

78029\_Auto\_Edited-check.docx

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

Zaiou M *et al.* Noncoding RNAs in nonalcoholic fatty liver disease

Mohamed Zaiou

**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 nonalcoholic 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

Zaiou M. Noncoding RNAs as additional mediators of epigenetic regulation in nonalcoholic fatty liver disease. *World J Gastroenterol* 2022; In press

**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.

## 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)<sup>[1]</sup>. 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<sup>[2,3]</sup>. The prevalence of NAFLD depends on race and ethnicity. In the United States, the estimated prevalence of NAFLD was reported to be about 32%<sup>[4]</sup>. 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<sup>[5,6]</sup>.

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. <sup>29</sup> Currently, liver biopsy remains the gold standard method for NAFLD diagnosis and degree of liver injury evaluation<sup>[7]</sup>. Computed tomography scans and ultrasound can also be performed as part of the standard evaluation of NAFLD. <sup>36</sup> However, these methods have a number of limitations, including invasiveness, low sensitivity, sampling variability, and inaccurate diagnosis<sup>[8,9]</sup>. 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<sup>[10]</sup>. 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<sup>[11,12]</sup>. 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”<sup>[13]</sup>. 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<sup>[3,14]</sup>. 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<sup>[15,16]</sup>, 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”<sup>[17]</sup>. 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<sup>[18,19]</sup>. 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<sup>[20]</sup>. 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<sup>[21]</sup>. Regulatory ncRNAs mainly consist of microRNAs (miRNAs) (< 30 nucleotides), long noncoding RNAs (lncRNAs) (≥ 200

nucleotides)<sup>[19]</sup>, 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<sup>[22,23]</sup>. Moreover, ncRNAs reveal significant differences in expression according to the severity of NAFLD and histological features<sup>[24]</sup>. 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<sup>[25]</sup>. They are transcribed in the cell nucleus and transported to the cytoplasm, where they are processed into mature miRNAs<sup>[26]</sup>. 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<sup>[27]</sup>. Mounting evidence reveals that dysregulation in miRNAs' expression is associated with molecular processes of various forms of metabolic and liver diseases, including NAFLD conditions<sup>[3,28-30]</sup>. Indeed, several differentially expressed miRNAs play key roles in the development of NAFLD in animal models and humans<sup>[30-33]</sup>, essentially through the regulation of several pathogenic processes including altered lipid and glucose metabolism, insulin resistance, and inflammation pathways<sup>[34,35]</sup>. 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<sup>[36,37]</sup>. 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<sup>[38]</sup>. 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<sup>[39-41]</sup>. Likewise, circulating miR-21 levels are significantly increased in patients suffering from NASH compared to NAFL and healthy controls<sup>[42]</sup>. Other studies have shown that inhibiting miR-21 can alleviate steatosis by activating peroxisome proliferator-activated receptor alpha (PPAR $\alpha$ )<sup>[40,43]</sup>. 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<sup>[44]</sup>. Similarly, miR-21 abrogation along with obeticholic acid treatment significantly reduced NASH in mice<sup>[45]</sup>.

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)<sup>[46]</sup> and 3-hydroxy-3-methylglutaryl-co-enzyme A reductase (HMGCR)<sup>[47]</sup>. Additionally, miR-21 can target phosphatase and tensin homolog, which prevents hepatic steatosis<sup>[48]</sup>, and PPAR $\alpha$  expression, which induces inflammation and fibrosis progression and activates lipid oxidation in NAFLD<sup>[40]</sup>. Other investigations have revealed that miR-21 can inactivate the Wnt/ $\beta$ -catenin signaling pathway by targeting low-density lipoprotein (LDL) receptor-related protein 6, thereby aggravating lipid accumulation and inflammation<sup>[49]</sup>. Mechanistic studies have also

34 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- $\alpha$ )<sup>[44]</sup>. 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

6 The miR-29 family of miRNAs consists of miR-29a, miR-29b, and miR-29c members<sup>[50]</sup>, and are mainly expressed in hepatocytes and hepatic stellate cells (HSCs)<sup>[51,52]</sup>. A body of evidence suggests that miR-29a is significantly associated with diagnostic relevance of NAFLD<sup>[31,53]</sup>, NASH<sup>[54]</sup> and liver fibrosis<sup>[54,55]</sup>, as well as aggressiveness and prognosis of HCC<sup>[31]</sup>. Lopez-Riera *et al*<sup>[53]</sup> identified circulating miR-29a as one of the potential biomarkers that could predict drug-induced NAFLD in humans<sup>[56]</sup>. Jampoka *et al*<sup>[57]</sup> 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 3 $\beta$  (DNMT3 $\beta$ ) to improve diet-induced NASH in mice. Mattis *et al*<sup>[58]</sup> used a mouse model to demonstrate that miR-29a protects hepatocytes from steatosis by repressing lipoprotein lipase in hepatocytes. Moreover, 16 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<sup>[59]</sup>. Roderburg *et al*<sup>[52]</sup> 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)<sup>[31]</sup>. 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, <sup>2</sup> miR-33a and miR-33b (miR-33a/b), which <sup>14</sup> 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<sup>[60,61]</sup>. In mice, <sup>14</sup> there is only one miR-33 isoform, which is an ortholog form of human miR-33a<sup>[60]</sup>.

In addition, expression levels of miR-33 are increased in the liver tissues of patients with NAFLD<sup>[62]</sup>. Circulating <sup>15</sup> 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<sup>[63]</sup>. The expression of hepatic miR-33a/miR-144 is increased in NASH patients with morbid obesity<sup>[64]</sup>. 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<sup>[65]</sup>.

From a therapeutic perspective, several <sup>1</sup> 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<sup>[66-68]</sup>. However, a previously <sup>18</sup> published clinical trial indicated that increased expression of miR-33a in the liver is associated with steatohepatitis in morbidly obese humans and metabolic dysfunction<sup>[64]</sup>. 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<sup>[69,70]</sup>. miR-33 KO mice exposed to HFD developed marked worsening of obesity and liver steatosis *via* targeting SREBP1<sup>[71]</sup>. Recently, Price *et al*<sup>[61]</sup> 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*

<sup>27</sup> The miR-34 family comprises three members: miR-34a, miR-34b, and miR-34c. <sup>6</sup> 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<sup>[72,73]</sup>. miR-34 regulates many transcription factors, such as HNF4- $\alpha$ , SIRT1, and p53, which are involved in lipid metabolism, cholesterol synthesis, and fatty acid  $\beta$ -oxidation<sup>[72,74]</sup>. In addition, <sup>8</sup> Xu *et al.*<sup>[73]</sup> demonstrated that miR-34a inhibits hepatic very LDL secretion by promoting steatosis through interaction with HNF4- $\alpha$  in patients with NASH and mice fed HFD. miR-34a regulates steatosis by directly targeting PPAR $\alpha$  expression in NAFLD<sup>[75]</sup>. Recently, another study <sup>16</sup> demonstrated that the miR-34a/SIRT1/AMPK pathway is involved in mitochondrial dysfunction in a mouse NASH model<sup>[76]</sup>. Higher circulating levels of miR-34a have been seen in patients with NAFLD and NASH and mice fed HFD<sup>[73,77]</sup>. An association of miR-34a and miR-122 with dyslipidemia among patients with NAFLD has also been reported<sup>[78]</sup>, and both miRNAs could be useful biomarkers in children with obesity and NAFLD<sup>[79]</sup>. Finally, in a meta-analysis study, <sup>1</sup> miR-34a, miR-122, and miR-192 were identified as potential diagnostic markers to segregate NAFL from NASH<sup>[32]</sup>. Here, miR-34 showed the best diagnostic accuracy for discriminating NASH *vs* NAFLD.

### *miR-122*

<sup>8</sup> miR-122 is the most abundant and extensively studied hepatic miRNA representing about 70% of the total miRNA in the liver<sup>[80]</sup>. 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<sup>[72,80,81]</sup>. 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<sup>[82,83]</sup>. 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<sup>[33,82,83]</sup>, 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<sup>[81,84]</sup>, whereas restoration of miR-122a expression reduces disease symptoms and tumorigenesis<sup>[84]</sup>. 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<sup>[72,80]</sup>. 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<sup>[74]</sup>.

Conversely, elevated serum levels of miR-122 have been found in patients with NAFLD compared to controls, and these levels are positively correlated with disease severity<sup>[85,86]</sup>. 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<sup>[80,87,88]</sup>. Additionally, NASH patients exhibit increased levels of miR-122 in the serum<sup>[80]</sup> and decreased hepatic expression of this RNA<sup>[72]</sup>. 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*<sup>[89]</sup> 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<sup>[90,91]</sup>. Several studies have reported that miR-155 is one of the biologically most relevant miRNAs in several liver diseases including NAFLD<sup>[92,93]</sup>. In this respect, a study by Wang *et al*<sup>[94]</sup> 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)- $\alpha$ , C/EBP- $\beta$ , PPAR- $\gamma$  and LXR $\alpha$ <sup>[94,95]</sup>. On the other hand, miR-155-deficient mice fed a HFD developed increased hepatic steatosis compared to controls<sup>[94]</sup>, while conditionally liver-specific overexpression of miR-155 reduced serum and hepatic levels of TC, TG, and high-density lipoprotein, and alleviated NAFLD<sup>[93]</sup>. 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<sup>[95]</sup>. 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<sup>[96]</sup>. 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<sup>[97]</sup>. 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<sup>[98]</sup>. 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<sup>[99]</sup>. 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<sup>[100]</sup>. Recently, Wang *et al*<sup>[101]</sup> 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<sup>[80]</sup>. 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<sup>[42,100]</sup>. A recent meta-analysis identified several miRNAs as potential biomarkers of NAFLD and NASH, including miR-34a, miR-122, and miR-192<sup>[32]</sup>. 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<sup>[102]</sup>. miR-122, miR-192, and miR-375 are significantly upregulated in NAFLD patients compared to controls<sup>[80]</sup>. miR-375 is involved in the pathogenesis of NAFLD and its inhibition suppresses the production

