The Emerging Role of MicroRNAs in NAFLD: Highlight of MicroRNA-29a in Modulating Oxidative Stress, Inflammation, and Beyond

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Abstract: Non-alcoholic fatty liver disease (NAFLD) is a common cause of chronic liver disease and ranges from steatosis to steatohepatitis and to liver fibrosis. Lipotoxicity in hepatocytes, elevated oxidative stress, and the activation of proinflammatory mediators of Kupffer cells, and fibrogenic pathways of activated hepatic stellate cells can contribute to the development of NAFLD. MicroRNAs (miRs) play a crucial role in the dysregulated metabolism and inflammatory signaling connected with NAFLD and its progression towards more severe stages. Of note, the protective effect of non-coding miR-29a on liver damage and its versatile action on epigenetic activity, mitochondrial homeostasis and immunomodulation may improve our perception of the pathogenesis of NAFLD. Herein, we review the biological functions of critical miRs in NAFLD, as well as highlight the emerging role of miR-29a in therapeutic application and the recent advances in molecular mechanisms underlying its liver protective effect.

Keywords: microRNAs; microRNA-29a; NAFLD; NASH; liver fibrosis; mitochondria; inflammation

1. Introduction

Non-alcoholic fatty liver disease (NAFLD), the most common cause of chronic liver disease, consists of fat deposited (steatosis) in the liver due to causes besides excessive alcohol use [1]. NAFLD is a hepatic manifestation of the metabolic syndrome [2] and is closely associated with cardio- and neurological complications, including cardiovascular disease, hypertension, cognitive dysfunction, and ischemic stroke [3,4]. NAFLD may result from “multiple and parallel hits” like lipotoxicity caused by the excessively elevated uptake of fatty acid (FA) into hepatocytes, subsequently elevated oxidative stress, and the activation of proinflammatory mediators of Kupffer cells (KC), as well as fibrogenic pathways of activated hepatic stellate cells (HSC), leading to non-alcoholic steatohepatitis (NASH) and non-alcoholic steatofibrosis (NASF) [5]. Considered a key predisposing factor for cirrhosis, NASH is implicated as a risk factor for non-viral hepatitis-related hepatocellular carcinoma (HCC) [6].
MicroRNAs (miRs) are small non-coding RNAs with about 22 nucleotides that have been found to have a regulatory role in transcriptional control mechanisms in guiding metabolic homeostasis. MiRs are first transcribed by RNA polymerase II or III in the nucleus to generate primary miRs (pri-miRs) which will be consequently processed to become precursor miRNAs (pre-miRs) [7]. The miRs then bind to 3′untranslated region (3′ UTR) of target mRNA(s) and can lead to mRNA degradation or translational repression [8]. Despite of this dogmatic view in the repressive activity, some miRs acting to enhance gene expression has been recognized [9]. In addition, other mechanisms have recently been reported, such as miRNAs binding to 5′ UTR or coding sequence of mRNA [10], Toll-like receptors [11,12] or mitochondrial transcripts [13]. There are increasing evidences reporting that some miRs regulate pathways governing lipid metabolism, oxidative stress and inflammation in the liver, playing a crucial role in the pathophysiology of NAFLD [14,15]. For example, miR-122, miR-34a, miR-33, miR-21, and miR-29 were acknowledged for their regulatory role in hepatic functions and for their therapeutic potential [14–16].

The miR-29 family in human includes miR-29a, -29b, and -29c. Mature miR-29s are highly similar between human, mouse, and rat [17]. Pathophysiological disturbance of various tissue or cell types could contribute to the alteration of circulating miR-29a level, as miR-29a level has been shown to correlate with diverse human diseases, including Alzheimer’s disease [18], Parkinson’s disease [19], ankylosing spondylitis [20], atherosclerosis [21], atrial fibrillation [22], active pulmonary tuberculosis [23], thoracic aneurysms [24], tendon disease [25], diabetes [26], scleroderma [27] and cholestatic pediatric liver disease [28].

In addition, miR-29a was tightly connected with diagnostic relevance of NAFLD [29], NASH [30], and liver fibrosis [30–32], as well as aggressiveness and prognosis of HCC [33–36]. Importantly, several lines of study have indicated the emerging roles of miR-29a through multiple signaling networks in experimental models simulating liver diseases, including NAFLD, NASH, fibrosis, and HCC (Table 1).

In this review, we focus on the latest findings regarding the biological role of miR-29a, as well as some important miRs in NAFLD. We also discuss recent advances in the molecular mechanisms underlying miR-29a-mediated protective effects against hepatic dysfunction.

### Table 1. Pleiotropic Role of miR-29a in in Liver Disease.

| Affected Pathway                  | Disease Model | miR-29a Targets                  | References          |
|----------------------------------|---------------|----------------------------------|---------------------|
| Apoptosis                        | liver fibrosis, HCC | COL1A1, FGL2, MAP4K4, PDGFC, BCL-2, DNMT3a, MCL-1 | [42,46,48,50–52]    |
| Autophagy                        | NASH, liver fibrosis, HCC | DNMT3b, SPARC | [36,37,51]          |
| Epigenetic                       | NASH, liver fibrosis, HCC | DNMT3b, HDAC4, DNMT3a, TET1 | [37–43]            |
| Oxidative stress/Inflammatory    | NASH, liver fibrosis, HCC | CD36, DNMT3b, HDAC4, ARRB1, PTEN | [37,40,44–49]    |
| Epithelial-mesenchymal transition| NASH, liver fibrosis | COL1A1, FGL2, MAP4K4, PDGFC | [37,39,44–46,48,51,53] |
| Cell cycle                       | HCC           | SIRT1, SPARC, HULC, TET1, TET2, TET3 | [56,41,43,54,55]    |
| Cell migration                   | HCC           | CLDN1, TET1, TET2, TET3, PTEN | [41,43,56]          |

2. MiRs as Markers in Liver Disease

The liver serves as a central organ in energy metabolism as it mainly contributes to regulate absorptive glucose storage and post-absorptive glucose release, amino acid metabolism, and lipid/lipoprotein metabolism. Since Lee et al. firstly identified the critical function of miRs in regulating the development of C. elegans [57], mounting lines of evidence have revealed that miRs are pivotal for controlling metabolic homeostasis and represents relevance in diagnosing liver diseases.
miR-122, which is the most abundant miRs in the liver, is involved in hepatic cholesterol and lipid metabolism [58], and presented an increased level in circulation in the context of NAFLD [59–62], making a well predictive panel when combined with miR-29a [29]. Moreover, dysregulated level of circulating miRs were also reported, including miR-122 [29], miR-34a [61,63], miR-33 [62], miR-21 [64], miR-192 [60], miR-221/222 [65], miR-375 [59], and miR-802 [66]. Table 2 exhibits a non-exhaustive list of miRs of important in the context of liver diseases.

In 2011, Roderburg et al. identified miR-29a as a non-invasive biomarker for liver fibrosis in cirrhosis patients and mouse model [32]. In the following year, Zhu et al. discovered the role of miR-29a as a prognostic marker in HCC patients receiving surgical resection [35]. At present, growing body of evidence has shown the significance of miR-29a as a diagnostic/prognostic tool in HCC [41,42,47,50,55,67–70] and alcoholic liver disease [71], as well as NAFLD. In 2017, Lopez-Riera et al. identified circulating miR-29a as one predictor of miRNAs biomarker set in NAFLD patients [72]. Studies from Lambrecht et al. as we as Jampoka et al. highlighted miR-29a as an essential part in predictive algorithm for NAFLD [29,31]. Furthermore, studies using mouse model also confirmed the close involvement of miR-29a in representing the progression of NAFLD [44,73] and NASH [74,75]. A non-exhaustive list of miR-29a with altered level in liver diseases is provided in Table 3.

| microRNA | Expression | Reference |
|----------|------------|-----------|
| miR-21   | Up         | [64]      |
| miR-33   | Up         | [62]      |
| miR-34a  | Up         | [61,63,64,76] |
| miR-103/107 | Up     | [77]      |
| miR-122  | Up         | [20,59–61,63,76] |
| miR-132  | Down       | [78]      |
| miR-146b | Down       | [78,79]   |
| miR-148a | Down       | [80,81]   |
| miR-181a | Up         | [82–84]   |
| miR-181d | Down       | [79]      |
| miR-192  | Up         | [59,60,63] |
| miR-197  | Down       | [79]      |
| miR-221/222 | Up       | [65,85]   |
| miR-375  | Up         | [59]      |
| miR-802  | Up         | [66]      |

| Source | Expression | Clinical Relevance | Reference |
|--------|------------|--------------------|-----------|
| Plasma | Down       | Biomarker implicated in miRFIB scoring algorithm for diagnosis of liver fibrosis | [31]      |
| Serum  | Down       | Reduced miR-29a along with elevated miR-122 serve as a diagnostic panel for NAFLD negatively correlated with necroinflammation and liver fibrosis | [29]      |
| Serum  | Down       | Biomarker of advanced liver cirrhosis | [32]      |
| Serum  | Up         | Biomarker of HCC | [67]      |
| Plasma | Down       | Prognostic marker of poor outcome of HCC | [33]      |
| Serum  | Up         | Predictor for poor survival of HCC | [70]      |
| HCC tissue | Up       | Predictor for recurrence of HCC | [35]      |
| HCC tissue | Down   | Prognostic marker of poor outcome of HCC | [55]      |
| HCC tissue | Down   | Predictor for low survival rate of HCC | [36]      |

3. MiR-29a Functions as an Epigenetic Modifier to Mitigate Liver Injury

Epigenetic regulation acts to alter hereditary gene expression by modifying chromatin structure and the DNA methylation and acetylation that is not related to change the primary DNA sequence [86]. Unlike the genome of an organism, the epigenome is not a consistent entity and may be modulated by different intrinsic, chemical, and environmental cues [87], and its changes may be inherited across
generations [88]. DNA methyltransferases (DNMTs), such as DNMT1, DNMT3a, and DNMT3b, enable DNA methylation, which is correlated with the conversion of quiescent HSC into hepatic myofibroblasts [89]. DNA methylation inhibitors exert a regulatory effect on hepatic wound healing and fibrogenesis [90,91]. Of particular note, our recent work demonstrated that miR-29a can repress DNMT3b expression by directly targeting its 3’UTR in the murine primary HSC [37]. Overexpression of miR-29a can alleviate steatosis, NASH, and NASF in methionine-choline-deficient diet-fed mice [37]. Another of our studies also showed that overexpression of miR-29a counteracts fibrosis in murine liver by reducing DNMT1 and DNMT3b [39], as well as the down-regulation of methyl CpG binding protein 2 (MeCP2) [38].

