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REVIEW

Noncoding RNAs as additional mediators of epigenetic regulation in nonalcoholic fatty liver disease

Mohamed Zaiou

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Mohamed Zaiou, Institut Jean Lamour, UMR CNRS 7198, CNRS, University of Lorraine, Nancy 54011, France

Corresponding author: Mohamed Zaiou, PhD, Professor, Institut Jean Lamour, UMR CNRS 7198, CNRS, University of Lorraine, 2 allée André Guinier, BP 50840, Nancy 54011, France. mohamed.zaiou@univ-lorraine.fr

Abstract

Nonalcoholic fatty liver disease (NAFLD) has emerged as the most common cause of chronic liver disorder worldwide. It represents a spectrum that includes a continuum of different clinical entities ranging from simple steatosis to non-alcoholic steatohepatitis, which can evolve to cirrhosis and in some cases to hepatocellular carcinoma, ultimately leading to liver failure. The pathogenesis of NAFLD and the mechanisms underlying its progression to more pathological stages are not completely understood. Besides genetic factors, evidence indicates that epigenetic mechanisms occurring in response to environmental stimuli also contribute to the disease risk. Noncoding RNAs (ncRNAs), including microRNAs, long noncoding RNAs, and circular RNAs, are one of the epigenetic factors that play key regulatory roles in the development of NAFLD. As the field of ncRNAs is rapidly evolving, the present review aims to explore the current state of knowledge on the roles of these RNA species in the pathogenesis of NAFLD, highlight relevant mechanisms by which some ncRNAs can modulate regulatory networks implicated in NAFLD, and discuss key challenges and future directions facing current research in the hopes of developing ncRNAs as next-generation non-invasive diagnostics and therapies in NAFLD and subsequent progression to hepatocellular carcinoma.

Key Words: MicroRNAs; Nonalcoholic fatty liver disease; Steatohepatitis; Noncoding RNAs; Circular RNAs; Biomarker

Core Tip: Nonalcoholic fatty liver disease (NAFLD) covers a spectrum of hepatic pathologies, ranging from simple steatosis to nonalcoholic steatohepatitis, all of which can evolve to cirrhosis and in some cases to hepatocellular carcinoma. There are now indications that noncoding RNAs (ncRNAs), a component of epigenetic mechanisms, contribute to the pathogenesis of NAFLD and may serve as potential prognostic and diagnostic biomarkers. However, little is known about the role of these RNA species in NAFLD and its progressive forms. This paper discusses the current state of research on the role of most clinically relevant ncRNAs in the pathogenesis of NAFLD.

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) has emerged as a liver disorder with an increasing prevalence but unclear etiology. The disease covers a wide spectrum of histologic lesions, ranging from simple steatosis to its subtype, nonalcoholic steatohepatitis (NASH), which is characterized by inflammation and hepatocyte injury. Over several years, NASH can progress to more serious disease stages, such as cirrhosis and hepatocellular carcinoma (HCC)[1]. Based on the close association between hepatic steatosis and metabolic dysregulation, international consensus guidelines recommended the renaming of NAFLD to metabolic-associated fatty liver disease[2,3]. The prevalence of NAFLD depends on race and ethnicity. In the United Sates, the estimated prevalence of NAFLD was reported to be about 32%[4]. However, estimates are likely higher in other populations that are currently witnessing the rapid rise in the incidence of type 2 diabetes mellitus (T2DM), obesity, metabolic and insulin resistance syndrome, and dyslipidemia rates[5,6].

NAFLD is sometimes called the "silent killer", because most patients with the condition are typically asymptomatic in the early stages until the liver is severely damaged. The unsuspected disease condition is often found incidentally when liver enzyme levels, such as alanine aminotransferase, are elevated in routine laboratory work-up or hepatic steatosis appears on imaging for reasons other than liver symptoms or signs. Currently, liver biopsy remains the gold standard method for NAFLD diagnosis and degree of liver injury evaluation[7]. Computed tomography scans and ultrasound can also be performed as part of the standard evaluation of NAFLD. However, these methods have a number of limitations, including invasiveness, low sensitivity, sampling variability, and inaccurate diagnosis[8,9]. The American Association for the Study of Liver Diseases has identified uncertainties about these diagnostic tools, which represent a barrier to the effective treatment of patients with NAFLD[10]. Thus, there is increased recognition of the need to develop non-invasive biomarkers that have the ability to identify simple steatosis from NASH patients who are at high risk of progression to cirrhosis and HCC conditions.

Many concepts important to understanding the pathogenesis of NAFLD have arisen. The traditional view of this complex disease suggests that an interplay between genetic and triggering and/or modifying environmental events is the fundamental basis for disease initiation and development[11,12]. Over the last several years, a growing body of functional evidence has pointed towards a central role of epigenetic factors in fatty liver diseases, including NAFLD. Epigenetics was redefined multiple times and Cavalli and Heard described it as "the study of molecules and mechanisms that can perpetuate alternative gene activity states in the context of the same DNA sequence"[13]. Epigenetic machinery could be another layer that orchestrates gene expression and provides a molecular link between genetic and environment effects on NAFLD. Thus, the integration of epigenetic information may represent another opportunity to tackle the complexity of NAFLD and identify new predictive biomarkers and potential therapeutic targets of this disease. Indeed, recent advancements in the emerging field of epigenetics have revealed that epigenetic mechanisms and associated systems may regulate many aspects of the pathogenesis of NAFLD[3,14]. Unlike genetic alterations, epigenetic alterations can be mostly heritable and reversible. Thus, further discoveries in the field could enable the development of epigenetic tools that can be used not only to complement current strategies for early disease diagnosis and optimal individualized patient risk stratification but also to improve therapy.

To date, the most studied epigenetic mechanisms include DNA methylation, histone modifications, and noncoding RNA (ncRNA)-based regulation. While certain epigenetic mechanisms underlying DNA and chromatin modifications in NAFLD were addressed elsewhere[15,16], only relevant studies shedding light on the roles played by ncRNAs' machinery will be reviewed next.