of inflammatory cytokines tumor necrosis factor-alpha<sup>11</sup> as well as interleukin-6, increased the expression of adiponectin, and suppressed lipid accumulation in palmitate (PA)-induced HepG2 cells<sup>[103]</sup>. 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<sup>[104]</sup>. They are regulatory molecules<sup>1</sup> 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<sup>[104]</sup>. 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<sup>[105]</sup> and decoys that bind targeted proteins or miRNAs to limit their availability and function by acting as a molecular sink<sup>[106]</sup>. 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<sup>21</sup> linked to the pathophysiology of various human diseases, such as cancer, diabetes, and cardiovascular diseases<sup>[107]</sup>. 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<sup>[108]</sup>. 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<sup>[109]</sup>. In this respect, existing evidence has shown that <sup>28</sup> overexpression of H19 results in hepatic metabolic reprogramming and exacerbates diet-induced fatty liver<sup>[110]</sup>. In agreement with this, Wang *et al*<sup>[111]</sup> 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/PPAR $\gamma$  axis in NAFLD<sup>[112]</sup>. 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<sup>[113]</sup> and may serve as a regulator of triacylglycerol biosynthesis. Recently, Zhao *et al*<sup>[114]</sup> reported that <sup>1</sup> hepatic Blnc1 expression was strongly linked to activation of lipogenesis in mouse models of obesity and NAFLD, whereas its liver-specific inactivation abrogated <sup>1</sup> 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<sup>[115]</sup>. Overall, these results suggest that Blnc1 has different regulatory mechanisms and distinct functions in the liver and white adipose tissue.

### ***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*<sup>[116]</sup> 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 <sup>19</sup> dyslipidemia in patients with NAFLD is atherogenic in nature and it is characterized by <sup>38</sup> increased levels of serum TG. Furthermore, elevated TG levels in the circulation are associated with metabolic syndrome and cardiovascular disease<sup>[117]</sup>.

### <sup>3</sup> ***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 <sup>1</sup> inhibition of MALAT1 expression decreased nuclear SREBP1c level and lipid accumulation both *in vitro* and *in vivo*<sup>[118]</sup>. Further analysis by these <sup>1</sup> 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<sup>[118]</sup>. 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<sup>[119]</sup>. Consistent with these observations, another study found that <sup>30</sup> MALAT1 expression was significantly increased in NASH patients compared to NAFLD individuals with simple steatosis and controls<sup>[120]</sup>. Previous studies have reported that MALAT is overexpressed in both HCC cell lines and clinical tissue samples<sup>[121,122]</sup>, providing additional evidence that this lncRNA could be used as a biomarker of liver damage and HCC development.

### <sup>5</sup> ***Nuclear enriched abundant transcript 1***

Nuclear enriched abundant transcript 1 (NEAT1) is a nuclear lncRNA involved in various liver diseases<sup>[123]</sup>. 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<sup>[124]</sup>. Additionally, NEAT1 plays an important role in the activation of estrogen receptor alpha to regulate water-glycerol transporter (AQP7)-mediated hepatic steatosis<sup>[125]</sup>. Chen *et al*<sup>[126]</sup> 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<sup>[127]</sup>. 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<sup>[128]</sup>. These results corroborate previous findings by Leti *et al*<sup>[119]</sup> 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<sup>[129]</sup>. 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<sup>[129]</sup>. These preliminary results suggest that UC372 may be a promising target for therapies combating hepatic steatosis.

### ***Maternally expressed gene 3***

<sup>7</sup> 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 <sup>7</sup> HSCs may be one of the main sources of the MEG3 Levels present in CCl4-treated livers<sup>[130]</sup>. The same study revealed that <sup>7</sup> MEG3 was also downregulated in human liver fibrotic tissues compared with control liver tissues. In line with these studies, Huang *et al*<sup>[131]</sup> showed <sup>13</sup> 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*<sup>[132]</sup>.

<sup>1</sup> In contradiction with these results, hepatic MEG3 Levels are significantly increased in liver fibrosis and NASH cirrhosis in human patients<sup>[133]</sup>. Similarly, MEG3 was shown to be <sup>26</sup> 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<sup>[134]</sup>. 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*

<sup>24</sup> 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<sup>[135]</sup>. HULC expression was found to be increased in the liver tissue of NAFLD rats<sup>[136]</sup>. 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<sup>[136]</sup>. 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<sup>[137]</sup>. 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<sup>[138]</sup>. Collectively, these findings suggest that HULC could be a promising target for NAFLD diagnosis, staging, and therapy.

#### ***Homeobox transcript antisense intergenic RNA***

<sup>1</sup> 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<sup>[139]</sup>. 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<sup>[140]</sup>. 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<sup>[141]</sup>. 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<sup>[141]</sup>.

#### ***Fatty liver-related lncRNA 2***

<sup>5</sup> 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 <sup>1</sup> nuclear-localized lncRNA is downregulated in the NAFLD mouse model, suggesting a role in the pathogenesis of this disease<sup>[142]</sup>. Further mechanistic studies have demonstrated that overexpression of FLRL2 alleviates NAFLD through activation of the Arntl-SIRT6 pathway, inhibits lipogenesis, and reduces hepatic steatosis in HFD mice<sup>[143]</sup>. 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<sup>[144-146]</sup>. Data from recent literature suggest that circRNAs are involved in several fundamental processes governing the onset and progression of NAFLD and display aberrant expression<sup>[147]</sup>. For instance, a <sup>4</sup> circRNA\_0046367 was decreased in HFD-induced hepatic steatosis<sup>[148]</sup>. 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 PPAR $\alpha$  downregulation. In a further analysis, the same research laboratory identified an additional <sup>4</sup> circRNA: circRNA\_0046366, whose expression was also diminished during free fatty acid-induced hepatocellular steatosis in high fat-treated HepG2



cells<sup>[149]</sup>. In HepG2 cells with hepatic steatosis induced by high-fat stimulation, circRNA\_021412 was associated with hepatic steatosis *via* the circRNA\_021412/miR-1972/LPIN1 axis<sup>[150]</sup>. 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<sup>[151]</sup>. 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<sup>[152]</sup>. circRNA profiling in a NASH mouse model identified circRNA\_29981 as the circRNA most significantly differentially expressed in this setting<sup>[153]</sup>.

More recently, Jin *et al*<sup>[147]</sup> 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*<sup>[154]</sup> 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 CCl<sub>4</sub>-induced mouse model of liver fibrosis, mmu\_circ\_34116 was able to inhibit HSCs activation<sup>[155]</sup>. In a mouse model of NAFLD, Chen *et al*<sup>[156]</sup> 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<sup>[157]</sup>. 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<sup>[157]</sup>.

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<sup>4</sup> 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 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<sup>[158]</sup>. 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.

## REFERENCES

- 1 **Baffy G**, Brunt EM, Caldwell SH. Hepatocellular carcinoma in non-alcoholic fatty liver disease: an emerging menace. *J Hepatol* 2012; **56**: 1384-1391 [PMID: 22326465 DOI: 10.1016/j.jhep.2011.10.027]
- 2 **Eslam M**, Sanyal AJ, George J; International Consensus Panel. MAFLD: A Consensus-Driven Proposed Nomenclature for Metabolic Associated Fatty Liver Disease. *Gastroenterology* 2020; **158**: 1999-2014.e1 [PMID: 32044314 DOI: 10.1053/j.gastro.2019.11.312]
- 3 **Eslam M**, Valenti L, Romeo S. Genetics and epigenetics of NAFLD and NASH: Clinical impact. *J Hepatol* 2018; **68**: 268-279 [PMID: 29122391 DOI: 10.1016/j.jhep.2017.09.003]
- 4 **Zou B**, Yeo YH, Nguyen VH, Cheung R, Ingelsson E, Nguyen MH. Prevalence, characteristics and mortality outcomes of obese, nonobese and lean NAFLD in the United States, 1999-2016. *J Intern Med* 2020; **288**: 139-151 [PMID: 32319718 DOI: 10.1111/joim.13069]
- 5 **Leite NC**, Salles GF, Araujo AL, Villela-Nogueira CA, Cardoso CR. Prevalence and associated factors of non-alcoholic fatty liver disease in patients with type-2 diabetes mellitus. *Liver Int* 2009; **29**: 113-119 [PMID: 18384521 DOI: 10.1111/j.1478-3231.2008.01718.x]
- 6 **Subichin M**, Clanton J, Makuszewski M, Bohon A, Zografakis JG, Dan A. Liver disease in the morbidly obese: a review of 1000 consecutive patients undergoing weight loss surgery. *Surg Obes Relat Dis* 2015; **11**: 137-141 [PMID: 25701959 DOI: 10.1016/j.soard.2014.06.015]
- 7 **Hardy T**, Oakley F, Anstee QM, Day CP. Nonalcoholic Fatty Liver Disease: Pathogenesis and Disease Spectrum. *Annu Rev Pathol* 2016; **11**: 451-496 [PMID: 26980160 DOI: 10.1146/annurev-pathol-012615-044224]