On the other hand, histone deacetylase (HDAC) 4, which acts to modify acetylation reactions in histones and non-histone proteins, has also been reported to have a positive role in activating liver fibrosis [92]. HDAC inhibitors administration exerts ameliorative effect both in experimental animal models and in in vitro cellular models of liver and kidney fibrosis [93]. In mechanistical term, miR-29a could exert suppressive effect on HDAC4 expression level by direct targeting 3’UTR of HDAC mRNA. Based on this molecular basis, our study demonstrated that overexpression of miR-29a in mice presents decreased HDAC4 activity and ameliorated liver fibrosis [40].

4. Role of miR-29a in Oxidative Stress and Inflammation

Under normal mitochondrial homeostasis conditions, physiological reactive oxygen species (ROS) can be effectively removed by antioxidant mechanisms and metabolic adaptations that inhibit substrate delivery to the tricarboxylic acid (TCA) cycle, a series of enzyme-catalyzed chemical reactions used by aerobic organisms to release energy [94]. However, in the context of NAFLD, both increased mitochondrial ROS production and the decreased activity of ROS scavenging mechanisms (e.g., glutathione, superoxide dismutase 2, and catalase) can increase oxidative stress, leading to lipid peroxidation, protein oxidation, and DNA oxidation, as well as mitochondrial damage [95,96]. Although the interaction between miR-29a and redox control in mitochondria is not fully understood, mice harbor miR-29a overexpression show mitigation of DNA oxidative damage and decreased stress-inducible marker heme oxidase-1 in NASH model, suggesting its role in neutralizing oxidative stress [37,97].

Elevated oxidative stress has been linked to altered mitochondrial membrane potential, as well as a loss of mitochondrial integrity in NAFLD. For example, cardiolipin, a unique phospholipid found in the inner mitochondrial membrane, is highly sensitive to oxidative stress, resulting in the induction of a mitochondrial permeability transition (MPT) pore opening, which has been suggested to provide routes for the cytosolic release of mitochondrial danger-associated molecular patterns (mtDAMPs) to trigger pro-inflammatory signaling [98–100]. For one, mtDNA that has escaped from mitochondria can activate innate immune signaling through NOD-like receptor family pyrin domain containing 3 (NLRP3) and toll-like receptors (TLRs) [101,102]. In high-fat diet (HFD)-fed mice, mtDNA has been shown to interact with the TLR9 on KC and HSC once released from damaged hepatocytes to trigger the signaling of innate immune and fibrogenesis, as has been suggested to occur in the pathogenesis of NASH [102–104]. The extracellular release of a mtDNA-associated protein, mitochondrial transcription factor A (TFAM), can also act as a mtDAMP to provoke pro-inflammatory macrophage activity [105]. mtdsRNA has been recently recognized as a novel mtDAMP that interacts with the dsRNA sensor to trigger innate immune signaling. In an alcoholic liver disease model, hepatocytes generate exosomal mtdsRNA to mediate TLR3 activation and subsequent IL-1β expression in KC [106]. Mitochondrial N-formyl peptides were released from hepatocyte trigger formyl peptide receptor 1 on KC, subsequently stimulating NF-κB activity [5]. Our recent work demonstrated that WT mice fed with HFD developed hepatic inflammation and fibrosis and had increased mtDNA and TFAM in the liver tissue, while those same phenomena in miR-29a transgene mice fed with HFD are greatly reduced [44], indicating that miR-29a may exert an anti-inflammatory effect on the pathogenesis of NAFLD by restricting mtDAMPs.
Nevertheless, how miR-29a performs on the mitochondrial restrictive mechanism over these danger signal molecules warrants further study.

Some other miRs also present impacts on pathways mastering mitochondrial functions in the liver. MiR-122 was shown to be required for mitochondrial translation of respiratory proteins, improvement of mitochondrial respiratory enzyme activity and enhancement of mitochondrial proteostasis in the liver [107]. Inhibition of miR-34a was shown to mitigate steatosis in an experimental NAFLD model [108]. As miR-34a presents repressive activity on PPARα by direct association with its mRNA 3’UTR [108], the consequence of miR-34a inhibition could be mediated by an increase of PPARα level, resulting in increased mitochondrial biogenesis, decreased oxidative stress, and reduced inflammatory response. In a similar manner, miR-21 also play a negative role through suppresses PPARα. Inhibition of miR-21 restores PPARα level to exert protective effect on liver inflammation and fibrosis in an experimental mouse NASH [109].

5. Role of miR-29a in Mitochondrial Metabolism

Mitochondrial dysfunction in hepatocytes is a major hallmark of NAFLD [110,111]. While the exact mechanism underlying hepatic mitochondrial dysfunction during NAFLD is not fully understood, one possible reason may be that the HFD-caused flux of free FA into the liver leads to lowered mitochondrial respiratory chain activity, incomplete β-oxidation, decreased ATP synthesis, and dysregulated TCA cycle metabolism, all of which may bring about oxidative stress and lipotoxicity which can contribute to hepatic inflammation, insulin resistance and fibrogenic signaling [112,113].

CD36, an FA translocase, acts as a multifunctional membrane protein that facilitates the uptake of long-chain FA [114]. CD36 is a shared target of LXR, PXR, and PPAR-γ in their mediation of lipid homeostasis [115]. CD36 upregulation has been shown to be coupled with the blunted breakdown of hepatic triglyceride in mice fed an HFD, while CD36 also binds to ox-LDL in the liver [116]. Furthermore, higher plasma concentrations of CD36 were associated with body adiposity, reflecting more severe liver damage in NAFLD in humans [117]. The knockdown of CD36 contributes to improving lipid accumulation in the human hepatic cell line HepG2 [118], suggesting that the liver-specific knockout of CD36 decreases hepatic lipid levels, increases FA oxidation (FAO), and reduces liver inflammatory markers in HF diet-induced steatosis [119]. FAO primarily occurs in mitochondria, as well as in peroxisomes and cytochromes [120,121]. Mitochondrial dysfunction is an important feature of excessive FA influx, while increased FAO produces ROS and induces oxidative stress [122]. This imbalanced redox status can further promote damage to the mitochondrial membranes, leading to compromised liver function [123]. Cholesterol, especially oxidized (ox)-LDL, can recruit infiltrating macrophages and regenerate KC to contribute to the progression of NASH [124]. CD36-mediated ox-LDL also triggers CEBP-β expression to directly upregulate Nogo-B and promote lipophagy, causing lysophosphatidic acid-enhanced yes-associated protein 1 (YAP) oncogenic activity, which subsequently induces carcinogetic signaling for NAFLD-associated HCC [2]. Ho et al. also revealed the perportal presents free cholesterol and ox-LDL accumulation that is associated with regional HSC activation and liver fibrosis in both human NAFLD [125] and mice [126]. Furthermore, Kawanishi et al. demonstrated that exercise training inhibits CD36 expression in KC and the liver of HFD and high-fructose water model mice [127].

In 2019, Chen et al. reported that ox-LDL/CD36 signaling in macrophage links dysregulated FA metabolism and oxidative stress from the mitochondria, which drove chronic inflammation in the atherosclerosis model [122]. Our group also discovered that miR-29a protects against glucocorticoid-mediated osteoporosis by suppressing the activity of osteoclasts and differentiating from macrophages [128], thus supporting its role in regulating immune cell activity. As a result, CD36 may play a role in linking FA metabolism with mitochondrial oxidative stress and inflammation, as well as be a promising target for reversing hepatic dysfunction in NAFLD.

On the bioinformatic basis that CD36 is a potential miR-29a target, our recent study further demonstrated that miR-29a in vitro directly binds to mRNA 3’UTR of CD36 and suppresses its
expression in HepG2 cells [44]. Under HFD, wild type mice develop steatosis and steatofibrosis and show an increased hepatic CD36 level, as well as elevated mtDAMPs and pro-inflammatory genes, while these phenotypes and markers are significantly reduced in miR-29aTg mice [44]. These findings support that lipid accumulation and hepatic inflammation could be effective counteracted on the basis of modulating the miR-29a/CD36/mitochondria axis (Figure 1). Nevertheless, the role of miR-29a in individual cell types (hepatocyte, KC, and HSC) and how it regulates intercellular cross-talk requires further study.

**Figure 1.** Role of miR-29a on modulating hepatic mtDAMPs release, lipid metabolism, inflammation, and fibrogenic signaling in the pathogenesis of NAFLD. Underlined genes represent miR-29a targets. BAX, Bcl-2-associated X protein; FGL2, fibrinogen-like 2; LPL, lipoprotein lipase; mtDAMPs, mitochondrial danger-associated molecular patterns; mtDNA, mitochondrial DNA; mtdsRNA, mitochondrial double-stranded RNA; NFP, N-formyl peptides; PRRs, pattern recognition receptors; NLRP3, NOD-like receptor family pyrin domain containing 3; TLR9, toll-like receptor 9.