EMERGING ROLE OF NCRNAS IN THE PATHOGENESIS OF NAFLD

For decades, only the portion of the genome that is transcribed into mRNA (approximately 2%) was the central focus of basic science and medical research. The remaining 98% was simply believed non-functional and referred to as "junk DNA" or "dark matter"[17]. Due to advances in high-throughput sequencing technologies enabling more in-depth genomic and transcriptomic analyses, the Encyclopedia of DNA Elements project revealed that up to 80% of the human genome is transcribed, generating a multitude of functional transcripts commonly referred to as ncRNAs[18,19]. The biological significance of these nonprotein coding transcripts is now becoming evident, with many ncRNAs found to have epigenetic activity and substantial roles in regulating diverse cellular processes. Indeed, they can affect gene expression by interacting with the transcriptional apparatus, and regulating chromatin structure and RNA processing mechanisms[20]. There is also proof that interaction and crosstalk between different species of ncRNA groups can create complicated and intertwined networks that can affect gene expression[21]. Regulatory ncRNAs mainly consist of microRNAs (miRNAs) (< 30 nucleotides), long noncoding RNAs (lncRNAs) (≥ 200 nucleotides)[19], and circular RNAs (circRNAs). Due to their stability and easy detection in biological fluids, ncRNAs are continuously investigated as promising diagnostic and therapeutic tools in metabolic diseases. A growing body of literature indicates that ncRNAs are abundantly expressed in the liver and their altered expression patterns are associated with various types of liver diseases including NAFLD[22,23]. Moreover, ncRNAs reveal significant differences in expression according to the severity of NAFLD and histological features[24]. In the next sections, the role of miRNAs, lncRNAs, and circRNAs will be discussed, to better improve our understanding of their appealing potential as biomarkers for early NAFLD/NASH staging and therapeutic targets.

miRNAs in NAFLD

miRNAs are small, highly conserved short single-stranded ncRNAs (approximately 18-22 nucleotides in length) with epigenetic functions able to transcriptionally regulate gene expression of other RNAs notably mRNAs[25]. They are transcribed in the cell nucleus and transported to the cytoplasm, where they are processed into mature miRNAs[26]. With respect to their function, miRNAs primarily regulate gene expression by promoting mRNA degradation or repressing their translation. They serve as master regulators that control the expression of thousands of coding and noncoding genes. Prior research suggests that more than 60% of human coding genes are potential targets of miRNAs[27]. Mounting evidence reveals that dysregulation in miRNAs' expression is associated with molecular processes of various forms of metabolic and liver diseases, including NAFLD conditions[3,28-30]. Indeed, several differentially expressed miRNAs play key roles in the development of NAFLD in animal models and humans[30-33], essentially through the regulation of several pathogenic processes including altered lipid and glucose metabolism, insulin resistance, and inflammation pathways[34,35]. Because miRNAs are stably detected in biofluids and can circulate within microvesicles, exosomes, or apoptotic bodies, or bound to RNA-binding proteins, interest in studying these molecules has increased tremendously. Additionally, considerable research has demonstrated that these RNA species may offer new insights into disease biology, and their easy profiling in the serum has raised enthusiasm about their potential use in clinical practice as biomarkers for early diagnosis and clinical monitoring of NAFLD progression [36,37]. While a plethora of miRNAs are associated with fatty liver diseases, only those shown to be repeatedly involved in different stages of NAFLD will be discussed next.

miR-21

There is evidence that miR-21-mediated regulation may play an important role in the pathogenesis of several types of liver diseases[38]. Dysregulated miR-21 expression has been reported in animal models of steatohepatitis and human NASH. Specifically, the levels of circulating miR-21 and its expression in the liver are heavily elevated in both NAFLD patients and mouse models[39-41]. Likewise, circulating miR-21 Levels are significantly increased in patients suffering from NASH compared to NAFL and healthy controls[42]. Other studies have shown that inhibiting miR-21 can alleviate steatosis by activating peroxisome proliferator-activated receptor alpha (PPARα)[40,43]. In support of these findings, another report indicated that hepatocyte-specific knockout (KO) of miR-21 in mice improved high-fat diet (HFD)-induced steatosis through upregulation of multiple miR-21-targeted pathways governing lipid metabolism[44]. Similarly, miR-21 abrogation along with obeticholic acid treatment significantly reduced NASH in mice[45].

Moreover, miR-21 plays a key role in hepatic lipid metabolism by promoting hepatic lipid accumulation *via* its interaction with several proteins including sterol regulatory element binding protein (SREBP1)[46] and 3-hydroxy-3-methylglutaryl-co-enzyme A reductase (HMGCR)[47]. Additionally, miR-21 can target phosphatase and tensin homolog, which prevents hepatic steatosis[48], and PPARα expression, which induces inflammation and fibrosis progression and activates lipid oxidation in NAFLD[40]. Other investigations have revealed that miR-21 can inactivate the Wnt/β-catenin signaling pathway by targeting low-density lipoprotein (LDL) receptor-related protein 6, thereby aggravating lipid accumulation and inflammation[49]. Mechanistic studies have also demonstrated that miR-21

promotes hepatic insulin resistance and steatosis in diet-induced obese mice through the regulation of several key transcription factors, such as forkhead box protein O1, insulin-induced gene 2, signal transducer and activator of transcription 3, and hepatocyte nuclear factor 4-alpha (HNF4-α)[44]. Together, these studies clearly show that miR-21 plays an essential role in key transitions of NAFLD pathogenesis. Such findings hold the potential to develop miR-21 as a reliable serum biomarker to identify patients "at risk" for NASH.