- 8 **Rinella ME.** Nonalcoholic fatty liver disease: a systematic review. *JAMA* 2015; **313**: 2263-2273 [PMID: 26057287 DOI: 10.1001/jama.2015.5370]
- 9 **Mazhar K.** The Future of Nonalcoholic Fatty Liver Disease Treatment. *Med Clin North Am* 2019; **103**: 57-69 [PMID: 30466676 DOI: 10.1016/j.mcna.2018.08.005]
- 10 **Younossi Z,** Tacke F, Arrese M, Chander Sharma B, Mostafa I, Bugianesi E, Wai-Sun Wong V, Yilmaz Y, George J, Fan J, Vos MB. Global Perspectives on Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis. *Hepatology* 2019; **69**: 2672-2682 [PMID: 30179269 DOI: 10.1002/hep.30251]
- 11 **Angulo P.** Nonalcoholic fatty liver disease. *N Engl J Med* 2002; **346**: 1221-1231 [PMID: 11961152 DOI: 10.1056/NEJMr011775]
- 12 **Anstee QM,** Daly AK, Day CP. Genetics of alcoholic and nonalcoholic fatty liver disease. *Semin Liver Dis* 2011; **31**: 128-146 [PMID: 21538280 DOI: 10.1055/s-0031-1276643]
- 13 **Cavalli G,** Heard E. Advances in epigenetics link genetics to the environment and disease. *Nature* 2019; **571**: 489-499 [PMID: 31341302 DOI: 10.1038/s41586-019-1411-0]
- 14 **Choudhary NS,** Duseja A. Genetic and epigenetic disease modifiers: non-alcoholic fatty liver disease (NAFLD) and alcoholic liver disease (ALD). *Transl Gastroenterol Hepatol* 2021; **6**: 2 [PMID: 33409397 DOI: 10.21037/tgh.2019.09.06]
- 15 **Pirola CJ,** Sookoian S. Epigenetics factors in nonalcoholic fatty liver disease. *Expert Rev Gastroenterol Hepatol* 2022; **16**: 521-536 [PMID: 32476509 DOI: 10.1080/17474124.2020.1765772]
- 16 **Zaiou M,** Amrani R, Rihn B, Hajri T. Dietary Patterns Influence Target Gene Expression through Emerging Epigenetic Mechanisms in Nonalcoholic Fatty Liver Disease. *Biomedicines* 2021; **9** [PMID: 34572442 DOI: 10.3390/biomedicines9091256]
- 17 **Mattick JS,** Makunin IV. Non-coding RNA. *Hum Mol Genet* 2006; **15 Spec No 1**: R17-R29 [PMID: 16651366 DOI: 10.1093/hmg/ddl046]
- 18 **ENCODE Project Consortium..** An integrated encyclopedia of DNA elements in the human genome. *Nature* 2012; **489**: 57-74 [PMID: 22955616 DOI: 10.1038/nature11247]

- 19 **Djebali S**, Davis CA, Merkel A, Dobin A, Lassmann T, Mortazavi A, Tanzer A, Lagarde J, Lin W, Schlesinger F, Xue C, Marinov GK, Khatun J, Williams BA, Zaleski C, Rozowsky J, Röder M, Kokocinski F, Abdelhamid RF, Alioto T, Antoshechkin I, Baer MT, Bar NS, Batut P, Bell K, Bell I, Chakraborty S, Chen X, Chrast J, Curado J, Derrien T, Drenkow J, Dumais E, Dumais J, Duttagupta R, Falconnet E, Fastuca M, Fejes-Toth K, Ferreira P, Foissac S, Fullwood MJ, Gao H, Gonzalez D, Gordon A, Gunawardena H, Howald C, Jha S, Johnson R, Kapranov P, King B, Kingswood C, Luo OJ, Park E, Persaud K, Preall JB, Ribeca P, Risk B, Robyr D, Sammeth M, Schaffer L, See LH, Shahab A, Skancke J, Suzuki AM, Takahashi H, Tilgner H, Trout D, Walters N, Wang H, Wrobel J, Yu Y, Ruan X, Hayashizaki Y, Harrow J, Gerstein M, Hubbard T, Reymond A, Antonarakis SE, Hannon G, Giddings MC, Ruan Y, Wold B, Carninci P, Guigó R, Gingeras TR. Landscape of transcription in human cells. *Nature* 2012; **489**: 101-108 [PMID: 22955620 DOI: 10.1038/nature11233]
- 20 **Adams BD**, Parsons C, Walker L, Zhang WC, Slack FJ. Targeting noncoding RNAs in disease. *J Clin Invest* 2017; **127**: 761-771 [PMID: 28248199 DOI: 10.1172/JCI84424]
- 21 **Yamamura S**, Imai-Sumida M, Tanaka Y, Dahiya R. Interaction and cross-talk between non-coding RNAs. *Cell Mol Life Sci* 2018; **75**: 467-484 [PMID: 28840253 DOI: 10.1007/s00018-017-2626-6]
- 22 **Ganguly N**, Chakrabarti S. Role of long non-coding RNAs and related epigenetic mechanisms in liver fibrosis (Review). *Int J Mol Med* 2021; **47** [PMID: 33495817 DOI: 10.3892/ijmm.2021.4856]
- 23 **Khalifa O**, Errafii K, Al-Akl NS, Arredouani A. Noncoding RNAs in Nonalcoholic Fatty Liver Disease: Potential Diagnosis and Prognosis Biomarkers. *Dis Markers* 2020; **2020**: 8822859 [PMID: 33133304 DOI: 10.1155/2020/8822859]
- 24 **Gim JA**, Bang SM, Lee YS, Lee Y, Yim SY, Jung YK, Kim H, Kim BH, Kim JH, Seo YS, Yim HJ, Yeon JE, Um SH, Byun KS. Evaluation of the severity of nonalcoholic fatty liver disease through analysis of serum exosomal miRNA expression. *PLoS One* 2021; **16**: e0255822 [PMID: 34358264 DOI: 10.1371/journal.pone.0255822]

- 25 **Szabo G**, Csak T. Role of MicroRNAs in NAFLD/NASH. *Dig Dis Sci* 2016; **61**: 1314-1324 [PMID: 26769057 DOI: 10.1007/s10620-015-4002-4]
- 26 **O'Brien J**, Hayder H, Zayed Y, Peng C. Overview of MicroRNA Biogenesis, Mechanisms of Actions, and Circulation. *Front Endocrinol (Lausanne)* 2018; **9**: 402 [PMID: 30123182 DOI: 10.3389/fendo.2018.00402]
- 27 **Friedman RC**, Farh KK, Burge CB, Bartel DP. Most mammalian mRNAs are conserved targets of microRNAs. *Genome Res* 2009; **19**: 92-105 [PMID: 18955434 DOI: 10.1101/gr.082701.108]
- 28 **Mahmoudi A**, Butler AE, Jamialahmadi T, Sahebkar A. The role of exosomal miRNA in nonalcoholic fatty liver disease. *J Cell Physiol* 2022; **237**: 2078-2094 [PMID: 35137416 DOI: 10.1002/jcp.30699]
- 29 **Ji C**, Guo X. The clinical potential of circulating microRNAs in obesity. *Nat Rev Endocrinol* 2019; **15**: 731-743 [PMID: 31611648 DOI: 10.1038/s41574-019-0260-0]
- 30 **Hajri T**, Zaiou M, Fungwe TV, Ouguerram K, Besong S. Epigenetic Regulation of Peroxisome Proliferator-Activated Receptor Gamma Mediates High-Fat Diet-Induced Non-Alcoholic Fatty Liver Disease. *Cells* 2021; **10** [PMID: 34072832 DOI: 10.3390/cells10061355]
- 31 **Lin HY**, Yang YL, Wang PW, Wang FS, Huang YH. The Emerging Role of MicroRNAs in NAFLD: Highlight of MicroRNA-29a in Modulating Oxidative Stress, Inflammation, and Beyond. *Cells* 2020; **9** [PMID: 32331364 DOI: 10.3390/cells9041041]
- 32 **Liu CH**, Ampuero J, Gil-Gómez A, Montero-Vallejo R, Rojas Á, Muñoz-Hernández R, Gallego-Durán R, Romero-Gómez M. miRNAs in patients with non-alcoholic fatty liver disease: A systematic review and meta-analysis. *J Hepatol* 2018; **69**: 1335-1348 [PMID: 30142428 DOI: 10.1016/j.jhep.2018.08.008]
- 33 **Gjorgjieva M**, Sobolewski C, Dolicka D, Correia de Sousa M, Foti M. miRNAs and NAFLD: from pathophysiology to therapy. *Gut* 2019; **68**: 2065-2079 [PMID: 31300518 DOI: 10.1136/gutjnl-2018-318146]

- 34 **Arner P**, Kulyté A. MicroRNA regulatory networks in human adipose tissue and obesity. *Nat Rev Endocrinol* 2015; **11**: 276-288 [PMID: 25732520 DOI: 10.1038/nrendo.2015.25]
- 35 **Sobolewski C**, Calo N, Portius D, Foti M. MicroRNAs in fatty liver disease. *Semin Liver Dis* 2015; **35**: 12-25 [PMID: 25632931 DOI: 10.1055/s-0034-1397345]
- 36 **Dongiovanni P**, Meroni M, Longo M, Fargion S, Fracanzani AL. miRNA Signature in NAFLD: A Turning Point for a Non-Invasive Diagnosis. *Int J Mol Sci* 2018; **19** [PMID: 30544653 DOI: 10.3390/ijms19123966]
- 37 **Arrese M**, Eguchi A, Feldstein AE. Circulating microRNAs: emerging biomarkers of liver disease. *Semin Liver Dis* 2015; **35**: 43-54 [PMID: 25632934 DOI: 10.1055/s-0034-1397348]
- 38 **Zhang T**, Yang Z, Kusumanchi P, Han S, Liangpunsakul S. Critical Role of microRNA-21 in the Pathogenesis of Liver Diseases. *Front Med (Lausanne)* 2020; **7**: 7 [PMID: 32083086 DOI: 10.3389/fmed.2020.00007]
- 39 **Dattaroy D**, Pourhoseini S, Das S, Alhasson F, Seth RK, Nagarkatti M, Michelotti GA, Diehl AM, Chatterjee S. Micro-RNA 21 inhibition of SMAD7 enhances fibrogenesis via leptin-mediated NADPH oxidase in experimental and human nonalcoholic steatohepatitis. *Am J Physiol Gastrointest Liver Physiol* 2015; **308**: G298-G312 [PMID: 25501551 DOI: 10.1152/ajpgi.00346.2014]
- 40 **Loyer X**, Paradis V, Hénique C, Vion AC, Colnot N, Guerin CL, Devue C, On S, Scetbun J, Romain M, Paul JL, Rothenberg ME, Marcellin P, Durand F, Bedossa P, Prip-Buus C, Baugé E, Staels B, Boulanger CM, Tedgui A, Rautou PE. Liver microRNA-21 is overexpressed in non-alcoholic steatohepatitis and contributes to the disease in experimental models by inhibiting PPAR $\alpha$  expression. *Gut* 2016; **65**: 1882-1894 [PMID: 26338827 DOI: 10.1136/gutjnl-2014-308883]
- 41 **Pillai SS**, Lakhani HV, Zehra M, Wang J, Dilip A, Puri N, O'Hanlon K, Sodhi K. Predicting Nonalcoholic Fatty Liver Disease through a Panel of Plasma Biomarkers and MicroRNAs in Female West Virginia Population. *Int J Mol Sci* 2020; **21** [PMID: 32933141 DOI: 10.3390/ijms21186698]



