrosis, and finally to cirrhosis or hepatocellular carcinoma (HCC). Existing research has mostly elucidated the etiology of NAFLD, yet its particular molecular processes remain uncertain. *Long non-coding RNAs* (*LncRNAs*) have been linked in a wide range of biological processes in recent years, with the introduction of microarray and high-throughput sequencing technologies, and previous studies have established their tight relationship with several stages of NAFLD development. Existing studies have shown that *lncRNAs* can regulate the signaling pathways related to hepatic lipid metabolism, NASH, NASH-related fibrosis and HCC. This review aims to provide a basic overview of NAFLD and *lncRNAs*, summarize and describe the mechanisms of *lncRNAs* action involved in the development of NAFLD, and provide an outlook on the future of *lncRNAs*-based therapy for NAFLD.

Abbreviation: SCD1, stearoyl-CoA desaturase-1; ACC, acetyl CoA carboxylase; FAS, Fatty acid synthase; CD36, cluster of differentiation 36; ROCK1, rho kinase 1; AMPK, 5-AMP activated protein kinase; SREBP, sterol-regulatory element binding proteins; ARNT, arylhydrocarbon receptor nuclear transporter; PPARα, peroxisome proliferator-activated receptor α; PPARγ, peroxisome proliferator-activated receptor γ; NOTCH2, notch homolog 2; USP10, deubiquitinase 10; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; IR, insulin resistnce; IRS-1, insulin receptor substrate-1; PDK1, 3′-phosphoinositide-dependent kinase 1; FoxO1, Forkhead Box Protein A1; EZH2, enhancer of zeste homolog 2; SIRT, sirtuin; HuR, human antigen R; Sphk2, sphingosine kinase 2; hnRNPA1, heterogeneous nuclear ribonucleoprotein A1; CALM, calmodulin; PI3K, phosphatidylinositol3-kinase; CaM, cell adhesion molecule; hnRNPU, heterogeneous nuclear ribonucleoprotein U; MTTP, microsomal triglyceride transfer protein; YAP, yes-associated protein 1; MLXIPL, MLX interacting protein-like; mTOR, mammalian target of rapamycin; ATGL, adipose triglyceride lipase; PEG3, paternally expressed gene 3; NF-kB, nuclear factor-k-gene binding; Arnt1, aryl hydrocarbon receptor nuclear translocator 1; TNF-α, tumor necrosis factor-α; IL-6, interleukin 6; IL-1β, interleukin 1β; PTEN, phosphatase and tensin homolog; α-SMA, α-smooth muscle actin; DNMT3b, DNA methyhransferase 3b; NLRC5, NOD-like receptor family caspase activation and recruitment domain containing 5; TGF, transforming growth factor; Hes1, hairy and enhancer of split 1; TTP, tocopherol transfer protein; MMP-2, matrix metalloproteinase 2; CUL4a, cullin 4 A; STAT6, signal transducer and activator of transcription 6.

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PALABRAS CLAVE
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Mecanismo;
Diana terapéutica

RNA largos no codificantes como moduladores y dianas terapéuticas en la enfermedad del hígado graso no alcohólico (NAFLD)

Resumen La enfermedad del hígado graso no alcohólico (NAFLD) es la enfermedad hepática más común en el mundo, con estudios epidemiológicos que indican una prevalencia del 25%. La NAFLD se considera una enfermedad progresiva que avanza de esteatosis hepática simple a esteatohepatitis no alcohólica (NASH), luego a fibrosis hepática y, finalmente, a cirrosis o carcinoma hepatocelular (HCC). La investigación existente ha dilucidado principalmente la etiología de NAFLD. Sin embargo, sus procesos moleculares particulares siguen siendo inciertos. Los ARN largos no codificantes (lncRNA) se han relacionado en una amplia gama de procesos biológicos en los últimos años, con la introducción de microarrays y tecnologías de secuenciación de alto rendimiento, y estudios previos han establecido su estrecha relación con varias etapas del desarrollo de NAFLD. Los estudios existentes han demostrado que los lncRNA pueden regular las vías de señalización relacionadas con el metabolismo lipídico hepático, NASH, fibrosis relacionada con NASH y HCC. Esta revisión tiene como objetivo proporcionar una visión general básica de NAFLD y lncRNA, resumir y describir los mecanismos de acción de lncRNA involucrados en el desarrollo de NAFLD, y proporcionar una perspectiva sobre el futuro de la terapia basada en lncRNA para NAFLD.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a chronic liver disease in which the fatty degeneration of the liver reaches 5–10% or more of the total liver weight. However, the disease is not due to excessive alcohol consumption ($\leq$20 g/d for women and $\leq$30 g/d for men) or other causes.[1] The prevalence of NAFLD in the general population is as high as 25%.[2] Current research suggests that NAFLD is close association with obesity and type 2 diabetes mellitus (T2DM).[3] It is estimated that 47.3–63.7% of patients with type 2 diabetes[4] and up to 80% of obese patients[5] develop symptoms related to NAFLD. NAFLD can progress from simple steatosis to non-alcoholic steatohepatitis (NASH). If not effectively controlled, it may eventually progress to cirrhosis or even hepatocellular carcinoma (HCC), seriously affecting physical health.[6] As scientists have studied NAFLD, they have found that the main risk factors associated with NAFLD progression include age, inflammation, intestinal-liver axis signaling, genetic polymorphisms such as single nucleotide polymorphisms in the *PNPLA3* gene[1] and metabolic abnormalities such as obesity, insulin resistance, and type 2 diabetes. In addition, diet can have a significant impact on NAFLD. In addition to the well-known high-fat diet, fructose intake has the potential to induce hepatic lipid deposition and hepatic steatosis in humans.[7]