miR-29a

The miR-29 family of miRNAs consists of miR-29a, miR-29b, and miR-29c members[50], and are mainly expressed in hepatocytes and hepatic stellate cells (HSCs)[51,52]. A body of evidence suggests that miR-29a is significantly associated with diagnostic relevance of NAFLD[31,53], NASH[54] and liver fibrosis [54,55], as well as aggressiveness and prognosis of HCC[31]. López-Riera *et al*[56] identified circulating miR-29a as one of the potential biomarkers that could predict drug-induced NAFLD in humans. Yang *et al*[57] found that serum miR-29a levels were significantly lower in NAFLD patients compared to controls. Furthermore, another study revealed that miR-29a disrupts DNA methyltransferase 3β (DNMT3β) to improve diet-induced NASH in mice. Mattis *et al*[58] used a mouse model to demonstrate that miR-29a protects hepatocytes from steatosis by repressing lipoprotein lipase in hepatocytes. Moreover, miR-29a inhibits glycogen synthase kinase 3 beta to repress sirtuin 1 (SIRT1)-mediated mitochondrial biogenesis and improve methionine–choline-deficient diet-induced NASH in mice[59]. Roderburg *et al*[52] reported that miR-29 family members are downregulated in mouse models of liver fibrosis and in human fibrotic livers. A recent study indicated that miR-29a plays a regulatory role in NAFLD by improving HFD-induced steatohepatitis and liver fibrosis through the suppression of cluster of differentiation 36 (CD36)[31]. Together, these findings highlight the potential of miR-29a-targeted therapy for the treatment of NAFLD and its advanced stages.

miR-33a/miR33b

In humans, the miR-33 family comprises two members, miR-33a and miR-33b (miR-33a/b), which are co-transcribed with the sterol regulatory element-binding protein 2 (SREBP2) and 1 respectively, and their main targets are SREBP and SREBP2 and ATP-binding cassette subfamily A member 1 (ABCA1). miR-33a/b is implicated in fatty liver disease and plays key roles in lipid metabolism and transport by targeting a number of genes involved in cholesterol homeostasis and insulin signaling pathways[60,61]. In mice, there is only one miR-33 isoform, which is an ortholog form of human miR-33a[60].

In addition, expression levels of miR-33 are increased in the liver tissues of patients with NAFLD[62]. Circulating miR-33a is associated with steatosis and inflammation in patients with NAFLD after liver transplantation and can serve as an independent predictor of these pathological conditions[63]. The expression of hepatic miR-33a/miR-144 is increased in NASH patients with morbid obesity[64]. A further study in mice also demonstrated that miR-33 can regulate hepatic lipogenesis signaling and may serve as a potential circulating biomarker of NAFLD[65].

From a therapeutic perspective, several studies have demonstrated that treatment with anti-miR-33 therapeutic agents can significantly reduce plaque burden in mouse models of atherosclerosis and offer promise for treating cardiovascular disease[66-68]. However, a previously published clinical trial indicated that increased expression of miR-33a in the liver is associated with steatohepatitis in morbidly obese humans and metabolic dysfunction[64]. In line with this, long-term therapeutic silencing of miR-33 in mice leads to the development of adverse outcomes, including hypertriglyceridemia and hepatic steatosis[69,70]. miR-33 KO mice exposed to HFD developed marked worsening of obesity and liver steatosis *via* targeting SREBP1[71]. Recently, Price *et al*[61] provided additional evidence that genetic loss of miR-33 results in an increase in food intake and promotes obesity and insulin resistance. Thus, further research is needed to fully understand the role of miR-33a/b in NAFLD, which may provide new insights into the physiopathology of various forms of this disease.

miR-34a

The miR-34 family comprises three members: miR-34a, miR-34b, and miR-34c. miR-34a expression levels are increased both in the liver and serum of patients with NAFLD and NASH compared to healthy controls and are positively correlated with total cholesterol (TC) and triglyceride (TG) levels[72, 73]. miR-34 regulates many transcription factors, such as HNF4-α, SIRT1, and p53, which are involved in lipid metabolism, cholesterol synthesis, and fatty acid b-oxidation[72,74]. In addition, Xu *et al*[73] demonstrated that miR-34a inhibits hepatic very LDL secretion by promoting steatosis through interaction with HNF4-α in patients with NASH and mice fed HFD. miR-34a regulates steatosis by directly targeting PPARα expression in NAFLD[75]. Recently, another study demonstrated that the miR-34a/SIRT1/AMPK pathway is involved in mitochondrial dysfunction in a mouse NASH model[76]. Higher circulating levels of miR-34a have been seen in patients with NAFLD and NASH and mice fed HFD[73,77]. An association of miR-34a and miR-122 with dyslipidemia among patients with NAFLD has also been reported[78], and both miRNAs could be useful biomarkers in children with obesity and NAFLD[79]. Finally, in a meta-analysis study, miR-34a, miR-122, and miR-192 were identified as potential diagnostic markers to segregate NAFL from NASH[32]. Here, miR-34 showed the best

diagnostic accuracy for discriminating NASH *vs* NAFLD.

miR-122

miR-122 is the most abundant and extensively studied hepatic miRNA representing about 70% of the total miRNA in the liver[80]. Current evidence indicates that miR-122 plays an essential role in different aspects of liver function as well as in the epigenetic modulation of several genes linked to chronic hepatic pathology[72,80,81]. miR-122 is involved in the regulation of lipid and cholesterol metabolism. Animal experiments have revealed that inhibition of miR-122 results in a decrease of hepatic fatty acid and cholesterol synthesis rate, reduction in plasma cholesterol levels, enhanced liver fatty acid oxidation, and protection of HFD-fed mice from hepatic steatosis[82,83]. Further investigations have reported that miR-122 targets specific genes of cholesterol biosynthesis, such as *HMGCR*, microsomal TG transfer protein, 3-hydroxy-3-methylglutaryl-coenzyme A (CoA) synthase 1, fatty acid synthase, and acetyl-CoA carboxylase[33,82,83], suggesting a role in the pathogenesis of NAFLD.

Excessive accumulation of TG in the cytoplasm of hepatocytes is a hallmark of NAFLD. Genetic deletion of miR-122 Locus in mice results in TG accumulation in the liver and hepatic steatosis that progresses to NASH, fibrosis, and HCC[81,84], whereas restoration of miR-122a expression reduces disease symptoms and tumorigenesis[84]. Consistent with the results from animal investigations, reduced expression of miR-122 is observed in hepatic tissues of NASH patients compared to that in simple steatosis and healthy controls[72,80]. Interestingly, changes in miRNA expression profiles were observed at various stages of NAFLD, including simple fatty liver, NASH, and liver fibrosis to HCC. In this respect, a study reported that in NAFLD patients, the hepatic miR-122 Levels were lower in patients with mild steatosis compared to those with severe steatosis, while hepatic and serum miR-122 Levels were significantly higher in patients with mild fibrosis than in those with severe fibrosis[74].

