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REVIEW

Role of microRNAs in alcohol-induced liver disorders and non-alcoholic fatty liver disease

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Abstract

MicroRNAs (miRNAs) are small non-coding RNAs that regulate multiple physiological and pathological functions through the modulation of gene expression at the post-transcriptional level. Accumulating evidence has established a role for miRNAs in the development and pathogenesis of liver disease. Specifically, a large number of studies have assessed the role of miRNAs

in alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD), two diseases that share common underlying mechanisms and pathological characteristics. The purpose of the current review is to summarize and update the body of literature investigating the role of miRNAs in liver disease. In addition, the potential use of miRNAs as biomarkers and/or therapeutic targets is discussed. Among all miRNAs analyzed, miR-34a, miR-122 and miR-155 are most involved in the pathogenesis of NAFLD. Of note, these three miRNAs have also been implicated in ALD, reinforcing a common disease mechanism between these two entities and the pleiotropic effects of specific miRNAs. Currently, no single miRNA or panel of miRNAs has been identified for the detection of, or staging of ALD or NAFLD. While promising results have been shown in murine models, no therapeutic based-miRNA agents have been developed for use in humans with liver disease.

Key words: Alcohol use disorder; Alcoholic liver disease; Non-alcoholic fatty liver disease; Steatosis; Obesity; miRNA; Biomarkers

Core tip: MicroRNAs (miRNAs) are small RNAs that regulate gene expression at a post-transcriptional level. Altered miRNA expression has been found in a variety of liver diseases, including non-alcoholic fatty liver disease and alcoholic liver disease. A group of miRNAs (miR-155, miR-122 and miR-34a) contributes to the pathogenesis of these two diseases and these miRNAs have potential use as biomarkers or therapeutic targets. Several technical limitations and a lack of clinical studies, however, preclude their clinical use.

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INTRODUCTION

MicroRNAs (miRNAs), small non-coding RNAs, can modulate gene expression at the post-transcriptional level by targeting messenger RNAs and inhibiting their translation or promoting their degradation[1,2]. Since the discovery of the first miRNA in 1993, lin-4[3], more than 2000 miRNAs have been described in humans and they are believed to regulate up to 60% of protein-coding genes in the human genome[4].

Human miRNAs are involved in virtually all physiological and pathological processes, including cell differentiation and proliferation, signal transduction, inflammation and immune response, metabolism, viral-host interaction, and oncogenesis[1,2]. The expression of a wide variety of miRNAs is potentially regulated by many factors, such as alcohol, but also diet, cigarette smoking and other drugs[5]. Therefore, it is not surprising that miRNAs have been increasingly recognized as key actors in the pathogenesis of a variety of diseases and as potential biomarkers for diagnosis or therapeutic targets[2]. The role of miRNAs in liver inflammation, fibrosis and cirrhosis has been widely described in the last twenty years[6-8]. The current paper reviews the existing literature pertaining to miRNA alteration, function, and the potential clinical application of miRNAs in alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD). While ALD and NAFLD differ in some aspects, they also share common features, including underlying mechanisms and clinical and histopathological characteristics[9]. Given the rapid expansion of research in miRNAs in recent years, an updated review on the topic will first be presented, followed by a summary of miRNA alterations that are common to both ALD and NAFLD.

ROLE OF MIRNAS IN ALD

Pathogenic role of miRNAs in ALD

The development of the different forms of ALD (steatosis, alcoholic hepatitis and cirrhosis) requires prolonged and heavy alcohol consumption along with susceptibility to the disease. Pathophysiological mechanisms of ALD are based both on the direct toxic effect of alcohol and also on ethanol-induced alterations in the inflammatory response[10]. A variety of enzymes, such as alcohol dehydrogenase (ADH) and the cytochrome P450 2E1 (CYP2E1), contribute to alcohol metabolism[11], leading to oxygen free radicals, nitric oxide and acetaldehyde, which ultimately can cause cellular damage and liver inflammation[12]. In addition, the toxic effect of acetaldehyde increases intestinal permeability to bacterial lipopolysaccharide (LPS)[13], which binds to toll-like receptors 4 (TLR4) and activates Kupffer and stellate cells through pro-inflammatory cytokines, such as tumour necrosis factor (TNF)-α, production[14]. This inflammatory signal is transmitted *via* the nuclear factor-κB (NF-κB) pathway, ultimately leading to liver damage[14].

While most immune mechanisms involved in ALD development are related to the TLR4-NF-κB pathway, the activation of TLR4 also triggers the transmission of pro-inflammatory stimuli through other signaling pathways, such us mitogen-activated protein kinases (MAPK) or TIR-domain-containing adapter-inducing interferon-β (TRIF)[14]. miRNAs can regulate this complex interplay between inflammatory signals *via* the regulation of cytokines and other components of the pathways[15]. Oxidative stress and free oxygen radicals generation involved in ALD development are also regulated by miRNAs through different pathways like Kelch-like ECH-associated protein 1 Kelch-like ECH-associated protein 1 (Keap1) / Nuclear factor-erythroid-2-related factor 2 (Nrf2) pathway[16-20]. In addition to this, miRNAs have also