Because of the complexity of the specific pathogenesis of NAFLD (Fig. 1), no definitive conclusions can be drawn about its pathogenesis. The ''two-hit theory'' is a classic theory that elucidates the pathogenesis of NAFLD. The theory states that NAFLD develops after two hits. The first being the excessive accumulation of fat in the liver, which subsequently triggers a second hit (cytotoxic event), including the release of inflammation-related cytokines (*e.g. TNFα, IL-1β, IL-6, etc.*) and adipokines, mitochondrial dysfunction, and oxidative stress, leading to hepatocyte damage.[8] However, this theory is somewhat flawed in failing to address the molecular and metabolic mechanisms behind the pathogenesis of steatosis and NASH. It does not fully explain the development of lipid deposition in hepatocytes during the development of NAFLD.

In some cases, inflammation may precede steatosis, so it is wrong to think of NAFLD as a disease continuum. In addition, simple steatosis can have a protective effect on the liver.[9] For these defects, scientists later developed the ''multiple hit theory,'' which states that excessive accumulation of liver fat remains the first hit but that hepatocytes are affected to varying degrees by genetic and epigenetic factors, changes in the gut microbiota and endoplasmic reticulum stress (ERS), resulting in widespread metabolic dysfunction and accelerated disease progression.[9]

Long non-coding RNAs (LncRNAs) are a group of molecules longer than 200 nucleotides that are not generally involved in protein-coding and are therefore often referred to by scholars as 'noisy sequences'.[10] *LncRNAs* can be classified into five categories depending on their position in the genome: antisense *lncRNAs*, intergenic *lncRNAs*, intronic *lncRNAs*, bidirectional *lncRNAs*, and sense *lncRNAs*. The *lncRNAs* has the exact transcription from corresponding genes as the *mRNAs*, and after shearing has 5′ cap and 3′ polyA tail that can turn the same gene into a different transcript by variable shearing.[11] The difference is that it does not have the ability of *mRNAs* to encode proteins, and it is differently located, with different *lncRNAs* differing in abundance inside (and outside) the cell.

Studies have shown that the influence mechanisms of lncRNAs mainly include the following: (a) Guiding target localization; (b) Acting as a molecular scaffold mediating protein-RNA interactions; (c) Act as a miRNA sponge; (d) Act as a molecular decoy to bind directly to proteins and inhibit downstream gene expression; (e) Encode transcription of upstream promoters of target genes and interfere with

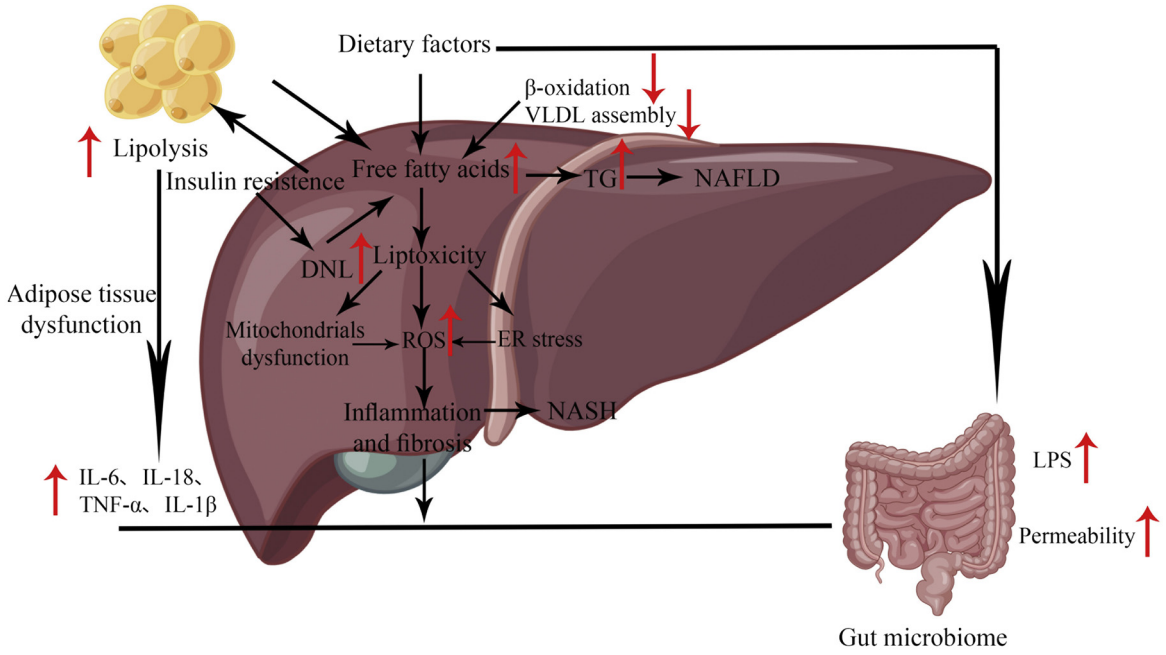

Figure 1 Pathogenesis of NAFLD.