Conversely, elevated serum levels of miR-122 have been found in patients with NAFLD patients compared to controls, and these levels are positively correlated with disease severity[85,86]. These data are in line with reports demonstrating that circulating levels of miR-122 are positively associated with fatty liver disease, T2DM, obesity, and atherosclerosis[80,87,88]. Additionally, NASH patients exhibit increased levels of miR-122 in the serum[80] and decreased hepatic expression of this RNA[72]. Although studies have consistently demonstrated that miR-122 expression differs between hepatocytes and blood, mechanisms underlying such an inverse correlation are certainly complex and need further attention. Attempts have been made to explain the observed difference in expression between the two tissues. The elevated levels of circulating miR-122 could be attributed to its secretion *via* liver exosomes. In agreement with this, Gallo *et al*[89] reported that miR-122 is localized in abundance to secreted liver exosomes. However, it must be acknowledged that the dynamic of miRNAs expression, secretion, and transport is complex and the contribution of other tissues such as adipose tissue to the pool of miR-122 Levels must not be ruled out.

miR-155

miR-155 is a multifunctional miRNA known to regulate numerous fundamental processes such as immunity, inflammation, lipid metabolism, and cancer[90,91]. Several studies have reported that miR-155 is one of the biologically most relevant miRNAs in several liver diseases including NAFLD[92,93]. In this respect, a study by Wang *et al*[94] demonstrated that the level of miR-155 is decreased in liver tissue and peripheral blood of NAFLD patients compared with healthy controls. Other studies indicated that miR-155 activity was also decreased in patients with NAFLD, which could be attributed to the adipogenic transcription factors CCAAT/enhancer binding protein (C/EBP)-α, C/EBP-β, PPAR-γ and LXRα[94,95]. On the other hand, miR-155-deficient mice fed a HFD developed increased hepatic steatosis compared to controls[94], while conditionally liver-specific overexpression of miR-155 reduced serum and hepatic levels of TC, TG, and high-density lipoprotein, and alleviated NAFLD[93]. These results suggest that miR-155 has a protective role in NAFLD and its pathological conditions. However, conflicting study results have somewhat dimmed the promise of using this miRNA to prevent NAFLD. For instance, miR-155 KO mice fed a methionine-choline-deficient diet showed a decrease in steatosis along with a reduction in the expression of genes involved in fatty acid metabolism and fibrosis, but not liver injury or inflammation[95]. Upon ingestion of a diet high in fat, high in cholesterol, and high in sucrose, miR-155 KO mice displayed less liver injury, decreased steatosis, and attenuation in fibrosis compared to control mice[96]. The ambiguous miR-155 roles suggest that this transcript may exert pleiotropic functions depending on the etiology and disease context. Another scenario is that miR-155-containing exosomes or miR-155-containing microvesicles released from cells into the surrounding tissue could contribute to the observed differences in results. As an example, adipose tissue-derived miR-155 upregulated by HFD was shown to induce hepatic insulin resistance in murine models[97]. Thus, further studies are warranted to clarify the contradictory results and determine the role of miR-155 in intracellular lipid accumulation and NAFLD development and progression.

miR-192

miR-192 is highly expressed in quiescent HSCs. Overexpression of miR-192 significantly suppresses the activity of these cells by reducing the proliferation and migratory potential of primary mouse HSCs[98].

A previous study found that circulating miR-192 is differentially expressed in NAFLD patients and even identified a miRNA panel (hsa-miR-122-5p, hsa-miR-1290, hsa-miR-27b-3p, and hsa-miR-192-5p) with high diagnostic accuracy for this disease[99]. Another study indicated that serum levels of miR-192-5p were significantly elevated in NAFLD patients and positively associated with hepatic inflammatory activity score and disease progression[100]. Recently, Wang *et al*[101] observed that miR-34a, miR-122, and miR-192 represent suitable biomarkers to distinguish NAFLD and NASH severity. Another study found that in NASH patients levels of miR-192 were elevated in serum, while decreased in the liver[80]. Similar to miR-122, miR-192 was increased in NASH serum compared with steatosis and downregulated in NASH liver, both in human and animal models, suggesting that these miRNAs are released from hepatocytes during pathophysiological states associated with cell membrane impairment[42,100]. A recent meta-analysis identified several miRNAs as potential biomarkers of NAFLD and NASH, including miR-34a, miR-122, and miR-192[32]. Together, these findings suggest that circulating miRNA-192 Levels may represent a potential noninvasive diagnostic biomarker and therapeutic target for the different stages of NAFLD.

miR-375

miR-375 is highly expressed in pancreatic islets and considered to be an essential regulator of glucose homeostasis and insulin secretion[102]. miR-122, miR-192, and miR-375 are significantly upregulated in NAFLD patients compared to controls[80]. miR-375 is involved in the pathogenesis of NAFLD and its inhibition suppresses the production of inflammatory cytokines tumor necrosis factor-alpha as well as interluekin-6, increased the expression of adiponectin, and suppressed lipid accumulation in palmitate (PA)-induced HepG2 cells[103]. These preliminary data suggest that miR-375 as well as the above discussed miRNAs (Table 1) could be promising targets for the prevention and progression of NAFLD.

LncRNAs in NAFLD pathogenesis

LncRNAs are relatively long RNA transcripts (> 200 nucleotides) that lack coding potential[104]. They are regulatory molecules transcribed from intergenic, exonic, or the distal protein-coding regions by RNA polymerase II and capped at the 5′-end and polyadenylated at the 3′-end[104]. Regarding their functions, there are subsets of lncRNAs that act as guides by binding to proteins and directing their localization, providing dynamic scaffolds providing a central platform for the transient assembly of multiple proteins and RNAs[105] and decoys that bind targeted proteins or miRNAs to limit their availability and function by acting as a molecular sink[106]. However, other functions related to these RNA species may arise as research in the field rapidly progresses. Over the last decade, dysregulation of lncRNAs has been linked to the pathophysiology of various human diseases, such as cancer, diabetes, and cardiovascular diseases[107]. In the context of NAFLD, some reports have noted that lncRNA expression patterns are dysregulated, suggesting that these molecules may represent potential drivers of NAFLD biology and have utility as clinical biomarkers. However, the role of lncRNAs in the development and progression of NAFLD still remains relatively unexplored. Herein, we provide a scientific update on lncRNAs relevant to NAFLD and its stages.