Table 1 MicroRNA targets involved in alcoholic liver disease pathogenesis

miRNA	Source of sample	miRNA target
let-7[27]	Animal models	Lin28, HMGA2
	Human HSCs	
miR-19b[28]	Animal models	TGFβRII, Col1α2, MeCP2
	Human HSCs	
miR-21[36,37]	Animal models	FASLG, DR5, Crebl2
miR-26a[35]	Animal models	DUSP4, DUSP5
miR-27a[44,52]	Animal models	Sprouty2, CD206
	HMC	
	Humans (plasma)	
miR-34a[29,43]	Animal models	SIRT1, CASP2
	Human HSCs	
	NHH	
	HiBECs	
	Humans (liver biopsy)	
miR-103 and miR-107[53]	Humans (liver biopsy)	Caveolin-1
miR-122[32,124,125]	Animal models	P4HA1, HO-1, Cyclin G1, Bcl-w, HIF-1α
miR-155[38,39,97,126,127]	Animal models	TNFα, SHIP1, SOCS1, IRAKM, C/EBPβ
miR-181b-3p[40]	Animal models	Importin α1
miR-182[30]	Animal models	SLC1A1, Cofilin 1, CCL20, CXCL1, IL-8, Cyclin D1, IL-6
	Humans (serum samples and liver biopsy)	
miR-199[128]	Animal models	ET-1, ET-BR
miR-200a[31]	Animal models	ZEB-2
miR-212[46]	Caco-2 cells	ZO-1
	Humans (colon biopsy)	
miR-214[24,34]	Animal models	POR, GSR, CYP2E1
	HHCs	
miR-217[41]	Animal models	SIRT-1
miR-223[45]	Animal models	$p47^{phox}$, IL-6
	Humans (serum)	
miR-291b[42]	Animal models	Tollip
	HPBMs	
miR-378[59]	Animal models	Gli-3
miR-497[25]	Animal models	Btg2, Yy1

HSCs: Hepatic stellate cells; HMGA2: High mobility group AT-hook 2; TGFβRII: Transforming growth factor β receptor II; Col1α2: Collagen type I α 2 chain; MeCP2: Methyl-CpG binding protein 2; FASLG: Fas ligand; DR5: Death receptor 5; Crebl2: cAMP responsive element binding protein like 2; DUSP: Dual specificity phosphatase; HMC: Human Monocyte Cells; NHH: Normal Human Hepatocytes; HiBECs: Human intrahepatic Biliary Epithelial Cells; SIRT1: sirtuin 1; CASP2: caspase 2; P4HA1: prolyl 4-hydroxylase subunit α 1; HO-1: heme oxygenase-1; BCL-W: Bcl-2-like protein 2; HIF-1α: Hypoxia inducible factor 1 α; TNFα: Tumor necrosis factor α; SHIP1: Src homology 2 domain-containing inositol phosphatase 1; SOCS1: Suppressor of cytokine signaling 1; IRAKM: Interleukin 1 receptor associated kinase 3; C/EBPβ: CCAAT/enhancer binding protein β; SLC1A1: Solute carrier family 1 member 1; CCL20: C-C motif chemokine ligand 20; CXCL1: C-X-C motif chemokine ligand 1; IL: Interleukin; ET-1: Endothelin-1; ET-BR: Endothelin-B receptor; ZEB-2: Zinc finger E-box binding homeobox 2; ZO-1: Zonula occludens 1; HHCs: Human Hepatoma Cells; POR: Cytochrome P450 oxidoreductase; GSR: Glutathione reductase; CYP2E1: Cytochrome P450 2E1; p47phox: Neutrophil cytosolic factor 1-like; HPBMs: Human Peripheral Blood Monocytes; Tollip: Toll interacting protein; Gli3: GLI Family Zinc Finger 3; Btg2: B-cell translocation gene 2; YY1: Yin yang 1; miRNA: MicroRNA.

been shown to exert an important modulatory function on macrophage activation and differentiation[21,22]. Moreover, recent studies have shown even broader effects of miRNAs in ALD development, including a role in intercellular communication, in secretion in exosomes[23], in the expression of enzymes directly linked to alcohol metabolism (*e.g.*, regulation of CYP2E1 by miR-214[24]) and in the modulation of pro-inflammatory pathways such as the B-cell translocation gene 2/Yin-yang 1 (BTG2/YY1) signaling pathway by miR-497[25]. Finally, alcohol consumption, with or without concurrent ALD, has also been linked to altered expression of several miRNAs[5,26].

Numerous studies, therefore, have addressed the relationship between ALD development and miRNAs. While animal models have been used in the majority of these studies, there is an increasing number of studies in human cells, tissues and serum, confirming the key role of miRNAs in ALD[27-30]. A summary of all available studies is shown in Table 1. In addition, a summary of the regulatory actions of miRNAs in the inflammatory response according to the different cell types involved, is displayed in Figure 1.