chromatin remodeling and histone modification to affect downstream gene expression; (f) As a precursor of small RNA. In addition, studies have also confirmed that *lncRNAs* can interact directly with signaling receptors.[12] Scientists have discovered that *lncRNAs* can be involved in a wide range of biological activities, including epigenetic regulation, regulation of protein complexes, chromosome recruitment as well as inactivation, and regulation of cell growth and apoptosis, *etc*. For example, the *lncRNA DANCR* can promote migration, invasion, and relocation of pre-eclamptic trophoblast cells via *miR-214-5p*.[13] The abnormal functional expression of *lncRNAs* has also been reported to be closely associated with developing various diseases, such as cancer, inflammation, and liver disease. The *lncRNA HSD11B1-AS1* is upregulated in the acute phase of Kawasaki disease, and interaction between *HSD11B1-AS1* and *G0S2* can occur to control inflammation in the acute phase of Kawasaki disease.[14]

A variety of dysregulated *lncRNAs* have been reported in NAFLD, which can play a crucial role in lipid accumulation, NASH, NASH-related fibrosis, and HCC through a variety of mechanisms, such as acting as competitive endogenous *RNAs* (*ceRNAs*), binding to *RNA*-binding proteins and controlling their phosphorylation, acetylation, and ubiquitination at the post-translational level. This review aims to examine the role of *lncRNAs* in the development of NAFLD and its future therapeutic prospects, further illuminating the future direction of NAFLD.

The role of *lncRNAs* in the development of NAFLD

To date, scientists have identified many abnormal *lncRNAs* expressions in NAFLD. Studies have shown that 1735 *lncRNAs* and 1485 *mRNAs* are differentially expressed in NAFLD samples compared to standard liver samples.[15] They are widely involved in hepatic lipid metabolism, NASH, NASH-associated fibrosis and NAFLD-related HCC (Table 1). This chapter will outline the mechanisms of *lncRNAs* action in NAFLD (Fig. 2).

The role of *lncRNAs* in hepatic lipid metabolism

The early stage of NAFLD is hepatic steatosis, mainly characterized by excessive triglyceride (TG) deposition in the hepatocytes. This is mainly caused by an imbalance between TG/fatty acid acquisition and removal, which involves an increase in the uptake of circulating lipids and de novo lipogenesis (DNL), as well as a decrease in fatty acid oxidation (FAO) and lipid output from very low-density lipoproteins (VLDL). DNL is an essential source of TG deposition in the liver, and the transcription factors *ChREBP* and *SREBP-1c* play a vital role in this process. Their activation promotes the expression of downstream lipogenic genes (*FAS*, *ACC1*, *etc*.), thereby stimulating DNL. In addition, hepatic TG utilization is primarily β-oxidation of fatty acids, with *PPARα/PGC-1α* playing a crucial role. *PPARα* is activated by fatty acids, and upon their binding, it can promote the expression of fatty acid metabolism precursor genes.

NAFLD has been treated as a metabolic disease, which has led to impaired lipid metabolism being seen as key to the pathogenesis of NAFLD. The role of *lncRNAs* in regulating hepatic lipid metabolism has been widely studied. *lncRNAs* can protect their protein-coding counterparts from post-translational regulation by isolating *miRNAs*. This *ceRNA* mechanism has been adopted as the primary molecular mechanism regulating lipid metabolism in NAFLD. For example, *lncRNA uc.372* was reported to reduce the expression inhibition of target genes related to lipid synthesis and uptake (*ACC*, *FAS*, *SCD1*, *CD36*) by binding to

Table 1 The mechanism of *lncRNAs* in NAFLD.

Progression	*LncRNAs*	Expression	Biological function	Potential targets	Downstream targets	Sample source	References
Lipid accumulation	*NEAT1*	Up	Promoting lipid accumulation	*miR-146a-5p*	*ROCK1*	Animal and cell models	17
				miR-140	*AMPK/SREBP1*		18
				miR-212-5p	*GRIA3*	Cell model, human samples	26
	MALAT1	Up	Promoting lipid accumulation	*miR-206*	*ARNT*	Animal and cell models, human samples	19
	H19	Up	Promoting hepatic steatosis and degeneration	*miR-130a*	*PPARγ*	Animal and cell models	20
				MLXIPL/mTORC1	–	Animal and cell models	33
	HOTAIR	Up	Promoting lipid accumulation	*miR-130b-3p*	*ROCK1*	Animal and cell models	21
	ACO12668	Down	Inhibiting lipid production and accumulation	*miR-380-5p*	*LRP2*	Animal and cell models	22
	LncNONMMUG027912	Down	Inhibiting lipid accumulation	*AMPKα/mTOR/SREBP1C*	–	Animal and cell models	23
Lipid accumulation	*MEG3*	Down	Inhibiting lipid accumulation and inflammation	*EZH2*	*Sirtuin6*	Animal models	27
			Relieving lipid excess deposition	*miR-21*	*LRP6*	Animal and cell models	24
	SRA	Up	Promoting hepatic steatosis	*FoxO1*	*ATGL*	Animal and cell models	36
			Promoting lipid accumulation	*JNK/p38 MAPK*	*IR,IRS-1/Akt*	Animal and cell models	25
	APOA4-AS	Up	Promoting lipid accumulation	*HuR*	–	Animal and cell models, human samples	28
	Blnc1	Up	Increasing insulin resistance and liver steatosis	*hnRNPA1*	*Pgc1β*	Animal and cell models	30
	LncRHL	Up	Inhibiting VLDL secretion from hepatocytes	*hnRNPU/Bmal1*	*MTTP*	Animal and cell models	31
	ARSR	Up	Promoting lipid accumulation	*YAP1*	*IRS2/AKT*	Animal and cell models, human samples	32

