

REVIEW

Emerging role of microRNAs in lipid metabolism


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Abstract microRNAs (miRNAs or miRs) are small non-coding RNAs that are involved in post-transcriptional regulation of their target genes in a sequence-specific manner. Emerging evidence demonstrates that miRNAs are critical regulators of lipid synthesis, fatty acid oxidation and lipoprotein formation and secretion. Dysregulation of miRNAs disrupts gene regulatory network, leading to metabolic syndrome and its related diseases. In this review, we introduced epigenetic and transcriptional regulation of miRNAs expression. We emphasized on several representative miRNAs that are functionally involved into lipid metabolism, including miR-33/33*, miR122, miR27a/b, miR378/378*, miR-34a and miR-21.

Abbreviations: ABCA1, adenosine triphosphate-binding cassette transporter A1; ABCG1, adenosine triphosphate-binding cassette transporter G1; Ago2, argonaute 2; AMPK α , AMP-activated protein kinase α ; ApoA1, apolipoprotein A1; ATP8B1, aminophospholipid transporter, class I, type 8B, member 1; BDL, bile-duct ligation; CPT1A, carnitine palmitoyltransferase 1A; CRAT, carnitine O-acetyltransferase; CYP26, cytochrome P450 family 26; CYP3A4, cytochrome P450 family 3 subfamily A polypeptide 4; ERR γ , estrogen-related receptor gamma; FABP7, fatty acid-binding protein 7; FASN, fatty acid synthase; FGF21, fibroblast growth factor 21; FGFR1, fibroblast growth factor receptor 1; FXR, farnesoid X receptor; GABPA, GA binding protein transcription factor alpha subunit; GPC6, glypican 6; HADHB, hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase trifunctional protein, beta subunit; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HMGCR, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; HMGCS1, 3-hydroxy-3-methylglutaryl-coenzyme A synthase 1; HNE, 4-hydroxynonenal; IGF1R, insulin-like growth factor 1 receptor; IGFBP3, insulin-like growth factor binding protein 3; INSIG1, insulin induced gene 1; LIPE, lipase hormone-sensitive; LNA, locked nucleic acids; LNPs, lipid-based nanoparticles; LPS, lipopolysaccharide; MED13, mediator complex subunit 13; MHV68, murine γ -herpesvirus 68; miRNAs or miRs, microRNAs; MTP, microsomal TG transfer protein; NR1D1/REV-ERB α , transcriptional repressor nuclear receptor subfamily 1 group D member 1; NRS, nuclear receptors; PCK1, phosphoenolpyruvate carboxykinase 1; PDCD4, programmed cell death 4; PGC-1, peroxisome proliferator-activated receptor gamma coactivator; PLIN1, perilipin 1; PNA, peptide nucleic acid; PNPLA2, patatin-like phospholipase domain containing 2; PPAR γ , peroxisome proliferator-activated receptor gamma; pre-miRNAs, precursor-miRNAs; pri-miRNAs, primary-miRNAs; RTL1, retrotransposon-like 1; RXR α , retinoid X receptor alpha; SHP, small heterodimer partner; SIRT1, sirtuin 1; SIRT6, sirtuin 6; TG, triglyceride; TLR4, toll-like receptor 4

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Understanding the function of miRNAs in lipid homeostasis may provide potential therapeutic strategies for fatty liver disease.

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1. Introduction

Gene regulation networks are the representation of multiple levels within a cell¹. They provide a global view intended to help understand how relationships between molecules dictate cellular behavior. The recent advances in molecular biology and cutting-edge technologies reveal the emerging role of microRNAs in major physiological and pathological processes. microRNAs are small non-coding RNAs involving in post-transcriptional regulation of gene expression by binding to the 3'-UTRs of the target mRNAs. Many microRNA targets are key regulators of lipid metabolism and disease in the liver, suggesting the functional involvement of microRNAs in this process. In this review, we provide new insight into the specific role of microRNAs in lipid metabolism.