In addition to nutrient metabolism, the dynamic properties of mitochondria—including their fusion, fission, and degradation—are vital for their optimal function and quality control [129]. Recent studies have suggested that mitochondrial dynamics and quality control mechanism mitophagy play a key role in NAFLD [130]. Several lines of evidence have revealed that miR-29a can modulate mitochondrial homeostasis by directly targeting key genes. With regard to protecting mitochondrial structural integrity, miR-29a can target voltage-dependent anion channel [131] and Bcl-2-associated X (BAX) genes [132], whose oligomerization is involved in MPT pore opening and mtDAMPs release [100,133]. The p53 upregulated modulator of apoptosis (PUMA), an activator of BAX/BAK for the induction of MPT and subsequent apoptosis, can also be targeted by miR-29a [134]. Moreover, one computational analysis revealed that miR-29a targets dyanin-related protein 1 (DRP1) [135], implying its potential role in regulating mitochondrial dynamics and mitophagy. In line with the aforementioned studies, our experimental results have shown that liver protective-miR-29a can reduce BAX expression [46]. More in-depth studies are warranted to investigate the therapeutic potential of miR-29a and shed light on the sophisticated interplay between miR-29a, mitochondrial repurposing, and inflammatory signaling.

In this regard, miR-34a/SIRT1/AMPK pathway was shown to cause mitochondrial dysfunction in mouse NASH model [136]. Another late study presented that miR-34a impair
mitochondria quality control mechanism through Sirt3/FoxO3a/PINK1 signaling in an experimental mouse model of liver inflammation [137].

### 6. MiRNAs Involved in Lipid Metabolism of NALFD

In the context of NAFLD, dysregulated miRs critically contribute to perturb pathways for lipid metabolism, including (i) synthesis of FA, triglycerides, and cholesterol, (ii) uptake of lipid in the blood, (iii) hepatic export of lipid and (iv) lipid oxidation [14]. These aberrations could aggravate steatosis and impair cellular redox, leading to lipid peroxidation [138]. Furthermore, lipid peroxidation-produced 1,4-hydroxy-trans-2-nonenal (HNE) was shown to activate proinflammatory transcription factor NF-κB [139]. In this regard, miR-122 which is the most abundant miRs in the liver was recognized as a prominent example in these metabolic processes. Overexpression of miR-122 was shown to counteract lipid accumulation in cultured hepatocytes or in the liver of NASH mouse model through several mechanisms, such as: (i) Yin Yang 1, farnesoid X receptor, and small heterodimer partner (YY1/FXR/SHP) axis [140]; (ii) hypoxia-inducible factor-1alpha, vimentin, and mitogen-activated protein kinase kinase kinase 3 (HIF-1α/vimentin/MAP3K3) axis [141]; (iii) hepatocyte nuclear factor 4α (HNF4α) pathway [142]; stearyl-CoA desaturase gene (SCD) [143].

In addition, the key role of miR-21 in hepatic lipid metabolism has recently been highlighted [14,144]. miR-21 can target phosphatase and tensin homolog (PTEN), which prevents hepatic steatosis, and PPARα, which activates lipid oxidation. Hepatocyte-specific knockout of miR-21 in mice improved HFD-induced steatosis through upregulation of multiple miR-21-targeted pathways governing lipid metabolism [145]. In lung cancer cells, inhibition of miR-21 was shown to restrain FA uptake by down-regulating CD36 protein expression [146].

MiR-33 is intimately implicated in both cholesterol and FA metabolism. In hepatic cell lines, miR-33 targets ABCA1 and ABCG1, which are cholesterol efflux regulatory proteins, and carnitine Palmitoyltransferase 1A (CPT1A) and AMPKα [147,148], which regulate FA β-oxidation. However, the effect of miR-33 in the pathogenesis of NAFLD appears to be debatable. Horie et al. showed that deletion of miR-33 in mice results in aggravating obesity and liver fibrosis induced by HFD via targeting sterol regulatory element-binding protein 1 (SREBP1) [149]. As well, Price et al. demonstrated that abrogation of miR-33 promotes obesity and insulin resistance [150]. On the contrary, Karunakaran et al. presented therapeutic effect of miR-33 inhibitor on promoting FA oxidation and preventing atherosclerosis in mice [151].

Of particular note, the central role of miR-29a in lipid metabolism was identified by Mattis et al. Their study conducted a bias-free, hepatocyte-specific global miRNAs deficiency in mouse and combined gene/miR profiling, demonstrating that miR-29a acts to prevent lipid accumulation in the liver by targeting lipoprotein lipase (LPL) 3′UPR [152]. These evidences underscore miR-29a/LPL axis’s close involvement in the reprogramming of lipid distribution in the liver, which may account for preventing steatosis-steatohepatitis transition (Figure 1).

### 7. The Role of miR-29a in Fibrogenesis

Stressed hepatocyte release mtDAMPs, which leads to KC activation. Inflammatory mediators secreted by activated KC trigger activation of HSC. HSC activation consequently plays a central role for liver fibrogenesis, because these cells transdifferentiate into myofibroblasts and represent the major extracellular matrix producing cells [5,153,154]. Free cholesterol accumulation caused-lipotoxicity sensitizes HSCs to TGFβ-induced activation through TLR4 signaling in NASH mouse model [155]. Our previous work showed that overexpression of miR-29a exerts anti-fibrotic effect in BDL mouse model, and acts to reduce fibrogenesis by down-regulating COL1A1 and induce HSC apoptosis by enhancing PTEN [39]. Meanwhile, our findings revealed that miR-29a also regulates innate immune response through surpassing pattern recognition receptors TLR2/TLR4 in HSC. This effect in vivo contributes to a reduction of MyD88 and NK-kB, leading to decreased proinflammatory cytokines [45]. In NASH mouse model, we demonstrated that miR-29aTg provides protective effect through suppressing TGF-β...
and SMAD3 [37], two critical positive regulator of HSC activation [156]. Furthermore, we recently uncovered that anti-fibrotic effect of miR-29a is associated with inhibition of bromodomain-containing protein 4 (BRD4) in HSC [38], which represents a novel therapeutic target of liver fibrosis [157]. In view of using miR-29a as an interventional approach, Matsumoto et al. have demonstrated that administration of miR-29a can reverse liver fibrosis in CCl4- and thioacetamide-treated mice. Mechanical study revealed that miR-29 in HSC inhibits extracellular matrix production via targeting COL1A1 and FGL2, proliferation via targeting mitogen-activated protein kinase kinase kinase kinase 4 (MAP4K4) and platelet-derived growth factor C (PDGFC). It also acts to anti-inflammation and pro-apoptosis through repressing IL-1β and BCL-2 [48]. In addition, Knabel et al. demonstrated that administration of adeno-associated virus (AAV) serotype 8-encoded miR-29a prevents CCl4-induced liver fibrosis [158].

In contrast to miR-29a, studies with reference to miR-34a is still in dispute. MiR-29a was reported to exert detrimental effect in promoting HSC activation and liver fibrosis via targeting Sirt1 [159], while another study demonstrated that overexpression of miR-34 in HSCs ameliorated the development and progression of liver fibrosis by targeting Smad4 and regulating TGF-β1/Smad3 pathway [160]. In addition, exogenous mir-122 was shown to exerts inhibitory effect on mouse liver fibrosis and HSC activation via a mutual modulation with sterol regulatory element-binding protein-1c (SREBP-1c) [161].

8. Conclusions

NAFLD can be caused by lipid dysregulation in hepatocytes, elevated ROS, and the activation of proinflammatory mediators of KC, as well as fibrogenic pathways of activated HSC, thus leading to NASH and NASF and rendering a predisposed milieu for cirrhosis and HCC. Therefore, curative approaches focused on modulating epigenetic modification and the inhibition of metabolic damage, oxidative stress, inflammation, and fibrogenic signaling to treat NAFLD is vital but challenging. As such, the role of miR-29a is emerging because its versatile function on epigenetic activity, mitochondrial homeostasis, and immunomodulation may improve our understanding of NAFLD (Figure 1). Increasing evidence has emphasized that miR-based therapeutic tools have potential and the significance of miR-29a is emerging, paving an innovative path for the future treatment of NAFLD.