Hepatocytes: Some miRNAs (*e.g.*, miR-34a and miR-200a) are responsible for the induction of hepatocytic apoptosis during ALD development[29,31]. In addition, secretion of miRNAs in exosomes (*e.g.*, miR-122) can cause an increase in inflammatory response by targeting monocyte/macrophage cells[32], ultimately leading to hepatocytic injury. MiRNAs action and pleiotropic effects could be different depending on the cell in which they act; thus, miR-122 could have a protective role inside the hepatocyte during alcohol-induced liver damage[33]. Increase in oxidative stress

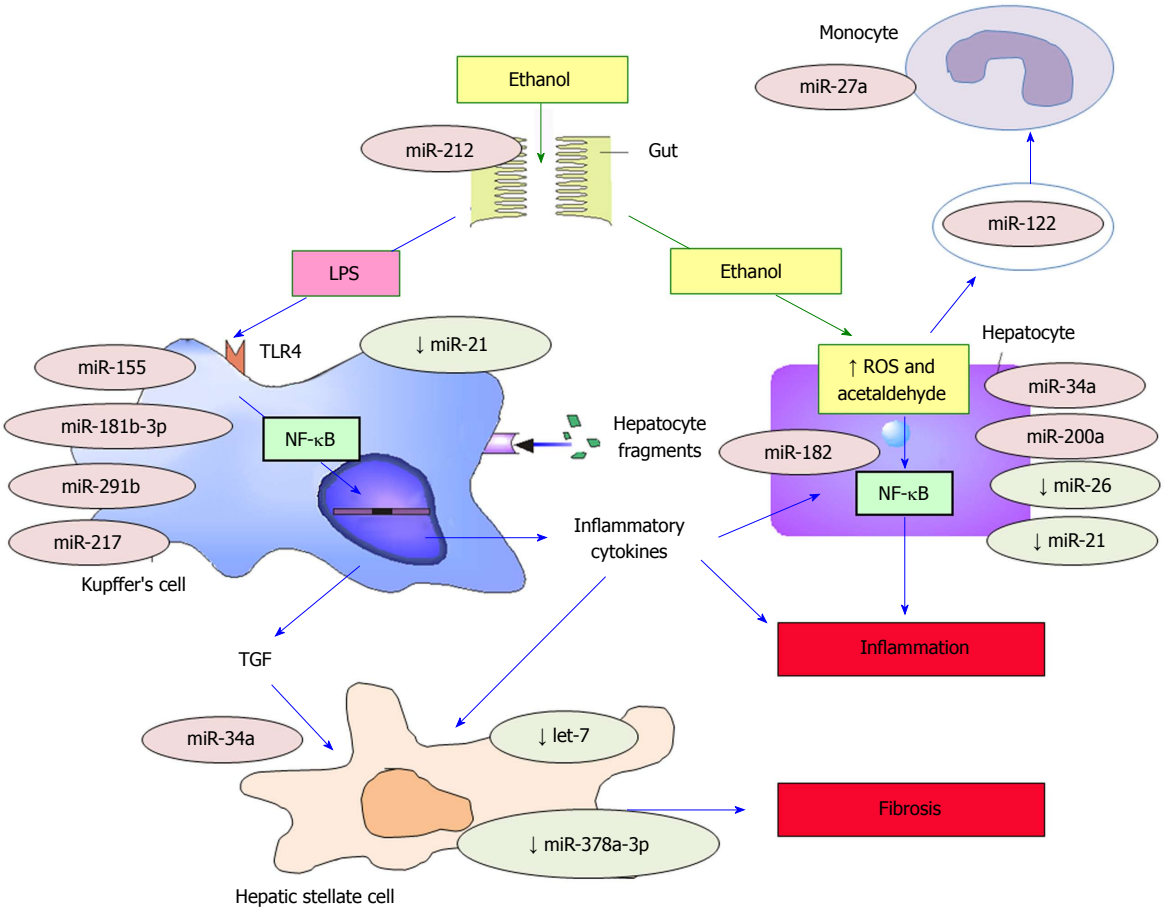

Figure 1 MicroRNAs involved in the pathogenesis of alcoholic liver disease. miRNAs preceded by a ↓ symbol are decreased in ALD or inhibit the development of ALD. The remainder of miRNAs promotes the development of ALD. TLR4: Toll-like receptor 4; TFG: Transforming growth factor; ALD: Alcoholic liver disease; ROS: Reactive oxygen species; NF-κB: Nuclear factor-κB. Figure adapted from Laso *et al*[10].

and alterations of enzymatic function in hepatocytes are also regulated by miRNAs[24,34]. Conversely, miRNAs may also have a protective role in ALD. For example miR-26a can increase autophagy[35] and miR-21 can inhibit alcohol-induced apoptosis[36,37].

Kupffer cells (KCs): miR-155, which is increased by chronic alcohol consumption through NF-κB induction, has been shown to be the main regulator of KC activation and function[38]. miR-155 inhibits the expression of multiple TLR4/NF-κB inhibitory regulators such as Src homology 2 domain-containing inositol phosphatase 1 (SHIP1) and Suppressor of cytokine signaling 1 (SOCS1)[38,39] leading to an increase in KC response to LPS and ultimately the development of liver fibrosis[39]. The Keap1/Nrf2 pathway could also be involved in miR-155 role in ALD development and KCs regulation[17]. Other miRNAs, such as miR-181b-3p, are also linked to increased LPS-sensitivity through the TLR4-NF-κB pathway[40]. In addition, miRNAs have been shown to regulate Sirtuin-1-Lipin-1, an inflammatory response mediator, leading to the down-regulation of the NF-κB pathway *via* de-acetylation. Alcohol consumption increases miR-217 expression, which in turn down-regulates sirtuin-1-Lipin-1[41], consequently leading to more hepatic inflammation[41]. Toll Interacting Protein (Tollip), another down-regulator of the TLR4-NF-κB pathway, is inhibited by miR-291b[42].