H19 LncRNA

The lncRNA H19 (H19) is a transcription product of the *H19* gene and represents one of the first discovered lncRNAs. H19 predominantly acts to affect miRNAs stability in different physiological and pathological conditions[108]. In recent years, H19 has attracted great attention in the research of liver diseases due to its aberrant expression and extensive involvement in several hepatic metabolic processes [109]. In this respect, existing evidence has shown that overexpression of H19 results in hepatic metabolic reprogramming and exacerbates diet-induced fatty liver[110]. In agreement with this, Liu *et al* [111] reported that expression of H19 induces hepatic steatosis by activating both the lipogenic transcription factor MLX interacting protein-like and the mammalian target of rapamycin complex 1 signaling pathways. In animal models, knockdown of H19 inhibited steatosis and alleviated hepatic lipogenesis by directly regulating the miR-130a/PPARγ axis in NAFLD[112]. However, further studies would be useful for determining the precise contribution of H19 to the pathogenesis of NAFLD.

Blnc1

Brown fat lncRNA 1 (Blnc1) is implicated in the regulation of adipocyte differentiation and function [113] and may serve as a regulator of triacylglycerol biosynthesis. Recently, Zhao *et al*[114] reported that hepatic Blnc1 expression was strongly linked to activation of lipogenesis in mouse models of obesity and NAFLD, whereas its liver-specific inactivation abrogated HFD-induced hepatic steatosis and insulin resistance, and protected mice from diet-induced NASH pathogenesis. Conversely, overexpression of Blnc1 in epididymal white fat tissue improved whole body insulin sensitivity, partially attenuated systemic dyslipidemia and glucose metabolism, and markedly protected against diet-induced obesity hepatic steatosis, probably *via* enhancement of mitochondrial biogenesis and function in white fat[115]. Overall, these results suggest that Blnc1 has different regulatory mechanisms and distinct functions in the liver and white adipose tissue.

Table 1 Selected microRNAs shown to be highly involved in the pathogenesis of nonalcoholic fatty liver disease

miRNA	Circulation level	Tissue expression	Main functional and pathophysiological impacts	Ref.
miR-21	↑	↑	Promotes lipogenesis Involved in NASH, fibrosis, and HCC Targets several metabolic and inflammatory signaling pathways related to the pathogenesis of NAFLD	[38-40,42,44]
miR-29a	↑	↓	Highly connected with the diagnostic relevance of NAFLD, NASH, and HCC Modulates oxidative stress and inflammation in the context of NAFLD	[31,53,52,58]
miR-33a/b	↑	↑	Involved in lipid metabolism, glucose homeostasis and hepatic lipogenesis Associated with steatosis and inflammation in patients with NAFLD/NASH	[61-63,65]
miR-34a	↑	↑	Regulates lipoprotein metabolism and promotes liver steatosis Involved in NAFLD/NASH Correlates with the severity of hepatic inflammatory activity Can serve as a biomarker to distinguish NAFLD from NASH patients	[72,73,75]
miR-122	↑	↓	Modulates several genes linked to chronic hepatic pathology and lipid metabolism Promotes hepatic steatosis Serum miR-122 correlates positively with markers of NAFLD severity as well as with NASH	[74,82-84]
miR-155	↑	↑	Regulates key cellular events in NAFLD/NASH Promotes insulin resistance	[96,97]
miR-192	↑	↓	Significantly elevated in NAFLD patients and positively associated with hepatic inflammatory activity score and disease progression Increased in serum from NASH patients compared with steatosis Could be a potential biomarker of NAFLD and NASH	[32,80,100]
miR-375	↑	↑	Involved in the pathogenesis of NAFLD/NASH/fibrosis Key regulator of glucose homeostasis and insulin secretion	[80,102]

HCC: Hepatocellular carcinoma; miRNAs: MicroRNAs; NAFLD: Nonalcoholic fatty liver disease; NASH: Nonalcoholic steatohepatitis.

lncHR1

The lncRNA HCV regulated 1 (lncHR1) was recently identified as a novel human-specific lncRNA that has an effect on lipid metabolism. A study by Li *et al*[116] reported that in an HFD mouse model, overexpression of lncHR1 inhibited fatty acid synthase and lowered oleic acid-induced hepatic cell TG and lipid droplets' accumulation by inhibiting *SREBP1c* gene expression. These findings are relevant to NAFLD since dyslipidemia in patients with NAFLD is atherogenic in nature and it is characterized by increased levels of serum TG. Furthermore, elevated TG levels in the circulation are associated with metabolic syndrome and cardiovascular disease[117].

Metastasis-associated lung adenocarcinoma transcript 1

Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is one of the highly conserved lncRNAs shown to play a significant role in many diseases, including cancer, diabetes, and insulin resistance. A previous study showed that excess PA increases MALAT1 expression, activated SREBP1c and induced intracellular lipid accumulation in hepatocytes, whereas inhibition of MALAT1 expression decreased nuclear SREBP1c level and lipid accumulation both *in vitro* and *in vivo*[118]. Further analysis by these authors revealed that the reduction of MALAT1 in the liver improved insulin sensitivity in ob/ob mice. They concluded that MALAT1 may promote hepatic steatosis and insulin resistance by increasing nuclear SREBP1c protein stability in hepatocytes[118]. Furthermore, results from lncRNA profiling in the liver biopsies of NAFLD patients demonstrated the potential of MALAT1 as a regulator of liver inflammation and fibrosis and insulin resistance by targeting the C-X-C motif chemokine ligand 5[119]. Consistent with these observations, another study found that MALAT1 expression was significantly increased in NASH patients compared to NAFLD individuals with simple steatosis and controls[120]. Previous studies have reported that MALAT is overexpressed in both HCC cell lines and clinical tissue samples[121,122], providing additional evidence that this lncRNA could be used as a

biomarker of liver damage and HCC development.