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References

1. Rinella, M.E. Nonalcoholic fatty liver disease: A systematic review. JAMA 2015, 313, 2263–2273. [CrossRef] [PubMed]
2. Tian, Y.; Yang, B.; Qiu, W.; Hao, Y.; Zhang, Z.; Yang, B.; Li, N.; Cheng, S.; Lin, Z.; Rui, Y.C.; et al. ER-residential Nogo-B accelerates NAFLD-associated HCC mediated by metabolic reprogramming of oxLDL lipophagy. Nat. Commun. 2019, 10, 3391. [CrossRef] [PubMed]
3. El Hadi, H.; Di Vincenzo, A.; Vettor, R.; Rossato, M. Cardio-Metabolic Disorders in Non-Alcoholic Fatty Liver Disease. Int. J. Mol. Sci. 2019, 20, 2215. [CrossRef] [PubMed]
4. Lombardi, R.; Fargion, S.; Fracanzani, A.L. Brain involvement in non-alcoholic fatty liver disease (NAFLD): A systematic review. Dig. Liver Dis. 2019, 51, 1214–1222. [CrossRef] [PubMed]
5. Lee, J.; Park, J.S.; Roh, Y.S. Molecular insights into the role of mitochondria in non-alcoholic fatty liver disease. Arch. Pharm. Res. 2019, 42, 935–946. [CrossRef] [PubMed]
6. Leveille, M.; Estall, J.L. Mitochondrial Dysfunction in the Transition from NASH to HCC. Metabolites 2019, 9, 233. [CrossRef] [PubMed]
7. Stavast, C.J.; Erkeland, S.J. The Non-Canonical Aspects of MicroRNAs: Many Roads to Gene Regulation. *Cells* 2019, 8, 1465. [CrossRef]
8. Bartel, D.P. MicroRNAs: Genomics, biogenesis, mechanism, and function. *Cell* 2004, 116, 281–297. [CrossRef]
9. Xiao, M.; Li, J.; Li, W.; Wang, Y.; Wu, F.; Xi, Y.; Zhang, L.; Ding, C.; Luo, H.; Li, Y.; et al. MicroRNAs activate gene transcription epigenetically as an enhancer trigger. *RNA Biol.* 2017, 14, 1326–1334. [CrossRef]
10. Lee, I.; Ajay, S.S.; Yook, J.I.; Kim, H.S.; Hong, S.H.; Kim, N.H.; Dhanasekaran, S.M.; Chinnaiyan, A.M.; Athey, B.D. New class of microRNA targets containing 5′-UTR and 3′-UTR interaction sites. *Genome Res.* 2009, 19, 1175–1183. [CrossRef]
11. Fabbri, M.; Paone, A.; Calore, F.; Galli, R.; Croce, C.M. A new role for microRNAs, as ligands of Toll-like receptors. *RNA Biol.* 2013, 10, 169–174. [CrossRef] [PubMed]
12. Fabbri, M.; Paone, A.; Calore, F.; Galli, R.; Gaudio, E.; Santhanam, R.; Lovat, F.; Fadda, P.; Mao, C.; Nuovo, G.J.; et al. MicroRNAs bind to Toll-like receptors to induce prometastatic inflammatory response. *Proc. Natl. Acad. Sci. USA* 2012, 109, E2110–E2116. [PubMed]
13. Das, S.; Bedja, D.; Campbell, N.; Dunkerly, B.; Chenna, V.; Steenbergen, C. miR-181c regulates the mitochondrial genome, bioenergetics, and propensity for heart failure in vivo. *PLoS ONE* 2014, 9, e96820. [CrossRef] [PubMed]
14. Gjorgjieva, M.; Sobolewski, C.; Dolicka, D.; Correia de Sousa, M.; Foti, M. microRNAs and NAFLD: From pathophysiology to therapy. *Gut.* 2019, 68, 2065–2079. [CrossRef] [PubMed]
15. Vienberg, S.; Geiger, J.; Madsen, S.; Dalgaard, L.T. MicroRNAs in metabolism. *Acta Physiol.* 2017, 219, 346–361. [CrossRef] [PubMed]
16. Huang, Y.H.; Yang, Y.L.; Wang, F.S. The Role of miR-29a in the Regulation, Function, and Signaling of Liver Fibrosis. *Int. J. Mol. Sci.* 2018, 19, 1889. [CrossRef]
17. Kriegel, A.J.; Liu, Y.; Fang, Y.; Ding, X.; Liang, M. The miR-29 family: Genomics, cell biology, and relevance to renal and cardiovascular injury. *Physiol. Genom.* 2012, 44, 237–244. [CrossRef]
18. Muller, M.; Jakel, L.; Bruinsma, I.B.; Claassen, J.A.; Kuiperij, H.B.; Verbeek, M.M. MicroRNA-29a Is a Candidate Biomarker for Alzheimer’s Disease in Cell-Free Cerebrospinal Fluid. *Mol. Neurobiol.* 2016, 53, 2894–2899. [CrossRef]
19. Goh, S.Y.; Chao, Y.X.; Dheen, S.T.; Tan, E.K.; Tay, S.S. Role of MicroRNAs in Parkinson’s Disease. *Int. J. Mol. Sci.* 2019, 20, 5649. [CrossRef] [PubMed]
20. Huang, J.; Song, G.; Yin, Z.; Fu, Z.; Ye, Z. MiR-29a and Messenger RNA Expression of Bone Turnover Markers in Canonical Wnt Pathway in Patients with Ankylosing Spondylitis. *Clin. Lab.* 2017, 63, 955–960. [CrossRef]
21. Huang, Y.Q.; Cai, A.P.; Chen, J.Y.; Huang, C.; Li, J.; Feng, Y.Q. The Relationship of Plasma miR-29a and Oxidized Low Density Lipoprotein with Atherosclerosis. *Cell Physiol. Biochem.* 2016, 40, 1521–1528. [CrossRef] [PubMed]
22. Zhao, Y.; Yuan, Y.; Qiu, C. Underexpression of CACNA1C Caused by Overexpression of microRNA-29a Underlies the Pathogenesis of Atrial Fibrillation. *Med. Sci. Monit.* 2016, 22, 2175–2181. [CrossRef] [PubMed]
23. Afum-Adjei Awuah, A.; Ueberberg, B.; Owusu-Dabo, E.; Frempong, M.; Jacobsen, M. Dynamics of T-cell IFN-gamma and miR-29a expression during active pulmonary tuberculosis. *Int. Immunol.* 2014, 26, 579–582. [CrossRef] [PubMed]
24. Jones, J.A.; Stroud, R.E.; O’Quinn, E.C.; Black, L.E.; Barth, J.L.; Elefteriades, J.A.; Bavaria, J.E.; Gorman, J.H., 3rd; Gorman, R.C.; Spinale, F.G.; et al. Selective microRNA suppression in human thoracic aneurysms: Relationship of miR-29a to aortic size and proteolytic induction. *Circ. Cardiovasc. Genet.* 2011, 4, 605–613. [CrossRef] [PubMed]
25. Millar, N.L.; Gilchrist, D.S.; Akbar, M.; Reilly, J.H.; Kerr, S.C.; Campbell, A.L.; Murrell, G.A.C.; Liew, F.Y.; Kurowska-Stolarska, M.; McInnes, I.B. MicroRNA29a regulates IL-33-mediated tissue remodelling in tendon disease. *Nat. Commun.* 2015, 6, 6774. [CrossRef]
26. Hsu, Y.C.; Chang, P.J.; Ho, C.; Huang, Y.T.; Shih, Y.H.; Wang, C.J.; Lin, C.L. Protective effects of miR-29a on diabetic glomerular dysfunction by modulation of DKK1/Wnt/beta-catenin signaling. *Sci Rep.* 2016, 6, 30575. [CrossRef]
27. Kawashita, Y.; Jinnin, M.; Makino, T.; Kajihara, I.; Makino, K.; Honda, N.; Masuguchi, S.; Fukushima, S.; Inoue, Y.; Ihn, H. Circulating miR-29a levels in patients with scleroderma spectrum disorder. *J. Derm. Sci.* 2011, 61, 67–69. [CrossRef] [PubMed]
28. Goldschmidt, I.; Thum, T.; Baumann, U. Circulating miR-21 and miR-29a as Markers of Disease Severity and Etiology in Cholestatic Pediatric Liver Disease. *J. Clin. Med.* 2016, 5, 28. [CrossRef]

29. Jampoka, K.; Muangpaisarn, P.; Khongnomnan, K.; Treeprasertsuks, S.; Tangkijvanich, P.; Payungporn, S. Serum miR-29a and miR-122 as Potential Biomarkers for Non-Alcoholic Fatty Liver Disease (NAFLD). *Microrna* 2018, 7, 215–222. [CrossRef]

30. Huang, C.; Zheng, J.M.; Cheng, Q.; Yu, K.K.; Ling, Q.X.; Chen, M.Q.; 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. [CrossRef]

31. Lambrecht, J.; Verhulst, S.; Reynaert, H.; van Grunsven, L.A. The miRFIB-Score: A Serological miRNA-Based Scoring Algorithm for the Diagnosis of Significant Liver Fibrosis. *Cells* 2019, 8, 1003. [CrossRef] [PubMed]

32. Roderburg, C.; Urban, G.W.; Bettermann, K.; Vucur, M.; Zimmermann, H.; Schmidt, S.; Janssen, J.; Koppe, C.; Knolle, P.; Castoldi, M.; et al. Micro-RNA profiling reveals a role for miR-29 in human and murine liver fibrosis. *Hepatology* 2011, 53, 209–218. [CrossRef] [PubMed]

33. Cho, H.J.; Kim, S.S.; Nam, J.S.; Kim, J.K.; Lee, J.H.; Kim, B.; Wang, H.J.; Kim, B.W.; Lee, J.D.; Kang, D.Y.; et al. Low levels of circulating microRNA-26a/29a as poor prognostic markers in patients with hepatocellular carcinoma who underwent curative treatment. *Clin. Res. Hepatol. Gastroenterol.* 2017, 41, 181–189. [CrossRef] [PubMed]

34. Wang, J.Y.; Zhang, Q.; Wang, D.D.; Yan, W.; Sha, H.H.; Zhao, J.H.; Yang, S.J.; Zhang, H.D.; Hou, J.C.; Xu, H.Z.; et al. MiR-29a: A potential therapeutic target and promising biomarker in tumors. *Biosci. Rep.* 2018, 38, BSР20171265. [CrossRef] [PubMed]

35. Zhu, H.T.; Dong, Q.Z.; Sheng, Y.Y.; Wei, J.W.; Wang, G.; Zhou, H.J.; Ren, N.; Jia, H.L.; Ye, Q.H.; Qin, L.X. MicroRNA-29a-5p is a novel predictor for early recurrence of hepatitis B virus-related hepatocellular carcinoma after surgical resection. *PLoS ONE* 2012, 7, e52393. [CrossRef] [PubMed]

36. Zhu, X.C.; Dong, Q.Z.; Zhang, X.F.; Deng, B.; Jia, H.L.; Ye, Q.H.; Qin, L.X.; Wu, X.Z. microRNA-29a suppresses cell proliferation by targeting SPARC in hepatocellular carcinoma. *Int. J. Mol. Med.* 2012, 30, 1321–1326. [CrossRef]