- 42 **Becker PP**, Rau M, Schmitt J, Malsch C, Hammer C, Bantel H, Müllhaupt B, Geier A. Performance of Serum microRNAs -122, -192 and -21 as Biomarkers in Patients with Non-Alcoholic Steatohepatitis. *PLoS One* 2015; **10**: e0142661 [PMID: 26565986 DOI: 10.1371/journal.pone.0142661]
- 43 **Pawlak M**, Lefebvre P, Staels B. Molecular mechanism of PPAR $\alpha$  action and its impact on lipid metabolism, inflammation and fibrosis in non-alcoholic fatty liver disease. *J Hepatol* 2015; **62**: 720-733 [PMID: 25450203 DOI: 10.1016/j.jhep.2014.10.039]
- 44 **Calo N**, Ramadori P, Sobolewski C, Romero Y, Maeder C, Fournier M, Rantakari P, Zhang FP, Poutanen M, Dufour JF, Humar B, Nef S, Foti M. Stress-activated *miR-21/miR-21\** in hepatocytes promotes lipid and glucose metabolic disorders associated with high-fat diet consumption. *Gut* 2016; **65**: 1871-1881 [PMID: 27222533 DOI: 10.1136/gutjnl-2015-310822]
- 45 **Rodrigues PM**, Afonso MB, Simão AL, Carvalho CC, Trindade A, Duarte A, Borralho PM, Machado MV, Cortez-Pinto H, Rodrigues CM, Castro RE. miR-21 ablation and obeticholic acid ameliorate nonalcoholic steatohepatitis in mice. *Cell Death Dis* 2017; **8**: e2748 [PMID: 28406477 DOI: 10.1038/cddis.2017.172]
- 46 **Wu H**, Ng R, Chen X, Steer CJ, Song G. MicroRNA-21 is a potential link between non-alcoholic fatty liver disease and hepatocellular carcinoma via modulation of the HBP1-p53-Srebp1c pathway. *Gut* 2016; **65**: 1850-1860 [PMID: 26282675 DOI: 10.1136/gutjnl-2014-308430]
- 47 **Sun C**, Huang F, Liu X, Xiao X, Yang M, Hu G, Liu H, Liao L. miR-21 regulates triglyceride and cholesterol metabolism in non-alcoholic fatty liver disease by targeting HMGCR. *Int J Mol Med* 2015; **35**: 847-853 [PMID: 25605429 DOI: 10.3892/ijmm.2015.2076]
- 48 **Meng F**, Henson R, Wehbe-Janek H, Ghoshal K, Jacob ST, Patel T. MicroRNA-21 regulates expression of the PTEN tumor suppressor gene in human hepatocellular cancer. *Gastroenterology* 2007; **133**: 647-658 [PMID: 17681183 DOI: 10.1053/j.gastro.2007.05.022]

- 49 **Wang XM**, Wang XY, Huang YM, Chen X, Lü MH, Shi L, Li CP. Role and mechanisms of action of microRNA-21 as regards the regulation of the WNT/ $\beta$ -catenin signaling pathway in the pathogenesis of non-alcoholic fatty liver disease. *Int J Mol Med* 2019; **44**: 2201-2212 [PMID: 31638173 DOI: 10.3892/ijmm.2019.4375]
- 50 **Zhao W**, Cheng L, Quek C, Bellingham SA, Hill AF. Novel miR-29b target regulation patterns are revealed in two different cell lines. *Sci Rep* 2019; **9**: 17449 [PMID: 31767948 DOI: 10.1038/s41598-019-53868-x]
- 51 **Kriegel AJ**, Liu Y, Fang Y, Ding X, Liang M. The miR-29 family: genomics, cell biology, and relevance to renal and cardiovascular injury. *Physiol Genomics* 2012; **44**: 237-244 [PMID: 22214600 DOI: 10.1152/physiolgenomics.00141.2011]
- 52 **Roderburg C**, Urban GW, Bettermann K, Vucur M, Zimmermann H, Schmidt S, Janssen J, Koppe C, Knolle P, Castoldi M, Tacke F, Trautwein C, Luedde T. Micro-RNA profiling reveals a role for miR-29 in human and murine liver fibrosis. *Hepatology* 2011; **53**: 209-218 [PMID: 20890893 DOI: 10.1002/hep.23922]
- 53 **Jampoka K**, Muangpaisarn P, Khongnomnan K, Treeprasertsuk S, Tangkijvanich P, Payungporn S. Serum miR-29a and miR-122 as Potential Biomarkers for Non-Alcoholic Fatty Liver Disease (NAFLD). *Microna* 2018; **7**: 215-222 [PMID: 29848284 DOI: 10.2174/2211536607666180531093302]
- 54 **Huang C**, Zheng JM, Cheng Q, Yu KK, Ling QX, Chen MQ, Li N. Serum microRNA-29 levels correlate with disease progression in patients with chronic hepatitis B virus infection. *J Dig Dis* 2014; **15**: 614-621 [PMID: 25138057 DOI: 10.1111/1751-2980.12185]
- 55 **Lambrecht J**, Verhulst S, Reynaert H, van Grunsven LA. The miRFIB-Score: A Serological miRNA-Based Scoring Algorithm for the Diagnosis of Significant Liver Fibrosis. *Cells* 2019; **8** [PMID: 31470644 DOI: 10.3390/cells8091003]
- 56 **López-Riera M**, Conde I, Tolosa L, Zaragoza Á, Castell JV, Gómez-Lechón MJ, Jover R. New microRNA Biomarkers for Drug-Induced Steatosis and Their Potential to Predict the Contribution of Drugs to Non-alcoholic Fatty Liver Disease. *Front Pharmacol* 2017; **8**: 3 [PMID: 28179883 DOI: 10.3389/fphar.2017.00003]

- 57 **Yang YL**, Kuo HC, Wang FS, Huang YH. MicroRNA-29a Disrupts DNMT3b to Ameliorate Diet-Induced Non-Alcoholic Steatohepatitis in Mice. *Int J Mol Sci* 2019; **20** [PMID: 30917489 DOI: 10.3390/ijms20061499]
- 58 **Mattis AN**, Song G, Hitchner K, Kim RY, Lee AY, Sharma AD, Malato Y, McManus MT, Esau CC, Koller E, Koliwad S, Lim LP, Maher JJ, Raffai RL, Willenbring H. A screen in mice uncovers repression of lipoprotein lipase by microRNA-29a as a mechanism for lipid distribution away from the liver. *Hepatology* 2015; **61**: 141-152 [PMID: 25131933 DOI: 10.1002/hep.27379]
- 59 **Yang YL**, Wang PW, Wang FS, Lin HY, Huang YH. miR-29a Modulates GSK3 $\beta$ /SIRT1-Linked Mitochondrial Proteostatic Stress to Ameliorate Mouse Non-Alcoholic Steatohepatitis. *Int J Mol Sci* 2020; **21** [PMID: 32961796 DOI: 10.3390/ijms21186884]
- 60 **Najafi-Shoushtari SH**, Kristo F, Li Y, Shioda T, Cohen DE, Gerszten RE, Näär AM. MicroRNA-33 and the SREBP host genes cooperate to control cholesterol homeostasis. *Science* 2010; **328**: 1566-1569 [PMID: 20466882 DOI: 10.1126/science.1189123]
- 61 **Price NL**, Singh AK, Rotllan N, Goedeke L, Wing A, Canfrán-Duque A, Diaz-Ruiz A, Araldi E, Baldán Á, Camporez JP, Suárez Y, Rodeheffer MS, Shulman GI, de Cabo R, Fernández-Hernando C. Genetic Ablation of miR-33 Increases Food Intake, Enhances Adipose Tissue Expansion, and Promotes Obesity and Insulin Resistance. *Cell Rep* 2018; **22**: 2133-2145 [PMID: 29466739 DOI: 10.1016/j.celrep.2018.01.074]
- 62 **Lendvai G**, Jármai K, Karácsony G, Halász T, Kovalszky I, Baghy K, Wittmann T, Schaff Z, Kiss A. Elevated miR-33a and miR-224 in steatotic chronic hepatitis C liver biopsies. *World J Gastroenterol* 2014; **20**: 15343-15350 [PMID: 25386083 DOI: 10.3748/wjg.v20.i41.15343]
- 63 **Erhartova D**, Cahova M, Dankova H, Heczkova M, Mikova I, Sticova E, Spicak J, Seda O, Trunecka P. Serum miR-33a is associated with steatosis and inflammation in patients with non-alcoholic fatty liver disease after liver transplantation. *PLoS One* 2019; **14**: e0224820 [PMID: 31703079 DOI: 10.1371/journal.pone.0224820]