Table 1 (*Continued*)

Progression	*LncRNAs*	Expression	Biological function	Potential targets	Downstream targets	Sample source	References
				PI3K/Akt	*SREBP-1c*	Animal and cell models	[34]
Inflammation	*NEAT1*	Up	Promoting inflammatory response	*miR-506*	*GLI3*	Cell models	[36]
	Platr4	Up	Alleviating NASH	*NF-κB*	*Nlrp3*	Animal and cell models	[37]
	FLRL2	Down	Inhibiting adipogenesis, inflammation and endoplasmic reticulum stress	*Arntl*	*Sirt1*	Animal and cell models	[38]
	GM9795	Up	Aggravating NASH	*NF-κB/JNK*	*TNFα,IL-6,IL-1β*	Animal and cell models	[39]
Fibrosis	*GAS5*	Up	Activating HSC	*miR-23a*	*PTEN*	Animal and cell models	[40]
	HOTAIR	Up	Activating HSC	*miR-29b*	*DNMT3b/PTEN*	Animal and cell models, human samples	[42]
	MEG3	Down	Inhibiting HSC activation	*NLRC5*	–	Animal and cell models	[44]
	MALAT1	Up	Activating HSC	*miR-101b*	*Rac1*	Animal and cell models, human samples	[43]
	LFAR1	Up	Activating HSC	*Smad2/3 and TGFβR1*	*TGFβ/Notch*	Animal and cell models	[45]
	SCRG1	Up	Activating HSC	*TTP*	*MMP-2,TNF-α*	Animal models, human samples	[46]
HCC	*LINC01468*	Up	Promote the development of NAFLD-HCC	*SHIP2*	*PI3K/AKT/mTOR*	Animal models, human samples	[47]
	SNHG20	Up	Inducing liver KCs M2 polarization	*STAT6*	–	Animal and cell models, human samples	[49]
	SNHG6	Up	Accelerate cholesterol-driven NAFLD to HCC transition	*FAF2*	*mTORC1*	Animal and cell models, human samples	[48]