37. Yang, Y.L.; Kuo, H.C.; Wang, F.S.; Huang, Y.H. MicroRNA-29a Disrupts DNMT3b to Ameliorate Diet-Induced Non-Alcoholic Steatohepatitis in Mice. *Int. J. Mol. Sci.* 2019, 20, 1499. [CrossRef]

38. Huang, Y.H.; Kuo, H.C.; Yang, Y.L.; Wang, F.S. MicroRNA-29a is a key regulon that regulates BRD4 and mitigates liver fibrosis in mice by inhibiting hepatic stellate cell activation. *Int. J. Med. Sci.* 2019, 16, 212–220. [CrossRef]

39. Yang, Y.L.; Wang, F.S.; Li, S.C.; Tiao, M.M.; Huang, Y.H. MicroRNA-29a Alleviates Bile Duct Ligation Exacerbation of Hepatic Fibrosis in Mice through Epigenetic Control of Methyltransferases. *Int. J. Mol. Sci.* 2017, 18, 192. [CrossRef]

40. Huang, Y.H.; Tiao, M.M.; Huang, L.T.; Chuang, J.H.; Kuo, K.C.; Yang, Y.L.; Wang, F.S. Activation of Mir-29a in Activated Hepatic Stellate Cells Modulates Its Profibrogenic Phenotype through Inhibition of Histone Deacetylases 4. *PLoS ONE* 2015, 10, e0136453. [CrossRef]

41. Weidle, U.H.; Schmid, D.; Birzele, F.; Brinkmann, U. MicroRNAs Involved in Metastasis of Hepatocellular Carcinoma: Target Candidates, Functionality and Efficacy in Animal Models and Prognostic Relevance. *Cancer Genom. Proteom.* 2020, 17, 1–21. [CrossRef] [PubMed]

42. Song, G.; Tian, L.; Cheng, Y.; Liu, J.; Wang, K.; Li, S.; Li, T. Antitumor activity of sevoflurane in HCC cell line is mediated by miR-29a-induced suppression of Dnmt3a. *J. Cell Biochem.* 2019, 120, 18152–18161. [CrossRef] [PubMed]

43. Chen, Q.; Yin, D.; Zhang, Y.; Yu, L.; Li, X.D.; Zhou, Z.J.; Zhou, S.L.; Gao, D.M.; Hu, J.; Jin, C.; et al. MicroRNA-29a induces loss of 5-hydroxymethylcytosine and promotes metastasis of hepatocellular carcinoma through a TET-SONC-MMP9 signaling axis. *Cell Death Dis.* 2017, 8, e2906. [CrossRef] [PubMed]

44. Lin, H.Y.; Wang, F.S.; Yang, Y.L.; Huang, Y.H. MicroRNA-29a Suppresses CD36 to Ameliorate High Fat Diet-Induced Steatohepatitis and Liver Fibrosis in Mice. *Cells* 2019, 8, 1298. [CrossRef] [PubMed]

45. Lin, Y.C.; Wang, F.S.; Yang, Y.L.; Chuang, Y.T.; Huang, Y.H. MicroRNA-29a mitigation of toll-like receptor 2 and 4 signaling and alleviation of obstructive jaundice-induced fibrosis in mice. *Biochem. Biophys. Res. Commun.* 2018, 496, 880–886. [CrossRef] [PubMed]
46. Tiao, M.M.; Wang, F.S.; Huang, L.T.; Chuang, J.H.; Kuo, H.C.; Yang, Y.L.; Huang, Y.H. MicroRNA-29a protects against acute liver injury in a mouse model of obstructive jaundice via inhibition of the extrinsic apoptosis pathway. *Apoptosis* 2014, 19, 30–41. [CrossRef]
47. Ma, J.H.; Bu, X.; Wang, J.J.; Xie, Y.X. MicroRNA-29-3p Regulates Hepatocellular Carcinoma Progression Through NF-kappaB Pathway. *Clin. Lab.* 2019, 65. [CrossRef]
48. Matsumoto, Y.; Itami, S.; Kuroda, M.; Yoshizato, K.; Kawada, N.; Murakami, Y. MiR-29a Assists in Preventing the Activation of Human Stellate Cells and Promotes Recovery From Liver Fibrosis in Mice. *Mol. Ther.* 2016, 24, 1848–1859. [CrossRef]
49. Xuan, J.; Guo, S.L.; Huang, A.; Xu, H.B.; Shao, M.; Yang, Y.; Wen, W. MiR-29a and miR-652 Attenuate Liver Fibrosis by Inhibiting the Differentiation of CD4+ T Cells. *Cell Struct. Funct.* 2017, 42, 95–103. [CrossRef]
50. Song, S.; Sun, K.; Dong, J.; Zhao, Y.; Liu, F.; Liu, H.; Sha, Z.; Mao, J.; Ding, G.; Guo, W.; et al. microRNA-29a regulates liver tumor-initiating cells expansion via Bcl-2 pathway. *Exp. Cell Res.* 2019, 387. [CrossRef]
51. Huang, Y.H.; Yang, Y.L.; Huang, F.C.; Tiao, M.M.; Lin, Y.C.; Tsai, M.H.; Wang, F.S. MicroRNA-29a mitigation of endoplasmic reticulum and autophagy aberrancy counteracts in obstructive jaundice-induced fibrosis in mice. *Exp. Biol Med. (Maywood)* 2018, 243, 13–21. [CrossRef] [PubMed]
52. Xiong, Y.; Fang, J.H.; Yun, J.P.; Yang, J.; Zhang, Y.; Jia, W.H.; Zhuang, S.M. Effects of microRNA-29 on apoptosis, tumorigenicity, and prognosis of hepatocellular carcinoma. *Hepatology* 2010, 51, 836–845. [CrossRef] [PubMed]
53. Li, S.C.; Wang, F.S.; Yang, Y.L.; Tiao, M.M.; Chuang, J.H.; Huang, Y.H. Microarray Study of Pathway Analysis Expression Profile Associated with MicroRNA-29a with Regard to Murine Cholestatic Liver Injuries. *Int. J. Mol. Sci.* 2016, 17, 324. [CrossRef] [PubMed]
54. Zhu, L.R.; Feng, J.L.; Liu, X.J.; Wang, J.M. LncRNA HULC promotes HCC growth by downregulating miR-29. *Zhonghua Zhong Liu Za Zhi* 2019, 41, 659–666. [PubMed]
55. Zhang, Y.; Yang, L.; Wang, S.; Liu, Z.; Xiu, M. MiR-29a suppresses cell proliferation by targeting SIRT1 in hepatocellular carcinoma. *Cancer Biomark.* 2018, 22, 151–159. [CrossRef] [PubMed]
56. Kong, G.; Zhang, J.; Zhang, S.; Shan, C.; Ye, L.; Zhang, X. Upregulated microRNA-29a by hepatitis B virus X protein enhances hepatoma cell migration by targeting PTEN in cell culture model. *PLoS ONE* 2011, 6, e19518. [CrossRef] [PubMed]
57. Lee, R.C.; Feinbaum, R.L.; Ambros, V. The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. *Cell* 1993, 75, 843–854. [CrossRef]
58. Krutzfeldt, J.; Rajewsky, N.; Braich, R.; Rajeev, K.G.; Tuschl, T.; Manoharan, M.; Stoffel, M. Silencing of microRNAs in vivo with ‘antagomirs’. *Nature* 2005, 438, 685–689. [CrossRef]
59. Pirola, C.J.; Fernandez Gianotti, T.; Castano, G.O.; Mallardi, P.; San Martino, J.; Mora Gonzalez Lopez, P.; et al. 9p24.1 microRNA-29a protects against acute liver injury in a mouse model of obstructive jaundice via inhibition of the extrinsic apoptosis pathway. *Apoptosis* 2014, 19, 30–41. [CrossRef]
60. Becker, P.P.; Rau, M.; Schmitt, J.; Malsch, C.; Hammer, C.; Bantel, H.; Mullhaupt, B.; Geier, A. Performance of Serum microRNAs -122, -192 and -21 as Biomarkers in Patients with Non-Alcoholic Steatohepatitis. *PLoS ONE* 2015, 10, e0142661. [CrossRef]
61. Cermelli, S.; Ruggieri, A.; Marrero, J.A.; Ioannou, G.N.; Beretta, L. Circulating microRNAs in patients with chronic hepatitis C and non-alcoholic fatty liver disease. *PLoS ONE* 2011, 6, e23937. [CrossRef] [PubMed]
62. Auguet, T.; Aragones, G.; Berlanga, A.; Guiu-Jurado, E.; Marti, A.; Martinez, S.; Sabench, F.; Hernandez, M.; Aguilar, C.; Sirvent, J.J.; et al. miR33a/miR33b* and miR122 as Possible Contributors to Hepatic Lipid Metabolism in Obese Women with Nonalcoholic Fatty Liver Disease. *Int. J. Mol. Sci.* 2016, 17, 1620. [CrossRef] [PubMed]
63. Liu, X.L.; Pan, Q.; Zhang, R.N.; Shen, F.; Yan, S.Y.; Sun, C.; Xu, Z.J.; Chen, Y.W.; Fan, J.G. Disease-specific miR-34a as diagnostic marker of non-alcoholic steatohepatitis in a Chinese population. *World J. Gastroenterol.* 2016, 22, 9844–9852. [CrossRef] [PubMed]
64. Yamada, H.; Suzuki, K.; Ichino, N.; Ando, Y.; Sawada, A.; Osakabe, K.; Sugimoto, K.; Ohashi, K.; Teradaira, R.; Inoue, T.; et al. Associations between circulating microRNAs (miR-21, miR-34a, miR-122 and miR-451) and non-alcoholic fatty liver. *Clin. Chim. Acta* 2013, 424, 99–103. [CrossRef] [PubMed]
65. Ogawa, T.; Enomoto, M.; Fujii, H.; Sekiya, Y.; Yoshizato, K.; Ikeda, K.; Kawada, N. MicroRNA-221/222 upregulation indicates the activation of stellate cells and the progression of liver fibrosis. Gut 2012, 61, 1600–1609. [CrossRef] [PubMed]