2. microRNA regulation network

microRNA genes are normally transcribed by Polymerase II or III² to generate primary-miRNAs (pri-miRNAs). These large RNA transcripts often contain several hundreds of base pairs in length and encode sequences for multiple miRNA genes. Before exported out of the nucleus by exportin-5, pri-miRNAs, which are capped and polyadenylated, need to be cleaved by Drosha to form hairpin-shaped stem-loop structures of approximately 60–70 nucleotides (nt), namely precursor-miRNAs (pre-miRNAs). In the cytoplasm, the pre-miRNAs are further processed by a second RNase III enzyme, named Dicer, into a miRNA-miRNA* duplex. One strand of the duplex, serving as the “guide” strand, is loaded into miRNP, a large multi-protein miRNA ribonucleoprotein complex, and is used to modulate target gene expression. The other strand of the duplex, namely miRNA*, is excluded and degraded¹. When the two strands of the pre-miRNA are more equal in their distribution, the opposite strand is named miRNA-3p instead of miRNA*. In turn, the guide strand is referred to as miRNA-5p, depending on the location to either 5' or 3' of the target miRNA molecule. Both strands could potentially have biological effects³.

In addition to the canonical miRNA biogenesis pathway, alternative pathways are emerging, including Drosha/DGCR8-independent or Dicer-independent pathway⁴. In the Drosha/DGCR8-independent pathway, three groups of miRNAs can generate pre-miRNA-like hairpins that serve directly as Dicer substrates without Drosha/DGCR8 processing, such as Mirtrons, endo-shRNAs and murine γ -herpesvirus 68 (MHV68) tRNA-shRNA fusions². In the Dicer-independent pathway, pri-miR-451 is processed by Drosha/DGCR8 to generate pre-miR-451 to be incorporated into argonaute 2 (Ago2), the latter cleaves the 3' arm of pre-miR-451. However, how the mature miR-451 is generated remains unclear^{5,6}.

2.1. Epigenetic control of microRNA expression

Although much effort has been focused on elucidating the mechanism of miRNA biogenesis and target gene regulation,

relatively little is known and published about the regulation of miRNA genes themselves. Based on the location in the genome, miRNA promoters are classified into three different conditions: 1) if miRNAs are embedded within introns or exons of host genes, they can share the same transcriptional control; 2) the embedded miRNAs also can have their own promoters; 3) if miRNAs are located in the intergenic regions, they will only be regulated by their own promoters^{1,7,8}. miR-127 is located in the intron of retrotransposon-like 1 (*Rtl1*), an imprinted mouse retrotransposon-like gene⁹. It is co-regulated by the *Rtl1* promoter, but is also under the control of its own promoter. The miR-127 gene overlaps with the miR-433 gene in a compact genomic space¹⁰. Their expression regulation involves epigenetic modification *via* DNA methylation and histone modification¹¹. The miR-127 promoter represents an example of the complicated miRNAs transcriptional and epigenetic regulation^{10,12–15}. The nature of miRNA promoter elements remains one of the most interesting, open problems in the study of miRNA biogenesis, since their identification would aid the understanding of regulatory networks in which miRNAs play a crucial role¹.

2.2. Transcriptional control of microRNA expression by nuclear receptors

Nuclear receptors (NRs) are ligand-activated transcription factors that regulate the expression of target genes by binding to the promoters^{14–16}. Members of the nuclear receptor superfamily have been proved as dominant regulators in lipid metabolism. Numerous NRs regulate miRNAs transcription, including farnesoid X receptor (FXR) and small heterodimer partner (SHP)¹. miR-29a promoter activity was significantly increased by FXR through a likely FXR-responsive element¹⁷. FXR plays a key role in homeostasis of cholesterol and bile acids, indicating the involvement of miR-29a in such processes. A recent study by Roderburg et al.¹⁸ showed that all three members of the miR-29a family (a, b and c) were significantly down-regulated in mouse liver in both CCl₄ and common bile-duct ligation (BDL) models. miR-199a-3p was also reported to be repressed by FXR¹⁹.

SHP is another important nuclear receptor to maintain cholesterol and bile acid homeostasis by inhibiting the conversion of cholesterol to bile acids. A microarray profiling revealed 21 upregulated miRNAs clustered on chromosome 12, including miR-433 and miR-127, in *Shp*^{-/-} mice^{10,12,13,20–22}. Further study identified CREB, which controls hepatic lipid metabolism by repression of peroxisome proliferator-activated receptor gamma (PPAR γ) and induction of peroxisome proliferator-activated receptor gamma coactivator (PGC-1), is one of the targets of miR-433^{20,23}. In addition, miR-433 expression is altered in the adipose tissue of patients with non-alcoholic fatty liver disease²⁴.