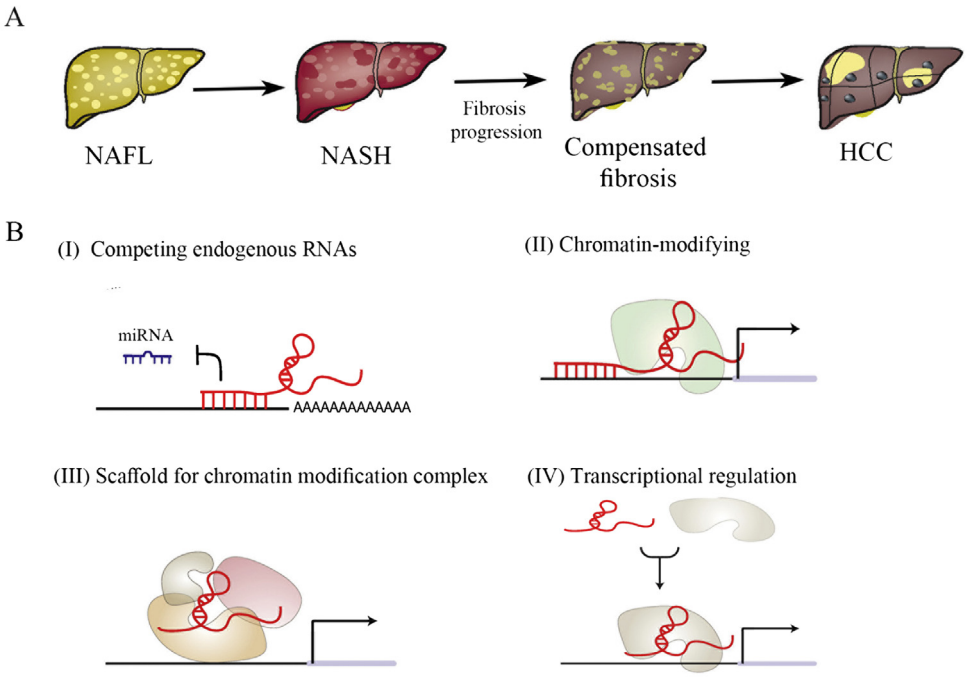

Figure 2 (A) Progression of NAFLD. (B) The mechanism of *lncRNAs* in NAFLD: (I) *LncRNAs* function as molecular sponges and compete for *miRNA* binding to *mRNAs*, thus inhibiting *miRNA*-mediated gene repression; (II) *LncRNAs* act as guide by recruiting chromatin-modifying enzymes to target genes, either in cis or in trans to distant target genes; (III) *LncRNAs* bring together multiple proteins to form ribonucleoprotein complexes, thus acting as a scaffold; (IV) *LncRNAs* interact directly with transcription factors to activate/inhibit the expression of target genes. The pathogenesis of NAFL includes the above four mechanisms. The pathogenesis of NASH is mainly mechanism (I) and (IV), while the relevant mechanism of NASH-related fibrosis is (I) and (II). The pathogenesis of NAFLD-HCC is mainly mechanism (II) and (III).
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pri-miR-195/pri-miR-4668 and inhibiting the maturation of *miR-195/miR-4668*.[16] This leads to lipid accumulation in the liver and aggravates NAFLD. In addition, *AMPK* is an essential regulator of lipid and glucose metabolism, and activation of *AMPK* inhibits *SREBP1* expression. Chen et al. showed that *lncRNA NEAT1* could affect lipid accumulation in NAFLD by targeting *miR-146a-5p*, resulting in reduced expression of *miR-146a-5p* and increased expression of the downstream target *ROCK1*, which in turn affects the *AMPK/SREBP* pathway.[17] Sun et al. found another mechanism that *NEAT1* could also directly bind to *miR-140* and exert a synergistic effect with *miR-140* to inhibit *AMPK/SREBP1* signaling, thereby increasing lipid accumulation and aggravating NAFLD.[18] In NAFLD, *lncRNA MALAT1* can upregulate the expression of its target *ARNT* by binding to *miR-206*, which can bind to the *PPARα* promoter, thereby inhibiting *PPARα* expression and inducing upregulation of *CD36* expression, leading to hepatic fat accumulation.[19] In addition, *PPARγ* is another crucial transcription factor in liver metabolism and is highly expressed in fat. Liu et al. demonstrated that *lncRNA-H19* could bind to *miR-130a* and promote *PPARγ* expression through downregulating *miR-130a* expression levels, which promoted hepatic lipogenesis and degeneration and the expression of NAFLD-related genes.[20] That high expression of GW9662 (an antagonist of *miR-130a* and *PPARγ*) inhibited hepatic lipogenesis.[20] In addition, other *lncRNAs* are present in this mechanism, including *HOTAIR*,[21] *ACO12668*,[22] *LncNONMMUG027912*,[23] and *MEG3*.[24]

There are other molecular mechanisms for *lncRNAs* in this process. Some *lncRNAs* can also regulate protein degradation or production by interacting with histone-modifying enzymes to control their phosphorylation, acetylation, and ubiquitination, which affect their target genes expression levels. This mechanism has also proved to be expected in lipid metabolism. For example, *lncRNA SRA* can promote adipogenesis by inhibiting *JNK/p38 MAPK*, increasing insulin receptor (IR) gene expression, and increasing phosphorylation of the downstream target *IRS-1/Akt*.[25] *H3K27* is present at the promoter of *NEAT1* and is enriched here. *H3K27* acetylation promotes the transcriptional level of *lncRNA NEAT1*. Upregulation of *NEAT1* targets *miR-212-5p*, decreases *miR-212-5p* expression levels, and subsequently upregulates *GRIA3* expression, promoting hepatic lipid accumulation.[26] Overexpression of *lncRNA MEG3* can inhibit the development of NAFLD by promoting the ubiquitination and degradation of *EZH2*, downregulating the expression of *EZH2*, and upregulating the expression of *Sirtuin6* (a target gene of *EZH2*), which exerts inhibition of lipid accumulation and inflammation.[27]

Several studies have shown that the mechanism that *lncRNAs* can act as a central platform to bind to different proteins and facilitate their intermolecular interactions also plays an essential regulatory role in hepatic lipid

metabolism. It has been reported that *lncRNAs* can bind to RNA-binding proteins to take effect. For example, *lncRNA ApoA4-AS* is co-expressed with *APOA4*, and *ApoA4-AS* can physically interact with *HuR* (*mRNA* stabilizing protein) to form a complex with *APOA4 mRNA* to stabilize *APOA4 mRNA* and increase the expression of *APOA4-AS* and *APOA4*.[28] This increased plasma TG and total cholesterol levels in ob/ob mice and aggravated lipid accumulation in the liver.[29] Another recent study showed that *HuR* can also inhibit liver lipid accumulation by inhibiting the expression of *lncRNA H19* and reducing *SphK2* nuclear translocation.[29] *LncRNA Blnc1* can bind to *hnRNPA1* to increase the expression of *Pgc1*β, thereby aggravating insulin resistance and hepatic steatosis.[30] *LncRHL* can directly bind to *hnRNPU* to make it more stable and avoid degradation, activating the expression of Bmal1 and reducing the expression of its downstream target *MTTP*, thus inhibiting VLDL secretion in hepatocytes.[31] In addition, *lncRNAs* can also bind to other proteins and play a role. For example, *lncRNA ARSR* can specifically bind to *YAP1*, promote the nuclear translocation of *YAP1* and inhibit the phosphorylation of *YAP1*, thereby activating the *IRS2/AKT* pathway and further increasing lipid accumulation *in vivo* and *in vitro*.[32]

Recent studies have also revealed that *lncRNAs* can activate or inhibit the expression of genes involved in pathways related to hepatic lipid metabolism by regulating the interaction of cellular signaling pathways and transcription factors. For example, *lncRNA-H19* can induce hepatic steatosis by activating the *MLXIPL* and *mTORC1* networks in hepatocytes.[33] The *lncRNA ARSR* can regulate hepatic fat accumulation by increasing *SREBP-1c* expression by activating the *PI3K/Akt* pathway.[34] *LncRNA SRA* can promote steatosis by inhibiting the transcriptional activity of *FoxO1*, reducing the expression of its downstream target *ATGL* and then decreasing free fatty acid (FFA) β-oxidation in hepatocytes.[35]

In summary, various mechanisms extensively involve *lncRNAs* in hepatic lipid metabolism. This indicates the need for scientists to investigate the mechanisms of *lncRNAs* in lipid metabolism. In the future, we need to continue to conduct further mechanistic studies on the aberrantly expressed *lncRNAs*, to investigate further the deeper mechanisms of *lncRNAs* in the development of NAFLD.