Nuclear enriched abundant transcript 1

Nuclear enriched abundant transcript 1 (NEAT1) is a nuclear lncRNA involved in various liver diseases [123]. It is involved in adipogenesis processes, including lipolysis, lipid uptake, and LDL oxidation. A recent study indicated that the NEAT1 and mTOR signaling pathway proteins were increased in NAFLD *in vitro* and *in vivo* while downregulation of NEAT1 alleviated NAFLD *via* the mTOR/S6K1 signaling pathway in rat model[124]. Additionally, NEAT1 plays an important role in the activation of estrogen receptor alpha to regulate water-glycerol transporter (AQP7)-mediated hepatic steatosis[125]. Chen *et al*[126] found that NEAT1 promotes steatosis by sponging miR-146a-5p, subsequently increasing the expression of Rho-kinase1 (ROCK1) and significantly inducing the AMPK/SREBP pathway. Silencing of NEAT1 alleviated fibrosis and inflammatory responses by regulating the miR-506/GLI3 axis in an NAFLD cellular model[127]. A recent study indicated that NEAT1 and paternally expressed gene 3 were highly expressed in the liver and HSCs from NASH mice and silencing of NEAT1 effectively reduced the fibrotic characteristics of HSCs in the setting of NASH[128]. These results corroborate previous findings by Leti *et al*[119] indicating that NEAT1 is upregulated in the fibrosis of NASH patients compared to controls. Together, these studies highlight the potential value of NEAT1 for aiding in the prognosis and diagnosis of NASH.

Ultra-conserved element

Ultra-conserved element (UC372) is a lncRNA associated with impaired homeostasis of lipid metabolism and may play a role in the pathogenesis of NAFLD. UC372 is upregulated in a murine model of T2DM (db/db mice), HFD-fed mice, and NAFLD patients, indicating a role in liver steatosis and fatty liver[129]. Mechanistically, UC372 may drive hepatic steatosis through binding to pri-miR-195/pri-miR-4668, thus preventing miR-195/miR-4668 from regulating the expression of target genes associated with lipid synthesis and uptake, including acetyl-CoA carboxylase, fatty acid synthase, stearoyl-CoA desaturase 1, and lipid uptake-related genes such as CD36[129]. These preliminary results suggest that UC372 may be a promising target for therapies combating hepatic steatosis.

Maternally expressed gene 3

Maternally expressed gene 3 (MEG3), also known as gene trap locus 2, is another lncRNA that plays a regulatory role in the carcinogenesis and progression of several types of cancer. MEG3 is also suspected to be involved in the pathogenesis of NAFLD. In this respect, an early study reported that expression of hepatic MEG3 was consistently decreased in the chemokine (C-C motif) ligand 4 (CCl4)-induced mouse progressive liver fibrosis model compared to normal tissues, and HSCs may be one of the main sources of the MEG3 Levels present in CCl4-treated livers[130]. The same study revealed that MEG3 was also downregulated in human liver fibrotic tissues compared with control liver tissues. In line with this these studies, Huang *et al*[131] showed that the downregulation of MEG3 in *in vitro* and *in vivo* models of NAFLD is negatively correlated with lipogenesis-related genes, and that overexpression of MEG3 alleviates lipid overaccumulation in HepG2 cells. The downregulation of MEG3 in two models of NAFLD (free fatty acid-challenged primary hepatocytes and HFD-induced mouse) was also indicated in a more recent study by Zou *et al*[132].

In contradiction with these results, hepatic MEG3 Levels are significantly increased in liver fibrosis and NASH cirrhosis in human patients[133]. Similarly, MEG3 was shown to be one of the most differentially expressed lncRNAs in the vascular endothelium in diet-induced obese mice, and its expression was elevated in human nonalcoholic fatty livers and NASH livers, whereas its knockdown potentiated obesity-induced insulin resistance and impaired glucose homeostasis[134]. These conflicting results underline the complexity of MEG regulation, and further studies are required to clarify the biological significance of MEG3 and its potential role MEG3 either as a biomarker or a therapeutic target for NAFLD.

Highly upregulated in liver cancer

The lncRNA highly upregulated in liver cancer (HULC) was the first identified lncRNA specifically overexpressed in HCC. HULC, a functionally important lncRNA, promotes HCC growth, metastasis and drug resistance[135]. HULC expression was found to be increased in the liver tissue of NAFLD rats [136]. Inhibition of this lncRNA improves hepatic fibrosis and lipid deposition and decreases hepatocyte apoptosis in rats with NAFLD *via* inhibition of the mitogen-activated protein kinase signaling pathway in liver tissue[136]. Interestingly, the antidiabetic drug metformin was also reported to decrease HULC by inhibiting the expression of specificity protein 1 transcription factor in liver cancer cells[137]. Indeed, metformin was shown to improve insulin resistance and hyperinsulinemia and increase insulin sensitivity. This drug is now recommended and has proven to be effective for the treatment of NAFLD [138]. Collectively, these findings suggest that HULC could be a promising target for NAFLD diagnosis, staging, and therapy.

Homeobox transcript antisense intergenic RNA

Homeobox (HOX) transcript antisense intergenic RNA (HOTAIR) is a lncRNA that resides on a boundary of the HOXC locus on chromosome 12q13.13. HOTAIR is increased in different forms of cancers and involved in diverse cellular functions. In NAFLD, free fatty acid treatment promotes TG accumulation in HepG2 cells, significantly induces HOTAIR expression and inhibits phosphatase and tensin homolog expression[139]. A recent study reported that HOTAIR was activated in NAFLD, and HOTAIR knockdown significantly inhibited the development of NAFLD *via* mediation of miR-130b-3p/ROCK1/AMPK axis, further suggesting a target for NAFLD[140]. HOTAIR shows several oncogenic functions in HCC and its expression levels are increased in liver fibrosis, which causes acceleration of carcinogenesis in hepatitis B virus-infected patients[141]. Other investigations have reported that HOTAIR can serve as a competing endogenous RNA to sponge miR-29b and then repress DNMT3b, which contributes to hepatic fibrosis[141].