Hepatic stellate cells (HSCs): HSCs, responsible for the development of liver fibrosis, are regulated by several miRNAs, including let-7. The downregulation of let-7 by LPS and alcohol use causes an increase in HSCs activation[27]. In addition, chronic alcohol consumption has been linked to an overexpression of miR-34a, which increases the expression of proteins such as transforming growth factor-β1 (TFG-β1), leading to a higher survival of HSCs through apoptosis inhibition[43].

Other cell types: In addition to the cell types described above, other cells involved in ALD development, such as circulating monocytes (by miR-27a[44]), and circulating neutrophils, (by miR-223[45]) are regulated by miRNAs. In addition, miR-212 has been shown to increase permeability to LPS by altering cells of the intestinal mucosa[46].

Due to the role of miRNAs in ALD and the modulatory effects of alcohol consumption on miRNA expression, it is plausible to hypothesize that genetic variations in certain miRNAs may lead to altered miRNA function and

an increased risk of liver damage. Consequently, we and others have analyzed the relationship of alcohol-related diseases and polymorphisms within miRNA genes or miRNA targets[47,48]. Interestingly, the miR-146a C>G rs2910164 variant is linked to a susceptibility to alcohol use disorder[47] and the pre-miR-27a A>G rs895819 polymorphism is linked to a higher alcohol intake[49], suggesting a potential relationship between these genetic variants and alcohol-related diseases. The lack of replication studies precludes any conclusions regarding these SNPs, and to date, only rs738409 polymorphism within the *PNPLA3* gene is clearly linked to a higher susceptibility to ALD[50].

miRNAs as a target for diagnosis and treatment of ALD

The clinical use of miRNAs as a diagnostic tool or therapeutic agent in ALD has not been well studied[51]. However, over the last years, an increasing number of miRNAs have been proposed as potential biomarkers of ALD. The following is a review of the most promising results.

miR-192 and miR-30a: It has been shown that serum levels of miR-192 and miR-30a are significantly correlated with the diagnosis of alcoholic hepatitis. Therefore, these miRNAs may be useful in the diagnosis, staging, and monitoring of patients with this specific form of ALD[23].

miR-27a: miR-27a has been linked to monocyte differentiation and is increased in extracellular plasmatic vesicles of patients with alcoholic hepatitis, making it a potentially useful diagnostic tool[52].

miR-182: An elevated level of miR-182 has been linked to greater disease severity and liver injury in alcoholic hepatitis. The correlation between miR-182 and disease severity, however, has only been shown in liver biopsies, limiting its application as a diagnostic tool[30].

miR-103 and miR-107: A prior study found that miR-103 and miR-107 were increased in liver from patients with ALD and with NAFLD, but not in healthy livers or in subjects with viral hepatitis[53].

miR-155 and miR-122: Increased blood levels of miR-155[32,54] and miR-122[55] have been found in healthy individuals after binge drinking and in a murine model of liver damage. While these miRNAs could be potential biomarkers of alcohol intake or alcohol liver damage, they are increased in several types of liver disease and therefore are unlikely to be specific to ALD[54].

Therapeutic application of miRNAs in ALD

There are no studies to date supporting a therapeutic role for miRNAs in ALD. Available data, however, suggest a potential role for the inhibition or activation of some miRNAs in the treatment of liver disease. A recent study found that treatment with hyaluronic acid normalized miR-181b-3p and Importin α5 levels in ethanol-fed mice, protecting them from ethanol-induced liver and intestinal damage[40]. In addition, hyaluronic acid normalized the miR-291b/Tollip pathway, leading to a lower sensitization of monocytes/macrophages to ethanol-induced activation *via* TLR4[42]. While both studies were performed in animal models, taken together they suggest a potential role for hyaluronic acid as a therapeutic regulator of the KC response to ethanol *via* miRNA modulation.

The role of miR-155 in KC and miR-122 in hepatocytes suggest that these miRNAs may serve as potential targets for treatment of ALD. Miravirsen, an miR-122 inhibitor, has shown promising results in chronic hepatitis C treatment[56,57], suggesting its potential usefulness in ALD. A recent study showed that the restoration of miR-122 in hepatocytes could have a protective role against ALD development[33]. These apparently contradictory results could reflect the ability of miRNAs to develop different actions in different cells and also its relevance in inter-cellular communications[32]. In this sense, the therapeutic action of Miravirsen over viral replication could be explained by the interruption of these communications[57]. In addition, other potential therapeutic miRNAs currently under development for other diseases, such as cardiac fibrosis and remodeling or vascular disease[58], could serve as potential targets for ALD. There is indirect data that inhibition of miR-155, may lead to decreased sensitivity of KC to LPS-mediated activation[39].

In addition to the inhibition of detrimental miRNAs, stimulation of protective miRNAs could also serve as a potential therapeutic target. For example, miR-21, which aids hepatocyte regeneration[36]; miR26a, which protects hepatocytes from fibrosis development[35]; miR-223, which inhibits neutrophil activation and liver infiltration[45]; and miR-378, which exerts a stop-signaling action in HSC[59], are all potential targets for treatment. There are no clinical trials to date involving these miRNAs as therapeutic targets in ALD and further studies will be necessary before clinical application.