The role of *lncRNAs* in NASH

NAFLD stimulates NASH by sustaining lipid degeneration in the liver and promoting the formation of toxic lipid metabolites. Available studies also confirm that NASH is the next step in developing NAFLD. Pro-inflammatory factors play a vital role in this development. After years of research, scientists found that *lncRNAs* are potential regulators in NASH that can mediate inflammation by enhancing endoplasmic reticulum stress or directly activating inflammation-related signaling pathways.

In NASH, *lncRNAs* act by a molecular mechanism similar to *lncRNA*-mediated fat accumulation. It can act as *ceRNAs* to mediate the production of inflammation in hepatocytes. For example, it has been confirmed that *lncRNA NEAT1* is highly expressed and *miR-506* is lowly expressed in NAFLD progression, and they have also been shown to regulate inflammatory response. Further mechanistic studies showed that *miR-506* could bind to *NEAT1* and *GLI3*, and *NEAT1* could sponge *miR-506* to regulate *GLI3* expression. This suggests that *NEAT1* regulates the inflammatory response of NASH through the *miR-506/GLI3* axis.[36]

Several studies have shown that *lncRNAs* mediate NASH production through other mechanisms. It is reported that *lncRNAs* can be regulated through the activation and inflammatory signaling pathways that play the role of NASH. For example, *lncRNA Platr4* improves NASH by preventing *NF-*κ*B/Rxr*α complexes from binding to κ*B* sites through physical interactions, thereby blocking the *NF-*κ*B* signaling pathway to inactivate *Nlrp3* inflammatory vesicles.[37] *LncRNA FLRL2* inhibits adipogenesis, inflammation, and ERS by activating the *Arntl-Sirt1* axis.[38] *LncRNA GM9795* is highly expressed in the liver tissue of the NASH animal and NASH cell models. It can enhance ERS and activate *NF-*κ*B/JNK* signaling pathway, thereby affecting the expression of inflammatory factors (*TNF*α, *IL-6*, *IL-1*β) and promoting the development of NASH.[39]

The above shows that *lncRNAs* is also essential in the inflammatory response of NASH, but the mechanism of this aspect still needs to be better studied as lipid metabolism. In the future, we need to study more inflammation-related pathways to find new mechanisms and provide new possibilities for treating NASH. In addition, *lncRNAs* can regulate the inflammatory response of NASH patients, which may become a potential non-invasive biomarker to provide more convenience for clinical diagnosis and treatment.

The role of *lncRNAs* in NASH-associated fibrosis

Fibrosis results from the further development of NASH and is a severe stage of the development of NAFLD. Hepatic stellate cells (HSC) are the key cells that influence the development of liver fibrosis. In the ordinary course of events, the HSC is stable. However, when the HSC is stimulated by inflammation, pathological accumulation of extracellular matrix (ECM) components in the liver can occur, leading to fibrosis. Through years of research, new pathways and mediators mediating the development of fibrosis have been identified, not least endoplasmic reticulum stress, oxidative stress, epigenetics, and receptor-mediated signaling. This suggests that the mechanisms of HSC activation are complex. Existing studies confirm that many types of *lncRNAs* can play a crucial role in the activation, proliferation, or apoptosis of HSC, which can further influence the progression of liver fibrosis.

The most common of the multiple mechanisms by which *lncRNAs* mediate NASH-associated fibrosis is their involvement in regulating liver fibrosis as *ceRNAs* that bind to *miRNAs*. For example, the *lncRNA GAS5* can act as a sponge for *miR-23a*, competitively reducing the expression of *miR-23a*, which can target *PTEN*, thereby activating the downstream signaling molecule *PI3K - p85/Akt/mTOR* pathway, resulting in decreased levels of the epithelial marker *E-cadherin* and increased levels of the myofibroblast marker α*-SMA* and the extracellular matrix protein *collagen I*, ultimately leading to liver fibrosis and HSC activation.[40] Another study confirmed that *GAS5* is not only associated with NASH-related fibrosis but also closely related to cirrhosis.[41] This

could perhaps be another direction for our future research. In addition, *lncRNA HOTAIR* can competitively bind to *miR-29b*, reducing the expression of *miR-29b*, restoring its target *DNMT3b*, and enhancing *PTEN* methylation, thereby reducing *PTEN* and increasing the expression of *collagen I* and *α-SMA*, leading to HSC activation and promoting the development of liver fibrosis. Knockdown of *HOTAIR* can inhibit liver fibrosis by restoring *miR-29b* and inhibiting *DNMT3b*, reduce *PTEN* methylation and increase *PTEN* level, thereby inhibiting liver fibrosis.[42] The *lncRNA MALAT1* can act as a *ceRNA* for *miR-101b*, reducing the expression of *miR-101b* and increasing the expression of its target *Rac1*, thereby promoting HSC proliferation and activation.[43]