Fatty liver-related lncRNA 2

The lncRNA fatty liver-related lncRNA 2 (FLRL2) is located in the intronic region of the aryl hydrocarbon receptor nuclear translocator-like (*Arntl*) gene, and *Arntl* is predicted as a cis target of FLRL2. FLRL2 was identified as a potential key molecule in the pathogenesis of NAFLD. This nuclear-localized lncRNA is downregulated in the NAFLD mouse model, suggesting a role in the pathogenesis of this disease[142]. Further mechanistic studies have demonstrated that overexpression of FLRL2 alleviates NAFLD through activation of the Arntl-SIRTA pathway, inhibits lipogenesis, and reduces hepatic steatosis in HFD mice[143]. These results render FLRL2 another promising therapeutic candidate for the treatment of NAFLD and its complications. Finally, the above-discussed lncRNAs with their potential functions in NAFLD are also summarized in Table 2.

circRNAs in NAFLD

As their name implies, circRNAs are single-stranded covalently closed RNA species formed through back-splicing. Distinct characteristics of circRNAs, such as high stability, evolutionary conservation among species, exonuclease resistance, and existence in body fluids endow this class of RNAs with numerous potential functions ranging from miRNA and protein sponges to gene transcriptional regulators and protein/peptide translators. Moreover, circRNAs are dysregulated in numerous pathological conditions and may potentially serve as novel diagnostic biomarkers and therapeutic targets.

Although there is increasing evidence linking circRNAs to the pathogenesis of metabolic diseases, studies centered on the investigation of circRNAs in NAFLD were only recently conducted[144-146]. Data from recent literature suggest that circRNAs are involved in several fundamental processes governing the onset and progression of NAFLD and display aberrant expression[147]. For instance, a circRNA_0046367 was decreased in HFD-induced hepatic steatosis[148]. Subsequently, the authors of this study demonstrated that normalization of circRNA_0046367 Levels prevents lipid peroxidation and mitochondrial dysfunction in steatosis through miR-34a sponging and PPARα downregulation. In a further analysis, the same research laboratory identified an additional circRNA: circRNA_0046366, whose expression was also diminished during free fatty acid-induced hepatocellular steatosis in high fat-treated HepG2 cells[149]. In HepG2 cells with hepatic steatosis induced by high-fat stimulation, circRNA_021412 was associated with hepatic steatosis *via* the circRNA_021412/miR-1972/LPIN1axis [150]. circRNA microarrays analysis in an HFD mouse model revealed that circScd1 expression was significantly decreased in NAFLD tissues compared to that in controls. Consistent with this, knockdown of circScd1 promoted hepatosteatosis through the regulation of the Janus kinase 2 and signal transducer and activator of transcription 5 signaling pathway[151]. In an *in vitro* model of NAFLD, Hsa_circ_0048179 was shown to attenuate free fatty acid-induced steatosis *via* Hsa_circ_0048179/miR-188-3p/glutathione peroxidase 4 signaling[152]. circRNA profiling in a NASH mouse model identified circRNA_29981 as the circRNA most significantly differentially expressed in this setting[153].

More recently, Jin *et al*[147] indicated that the circRNA_002581-miR-122-CPEB1 axis aggravates NASH partially through autophagy suppression, while silencing of circRNA_002581 significantly attenuated lipid droplet accumulation, eliminated liver damage in both mouse and cellular models of NASH. Chen *et al*[154] indicated that silencing of circ_0071410 alleviates hepatic stellate activation, a key step of liver cirrhosis. HSCs are the primary cell type responsible for liver fibrosis. In the CCl4-induced mouse model of liver fibrosis, mmu_circ_34116 was able to inhibit HSCs activation[155]. In a mouse model of NAFLD, Chen *et al*[156] found that circ_0057558 can promote NAFLD by regulating ROCK1/AMPK signaling through targeting miR-206. Interestingly, a novel mitochondrial genome-encoded circRNA termed mitochondrial steatohepatitis-associated circRNA ATP5B regulator (SCAR) was identified recently[157]. The latter study found SCAR to be significantly downregulated in liver fibroblasts from patients with NASH. Additionally, the overexpression of SCAR inhibited mitochondrial reactive oxygen species output and fibroblast activation *via* shutting down mitochondrial permeability transition pore. More importantly, *in vivo* targeting of SCAR alleviated HFD-induced cirrhosis and insulin resistance implying that circRNA SCAR may serve as a therapeutic target for NASH[157].

Table 2 Relevant dysregulated long noncoding RNAs associated with alterations in liver metabolism and nonalcoholic fatty liver disease

lncRNA	Expression	Main functional and pathophysiological effects	Ref.
MALAT1	↑	Promotes cell proliferation, migration, and invasion in several different human cancers including HCC Promotes hepatic steatosis and insulin resistance Hepatic MALAT1 levels are higher in NASH patients with fibrosis Promotes NAFLD progression and increase with the severity of the disease	[119-122]
NEAT1	↑	Promotes adipogenesis, lipogenesis, and lipid absorption Modulates fibrosis and inflammatory responses Silencing NEAT1 alleviated fibrosis and inflammatory in a NAFLD cellular model	[124,126,127]
MEG3	↓	Involved in lipid metabolism and glucose homeostasis Correlates with steatosis and inflammation (NASH) in patients with NAFLD	[131-134]
HULC	↑	Promotes HCC growth and metastasis Promotes NAFLD development Metformin decreases HULC expression	[135,136]
HOTAIR	↑	Activates lipid accumulation in hepatocytes and promotes hepatic steatosis development Expression profile is significantly increased in oleic acid-induced steatosis and during the development of HFD-induced NAFLD Accelerates liver fibrosis and carcinogenesis	[139-141]
FLRL2	↓	Decreases endoplasmic reticulum stress and liver inflammation Alleviates NAFLD and steatosis in mouse model	[143]

FLR2: Fatty liver-related lncRNA 2; H19: H19 imprinted maternally expressed transcript; HCC: Hepatocellular carcinoma; HFD: High-fat diet; HOTAIR: HOX transcript antisense RNA; MALAT1: Metastasis-associated lung adenocarcinoma transcript 1; lncRNAs: Long noncoding RNAs; MEG3: Maternally expressed 3; NAFLD: Nonalcoholic fatty liver disease; NASH: Nonalcoholic steatohepatitis; NEAT1: Nuclear paraspeckle assembly transcript 1; HULC: Hepatocellular carcinoma upregulated long noncoding RNA.