ROLE OF MIRNAS IN NAFLD

NAFLD is defined as the accumulation of fat in the liver in the absence of alcohol intake, viral infection or other specific causes of liver disease. NAFLD represents a spectrum of disorders ranging from the simple accumulation of triglycerides in hepatocytes (hepatic steatosis) to steatosis with inflammation [non-alcoholic steatohepatitis (NASH)], fibrosis and cirrhosis[60]. NAFLD and NASH have rapidly become the most common cause of chronic liver disease worldwide in recent decades. The prevalence of these diseases has been estimated between 25% to 45% of the general population[61] with a greater prevalence in patients with obesity, diabetes mellitus or metabolic syndrome, in which case, the

prevalence of NAFLD can reach 70% to 90%[62-64]. It is estimated that by 2020 cirrhosis related to NAFLD will be the first indication for liver transplantation[65].

Pathogenic role of miRNAs in NAFLD

The pathogenesis of NAFLD, along with the underlying mechanisms of progression from steatosis to steatohepatitis, has not been fully elucidated. Traditionally, the "two hit" theory[66] has been upheld. The "first hit", which includes insulin resistance leading to the accumulation of fat in the liver, is followed by a "second hit", consisting of the interaction of inflammatory cytokines, mitochondrial dysfunction and oxidative stress, leading to hepatocellular injury, inflammation and fibrosis[67]. However, more recently, multiple factors have been implicated in the pathogenesis of NAFLD, such that the "two hit" theory has been replaced by a "multiple-hit" hypothesis[68]. The "multiple-hit" theory includes the involvement of insulin resistance, adipose tissue dysfunction, mitochondrial dysfunction, endoplasmic reticulum stress, dietary factors, fatty acids, iron overload, inflammatory activation, LPS produced by gut microbiota, a chronic inflammatory state, and genetic and epigenetic factors in the pathogenesis and progression of NAFLD[68-70]. Accordingly, the following is a summary of the research implicating several miRNAs in the regulation of key targets in the development of NAFLD[8]. It is of special interest that recent studies have reported differences in miRNA expression between liver samples from patients with NAFLD and controls. Specifically, livers from patients with NAFLD express an upregulation of miR-31, miR-33a, miR-34a, miR-144, miR-146b, miR-150, miR-182, miR-183, miR-200a, miR-224, and miR-301a and a down regulation of miR-17, miR-122, miR-296, miR-373, miR-375 and miR-378c[71-76]. Among these miRNAs, miR-34a, miR-122, and miR-155 have been most often associated with the pathogenesis of NAFLD and as such, the following is a review of these miRNAs in detail. Table 2 displays a list of all miRNAs that have been associated with NAFLD through February 2018.

miR-122: miR-122 is the most abundant miRNA in the liver and plays a fundamental role in liver physiology[77-79] and lipid metabolism[80]. miR-122 interacts with multiple important lipogenic factors in human NAFLD, such as acetyl coA carboxylase-2 (ACC2) and the sterol regulatory element binding protein (SREBP)[71,81,82]. miR-122 is decreased in liver samples[83-85] but increased in serum[84,86,87] from patients with NAFLD compared to healthy controls. Despite this somewhat paradoxical finding, the association of miR-122 with NAFLD pathogenesis is well established. Inhibition of miR-122 in high-fat fed mice is associated with a significant reduction in hepatic steatosis and plasma cholesterol levels, which was associated with a reduction in hepatic sterol and fatty acid synthesis rates and stimulation of hepatic fatty-acid oxidation mediated by activation of adenosine 5'-monophosphate-activated protein kinase (AMPK)[80]. Moreover, the relationship of miR-122 with the development and progression of hepatic fibrosis has been demonstrated *in vitro*, through the regulation of HSC proliferation and production of collagen by targeting prolyl 4-hydroxylase subunit α-1 (P4HA1)[88].

miR-34a: miR-34a is overexpressed in both murine models of NAFLD (*e.g.*, mice fed a high-fat diet) and liver and serum from patients with NAFLD[81,87,89,90]. The main target of miR-34a is Sirtuin 1 (SIRT1), which regulates energy homeostasis by activating transcription factors such as peroxisome proliferator activated receptors (PPAR) α and liver X receptor (LXR). In addition, SIRT1 inhibits the co-activator 1α of the PPAR-γ (PGC1-α), the SREBP-1c and the farnesoid X receptor (FXR). SIRT1 is downregulated in the liver of NAFLD patients[91] and the inhibition of miR-34a restores the expression of SIRT1 and PPAR-α, leading to the activation of AMP-activated protein kinase (AMPK) and several target genes of PPAR-α. These findings suggest a fundamental role for miR-34a in the dysregulation of lipid metabolism associated with NAFLD[92].

miR-155: miR-155 is an important regulator of immune cells in both humans and mice and is involved in several inflammatory processes, such as rheumatic diseases[93], lipid metabolism[94] and in ALD (as described above). In patients with NAFLD, miR-155 is dysregulated by adipogenic transcription factors CCAAT/enhancer binding protein (C/EBP)-α, C/EBP-β, PPAR-γ and LXRα[95,96], fibrosis targets platelet derived growth factor (PDGF), Smad3 and C/EBP-β[97], and a tumor suppressor in the liver, SOCS-1[90,98]. However, animal models of NAFLD show contradictory results. For example, miR-155 deficient mice fed a high-fat diet showed a significant increase in hepatic steatosis[98], while miR-155 KO mice fed a methionine-choline-deficient diet showed a decrease in steatosis and expression of genes involved in fatty acid metabolism and fibrosis, with no concomitant liver injury or inflammation[97]. In addition, miR-155 may also be involved in hepatocarcinoma development[99]. These findings suggest that miR-155 may have different roles in fat storage and lipid accumulation in liver diseases and healthy subjects. However, additional research is warranted[97].