- 64 **Vega-Badillo J**, Gutiérrez-Vidal R, Hernández-Pérez HA, Villamil-Ramírez H, León-Mimila P, Sánchez-Muñoz F, Morán-Ramos S, Larrieta-Carrasco E, Fernández-Silva I, Méndez-Sánchez N, Tovar AR, Campos-Pérez F, Villarreal-Molina T, Hernández-Pando R, Aguilar-Salinas CA, Canizales-Quinteros S. Hepatic miR-33a/miR-144 and their target gene ABCA1 are associated with steatohepatitis in morbidly obese subjects. *Liver Int* 2016; **36**: 1383-1391 [PMID: 26945479 DOI: 10.1111/liv.13109]
- 65 **Pan JH**, Cha H, Tang J, Lee S, Lee SH, Le B, Redding MC, Kim S, Batish M, Kong BC, Lee JH, Kim JK. The role of microRNA-33 as a key regulator in hepatic lipogenesis signaling and a potential serological biomarker for NAFLD with excessive dietary fructose consumption in C57BL/6N mice. *Food Funct* 2021; **12**: 656-667 [PMID: 33404569 DOI: 10.1039/d0fo02286a]
- 66 **Rayner KJ**, Esau CC, Hussain FN, McDaniel AL, Marshall SM, van Gils JM, Ray TD, Sheedy FJ, Goedeke L, Liu X, Khatsenko OG, Kaimal V, Lees CJ, Fernandez-Hernando C, Fisher EA, Temel RE, Moore KJ. Inhibition of miR-33a/b in non-human primates raises plasma HDL and lowers VLDL triglycerides. *Nature* 2011; **478**: 404-407 [PMID: 22012398 DOI: 10.1038/nature10486]
- 67 **Rotllan N**, Ramírez CM, Aryal B, Esau CC, Fernández-Hernando C. Therapeutic silencing of microRNA-33 inhibits the progression of atherosclerosis in *Ldlr*<sup>-/-</sup> mice--brief report. *Arterioscler Thromb Vasc Biol* 2013; **33**: 1973-1977 [PMID: 23702658 DOI: 10.1161/ATVBAHA.113.301732]
- 68 **Karunakaran D**, Richards L, Geoffrion M, Barrette D, Gotfrit RJ, Harper ME, Rayner KJ. Therapeutic Inhibition of miR-33 Promotes Fatty Acid Oxidation but Does Not Ameliorate Metabolic Dysfunction in Diet-Induced Obesity. *Arterioscler Thromb Vasc Biol* 2015; **35**: 2536-2543 [PMID: 26427794 DOI: 10.1161/ATVBAHA.115.306404]
- 69 **Goedeke L**, Salerno A, Ramírez CM, Guo L, Allen RM, Yin X, Langley SR, Esau C, Wanschel A, Fisher EA, Suárez Y, Baldán A, Mayr M, Fernández-Hernando C. Long-term therapeutic silencing of miR-33 increases circulating triglyceride levels and hepatic lipid accumulation in mice. *EMBO Mol Med* 2014; **6**: 1133-1141 [PMID: 25038053 DOI: 10.15252/emmm.201404046]

- 70 **Allen RM**, Marquart TJ, Jesse JJ, Baldán A. Control of very low-density lipoprotein secretion by N-ethylmaleimide-sensitive factor and miR-33. *Circ Res* 2014; **115**: 10-22 [PMID: 24753547 DOI: 10.1161/CIRCRESAHA.115.303100]
- 71 **Horie T**, Nishino T, Baba O, Kuwabara Y, Nakao T, Nishiga M, Usami S, Izuhara M, Sowa N, Yahagi N, Shimano H, Matsumura S, Inoue K, Marusawa H, Nakamura T, Hasegawa K, Kume N, Yokode M, Kita T, Kimura T, Ono K. MicroRNA-33 regulates sterol regulatory element-binding protein 1 expression in mice. *Nat Commun* 2013; **4**: 2883 [PMID: 24300912 DOI: 10.1038/ncomms3883]
- 72 **Cheung O**, Puri P, Eicken C, Contos MJ, Mirshahi F, Maher JW, Kellum JM, Min H, Luketic VA, Sanyal AJ. Nonalcoholic steatohepatitis is associated with altered hepatic MicroRNA expression. *Hepatology* 2008; **48**: 1810-1820 [PMID: 19030170 DOI: 10.1002/hep.22569]
- 73 **Xu Y**, Zalzal M, Xu J, Li Y, Yin L, Zhang Y. A metabolic stress-inducible miR-34a-HNF4 $\alpha$  pathway regulates lipid and lipoprotein metabolism. *Nat Commun* 2015; **6**: 7466 [PMID: 26100857 DOI: 10.1038/ncomms8466]
- 74 **Miyaaki H**, Ichikawa T, Kamo Y, Taura N, Honda T, Shibata H, Milazzo M, Fornari F, Gramantieri L, Bolondi L, Nakao K. Significance of serum and hepatic microRNA-122 levels in patients with non-alcoholic fatty liver disease. *Liver Int* 2014; **34**: e302-e307 [PMID: 24313922 DOI: 10.1111/liv.12429]
- 75 **Ding J**, Li M, Wan X, Jin X, Chen S, Yu C, Li Y. Effect of miR-34a in regulating steatosis by targeting PPAR $\alpha$  expression in nonalcoholic fatty liver disease. *Sci Rep* 2015; **5**: 13729 [PMID: 26330104 DOI: 10.1038/srep13729]
- 76 **Simão AL**, Afonso MB, Rodrigues PM, Gama-Carvalho M, Machado MV, Cortez-Pinto H, Rodrigues CMP, Castro RE. Skeletal muscle miR-34a/SIRT1:AMPK axis is activated in experimental and human non-alcoholic steatohepatitis. *J Mol Med (Berl)* 2019; **97**: 1113-1126 [PMID: 31139863 DOI: 10.1007/s00109-019-01796-8]
- 77 **Ezaz G**, Trivedi HD, Connelly MA, Filozof C, Howard K, L Parrish M, Kim M, Herman MA, Nasser I, Afdhal NH, Jiang ZG, Lai M. Differential Associations of



Circulating MicroRNAs With Pathogenic Factors in NAFLD. *Hepatol Commun* 2020; **4**: 670-680 [PMID: 32363318 DOI: 10.1002/hep4.1501]

78 **Salvoza NC**, Klinzing DC, Gopez-Cervantes J, Bacilig MO. Association of Circulating Serum miR-34a and miR-122 with Dyslipidemia among Patients with Non-Alcoholic Fatty Liver Disease. *PLoS One* 2016; **11**: e0153497 [PMID: 27077736 DOI: 10.1371/journal.pone.0153497]

79 **Oses M**, Margareto Sanchez J, Portillo MP, Aguilera CM, Labayen I. Circulating miRNAs as Biomarkers of Obesity and Obesity-Associated Comorbidities in Children and Adolescents: A Systematic Review. *Nutrients* 2019; **11** [PMID: 31783635 DOI: 10.3390/nu11122890]

80 **Pirola CJ**, Fernández Gianotti T, Castaño GO, Mallardi P, San Martino J, Mora Gonzalez Lopez Ledesma M, Flichman D, Mirshahi F, Sanyal AJ, Sookoian S. Circulating microRNA signature in non-alcoholic fatty liver disease: from serum non-coding RNAs to liver histology and disease pathogenesis. *Gut* 2015; **64**: 800-812 [PMID: 24973316 DOI: 10.1136/gutjnl-2014-306996]

81 **Hsu SH**, Wang B, Kota J, Yu J, Costinean S, Kutay H, Yu L, Bai S, La Perle K, Chivukula RR, Mao H, Wei M, Clark KR, Mendell JR, Caligiuri MA, Jacob ST, Mendell JT, Ghoshal K. Essential metabolic, anti-inflammatory, and anti-tumorigenic functions of miR-122 in liver. *J Clin Invest* 2012; **122**: 2871-2883 [PMID: 22820288 DOI: 10.1172/JCI63539]

82 **Krützfeldt J**, Rajewsky N, Braich R, Rajeev KG, Tuschl T, Manoharan M, Stoffel M. Silencing of microRNAs in vivo with 'antagomirs'. *Nature* 2005; **438**: 685-689 [PMID: 16258535 DOI: 10.1038/nature04303]

83 **Esau C**, Davis S, Murray SF, Yu XX, Pandey SK, Pear M, Watts L, Booten SL, Graham M, McKay R, Subramaniam A, Propp S, Lollo BA, Freier S, Bennett CF, Bhanot S, Monia BP. miR-122 regulation of lipid metabolism revealed by in vivo antisense targeting. *Cell Metab* 2006; **3**: 87-98 [PMID: 16459310 DOI: 10.1016/j.cmet.2006.01.005]

84 **Tsai WC**, Hsu SD, Hsu CS, Lai TC, Chen SJ, Shen R, Huang Y, Chen HC, Lee CH, Tsai TF, Hsu MT, Wu JC, Huang HD, Shiao MS, Hsiao M, Tsou AP. MicroRNA-122

plays a critical role in liver homeostasis and hepatocarcinogenesis. *J Clin Invest* 2012; **122**: 2884-2897 [PMID: 22820290 DOI: 10.1172/JCI63455]

85 **Cermelli S**, Ruggieri A, Marrero JA, Ioannou GN, Beretta L. Circulating microRNAs in patients with chronic hepatitis C and non-alcoholic fatty liver disease. *PLoS One* 2011; **6**: e23937 [PMID: 21886843 DOI: 10.1371/journal.pone.0023937]

86 **Pirola CJ**, Gianotti TF, Castaño GO, Sookoian S. Circulating MicroRNA-122 signature in nonalcoholic fatty liver disease and cardiovascular disease: a new endocrine system in metabolic syndrome. *Hepatology* 2013; **57**: 2545-2547 [PMID: 23111985 DOI: 10.1002/hep.26116]

87 **Jones A**, Danielson KM, Benton MC, Ziegler O, Shah R, Stubbs RS, Das S, Macartney-Coxson D. miRNA Signatures of Insulin Resistance in Obesity. *Obesity (Silver Spring)* 2017; **25**: 1734-1744 [PMID: 28834285 DOI: 10.1002/oby.21950]

88 **Willeit P**, Skrobilin P, Moschen AR, Yin X, Kaudewitz D, Zampetaki A, Barwari T, Whitehead M, Ramírez CM, Goedeke L, Rotllan N, Bonora E, Hughes AD, Santer P, Fernández-Hernando C, Tilg H, Willeit J, Kiechl S, Mayr M. Circulating MicroRNA-122 Is Associated With the Risk of New-Onset Metabolic Syndrome and Type 2 Diabetes. *Diabetes* 2017; **66**: 347-357 [PMID: 27899485 DOI: 10.2337/db16-0731]

89 **Gallo A**, Tandon M, Alevizos I, Illei GG. The majority of microRNAs detectable in serum and saliva is concentrated in exosomes. *PLoS One* 2012; **7**: e30679 [PMID: 22427800 DOI: 10.1371/journal.pone.0030679]