Together, these findings suggest that certain circRNAs, including those summarized in Table 3, are likely to contribute to NAFLD phenotype, which makes them attractive targets for the development of diagnostic and interventional pharmacology. However, circRNA data are still lacking functional evidence and their underlying mechanisms are still awaiting elucidation. Nevertheless, further carefully designed prospective studies to emphasize and validate the potential use of circRNAs as NAFLD biomarkers are expected to yield new insights into the pathogenesis of this disease state.

CONCLUSION

The findings from the above research clearly indicate that alterations in miRNA, circRNA and lncRNA expression play critical roles in cellular physiology and many diseases, including NAFLD and cancer. Thus, these ncRNA subsets are promising non-invasive biomarkers for the diagnosis and stratification of patients with NAFLD and could inform future personalized treatments designed for this condition. Even though the concept is promising and optimism is high, there is a consensus that research in the field still has limitations and technical challenges. (1) Sustained research efforts in the ncRNAs field have aimed to develop biomarkers to support the diagnostic process in patients with NAFLD. Unfortunately, most of the studies were carried out in subjects who already display patterns of worsening symptoms and are seeking medical care. To overcome this challenge, an alternative option would be to investigate the status of ncRNAs in the general population, which may assess the risk and capture early stages of disease initiation and evolution. This strategy could help achieve early diagnosis in individuals at risk for NAFLD but yet asymptomatic, and determine whether the overserved aberration in ncRNA

Table 3 Relevant dysregulated circular RNAs associated with alterations in liver metabolism and nonalcoholic fatty liver disease

circRNA	Expression level	Main functional and pathophysiological effects	Ref.
circRNA_0046367	↑	Inhibits hepatic steatosis by preventing hepatotoxicity of lipid peroxidation	[148]
circRNA_0046366	↑	Inhibits hepatic steatosis through miR-34a/PPARα	[149]
circRNA_021412	↑	Associated with hepatic steatosis	[150]
circScd1	↓	Affects steatosis on NAFLD *via* JAK2/STAT5 signaling pathways	[151]
hsa_circ_0048179	↓	Attenuates free fatty acid-induceded steatosis by sponging of miR-188-3p *in vitro*	[152]
mmu_circRNA_29981	↑	Regulatory role in NASH mousee model	[153]
Circ_0057558	↑	Involved in lipogenesis	[156]
		Promotes nonalcoholic fatty liver disease by sponging miR-206	
SCAR	↓	Correlates with steatosis-to-NASH progression	[157]
		In vivo, targeting circRNA SCAR alleviates HFD-induced cirrhosis and insulin resistance	

circRNAs: Circular RNAs; HCC: Hepatocellular carcinoma; HFD: High-fat diet; JAK2: Janus Kinase 2; NAFLD: Nonalcoholic fatty liver disease; NASH: Nonalcoholic steatohepatitis; PPARα: Peroxisome proliferator-activated receptor α; STAT5: Signal transducer and activator of transcription 5.

expression is the trigger or it is just a consequence of other causes such as those associated with lipid metabolism disorder, inflammation and immune system; (2) The role of ncRNAs as mediators of cell and organ crosstalk as well as their impact on different signaling pathways involved in NAFLD pathogenesis are not fully understood. It is now recognized that some ncRNAs are present in the extracellular environment and may be involved in pathophysiological condition. They may act to affect their targets either in an autocrine or paracrine fashion. Hence, special attention should be drawn to further research addressing the role of ncRNAs and their carriers (extracellular vesicles) in mediating potential inter-organ crosstalk in NAFLD condition, and the dynamic interaction of ncRNAs with metabolism cell signaling pathways. While these strategies may seem difficult to carry out and complete, they can be a starting point for increasing our knowledge on the role of circulating ncRNAs in organ crosstalk and may represent an opportunity to better understand how they affect metabolic homeostasis to drive the onset and progression of NAFLD and related pathological conditions; and (3) From a clinical perspective, approaches based on an individual ncRNA targeting or overexpression are what researchers are shooting for. However, each ncRNA has highly redundant roles and multiple functions. Indeed, a previous study revealed that a miRNA can affect a phenotype not only through a simple regulatory process, but *via* multiple targets redundantly and often incoherently, and such a complex regulation is difficult to assemble and control[158]. Indeed, it is becoming evident that it is difficult to diagnose a multifactorial disease such as NAFLD using a single ncRNA. Attempts were conducted to use a combination of serum circulating ncRNAs. Understanding the ncRNA-ncRNA crosstalk and their intricate interplay with different genetic and other epigenetic regulators including DNA methylation, chromatin remodeling, and components of the transcriptional and posttranscriptional machineries to regulate gene networks involved in NAFLD could certainly expand our knowledge on the molecular mechanisms driving this disease. This approach can also lead to a breakdown into NAFLD subtypes which would add resolution and inform about the regulation of molecular processes involved in each stage of the disease by specific ncRNAs.

To sum up, this review highlights the evidence for potential subsets of ncRNAs that are associated with NAFLD and its pathological conditions. The findings from various human and animal studies clearly suggest that dysregulation in ncRNA profiles are critical factors in the initiation and progression of fatty liver diseases, including NAFLD. This may be an appealing argument to further explore the mystery of these RNA molecules and consider their clinical application as biomarkers/therapeutics in the prevention and treatment of NAFLD and its progressive forms.

FOOTNOTES

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Country/Territory of origin: France

ORCID number: Mohamed Zaiou 0000-0002-4113-4350.

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