66. Jiang, C.; Liu, X.; Wang, M.; Lv, G.; Wang, G. High Blood miR-802 Is Associated With Poor Prognosis in HCC Patients by Regulating DNA Damage Response 1 (REDD1)-Mediated Function of T Cells. Oncol. Res. 2019, 27, 1025–1034. [CrossRef] [PubMed]

67. Xue, X.; Zhao, Y.; Wang, X.; Qin, L.; Hu, R. Development and validation of serum exosomal microRNAs as diagnostic and prognostic biomarkers for hepatocellular carcinoma. J. Cell Biochem. 2019, 120, 135–142. [CrossRef]

68. Kim, S.S.; Cho, H.J.; Nam, J.S.; Kim, H.J.; Kang, D.R.; Won, J.H.; Kim, J.; Kim, J.K.; Lee, J.H.; Kim, B.H.; et al. Plasma MicroRNA-21, 26a, and 29a-3p as Predictive Markers for Treatment Response Following Transarterial Chemoembolization in Patients with Hepatocellular Carcinoma. J. Korean Med. Sci. 2018, 33, e6. [CrossRef]

69. Zhang, Z.; Shen, S. Combined low miRNA-29s is an independent risk factor in predicting prognosis of patients with hepatocellular carcinoma after hepatectomy: A Chinese population-based study. Medicine (Baltim.) 2017, 96, e8795. [CrossRef]

70. Zhu, H.T.; Hasan, A.M.; Liu, R.B.; Zhang, Z.C.; Zhang, X.; Wang, J.; Wang, H.Y.; Wang, F.; Shao, J.Y. Serum microRNA profiles as prognostic biomarkers for HBV-positive hepatocellular carcinoma. Oncotarget 2016, 7, 45637–45648. [CrossRef]

71. Eguchi, A.; Lazaro, R.G.; Wang, J.; Kim, J.; Povero, D.; Williams, B.; Ho, S.B.; Starkel, P.; Schnabl, B.; Ohno-Machado, L.; et al. Extracellular vesicles released by hepatocytes from gastric infusion model of alcoholic liver disease contain a MicroRNA barcode that can be detected in blood. Hepatology 2017, 65, 475–490. [CrossRef] [PubMed]

72. Lopez-Riera, M.; Conde, I.; Tolosa, L.; Zaragoza, A.; Castell, J.V.; Gomez-Lechon, M.J.; 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. Pharm. 2017, 8, 3. [CrossRef] [PubMed]

73. Jia, N.; Lin, X.; Ma, S.; Ge, S.; Mu, S.; Yang, C.; Shi, S.; Gao, L.; Xu, J.; Bo, T.; et al. Amelioration of hepatic steatosis is associated with modulation of gut microbiota and suppression of hepatic miR-34a in Gynostemma pentaphylla (Thunb.) Makino treated mice. Nutr. Metab. (Lond.) 2018, 15, 86. [CrossRef] [PubMed]

74. Liu, J.; Xiao, Y.; Wu, X.; Jiang, L.; Yang, S.; Ding, Z.; Fang, Z.; Hua, H.; Kirby, M.S.; Shou, J. A circulating microRNA signature as noninvasive diagnostic and prognostic biomarkers for nonalcoholic steatohepatitis. Bmc. Genom. 2018, 19, 188. [CrossRef] [PubMed]

75. Liu, M.X.; Gao, M.; Li, C.Z.; Yu, C.Z.; Yan, H.; Peng, C.; Li, Y.; Li, C.G.; Ma, Z.L.; Zhao, Y.; et al. Dicer1/miR-29/HMGCR axis contributes to hepatic free cholesterol accumulation in mouse non-alcoholic steatohepatitis. Acta. Pharm. Sin. 2017, 38, 660–671. [CrossRef] [PubMed]

76. Oses, M.; Margarote Sanchez, J.; Portillo, M.P.; Aguilera, C.M.; Labayen, I. Circulating miRNAs as Biomarkers of Obesity and Obesity-Associated Comorbidities in Children and Adolescents: A Systematic Review. Nutrients 2019, 11, 2890. [CrossRef] [PubMed]

77. Joven, J.; Espinel, E.; Rull, A.; Aragones, G.; Rodriguez-Gallego, E.; Camps, J.; Micol, V.; Herranz-Lopez, M.; Menendez, J.A.; Borras, I.; et al. Plant-derived polyphenols regulate expression of miRNA paralogs miR-103/107 and miR-122 and prevent diet-induced fatty liver disease in hyperlipidemic mice. Biochim. Biophys. Acta 2012, 1820, 894–899. [CrossRef] [PubMed]

78. Mehta, R.; Otgonsuren, M.; Younoszai, Z.; Allawi, H.; Raybuck, B.; Younossi, Z. Circulating miRNA in patients with non-alcoholic fatty liver and coronary artery disease. BMJ Open Gastroenterol. 2016, 3, e000096. [CrossRef]

79. Celikbilek, M.; Baskol, M.; Taheri, S.; Deniz, K.; Dogan, S.; Zararsiz, G.; Gursoy, S.; Guven, K.; Ozbakir, O. Circulating microRNAs in patients with non-alcoholic fatty liver disease. World J. Hepatol 2014, 6, 613–620. [CrossRef] [PubMed]

80. Babu, K.R.; Muckenthaler, M.U. miR-148a regulates expression of the transferrin receptor 1 in hepatocellular carcinoma. Sci. Rep. 2019, 9, 1518. [CrossRef] [PubMed]

81. Long, X.R.; He, Y.; Huang, C.; Li, J. MicroRNA-148a is silenced by hypermethylation and interacts with DNA methyltransferase 1 in hepatocellular carcinogenesis. Int. J. Oncol. 2014, 44, 1915–1922. [CrossRef] [PubMed]
82. Huang, R.; Duan, X.; Liu, X.; Cao, H.; Wang, Y.; Fan, J.; Wang, B. Upregulation of miR-181a impairs lipid metabolism by targeting PPARα expression in nonalcoholic fatty liver disease. Biochem. Biophys. Res. Commun. 2019, 508, 1252–1258. [CrossRef] [PubMed]

83. Du, X.; Yang, Y.; Xu, C.; Peng, Z.; Zhang, M.; Lei, L.; Gao, W.; Dong, Y.; Shi, Z.; Sun, X.; et al. Upregulation of miR-181a impairs hepatic glucose and lipid homeostasis. Oncotarget 2017, 8, 91362–91378. [CrossRef]

84. Tryndyak, V.P.; Latendresse, J.R.; Montgomery, B.; Ross, S.A.; Beland, F.A.; Rusyn, I.; Pogribny, I.P. Plasma microRNAs are sensitive indicators of inter-strain differences in the severity of liver injury induced in mice by a choline- and folate-deficient diet. Toxicol. Appl. Pharm. 2012, 262, 52–59. [CrossRef] [PubMed]

85. Dongiovanni, P.; Meroni, M.; Longo, M.; Fargion, S.; Fracanzani, A.L. miRNA Signature in NAFLD: A Turning Point for a Non-Invasive Diagnosis. Int. J. Mol. Sci 2018, 19, 3966. [CrossRef] [PubMed]

86. Portela, A.; Esteller, M. Epigenetic modifications and human disease. Nat. Biotechnol. 2010, 28, 1057–1068. [CrossRef] [PubMed]

87. Kanherkar, R.R.; Bhatia-Dey, N.; Csoka, A.B. Epigenetics across the human lifespan. Front. Cell Dev. Biol. 2014, 2, 49. [CrossRef] [PubMed]

88. Lind, M.I.; Spagopoulou, F. Evolutionary consequences of epigenetic inheritance. Hered. (Edinb) 2018, 121, 205–209. [CrossRef] [PubMed]

89. Chen, X.; Li, W.X.; Chen, Y.; Li, X.F.; Li, H.D.; Huang, H.M.; Bu, F.T.; Pan, X.Y.; Yang, Y.; Huang, C.; et al. Suppression of SUN2 by DNA methylation is associated with HSCs activation and hepatic fibrosis. Cell Death Dis. 2018, 9, 1021. [CrossRef]

90. Sheen-Chen, S.M.; Lin, C.R.; Chen, K.H.; Lee, C.T.; Huang, H.W.; Huang, C.Y. Epigenetic histone methylation regulates transforming growth factor beta-1 expression following bile duct ligation in rats. J. Gastroenterol. 2014, 49, 1285–1297. [CrossRef]

91. Perugorria, M.J.; Wilson, C.L.; Zeybel, M.; Walsh, M.; Amin, S.; Robinson, S.; White, S.A.; Burt, A.D.; Oakley, F.; Tsukamoto, H.; et al. Histone methyltransferase ASH1 orchestrates fibrogenic gene transcription during myofibroblast transdifferentiation. Hepatology 2012, 56, 1129–1139. [CrossRef] [PubMed]

92. Mantena, S.K.; Vaughn, D.P.; Andringa, K.K.; Eccleston, H.B.; King, A.L.; Abrams, G.A.; Doeller, J.E.; Kraus, D.W.; Darley-Usmar, V.M.; Bailey, S.M. High fat diet induces dysregulation of hepatic oxygen gradients and mitochondrial function in vivo. Biochem. J. 2009, 417, 183–193. [CrossRef]

93. Fan, W.X.; Wen, X.L.; Xiao, H.; Yang, Q.P.; Liang, Z. MicroRNA-29a enhances autophagy in podocytes as a protective mechanism against high glucose-induced apoptosis by targeting heme oxygenase-1. Eur. Rev. Mol. Pharm. Sci. 2018, 22, 8909–8917.