It has been reported that another common mechanism is that *lncRNAs* can directly bind to proteins to exert regulatory effects to mediate the production of NASH-associated fibrosis. The *lncRNA MEG3* inhibits HSC activation and reverses liver fibrosis by targeting the *NLRC5* protein.[44] *LncRNA LFAR1* can promote the binding between *Smad2/3* and *TGFβR1*, and promote the expression and phosphorylation of *Smad2/3*. It can also directly bind to *Smad2/3* to regulate the transcription of *TGFβ*, *Smad2*, *Smad3*, *Notch2*, *Notch3* and *Hes1*, activate *TGFβ/Notch* pathway to activate HSC and promote the progression of liver fibrosis.[45] The *lncRNA SCRG1* can bind specifically to the *RNA*-binding protein *TTP*. Its overexpression can lead to *TTP mRNA* instability, reducing *TTP* expression and decreasing *TTP* expression the expression of its targets *MMP-2* and *TNF-α* and promotes HSC activation and liver fibrosis progression.[46]

In conclusion, *lncRNAs* plays a vital role in NASH-related fibrosis and also illustrates that HSC activation is central to liver fibrosis. Existing studies have focused on the genes and signaling pathways associated with HSC activation. In the future, we could further research to explore other mechanisms of *lncRNAs* involvement in fibrosis. Furthermore, these studies suggest that *lncRNAs* have great potential in NAFLD research and new approaches to treat NASH-related fibrosis could be further explored.

Role of *lncRNAs* in NAFLD-related HCC

NAFLD-HCC is a complex and incompletely studied process. During this process, various pathophysiological changes such as insulin resistance, cytokine release, oxidative stress and mitochondrial damage may occur. However, hepatic lipid storage, the most important characteristic of NAFLD, is a key factor in promoting HCC development. FFA and diglycerol can facilitate ERS and reactive oxygen-species-mediated DNA damage, which leads to a chronically inflamed hepatic environment, resulting in NASH and liver fibrosis, which will further drive the oncogenesis of NAFLD-related HCC. NASH is key to this process. Studies have shown that *HOTAIR* and *MALAT1* are highly expressed in NASH and are associated with tumor cell proliferation, migration and invasion. This suggests that they may be important markers of NASH and NASH-HCC. However, more in-depth studies are still needed to reveal the specific expression of *lncRNAs* and their mechanism of action in NASH-HCC.

Most current studies focus on NAFLD-HCC. Recent studies have shown that *LINC01468* can activate the *PI3K/AKT/mTOR* signaling pathway by binding *SHIP2* and promoting the ubiquitination and degradation of *CUL4A*, thereby promoting lipogenesis and accelerating the development of HCC.[47] Previous studies have confirmed that hepatic cholesterol is one of the main lipotoxic molecules involved in the progression of NAFLD to HCC. However, *lncRNA SNHG6* is involved in this process. Because *SNHG6* is located at the endoplasmic reticulum – lysosome contact site, it can regulate cholesterol-dependent *mTORC1* lysosomal recruitment and activation, promote cholesterol synthesis, and accelerate NAFLD-HCC.[48] These studies indicate that it is necessary to investigate the role of *lncRNAs* in NAFLD-HCC, but there are still few studies on this topic. Furthermore, previous suggests that polarization of liver macrophage Kupffer cells (KCs) may be a contributing factor to NAFLD-associated HCC. Wang et al. found that *lncRNA SNHG20* expression was decreased in human NAFLD, but increased in human NAFLD-HCC liver. *SNHG20* may facilitate the progression of NALFD to HCC via inducing liver KCs M2 polarization via *STAT6* activation.[49]

Prospects for *lncRNAs*-based therapy for NAFLD

Because of the crucial role of *lncRNAs* in the development of NAFLD and the presence of multiple *lncRNAs* aberrantly expressed in NAFLD. This offers the possibility of *lncRNAs*-based therapies to correct this dysregulation. Currently, NAFLD is treated mainly through lifestyle changes. It has been reported that dietary intervention based on Mediterranean diet and lifestyle changes is the main means of treatment for NAFLD.[51] For example, aerobic exercise may inhibit the transcriptional activity of *FoxO1* by suppressing the expression of *lncRNA SRA*, which leads to upregulation of *ATGL* expression, reducing intrahepatic lipid accumulation, and inhibiting inflammatory proteins and the *JNK/p38MAPK* signaling pathway, allowing for further relief of inflammation.[52] However, compliance with this treatment is relatively poor and the therapeutic effect is difficult to maintain. Therefore, we need to develop new treatment strategies for NAFLD (Fig. 3).

Exogenous materials

In recent years, numerous achievements in studying the mechanisms of *lncRNAs* action in NAFLD have accelerated the research on *lncRNAs*-based therapies for NAFLD. Decaffeinated coffee has been reported to restore *lncRNA GM16551* to normal levels and to downregulate the expression of its target genes ACC1 and SCD1. In addition, it significantly reduces the expression of *lncRNA H19* and its target gene *collagen α-1(I)* chain and normalizes the expression level of *αSMA* protein, thereby preventing NAFLD.[53] Studies have confirmed that the biologically active substance flavopiridol (BBR) in Chinese medicine can be used to treat a various diseases.[54] BBR may treat NAFLD by upregulating the expression of the *lncRNA MRAK052686* and its associated gene *Nrf2*.[55] In addition, the probiotic mixture, which can be used alone or combined with prebiotic inulin fiber, can improve hepatic steatosis, inflammation, and fibrosis by modulating a panel of Hippo signaling pathway-associated *RNAs*, downregulating the expression of *YAP1* and