miRNAs as biomarkers in the diagnosis of NAFLD

As shown in Table 2, many miRNAs are differentially expressed in patients with NAFLD compared to healthy controls. These miRNAs may serve as potential biomarkers in the diagnosis and staging of NAFLD.

miR-122: Several studies have found that miR-122 is elevated in serum in NAFLD patients[81,86,100-102], even long before an alteration in transaminase levels occurs[103]. The diagnostic potential of miR-122 may extend to an indicator of disease severity and as a

Table 2 Summary of microRNAs associated with non-alcoholic fatty liver disease

miRNA	Source of samples	Change	Main targets
miR-9[129]	Human serum; Human hepatocyte cell line	Upregulated	Onecut2; SIRT1
miR-10b[130]	Human hepatocyte cell line	Downregulated	PPARα
miR-15b[131,132]	Animal models Human serum	Upregulated	
miR-16[104]	Human serum	Upregulated	
miR-17[74]	Human liver	Downregulated	
miR-19[84]	Human serum	Upregulated	
miR-21[86,87,99,133-136]	Animal models Human hepatocyte cell line Human liver and serum	Upregulated	PPARα; TGF-β PTEN
miR-21[85,89,137,138]	Animal models Human liver Human hepatocyte cell line	Downregulated	HMGCR; FABP7
miR-24[139]	Animal models Human hepatocyte cell line	Upregulated	Insig1; SREBP
miR-26[140]	Animal models	Downregulated	IL-6, IL-7
miR-27a[141]	Animal models	Downregulated	
miR-27b[102]	Human serum	Upregulated	
miR-29a[142,143]	Animal models	Downregulated	HMGCR; LPL
miR-29c[85,89,90]	Animal models	Downregulated	DNMT3A; DNMT3B
miR-30b[83]	Human liver Human hepatocyte cell line	Downregulated	ITGAX; FABP4
miR-30c[144]	Human serum	Upregulated	
miR-31[74,89]	Human liver Animal models	Upregulated	
miR-33a[73,76]	Human liver	Upregulated	ABCA1; ABCA2
miR-33a[85]	Human liver	Downregulated	
MiR-34a[71,81,82,85,87,89,90,92,104,105,145-148]	Animal models Human hepatocyte cell line Human liver and serum	Upregulated	SIRT1; HNF4α; PPARα
miR-99a[149]	Human serum	Downregulated	
miR-101[150]	Human hepatocyte cell line Human monocyte cell line	Upregulated	ABCA1
miR-103[53,89,151]	Animal models Human liver and serum	Upregulated	Cav1
miR-103a[152]	Human liver Human hepatocyte cell line	Upregulated	
miR-106b[152]	Human liver	Upregulated	
miR-107[53,89]	Animal models Human liver	Upregulated	Cav1
miR-122[81,84,86,87,101-104,106,153]	Animal models Human Serum	Upregulated	
miR-122[71,82-85,89,90,99,106,141,154,155]	Animal models Human liver	Downregulated	ACC-2; HAMP; FAS; HMGCR; SREBF-1c SREPBF-2; HIF-1α; Vimentin; MAP3K3
miR-125b[84]	Human serum	Upregulated	
miR-125b[156]	Animal models	Downregulated	FAS
miR-139-5p[83]	Human liver	Downregulated	TNFα
miR-144[76]	Human Liver	Upregulated	ABCA1
miR-144[157]	Animal models	Downregulated	TLR-2
miR-146a[158]	Animal models Human hepatocyte cell line	Upregulated	
miR-146a[132]	Animal models Human hepatocyte cell line	Downregulated	Wnt1; Wnt5
Mir-146b[149,159]	Animal models Human serum Human hepatocyte cell line	Downregulated	IRAK1 TRAF6
miR-146b[71,83,158]	Animal models Human liver Human hepatocyte cell line	Upregulated	
miR-149[160]	Animal models Human hepatocyte cell line	Upregulated	FGF-21
miR-150[74]	Human liver	Upregulated	
miR-152[158]	Animal models Human hepatocyte cell line	Upregulated	