94. Vringer, E.; Tait, S.W.G. Mitochondria and Inflammation: Cell Death Heats Up. Front. Cell Dev. Biol. 2019, 7, 100. [CrossRef]

95. Zhong, Z.; Liang, S.; Sanchez-Lopez, E.; He, F.; Shalapour, S.; Lin, X.J.; Wong, J.; Ding, S.; Seki, E.; Schnabl, B.; et al. New mitochondrial DNA synthesis enables NLRP3 inflammasome activation. Nature 2018, 560, 198–203. [CrossRef] [PubMed]

96. Dhir, A.; Dhir, S.; Borowski, L.S.; Jimenez, L.; Teitell, M.; Rotig, A.; Crow, Y.J.; Rice, G.I.; Duffy, D.; Tamby, C.; et al. Mitochondrial double-stranded RNA triggers antiviral signalling in humans. Nature 2018, 560, 238–242. [CrossRef] [PubMed]

97. Marques, P.E.; Oliveira, A.G.; Pereira, R.V.; David, B.A.; Gomides, L.F.; Saraiva, A.M.; Pires, D.A.; Novaes, J.T.; Patricio, D.O.; Cisalpino, D.; et al. Hepatic DNA deposition drives drug-induced liver injury and inflammation in mice. Hepatology 2015, 61, 348–360. [CrossRef] [PubMed]
102. Garcia-Martinez, I.; Santoro, N.; Chen, Y.; Hoque, R.; Ouyang, X.; Caprio, S.; Shlomchik, M.J.; Coffman, R.L.; Candida, A.; Mehal, W.Z. Hepatocyte mitochondrial DNA drives nonalcoholic steatohepatitis by activation of TLR9. *J. Clin. Investig.* 2016, **126**, 859–864. [CrossRef] [PubMed]

103. Murgia, M.; Giorgi, C.; Pinton, P.; Rizzuto, R. Controlling metabolism and cell death: At the heart of mitochondrial calcium signalling. *J. Mol. Cell Cardiol.* 2009, **46**, 781–788. [CrossRef] [PubMed]

104. Murphy, M.P. How mitochondria produce reactive oxygen species. *Biochem. J.* 2009, **417**, 1–13. [CrossRef] [PubMed]

105. Chaung, W.W.; Wu, R.; Ji, Y.; Dong, W.; Wang, P. Mitochondrial transcription factor A is a proinflammatory mediator in hemorrhagic shock. *Int. J. Mol. Med.* 2012, **30**, 199–203.

106. Lee, J.H.; Shim, Y.R.; Seo, W.; Kim, M.H.; Choi, W.M.; Kim, H.H.; Kim, Y.E.; Yang, K.; Ryu, T.; Jeong, J.M.; et al. Mitochondrial double-stranded RNA in exosome promotes interleukin-17 production through toll-like receptor 3 in alcoholic liver injury. *Hepatology* 2019. [CrossRef]

107. Zhang, R.; Wang, X.; Qu, J.H.; Liu, B.; Zhang, P.; Zhang, T.; Fan, P.C.; Wang, X.M.; Xiao, G.Y.; Su, Y.; et al. Caloric Restriction Induces MicroRNAs to Improve Mitochondrial Proteostasis. *iScience* 2019, **17**, 155–166. [CrossRef]

108. Ding, J.; Li, M.; Wan, X.; Jin, X.; Chen, S.; Yu, C.; Li, Y. Effect of miR-34a in regulating steatosis by targeting PPARalpha expression in nonalcoholic fatty liver disease. *Sci Rep.* 2015, **5**, 13729. [CrossRef]

109. Loyer, X.; Paradis, V.; Henrique, C.; Vion, A.C.; Colnot, N.; Guerin, C.L.; Devue, C.; On, S.; Scebtun, J.; Romain, M.; et al. Liver microRNA-21 is overexpressed in non-alcoholic steatohepatitis and contributes to the disease in experimental models by inhibiting PPARalpha expression. *Gut* 2016, **65**, 1882–1894. [CrossRef]

110. Rector, R.S.; Thyfault, J.P.; Uptergrove, G.M.; Morris, E.M.; Naples, S.P.; Borengasser, S.J.; Mikus, C.R.; Laye, M.J.; Laughlin, M.H.; Booth, F.W.; et al. Mitochondrial dysfunction precedes insulin resistance and hepatic steatosis and contributes to the natural history of non-alcoholic fatty liver disease in an obese rodent model. *J. Hepatol.* 2010, **52**, 727–736. [CrossRef]

111. Grattagliano, I.; de Bari, O.; Bernardo, T.C.; Oliveira, P.; Wang, D.Q.; Portincasa, P. Role of mitochondria in nonalcoholic fatty liver disease–from origin to propagation. *Clin. Biochem.* 2012, **45**, 610–618. [CrossRef] [PubMed]

112. Sunny, N.E.; Bril, F.; Cusi, K. Mitochondrial Adaptation in Nonalcoholic Fatty Liver Disease: Novel Mechanisms and Treatment Strategies. *Trends Endocrinol. Metab.* 2017, **28**, 250–260. [CrossRef] [PubMed]

113. Degli Esposti, D.; Hamelin, J.; Bosselut, N.; Saffroy, R.; Sebagh, M.; Pommier, A.; Martel, C.; Lemoine, A. Mitochondrial roles and cytoprotection in chronic liver injury. *Biochem. Res. Int.* 2012, **2012**, 387626. [CrossRef] [PubMed]

114. Zhong, S.; Zhao, L.; Wang, Y.; Zhang, C.; Liu, J.; Wang, P.; Zhou, W.; Yang, P.; Varghese, Z.; Moorhead, J.F.; et al. Cluster of Differentiation 36 Deficiency Aggravates Macrophage Infiltration and Hepatic Inflammation by Upregulating Monocyte Chemotactic Protein-1 Expression of Hepatocytes Through Histone Deacetylase 2-Dependent Pathway. *Antioxid. Redox Signal.* 2017, **27**, 201–214. [CrossRef] [PubMed]

115. Zhou, J.; Febbraio, M.; Wada, T.; Zhai, Y.; Kuruba, R.; He, J.; Lee, J.H.; Khadem, S.; Ren, S.; Li, S.; et al. Hepatic fatty acid transporter Cd36 is a common target of LXR, PXR, and PPARgamma in promoting steatosis. *Gastroenterology* 2008, **134**, 556–567. [CrossRef] [PubMed]

116. Zhan, Z.; Ren, H.; Peng, M.L. Role of CD36 in nonalcoholic fatty liver disease. *Zhonghua Gan Zang Bing Za Zhi* 2017, **25**, 953–956.

117. Wang, Y.; Koch, M.; di Giuseppe, R.; Evans, K.; Borggrefe, J.; Nothlings, U.; Handberg, A.; Jensen, M.K.; Lieb, W. Associations of plasma CD36 and body fat distribution. *J. Clin. Endocrinol. Metab.* 2019, **Jc.2019-00368. [CrossRef]

118. Li, Y.; Yang, P.; Zhao, L.; Chen, Y.; Zhang, X.; Zeng, S.; Wei, L.; Varghese, Z.; Moorhead, J.F.; Chen, Y.; et al. CD36 plays a negative role in the regulation of lipophagy in hepatocytes through an AMPK-dependent pathway. *J. Lipid Res.* 2019, **60**, 844–855. [CrossRef] [PubMed]

119. Wilson, C.G.; Tran, J.L.; Erion, D.M.; Vera, N.B.; Febbraio, M.; Weiss, E.J. Hepatocyte-Specific Disruption of CD36 Attenuates Fatty Liver and Improves Insulin Sensitivity in HFD-Fed Mice. *Endocrinology* 2016, **157**, 570–585. [CrossRef]

120. Begricher, K.; Massart, J.; Robin, M.A.; Bonnet, F.; Fromenty, B. Mitochondrial adaptations and dysfunctions in nonalcoholic fatty liver disease. *Hepatology* 2013, **58**, 1497–1507. [CrossRef]
121. Reddy, J.K.; Rao, M.S. Lipid metabolism and liver inflammation. II. Fatty liver disease and fatty acid oxidation. *Am. J. Physiol. Gastrointest Liver Physiol.* 2006, 290, G852–G858. [CrossRef] [PubMed]

122. Chen, Y.; Yang, M.; Huang, W.; Chen, W.; Zhao, Y.; Schulte, M.L.; Volberding, P.J.; Gerbec, Z.; Zimmermann, M.T.; Zeighammer, A.; et al. Mitochondrial Metabolic Reprogramming by CD36 Signaling Drives Macrophage Inflammatory Responses. *Circ. Res.* 2019, 125, 1087–1102. [CrossRef] [PubMed]

123. Ipsen, D.H.; Lykkesfeldt, J.; Tveden-Nyborg, P. Molecular mechanisms of hepatic lipid accumulation in non-alcoholic fatty liver disease. *Cell Mol. Life Sci.* 2018, 75, 3313–3327. [CrossRef]

124. McGettigan, B.; McMahan, R.; Orlicky, D.; Burchill, M.; Danhorn, T.; Francis, P.; Cheng, L.L.; Golden-Mason, L.; Jakubzick, C.V.; Rosen, H.R. Dietary Lipids Differentially Shape Nonalcoholic Steatohepatitis Progression and the Transcriptome of Kupffer Cells and Infiltrating Macrophages. *Hepatology* 2019, 70, 67–83. [CrossRef] [PubMed]