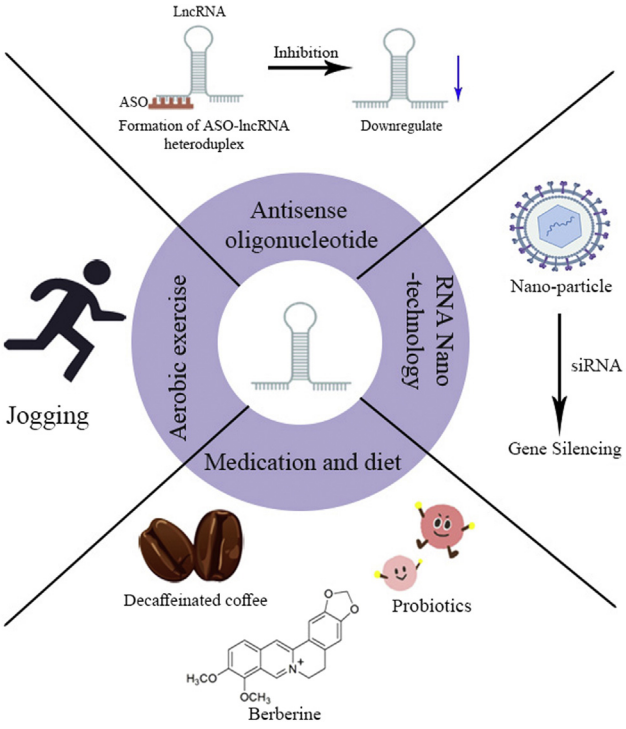

Figure 3 Aerobic exercise, diet and drugs (such as coffee, probiotics, berberine, *etc.*) can regulate the expression of *lncRNAs* to alleviate NAFLD. In addition, oligonucleotide and *RNA* nanotechnology can also achieve therapeutic goals by targeting silencing *lncRNAs*.

miR-1205, and regulating the expression of *LATS1*, *NF2*, and the *lncRNA SRD5A3-AS1*.[56] These studies reveal that these exogenous materials have the potential to alter *lncRNAs* expression, offering a new therapeutic approach for the treatment of NAFLD. However, research into its corresponding mechanisms should be deepened in the future.

Gene-targeted therapy

Antisense oligonucleotides (ASOs) are chemically synthesized nucleic acid analogs, usually around 12–30 nucleotides in length, which can regulate *RNAs* processing and protein expression through different mechanisms (promoting *RNAs* cleavage and degradation or occupancy-only mechanisms) and can act as targets for a variety of molecules. With advanced research into the structure and chemistry of ASOs, they are already being used as a valuable tool for the future treatment of many diseases. Many studies have confirmed the therapeutic role of ASOs in the disease. For example, *LINC00680* promotes proliferation, migration, and invasion of esophageal squamous cell carcinoma (ESCC) and is strongly associated with poor patient prognosis. Xue et al. designed specific targeting ASO *LINC00680* and negative form control ASO NC, transfected with ASOs into KYSE510 and KYSE140 cells, following injection of ASO *LINC00680*-targeted treatment in a mouse model of hetero-transplanted KYSE510 cells, they found that tumor growth was significantly inhibited in the ASO *LINC00680*-treated group compared to the ASO NC-treated group and that the expression levels of *LINC00680* were significantly reduced. This suggests that ASOs targeting *LINC00680* may be able to suppress it expression, with the promise of *lncRNAs*-based therapy for ESCC.[57] From the above description, we can draw a welcome conclusion that ASO can be used for *lncRNAs* function loss. It indicates that we can use the existing theory to design ASOs-targeted *lncRNAs*-based therapies for treating NAFLD.

In recent years, *RNA* nanotechnology has flourished and has been adopted as a novel delivery system for targeted therapies for various human diseases. The *lncRNA TMEM1-AS5* has been reported to be key in regulating GC drug resistance. Zhou *et al*. constructed a novel chitosan-gelatin-EGCG (CGE) nanocarrier for selective delivery of *si-TMEM44-AS1* to silence *TMEM44-AS1* expression and exert a reversal of 5-FU resistance in GC, thereby enhancing 5-FU efficacy in a GC xenograft nude mouse model.[58] In conclusion, nanoparticles can treat relevant diseases by selectively delivering *siRNAs*, thereby silencing the relevant disease-causing genes. These results suggest that this therapeutic approach based on *RNA* nanoparticle-mediated *lncRNAs* expression holds excellent promise. In the future, we can prepare *RNA* nanoparticles to silence the expression of NAFLD-related *lncRNAs* to treat NAFLD, which requires our future in-depth research.

Conclusion and outlook

In conclusion, many *lncRNAs* are expressed differently in NAFLD and are involved in multiple processes in the development of NAFLD. In this review, we summarize the mechanisms of *lncRNAs* involvement in hepatic lipid metabolism, NASH, NASH-associated fibrosis, and NAFLD-related HCC. In addition, we look forward to the future potential of *lncRNAs* in the treatment of NAFLD to be developed into a clinical *lncRNAs*-based treatment of NAFLD. For example, coffee, flavonoid, ASOs, and *RNA* nanotechnology are used. It has been shown that *lncRNAs* play a key role in diagnosing and treating NAFLD. Future research is needed to continue investigating the regulatory mechanisms of *lncRNAs* in NAFLD, further revealing their potential role as diagnostic and therapeutic targets and prognostic biomarkers of NAFLD.

Conflict of interest

The authors declare that they have no conflict of interest.

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