90 **Chen Y**, Siegel F, Kipschull S, Haas B, Fröhlich H, Meister G, Pfeifer A. miR-155 regulates differentiation of brown and beige adipocytes via a bistable circuit. *Nat Commun* 2013; **4**: 1769 [PMID: 23612310 DOI: 10.1038/ncomms2742]

91 **Chen JQ**, Papp G, Szodoray P, Zeher M. The role of microRNAs in the pathogenesis of autoimmune diseases. *Autoimmun Rev* 2016; **15**: 1171-1180 [PMID: 27639156 DOI: 10.1016/j.autrev.2016.09.003]

92 **Miller AM**, Gilchrist DS, Nijjar J, Araldi E, Ramirez CM, Lavery CA, Fernández-Hernando C, McInnes IB, Kurowska-Stolarska M. MiR-155 has a protective role in the

development of non-alcoholic hepatosteatosis in mice. *PLoS One* 2013; **8**: e72324 [PMID: 23991091 DOI: 10.1371/journal.pone.0072324]

93 **Lin X**, Jia J, Du T, Li W, Wang X, Wei J, Lin X, Zeng H, Yao L, Chen X, Zhuang J, Weng J, Liu Y, Lin J, Wu Q, Wang W, Yao K, Xu K, Xiao D. Overexpression of miR-155 in the liver of transgenic mice alters the expression profiling of hepatic genes associated with lipid metabolism. *PLoS One* 2015; **10**: e0118417 [PMID: 25799309 DOI: 10.1371/journal.pone.0118417]

94 **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 [PMID: 27832630 DOI: 10.1159/000447917]

95 **Csak T**, Bala S, Lippai D, Kodys K, Catalano D, Iracheta-Vellve A, Szabo G. MicroRNA-155 Deficiency Attenuates Liver Steatosis and Fibrosis without Reducing Inflammation in a Mouse Model of Steatohepatitis. *PLoS One* 2015; **10**: e0129251 [PMID: 26042593 DOI: 10.1371/journal.pone.0129251]

96 **Bala S**, Ganz M, Babuta M, Zhuang Y, Csak T, Calenda CD, Szabo G. 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 [PMID: 34453120 DOI: 10.1038/s41374-021-00626-1]

97 **Ying W**, Riopel M, Bandyopadhyay G, Dong Y, Birmingham A, Seo JB, Ofrecio JM, Wollam J, Hernandez-Carretero A, Fu W, Li P, Olefsky JM. Adipose Tissue Macrophage-Derived Exosomal miRNAs Can Modulate In Vivo and In Vitro Insulin Sensitivity. *Cell* 2017; **171**: 372-384.e12 [PMID: 28942920 DOI: 10.1016/j.cell.2017.08.035]

98 **Coll M**, El Taghdouini A, Perea L, Mannaerts I, Vila-Casadesús M, Blaya D, Rodrigo-Torres D, Affò S, Morales-Ibanez O, Graupera I, Lozano JJ, Najimi M, Sokal E, Lambrecht J, Ginès P, van Grunsven LA, Sancho-Bru P. Integrative miRNA and Gene Expression Profiling Analysis of Human Quiescent Hepatic Stellate Cells. *Sci Rep* 2015; **5**: 11549 [PMID: 26096707 DOI: 10.1038/srep11549]

- 99 **Tan Y**, Ge G, Pan T, Wen D, Gan J. A pilot study of serum microRNAs panel as potential biomarkers for diagnosis of nonalcoholic fatty liver disease. *PLoS One* 2014; **9**: e105192 [PMID: 25141008 DOI: 10.1371/journal.pone.0105192]
- 100 **Liu XL**, Pan Q, Cao HX, Xin FZ, Zhao ZH, Yang RX, Zeng J, Zhou H, Fan JG. 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 [PMID: 31782176 DOI: 10.1002/hep.31050]
- 101 **Wang X**, He Y, Mackowiak B, Gao B. MicroRNAs as regulators, biomarkers and therapeutic targets in liver diseases. *Gut* 2021; **70**: 784-795 [PMID: 33127832 DOI: 10.1136/gutjnl-2020-322526]
- 102 **Dumortier O**, Fabris G, Pisani DF, Casamento V, Gautier N, Hinault C, Lebrun P, Duranton C, Tauc M, Dalle S, Kerr-Conte J, Pattou F, Prentki M, Van Obberghen E. microRNA-375 regulates glucose metabolism-related signaling for insulin secretion. *J Endocrinol* 2020; **244**: 189-200 [PMID: 31697642 DOI: 10.1530/JOE-19-0180]
- 103 **Lei L**, Zhou C, Yang X, Li L. Down-regulation of microRNA-375 regulates adipokines and inhibits inflammatory cytokines by targeting AdipoR2 in non-alcoholic fatty liver disease. *Clin Exp Pharmacol Physiol* 2018; **45**: 819-831 [PMID: 29569260 DOI: 10.1111/1440-1681.12940]
- 104 **Quinn JJ**, Chang HY. Unique features of long non-coding RNA biogenesis and function. *Nat Rev Genet* 2016; **17**: 47-62 [PMID: 26666209 DOI: 10.1038/nrg.2015.10]
- 105 **Tsai MC**, Manor O, Wan Y, Mosammaparast N, Wang JK, Lan F, Shi Y, Segal E, Chang HY. Long noncoding RNA as modular scaffold of histone modification complexes. *Science* 2010; **329**: 689-693 [PMID: 20616235 DOI: 10.1126/science.1192002]
- 106 **Wang KC**, Chang HY. Molecular mechanisms of long noncoding RNAs. *Mol Cell* 2011; **43**: 904-914 [PMID: 21925379 DOI: 10.1016/j.molcel.2011.08.018]
- 107 **Huarte M**. The emerging role of lncRNAs in cancer. *Nat Med* 2015; **21**: 1253-1261 [PMID: 26540387 DOI: 10.1038/nm.3981]

- 108 **Giovarelli M**, Bucci G, Ramos A, Bordo D, Wilusz CJ, Chen CY, Puppo M, Briata P, Gherzi R. H19 long noncoding RNA controls the mRNA decay promoting function of KSRP. *Proc Natl Acad Sci U S A* 2014; **111**: E5023-E5028 [PMID: 25385579 DOI: 10.1073/pnas.1415098111]
- 109 **Li X**, Liu R. Long non-coding RNA H19 in the liver-gut axis: A diagnostic marker and therapeutic target for liver diseases. *Exp Mol Pathol* 2020; **115**: 104472 [PMID: 32454104 DOI: 10.1016/j.yexmp.2020.104472]
- 110 **Liu C**, Yang Z, Wu J, Zhang L, Lee S, Shin DJ, Tran M, Wang L. Long noncoding RNA H19 interacts with polypyrimidine tract-binding protein 1 to reprogram hepatic lipid homeostasis. *Hepatology* 2018; **67**: 1768-1783 [PMID: 29140550 DOI: 10.1002/hep.29654]
- 111 **Liu J**, Tang T, Wang GD, Liu B. LncRNA-H19 promotes hepatic lipogenesis by directly regulating miR-130a/PPAR $\gamma$  axis in non-alcoholic fatty liver disease. *Biosci Rep* 2019; **39** [PMID: 31064820 DOI: 10.1042/BSR20181722]
- 112 **Wang H**, Cao Y, Shu L, Zhu Y, Peng Q, Ran L, Wu J, Luo Y, Zuo G, Luo J, Zhou L, Shi Q, Weng Y, Huang A, He TC, Fan J. 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 [PMID: 31809000 DOI: 10.1111/jcmm.14818]
- 113 **Zhao XY**, Li S, Wang GX, Yu Q, Lin JD. A long noncoding RNA transcriptional regulatory circuit drives thermogenic adipocyte differentiation. *Mol Cell* 2014; **55**: 372-382 [PMID: 25002143 DOI: 10.1016/j.molcel.2014.06.004]
- 114 **Zhao XY**, Xiong X, Liu T, Mi L, Peng X, Rui C, Guo L, Li S, Li X, Lin JD. Long noncoding RNA licensing of obesity-linked hepatic lipogenesis and NAFLD pathogenesis. *Nat Commun* 2018; **9**: 2986 [PMID: 30061575 DOI: 10.1038/s41467-018-05383-2]
- 115 **Tang S**, Zhu W, Zheng F, Gui W, Zhang W, Lin X, Li H. The Long Noncoding RNA Blnc1 Protects Against Diet-Induced Obesity by Promoting Mitochondrial Function in White Fat. *Diabetes Metab Syndr Obes* 2020; **13**: 1189-1201 [PMID: 32368112 DOI: 10.2147/DMSO.S248692]