125. Ho, C.M.; Ho, S.L.; Jeng, Y.M.; Lai, Y.S.; Chen, Y.H.; Lu, S.C.; Chen, H.L.; Chang, P.Y.; Hu, R.H.; Lee, P.H. Accumulation of free cholesterol and oxidized low-density lipoprotein is associated with portal inflammation and fibrosis in nonalcoholic fatty liver disease. *J. Inflamm. (Lond)* 2019, 16, 7. [CrossRef] [PubMed]

126. Houben, T.; Oligschlaeger, Y.; Bitorina, A.V.; Hendrikx, T.; Walenbergh, S.M.A.; Lenders, M.H.; Gijbels, M.J.J.; Verheyen, F.; Lutjohann, D.; Hofker, M.H.; et al. Blood-derived macrophages prone to accumulate lysosomal lipids trigger oxLDL-dependent murine hepatic inflammation. *Sci. Rep.* 2017, 7, 12550. [CrossRef] [PubMed]

127. Kawanishi, N.; Mizokami, T.; Yada, K.; Suzuki, K. Exercise training suppresses scavenger receptor CD36 signalling and the pathogenesis of non-alcoholic fatty liver disease. *J. Hepatol.* 2018, 69, 927–947. [CrossRef] [PubMed]

128. Wu, R.W.; Lian, W.S.; Chen, Y.S.; Kuo, C.W.; Ke, H.C.; Hsieh, C.K.; Wang, S.Y.; Ko, J.Y.; Wang, F.S. Exercise training attenuates fibrosis in a murine model of non-alcoholic steatohepatitis. *Hepatology* 2019, 69, 1087–1102. [CrossRef] [PubMed]

129. Liu, Y.; Merrill, R.A.; Strack, S. A-Kinase Anchoring Protein 1: Emerging Roles in Regulating Mitochondrial Function and Form in Health and Disease. *Cells* 2020, 9, 298. [CrossRef]

130. Mansouri, A.; Gattolliat, C.H.; Asselah, T. Mitochondrial Dysfunction and Signaling in Chronic Liver Diseases. *Oxid Med. Cell Longev.* 2018, 2018, 690545. [CrossRef] [PubMed]

131. Bargaje, R.; Gupta, S.; Sarkeshik, A.; Park, R.; Xu, T.; Sarkar, M.; Halimani, M.; Roy, S.S.; Yates, J.; Pillai, B. Identification of novel targets for miR-29a using miRNA proteomics. *PLoS ONE* 2012, 7, e43243. [CrossRef] [PubMed]

132. Zhang, L.; Zhang, J.; Tong, Q.; Wang, G.; Dong, H.; Wang, Z.; Sun, Q.; Wu, H. Reduction of miR-29a-3p induced cardiac ischemia reperfusion injury in mice via targeting Bax. *Exp. Med.* 2019, 18, 1729–1737. [CrossRef] [PubMed]

133. Betaneli, V.; Petrov, E.P.; Schwille, P. The role of lipids in VDAC oligomerization. *Biophys. J.* 2012, 102, 523–531. [CrossRef] [PubMed]

134. OuYang, Y.B.; Xu, L.; Lu, Y.; Sun, X.; Yue, S.; Xiong, X.X.; Giffard, R.G. Astrocyte-enriched miR-29a targets PUMA and reduces neuronal vulnerability to forebrain ischemia. *Glia* 2013, 61, 1784–1794. [CrossRef] [PubMed]

135. Jan, M.I.; Khan, R.A.; Malik, A.; Ali, T.; Bilal, M.; Bo, L.; Sajid, A.; Ureham, N.; Waseem, N.; Nawab, J.; et al. Data of expression status of miR- 29a and its putative target mitochondrial apoptosis regulatory gene DRP1 upon miR-15a and miR-214 inhibition. *Data Brief.* 2018, 16, 1000–1004. [CrossRef]

136. Simao, A.L.; Afonso, M.B.; Rodrigues, P.M.; Gama-Carvalho, M.; Machado, M.V.; Cortez-Pinto, H.; Rodrigues, C.M.P.; Castro, R.E. Skeletal muscle miR-34a/SIRT1:AMPK axis is activated in experimental and human non-alcoholic steatohepatitis. *J. Mol. Med. (Berl)* 2019, 97, 1113–1126. [CrossRef]

137. Chen, F.; Feng, L.; Zheng, Y.L.; Lu, J.; Fan, S.H.; Shan, Q.; Zheng, G.H.; Wang, Y.J.; Wu, D.M.; Li, M.Q.; et al. 2′, 4′, 4′-tetrabromodiphenyl ether (BDE-47) induces mitochondrial dysfunction and related liver injury via eliciting miR-34a-5p-mediated mitophagy impairment. *Environ. Pollut.* 2020, 258, 113693. [CrossRef]

138. Lebeauvin, C.; Vallee, D.; Hazari, Y.; Hetz, C.; Chevet, E.; Bailly-Maître, B. Endoplasmic reticulum stress signalling and the pathogenesis of non-alcoholic fatty liver disease. *J. Hepatol.* 2018, 69, 927–947. [CrossRef] [PubMed]

139. Yadav, U.C.; Ramana, K.V. Regulation of NF-kappaB-induced inflammatory signaling by lipid peroxidation-derived aldehydes. *Oxid Med. Cell Longev.* 2013, 2013, 690545. [CrossRef]
140. Wu, G.Y.; Rui, C.; Chen, J.Q.; Sho, E.; Zhan, S.S.; Yuan, X.W.; Ding, Y.T. MicroRNA-122 Inhibits Lipid Droplet Formation and Hepatic Triglyceride Accumulation via Yin Yang 1. *Cell Physiol. Biochem.* 2017, **44**, 1651–1664. [CrossRef]

141. Csak, T.; Bala, S.; Lippai, D.; Sathishchandran, A.; Catalano, D.; Kody, K.; Szabo, G. microRNA-122 regulates hypoxia-inducible factor-1 and vimentin in hepatocytes and correlates with fibrosis in diet-induced steatohepatitis. *Liver Int.* 2015, **35**, 532–541. [CrossRef] [PubMed]

142. Li, Z.Y.; Xi, Y.; Zhu, W.N.; Zeng, C.; Zhang, Z.Q.; Guo, Z.C.; Hao, D.L.; Liu, G.; Feng, L.; Chen, H.Z.; et al. Positive regulation of hepatic miR-122 expression by HNF4alpha. *J. Hepatol.* 2011, **55**, 602–611. [CrossRef] [PubMed]

143. Qiang, J.; Tao, Y.F.; Bao, J.W.; Chen, J.; Li, H.X.; He, J.; Xu, P. High Fat Diet-Induced miR-122 Regulates Lipid Metabolism and Fat Deposition in Genetically Improved Farmed Tilapia (GIFT, Oreochromis niloticus) Liver. *Front. Physiol.* 2018, **9**, 1422. [CrossRef] [PubMed]

144. Rodrigues, P.M.; Rodrigues, C.M.P.; Castro, R.E. Modulation of liver steatosis by miR-21/PPARalpha. *Cell Death Discov.* 2018, **4**, 9. [CrossRef] [PubMed]

145. Calo, N.; Ramadori, P.; Sobolewski, C.; Romero, Y.; Maeder, C.; Fournier, M.; Rantakari, P.; Zhang, F.P.; Poutanen, M.; Dufour, J.F.; et al. 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. [CrossRef] [PubMed]

146. Ni, K.; Wang, D.; Xu, H.; Mei, F.; Wu, C.; Liu, Z.; Zhou, B. miR-21 promotes non-small cell lung cancer cells growth by regulating fatty acid metabolism. *Cancer Cell Int.* 2019, **19**, 219. [CrossRef] [PubMed]

147. Davalos, A.; Goedeke, L.; Smibert, P.; Ramirez, C.M.; Warrier, N.P.; Andreo, U.; Cirera-Salinas, D.; Rayner, K.; Suresh, U.; Pastor-Pareja, J.C.; et al. miR-33a/b contribute to the regulation of fatty acid metabolism and insulin signaling. *Proc. Natl. Acad. Sci. USA* 2011, **108**, 9232–9237. [CrossRef]

148. Rayner, K.J.; Suarez, Y.; Davalos, A.; Parathath, S.; Fitzgerald, M.L.; Rantakari, P.; Zhang, F.P.; Karhadkar, S.; Hwang, H.W.; Creamer, T.J.; Chivukula, R.R.; Sheikh, F.; Clark, K.R.; Torbenson, M.; Montgomery, R.A.; et al. Systemic Delivery of scAAV8-Encoded MiR-29a Ameliorates Hepatic Fibrosis in Carbon Tetrachloride-Treated Mice. *PLoS ONE* 2015, **10**, e0124411. [CrossRef]
159. Liu, Q.; Zhang, Y.; Yang, S.; Wu, Y.; Wang, J.; Yu, W.; Liu, Y. 1-deficient mice are resistant to thioacetamide-induced hepatic fibrosis: PU.1 finely regulates Sirt1 expression via transcriptional promotion of miR-34a and miR-29c in hepatic stellate cells. *Biosci. Rep.* 2017, 37, BSR20170926. [CrossRef]

160. Feili, X.; Wu, S.; Ye, W.; Tu, J.; Lou, L. MicroRNA-34a-5p inhibits liver fibrosis by regulating TGF-beta1/Smad3 pathway in hepatic stellate cells. *Cell Biol. Int.* 2018, 42, 1370–1376. [CrossRef]

161. Zhai, X.; Cheng, F.; Ji, L.; Zhu, X.; Cao, Q.; Zhang, Y.; Jia, X.; Zhou, Q.; Guan, W.; Zhou, Y. Leptin reduces microRNA-122 level in hepatic stellate cells in vitro and in vivo. *Mol. Immunol.* 2017, 92, 68–75. [CrossRef] [PubMed]

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