miR-155[90,97-99,161,162]	Animal models	Upregulated	SOCS1; C/EBP-B; CES3;
	Human hepatocyte cell line		PDGF; SMAD3
miR-155[96]	Animal models	Downregulated	LXRα
	Human liver and serum		
miR-181a[82]	Animal models	Upregulated	
miR-181d[149]	Human serum	Downregulated	
miR-182[74]	Human liver	Upregulated	FOXO3
miR-183[74]	Human liver	Upregulated	
miR-192[84,90]	Animal models	Downregulated	
	Human liver		
miR-192-5p[82,84,86,102,106]	Animal models	Upregulated	
	Human liver and serum		
miR-194[89]	Animal models	Upregulated	
miR-197[149]	Human serum	Downregulated	
miR-199[163]	Animal models	Upregulated	Cav1; PPARα
	Human hepatocyte cell line		
	Human liver		
miR-200a/b/c[74,82,89,90,141,158,162,164]	Animal models	Upregulated	ZEB1; CDH1; EZH2; IRP1
	Human hepatocyte cell line		
miR-203[90,132]	Animal models	Downregulated	
miR-212[165]	Animal models	Upregulated	FGF-21
	Human hepatocyte cell line		
miR-214[71,166]	Human liver	Upregulated	
	Animal models		
miR-216[167]	Animal models	Downregulated	
miR-219a[74]	Human liver	Downregulated	
miR-221[73]	Human liver	Downregulated	
miR-221[89,90,99]	Animal models	Upregulated	
miR-222[99]	Animal models	Upregulated	
miR-223[86,164]	Animals models	Upregulated	IRP1
	Human serum		
miR-224[73,74]	Human liver	Upregulated	
miR-291b[168]	Animal models	Upregulated	AMPKα1
miR-302a[167]	Animals model	Downregulated	ELOVL6
miR-331[144]	Human serum	Upregulated	
miR-335[89]	Animal models	Upregulated	
miR-375[84]	Human serum	Upregulated	
miR-378i[74]	Human liver	Downregulated	
miR-421[169]	Animal models	Upregulated	SIRT-3
miR-422a[83]	Human liver	Downregulated	
miR-429[141]	Animal models	Upregulated	
miR-451[87]	Human Serum	Upregulated	
miR-451[89,141,170]	Animal models	Downregulated	AMPK/AKT
	Human liver		
miR-467b[171]	Animal models	Downregulated	LPL
miR-576[152]	Human liver	Downregulated	RAC1
	Human hepatocyte cell line		
miR-590[74]	Human liver	Downregulated	
miR-892a[152]	Human liver	Upregulated	
	Human hepatocyte cell line		
miR-1290[102]	Human serum	Upregulated	

Onecut2: One cut homeobox 2; SIRT: Sirtuin; PPARα: Peroxisome proliferator activated receptor α; TGF-β: Transforming growth factor β; PTEN: Phosphatase and tensin homolog; HMGCR: 3-hydroxy-3-methylglutaryl-CoA reductase; FABP: Fatty acid binding protein; Insig1: Insulin induced gene 1; SREBP: Sterol regulatory element binding protein; IL: Interleukin; LPL: Lipoprotein lipase; DNMT: DNA methyltransferase; ITGAX: Integrin subunit α X; ABCA: ATP binding cassette subfamily A; HNF4α: Hepatocyte nuclear factor 4 α; Cav1: Caveolin 1; ACC-2: Acetyl-CoA carboxylase 2; SREBF: Sterol regulatory element binding transcription factor; HIF-1α: Hypoxia inducible factor 1 α; MAP3K3: Mitogen-activated protein kinase kinase kinase 3; FAS: Fatty acid synthase; TNFα: Tumour necrosis factor α; TLR-2: Toll-like receptor 2; Wnt: Wnt family member; IRAK1: Interleukin 1 receptor associated kinase 1; TRAF6: TNF receptor associated factor 6; FGF-21: Fibroblast growth factor 21; SOCS1: Suppressor of cytokine signaling 1; C/EBPβ: CCAAT/enhancer binding protein β; CES3: Carboxylesterase 3; PDGF: Platelet derived growth factor; SMAD3: SMAD family member 3; LXRα: Liver X receptor; FOXO3: Forkhead box O3; ZEB-1: Zinc finger E-box binding homeobox 1; CDH1: Cadherin 1; EZH2: Enhancer of zeste 2 polycomb repressive complex 2; IRP1: Iron regulatory protein 1; AMPKα1: AMPK: Adenosine monophosphate activated protein kinase α 1; ELOVL6: ELOVL fatty acid elongase 6; AMPK: Adenosine monophosphate activated protein kinase; AKT: AKT serine/threonine kinase 1; RAC1: Ras-related C3 botulinum toxin substrate 1.

predictor of hepatic fibrosis[82,84,87,104].

miR-34a: Similar to miR-122, miR-34a has also been shown to have potential as a biomarker of diagnosis and severity of NAFLD. Several studies have shown that miR-34a is upregulated in the liver and serum of patients with NAFLD[71,81,82,104]. Additionally, elevated serum levels of miR-34a correlate with disease severity from simple

steatosis to steatohepatitis, with liver enzyme levels, with fibrosis stage and with inflammation activity[82,104,105].

miR-192: Serum miR-192 levels are positively correlated with the severity of NAFLD-specific liver pathomorphological changes in mice fed a choline and folate deficient diet[82] and miR-192 upregulation in human serum has been demonstrated[82,84,86,102,106]. Interestingly, serum levels of miR-122 and mir-192 have been shown to be strongly correlated[84,86].

Panels: In addition to individual miRNAs, a serum panel comprised of hsa-miR-122-5p, hsa-miR-1290, hsa-miR-27b-3p, and hsa-miR-192-5p has shown high NAFLD diagnostic accuracy, regardless of NAFLD activity score (NAS) status[102]. Another research group found that NAFLD was associated with an miRNA signature based on up-regulation of miR-122, miR-192, miR-19a, miR-19b, miR-125b, and miR-375[84].

It is important to mention that most studies have compared patients with NAFLD to healthy controls or patients with chronic viral hepatitis B[105] or C[104]. However, no comparisons have been performed, to our knowledge, between patients with NAFLD and patients with ALD.