- 116 **Li D**, Cheng M, Niu Y, Chi X, Liu X, Fan J, Fan H, Chang Y, Yang W. Identification of a novel human long non-coding RNA that regulates hepatic lipid metabolism by inhibiting SREBP-1c. *Int J Biol Sci* 2017; **13**: 349-357 [PMID: 28367099 DOI: 10.7150/ijbs.16635]
- 117 **Hegele RA**. Plasma lipoproteins: genetic influences and clinical implications. *Nat Rev Genet* 2009; **10**: 109-121 [PMID: 19139765 DOI: 10.1038/nrg2481]
- 118 **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 [PMID: 26935028 DOI: 10.1038/srep22640]
- 119 **Leti F**, Legendre C, Still CD, Chu X, Petrick A, Gerhard GS, DiStefano JK. Altered expression of MALAT1 lncRNA in nonalcoholic steatohepatitis fibrosis regulates CXCL5 in hepatic stellate cells. *Transl Res* 2017; **190**: 25-39.e21 [PMID: 28993096 DOI: 10.1016/j.trsl.2017.09.001]
- 120 **Sookoian S**, Flichman D, Garaycoechea ME, San Martino J, Castaño GO, Pirola CJ. Metastasis-associated lung adenocarcinoma transcript 1 as a common molecular driver in the pathogenesis of nonalcoholic steatohepatitis and chronic immune-mediated liver damage. *Hepatol Commun* 2018; **2**: 654-665 [PMID: 29881817 DOI: 10.1002/hep4.1184]
- 121 **Lai MC**, Yang Z, Zhou L, Zhu QQ, Xie HY, Zhang F, Wu LM, Chen LM, Zheng SS. Long non-coding RNA MALAT-1 overexpression predicts tumor recurrence of hepatocellular carcinoma after liver transplantation. *Med Oncol* 2012; **29**: 1810-1816 [PMID: 21678027 DOI: 10.1007/s12032-011-0004-z]
- 122 **Konishi H**, Ichikawa D, Yamamoto Y, Arita T, Shoda K, Hiramoto H, Hamada J, Itoh H, Fujita Y, Komatsu S, Shiozaki A, Ikoma H, Ochiai T, Otsuji E. Plasma level of metastasis-associated lung adenocarcinoma transcript 1 is associated with liver damage and predicts development of hepatocellular carcinoma. *Cancer Sci* 2016; **107**: 149-154 [PMID: 26614531 DOI: 10.1111/cas.12854]
- 123 **Bu FT**, Wang A, Zhu Y, You HM, Zhang YF, Meng XM, Huang C, Li J. LncRNA NEAT1: Shedding light on mechanisms and opportunities in liver diseases. *Liver Int* 2020; **40**: 2612-2626 [PMID: 32745314 DOI: 10.1111/liv.14629]

- 124 **Wang X.** Down-regulation of lncRNA-NEAT1 alleviated the non-alcoholic fatty liver disease via mTOR/S6K1 signaling pathway. *J Cell Biochem* 2018; **119**: 1567-1574 [PMID: 28771824 DOI: 10.1002/jcb.26317]
- 125 **Fu X,** Zhu J, Zhang L, Shu J. Long non-coding RNA NEAT1 promotes steatosis via enhancement of estrogen receptor alpha-mediated AQP7 expression in HepG2 cells. *Artif Cells Nanomed Biotechnol* 2019; **47**: 1782-1787 [PMID: 31062612 DOI: 10.1080/21691401.2019.1604536]
- 126 **Chen X,** Tan XR, Li SJ, Zhang XX. LncRNA NEAT1 promotes hepatic lipid accumulation via regulating miR-146a-5p/ROCK1 in nonalcoholic fatty liver disease. *Life Sci* 2019; **235**: 116829 [PMID: 31484042 DOI: 10.1016/j.lfs.2019.116829]
- 127 **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 [PMID: 31957704 DOI: 10.1684/ecn.2019.0432]
- 128 **Zhang Z,** Wen H, Peng B, Weng J, Zeng F. Downregulated microRNA-129-5p by Long Non-coding RNA NEAT1 Upregulates PEG3 Expression to Aggravate Non-alcoholic Steatohepatitis. *Front Genet* 2020; **11**: 563265 [PMID: 33574830 DOI: 10.3389/fgene.2020.563265]
- 129 **Guo J,** Fang W, Sun L, Lu Y, Dou L, Huang X, Tang W, Yu L, Li J. Ultraconserved element uc.372 drives hepatic lipid accumulation by suppressing miR-195/miR4668 maturation. *Nat Commun* 2018; **9**: 612 [PMID: 29426937 DOI: 10.1038/s41467-018-03072-8]
- 130 **He Y,** Wu YT, Huang C, Meng XM, Ma TT, Wu BM, Xu FY, Zhang L, Lv XW, Li J. Inhibitory effects of long noncoding RNA MEG3 on hepatic stellate cells activation and liver fibrogenesis. *Biochim Biophys Acta* 2014; **1842**: 2204-2215 [PMID: 25201080 DOI: 10.1016/j.bbdis.2014.08.015]
- 131 **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 [PMID: 30711569 DOI: 10.1016/j.metabol.2019.01.018]

132 **Zou D**, Liu L, Zeng Y, Wang H, Dai D, Xu M. LncRNA MEG3 up-regulates SIRT6 by ubiquitinating EZH2 and alleviates nonalcoholic fatty liver disease. *Cell Death Discov* 2022; **8**: 103 [PMID: 35256601 DOI: 10.1038/s41420-022-00889-7]

133 **Zhang L**, Yang Z, Trottier J, Barbier O, Wang L. Long noncoding RNA MEG3 induces cholestatic liver injury by interaction with PTBP1 to facilitate shp mRNA decay. *Hepatology* 2017; **65**: 604-615 [PMID: 27770549 DOI: 10.1002/hep.28882]

134 **Cheng X**, Shihabudeen Haider Ali MS, Moran M, Viana MP, Schlichte SL, Zimmerman MC, Khalimonchuk O, Feinberg MW, Sun X. Long non-coding RNA Meg3 deficiency impairs glucose homeostasis and insulin signaling by inducing cellular senescence of hepatic endothelium in obesity. *Redox Biol* 2021; **40**: 101863 [PMID: 33508742 DOI: 10.1016/j.redox.2021.101863]

135 **Panzitt K**, Tschernatsch MM, Guelly C, Moustafa T, Stradner M, Strohmaier HM, Buck CR, Denk H, Schroeder R, Trauner M, Zatloukal K. Characterization of HULC, a novel gene with striking up-regulation in hepatocellular carcinoma, as noncoding RNA. *Gastroenterology* 2007; **132**: 330-342 [PMID: 17241883 DOI: 10.1053/j.gastro.2006.08.026]

136 **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 [PMID: 30908654 DOI: 10.1002/jcp.28450]

137 **Gandhy SU**, Imanirad P, Jin UH, Nair V, Hedrick E, Cheng Y, Corton JC, Kim K, Safe S. Specificity protein (Sp) transcription factors and metformin regulate expression of the long non-coding RNA HULC. *Oncotarget* 2015; **6**: 26359-26372 [PMID: 26317792 DOI: 10.18632/oncotarget.4560]

138 **Feng W**, Gao C, Bi Y, Wu M, Li P, Shen S, Chen W, Yin T, Zhu D. Randomized trial comparing the effects of gliclazide, liraglutide, and metformin on diabetes with non-alcoholic fatty liver disease. *J Diabetes* 2017; **9**: 800-809 [PMID: 28332301 DOI: 10.1111/1753-0407.12555]

- 139 **Li P**, Chen X, Lin M, Huang D. Up-regulated HOTAIR induced by fatty acids inhibits PTEN expression and increases triglycerides accumulation in HepG2 cells. *Food Nutr Res* 2017; **61**: 1412794 [DOI: 10.1080/16546628.2017.1412794]
- 140 **Guo B**, Cheng Y, Yao L, Zhang J, Lu J, Qi H, Chen H. LncRNA HOTAIR regulates the lipid accumulation in non-alcoholic fatty liver disease via miR-130b-3p/ROCK1 axis. *Cell Signal* 2022; **90**: 110190 [PMID: 34774989 DOI: 10.1016/j.cellsig.2021.110190]
- 141 **Yu F**, Chen B, Dong P, Zheng J. HOTAIR Epigenetically Modulates PTEN Expression via MicroRNA-29b: A Novel Mechanism in Regulation of Liver Fibrosis. *Mol Ther* 2017; **25**: 205-217 [PMID: 28129115 DOI: 10.1016/j.ymthe.2016.10.015]
- 142 **Chen Y**, Huang H, Xu C, Yu C, Li Y. Long Non-Coding RNA Profiling in a Non-Alcoholic Fatty Liver Disease Rodent Model: New Insight into Pathogenesis. *Int J Mol Sci* 2017; **18** [PMID: 28275212 DOI: 10.3390/ijms18010021]
- 143 **Chen Y**, Chen X, Gao J, Xu C, Xu P, Li Y, Zhu Y, Yu C. Long noncoding RNA FLRL2 alleviated nonalcoholic fatty liver disease through Arntl-Sirt1 pathway. *FASEB J* 2019; **33**: 11411-11419 [PMID: 31311301 DOI: 10.1096/fj.201900643RRR]
- 144 **Wu YL**, Li HF, Chen HH, Lin H. Emergent Roles of Circular RNAs in Metabolism and Metabolic Disorders. *Int J Mol Sci* 2022; **23** [PMID: 35162956 DOI: 10.3390/ijms23031032]
- 145 **Zaiou M**. The Emerging Role and Promise of Circular RNAs in Obesity and Related Metabolic Disorders. *Cells* 2020; **9** [PMID: 32560220 DOI: 10.3390/cells9061473]
- 146 **Xu ZX**, Li JZ, Li Q, Xu MY, Li HY. CircRNA608-microRNA222-PINK1 axis regulates the mitophagy of hepatic stellate cells in NASH related fibrosis. *Biochem Biophys Res Commun* 2022; **610**: 35-42 [PMID: 35436629 DOI: 10.1016/j.bbrc.2022.04.008]
- 147 **Jin X**, Gao J, Zheng R, Yu M, Ren Y, Yan T, Huang Y, Li Y. Antagonizing circRNA\_002581-miR-122-CPEB1 axis alleviates NASH through restoring PTEN-AMPK-mTOR pathway regulated autophagy. *Cell Death Dis* 2020; **11**: 123 [PMID: 32054840 DOI: 10.1038/s41419-020-2293-7]