Therapeutic application of miRNAs in NAFLD

As previously mentioned, miRNAs are involved in several stages of NAFLD development (from lipid metabolism or diabetes to liver inflammation), and are therefore potential therapeutic targets[7,107]. The expression of miR-103 and miR-107 is upregulated in obese mice[53,89]. Inactivation of miR-103/107 in murine adipocytes upregulates caveolin-1 (a critical mediator of the insulin receptor) leading to enhanced insulin signaling, decreased adipocyte size and enhanced insulin-stimulated glucose uptake[53,108]. An N-acetylgalactosamine (GalNAc)-conjugated anti-miR-103/107 (RG-125/AZD4076, Regulus Therapeutics) has been developed for the treatment of NAFLD and type 2 diabetes or pre-diabetes[108-110]. Currently, two clinical trials are registered using this drug in patients with NAFLD (ClinicalTrials.gov Identifier: NCT02826525 and NCT02612662), although Regulus has acknowledged that AstraZeneca intends to terminate the clinical development of RG-125/AZD4076[108,111].

miR-122 has also shown promising results as a treatment for NAFLD. There is a high concentration of miR-122 in liver tissue[112] and this miRNA plays an important role in liver development, differentiation, homeostasis and functioning[113]. Over-expression of miR-122 may affect the Ying Yan 1 and Farnesoid X Receptor (YY1-FXR-SHP) regulatory axis leading to a reduction in hepatic triglyceride levels, potentially serving as a target for NAFLD treatment[114]. miR-122 is also an essential host factor for hepatitis C virus (HCV) replication and anti-miR-122 efficiently reduces viral load in chronically infected HCV patients without detectable resistance[108]. The fact that miR-122 has protective effects on NAFLD, while imposing a deleterious impact on HCV infection, emphasizes the importance of cautious targeting of miRNAs therapy since the role of miRNAs can be highly context dependent[115].

circRNA_0046366 antagonizes miR-34a and normalizes PPARα signaling, leading to the amelioration of liver steatosis in a murine model[116]. However, a phase I study on the effects of a miR-34 mimic (MRX34) on primary liver cancer and advanced or metastatic cancer with liver involvement (ClinicalTrials.gov Identifier: NCT01829971) was prematurely terminated due to serious immune-related adverse events[108], highlighting the potential risks of miRNA based-therapies.

CONCLUSION

All except four (miR-199, miR-212, miR-214 and miR-497) of the 21 miRNAs associated with ALD, listed in Table 1, are also related to NAFLD or lipid metabolism (although the four have been associated with other diseases, such as cancer[117]). Conversely, miRNAs that are related to the pathogenesis of NAFLD (miR-122, miR-34a and miR-155) are also clearly linked to ALD. These results reflect the common mechanisms between NAFLD and ALD and also the pleiotropic effects of any particular miRNA.

Due to the lack of specificity of miRNAs, the development of a biomarker or treatment specific to ALD or NAFLD is difficult. It is more feasible that individual miRNAs or a panel of miRNAs would be useful in the staging of liver disease (*e.g.*, distinguishing simple steatosis in ALD or NAFLD from steatohepatitis)[118]. miR-122 is the most promising candidate as a biomarker due to its liver specificity. It is clear however, that miR-122 is also a marker of liver damage regardless of etiology[119]. Technical limitations, such as standardization of techniques and potential costs, add to the difficulties inherent to the development of a validated diagnostic biomarker. Circulating miRNAs are promising as biomarkers due to their stability and potential ability to detect advanced liver disease without a biopsy. However, rigorously validated studied are needed before they can be brought to the clinic[119].

The development of miRNA-targeted interventions for ALD and NAFLD is an intriguing area of research. However, despite the success in animal models and the potential targets described in this review, to the best of our knowledge there are no current clinical trials for miRNA interventions in ALD or NAFLD. The few studies that are being conducted on miRNA treatment in other diseases are phase 1 studies in the field of cancer research (*e.g.*, assessing the activity of miRNA-loaded minicells or TargomiRs in malignant pleural mesothelioma[120]). Theoretical miRNA-based therapies are pharmacologically complex and include miRNA inhibition (*e.g.*, synthetic

anti-miRNAs) or miRNA replacement therapy (*e.g.*, lipid vesicles or gold nanoparticles)[121]. One major challenge to the development of miRNA-based therapies is the improvement of drug delivery systems. Due to the biochemical instability of unmodified miRNAs and potential immunogenicity, specific delivery to target organs should be achieved. The high degree of redundancy among miRNAs and the multiple binding sites for any given miRNA must also be taken into account when designing efficacious and safe miRNA-based therapies[122].

To sum up, there is a large body of literature regarding miRNAs in NAFLD and ALD at various stages of the disease. These studies include expression data from microarrays and next generation sequencing from animal models and human studies, and cell-specific data from in situ hybridization and sensor constructs. The role of miRNAs in pathogenesis is well-documented and as such, their potential value as biomarkers or therapeutic targets is warranted. However, most miRNA modifications have a modest phenotypic effect, since miRNAs are unlikely to be the single key factor in chronic and multifactorial diseases such as liver steatosis[123]. Instead, most miRNAs act as fine-tuners in disease pathways and this characteristic, along with their lack of specificity must be considered before use in the clinic. To this end, we must improve our understanding of the interaction of different miRNAs in the development of advanced liver disease.

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