- 148 **Guo XY**, Chen JN, Sun F, Wang YQ, Pan Q, Fan JG. circRNA\_0046367 Prevents Hepatotoxicity of Lipid Peroxidation: An Inhibitory Role against Hepatic Steatosis. *Oxid Med Cell Longev* 2017; **2017**: 3960197 [PMID: 29018509 DOI: 10.1155/2017/3960197]
- 149 **Guo XY**, Sun F, Chen JN, Wang YQ, Pan Q, Fan JG. circRNA\_0046366 inhibits hepatocellular steatosis by normalization of PPAR signaling. *World J Gastroenterol* 2018; **24**: 323-337 [PMID: 29391755 DOI: 10.3748/wjg.v24.i3.323]
- 150 **Guo XY**, He CX, Wang YQ, Sun C, Li GM, Su Q, Pan Q, Fan JG. Circular RNA Profiling and Bioinformatic Modeling Identify Its Regulatory Role in Hepatic Steatosis. *Biomed Res Int* 2017; **2017**: 5936171 [PMID: 28717649 DOI: 10.1155/2017/5936171]
- 151 **Li P**, Shan K, Liu Y, Zhang Y, Xu L, Xu L. CircScd1 Promotes Fatty Liver Disease via the Janus Kinase 2/Signal Transducer and Activator of Transcription 5 Pathway. *Dig Dis Sci* 2019; **64**: 113-122 [PMID: 30259280 DOI: 10.1007/s10620-018-5290-2]
- 152 **Yang W**, Zhao J, Zhao Y, Li W, Zhao L, Ren Y, Ou R, Xu Y. 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 [PMID: 33221744 DOI: 10.18632/aging.104081]
- 153 **Ou Q**, Zhao Y, Zhou J, Wu X. Comprehensive circular RNA expression profiles in a mouse model of nonalcoholic steatohepatitis. *Mol Med Rep* 2019; **19**: 2636-2648 [PMID: 30720095 DOI: 10.3892/mmr.2019.9935]
- 154 **Chen Y**, Yuan B, Wu Z, Dong Y, Zhang L, Zeng Z. Microarray profiling of circular RNAs and the potential regulatory role of hsa\_circ\_0071410 in the activated human hepatic stellate cell induced by irradiation. *Gene* 2017; **629**: 35-42 [PMID: 28774651 DOI: 10.1016/j.gene.2017.07.078]
- 155 **Zhou Y**, Lv X, Qu H, Zhao K, Fu L, Zhu L, Ye G, Guo J. Preliminary screening and functional analysis of circular RNAs associated with hepatic stellate cell activation. *Gene* 2018; **677**: 317-323 [PMID: 30118889 DOI: 10.1016/j.gene.2018.08.052]
- 156 **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 [PMID: 34446693 DOI: 10.1038/s41419-021-04090-z]



- 157 **Zhao Q**, Liu J, Deng H, Ma R, Liao JY, Liang H, Hu J, Li J, Guo Z, Cai J, Xu X, Gao Z, Su S. Targeting Mitochondria-Located circRNA SCAR Alleviates NASH via Reducing mROS Output. *Cell* 2020; **183**: 76-93.e22 [PMID: 32931733 DOI: 10.1016/j.cell.2020.08.009]
- 158 **Liufu Z**, Zhao Y, Guo L, Miao G, Xiao J, Lyu Y, Chen Y, Shi S, Tang T, Wu CI. Redundant and incoherent regulations of multiple phenotypes suggest microRNAs' role in stability control. *Genome Res* 2017; **27**: 1665-1673 [PMID: 28904014 DOI: 10.1101/gr.222505.117]

# 20%

SIMILARITY INDEX

### PRIMARY SOURCES

1	<a href="http://www.ncbi.nlm.nih.gov">www.ncbi.nlm.nih.gov</a> Internet	348 words — 5%
2	<a href="http://www.mdpi.com">www.mdpi.com</a> Internet	130 words — 2%
3	<a href="http://www.wjgnet.com">www.wjgnet.com</a> Internet	88 words — 1%
4	<a href="http://link.springer.com">link.springer.com</a> Internet	70 words — 1%
5	<a href="http://Nutritionandmetabolism.biomedcentral.com">Nutritionandmetabolism.biomedcentral.com</a> Internet	63 words — 1%
6	Qiaozhu Su, Virender Kumar, Neetu Sud, Ram I. Mahato. "Role of MicroRNAs in the pathogenesis and treatment of progressive liver injury in NAFLD and liver fibrosis", Advanced Drug Delivery Reviews, 2018 Crossref	45 words — 1%
7	<a href="http://s3-eu-west-1.amazonaws.com">s3-eu-west-1.amazonaws.com</a> Internet	43 words — 1%
8	Guillermo Nahúm López-Sánchez, Mayra Dóminguez-Pérez, Misael Uribe, Norberto Carlos Chávez-Tapia et al. "Non-alcoholic fatty liver disease and	38 words — 1%

microRNAs expression, how it affects the development and progression of the disease", Annals of Hepatology, 2020

Crossref

9

[www.hindawi.com](http://www.hindawi.com)

Internet

36 words — 1%

10

Fang - tianang - tian Bu, Ao Wang, Yanan Zhu, Hong - mei You, Ya - fei Zhang, Xiao - ming Meng, Cheng Huang, Jun Li. " LncRNA : Shedding light on mechanisms and opportunities in liver diseases ", Liver International, 2020

Crossref

31 words — < 1%

11

Lei Lei, Chao Zhou, Xue Yang, Liangping Li. "Down-regulation of microRNA-375 regulates adipokines and inhibits inflammatory cytokines by targeting AdipoR2 in non-alcoholic fatty liver disease", Clinical and Experimental Pharmacology and Physiology, 2018

Crossref

31 words — < 1%

12

[ijbs.com](http://ijbs.com)

Internet

31 words — < 1%

13

[www.researchgate.net](http://www.researchgate.net)

Internet

28 words — < 1%

14

[www.tandfonline.com](http://www.tandfonline.com)

Internet

27 words — < 1%

15

[wjgnet.com](http://wjgnet.com)

Internet

26 words — < 1%

16

[www.nature.com](http://www.nature.com)

Internet

25 words — < 1%

17

[journals.plos.org](http://journals.plos.org)

Internet

23 words — < 1%

18 Denisa Erhartova, Monika Cahova, Helena Dankova, Marie Heczko et al. "Serum miR-33a is associated with steatosis and inflammation in patients with non-alcoholic fatty liver disease after liver transplantation", PLOS ONE, 2019

18 words — < 1%

Crossref

19 [www.science.gov](http://www.science.gov)

Internet

18 words — < 1%

20 [tgh.amegroups.com](http://tgh.amegroups.com)

Internet

17 words — < 1%

21 zengyuan zhou, Xue Zhao, Liang Chen, Yuzheng Li, Zhao Chen, Yuanyuan Wang, Zihao Zhou, Xia Chu. "Integrated analysis of differentially expressed long noncoding RNAs and mRNAs associated with high-fat diet-induced hepatic insulin resistance in mice", Research Square Platform LLC, 2020

17 words — < 1%

Crossref Posted Content

22 [cyberleninka.org](http://cyberleninka.org)

Internet

16 words — < 1%

23 Kai Lei, Lei Qu, Fangzhou Liu, Ninghui Hao, Jincheng Chen, Jian Liu, Aifu Lin. "Long non-coding RNAs regulate fatty acid and cholesterol metabolism", Genome Instability & Disease, 2022

15 words — < 1%

Crossref

24 [cancerres.aacrjournals.org](http://cancerres.aacrjournals.org)

Internet

15 words — < 1%

25 [coek.info](http://coek.info)

Internet

15 words — < 1%

26 [network.bepress.com](http://network.bepress.com)

15 words — &lt; 1%

[27 www.intechopen.com](http://www.intechopen.com)

Internet

15 words — &lt; 1%

28 Chune Liu, Zhihong Yang, Jianguo Wu, Li Zhang, Sangmin Lee, Dong-Ju Shin, Melanie Tran, Li Wang. "Long noncoding RNA H19 interacts with polypyrimidine tract-binding protein 1 to reprogram hepatic lipid homeostasis", *Hepatology*, 2018

Crossref

14 words — &lt; 1%

[29 journals.sagepub.com](http://journals.sagepub.com)

Internet

14 words — &lt; 1%

[30 mdpi.com](http://mdpi.com)

Internet

14 words — &lt; 1%

31 Jeong-An Gim, Soo Min Bang, Young-Sun Lee, Yoonseok Lee et al. "Evaluation of the severity of nonalcoholic fatty liver disease through analysis of serum exosomal miRNA expression", *PLOS ONE*, 2021

Crossref

13 words — &lt; 1%

32 Nie, Yu-Qiang, Jie Cao, Yong-Jian Zhou, Xia Liang, Yan-Lei Du, Yu-Jui Yvonne Wan, and Yu-Yuan Li. "The Effect of miRNA-122 in Regulating Fat Deposition in a Cell Line Model : miR-122 and fatty liver disease", *Journal of Cellular Biochemistry*, 2013.

Crossref

13 words — &lt; 1%

[33 coursepivot.com](http://coursepivot.com)

Internet

13 words — &lt; 1%

[34 www.frontiersin.org](http://www.frontiersin.org)

Internet

13 words — &lt; 1%



35	<a href="http://www.geneticsmr.com">www.geneticsmr.com</a> Internet	13 words — < 1 %
36	<a href="http://www.spandidos-publications.com">www.spandidos-publications.com</a> Internet	13 words — < 1 %
37	Charalampia Amerikanou, Efstathia Papada, Aristea Gioxari, Ilias Smyrnioudis et al. "Mastiha has efficacy in immune-mediated inflammatory diseases through a microRNA-155 Th17 dependent action", Pharmacological Research, 2021 Crossref	12 words — < 1 %
38	Coen van Solingen, Kaitlyn R. Scacalossi, Kathryn J. Moore. "Long noncoding RNAs in lipid metabolism", Current Opinion in Lipidology, 2018 Crossref	12 words — < 1 %
39	<a href="http://WWW.MDPI.COM">WWW.MDPI.COM</a> Internet	12 words — < 1 %
40	<a href="http://f6publishing.blob.core.windows.net">f6publishing.blob.core.windows.net</a> Internet	12 words — < 1 %
41	<a href="http://medworm.com">medworm.com</a> Internet	12 words — < 1 %
42	<a href="http://www.jscimedcentral.com">www.jscimedcentral.com</a> Internet	12 words — < 1 %
43	<a href="http://www.karger.com">www.karger.com</a> Internet	12 words — < 1 %
44	<a href="http://www.omicsonline.org">www.omicsonline.org</a> Internet	12 words — < 1 %

---

EXCLUDE QUOTES            ON

EXCLUDE BIBLIOGRAPHY   ON

EXCLUDE SOURCES           < 12 WORDS

EXCLUDE MATCHES           < 12 WORDS