3. miRNA regulation of lipid metabolism

Lipid metabolism was reviewed in great detail elsewhere²⁵. Dyslipidemia is strongly associated with metabolic syndrome,

obesity, diabetes and fatty liver disease²⁶. Recent studies identified miRNAs in the regulation of plasma levels of lipoproteins and intercellular signaling molecules^{27,28}. Several representative miRNAs have been shown to have a significant impact on lipid homeostasis^{29,30}.

3.1. miR-122

miR-122 is not only well known as the first identified miRNA to regulate lipid metabolism, but also the liver-enriched and liver-specific miRNA. miR-122-deletion in whole body or specifically in the liver showed a marked decrease in total serum cholesterol and triglyceride (TG) levels. Anti-miR-122 therapy resulted in a significant reduction (25%–30%) of circulating cholesterol levels^{27,29,31}. A set of cholesterol biosynthesis genes was down-regulated by an indirect mechanism³², including 3-hydroxy-3-methylglutaryl-coenzyme A synthase 1 (HMGCS1), 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) and microsomal TG transfer protein (MTTP)²⁹. The identification of SWI/SNF related matrix associated actin dependent regulator of chromatin subfamily d member 1 (*Smardc1/Baf60a*) as novel miR-122 targets suggests the direct regulation of these genes³³. Interestingly, the miR-122 locus is transcribed in a circadian fashion, involving the transcriptional repressor nuclear receptor subfamily 1 group D member 1 (NR1D1/REV-ERB α). In liver, most metabolic pathways are under the circadian control. Both lipid and cholesterol metabolism are well known for their daytime-dependent regulation, similar to many other hepatic functions that require coordination of food intake with nutrient-processing and energy homeostasis. The molecular mechanism of miR-122 could represent a novel way of regulation of the circadian rhythm and hepatic metabolism³³.

In addition, miR-122 is involved in several hepatic disorders, as down-regulation of miR-122 is often associated with hepatocellular carcinoma (HCC), and miR-122 is found to bind to two sites in the 5'-UTR of the hepatitis C virus (HCV) genome and enhance its translation and replication^{34,35}.

3.2. miR-33/33*

miR-33 is another extensively investigated microRNA that modulates genes involved in lipid metabolism³⁶. The family of miR-33 includes two members, miR-33a and miR-33b. miR-33a and miR-33b are located in intronic regions within sterol regulatory element-binding proteins SREBP-2 and SREBP-1, respectively³⁷. As key transcriptional regulators of lipid metabolism, SREBPs control many genes involved in cholesterol and fatty acid biosynthesis and uptake, along with TG and phospholipids production³⁸. Both miRNAs are co-transcribed with their host genes and regulate similar physiological processes. Silencing of miR-33 *in vivo* increased plasma HDL levels by targeting adenosine triphosphate-binding cassette transporter A1 (ABCA1) and adenosine triphosphate-binding cassette transporter G1 (ABCG1), thereby attenuating cholesterol efflux to apolipoprotein A1 (ApoA1) or reducing cholesterol efflux to nascent HDL^{39,40}. Moreover, miR-33-deficient mice had significantly higher serum HDL cholesterol levels⁴¹. Interestingly, in addition to other targets of miR-33, including AMP-activated protein kinase α (AMPK α), ATPase, aminophospholipid transporter, class I, type 8B, member 1 (ATP8B1), hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase (trifunctional protein), beta subunit

(HADHB), carnitine palmitoyltransferase 1A (CPT1A), sirtuin 6 (SIRT6), glypican 6 (GPC6) and phosphoenolpyruvate carboxykinase 1 (PCK1), the host gene *SREBP-1* is one of the targets of miR-33. This auto-feedback regulation fine-tuned the cholesterol homeostasis to a delicate balance⁴².

Intriguingly, as the opposite stand to miR-33, miR-33* shares similar lipid metabolic network. miR-33* also represses key regulators involved in cholesterol homeostasis and specifically targets cholesterol efflux (NPC1), fatty acid metabolism (CROT), insulin signaling (IRS2) and lipid metabolism (SRC1, SRC3 and NFYC)⁴³. Although antagonizing miR-33 may develop as an attractive strategy for raising plasma HDL and are against atherosclerosis, caution should be taken because long-term therapeutic silencing of miR-33 may increase circulating triglyceride levels^{44–46}.

3.3. miR-27a/27b

Retinoid X receptor alpha (RXR α) plays a central role in adipogenesis through forming a heterodimer with PPAR γ and other nuclear receptors. Both miR-27a and miR-27b are demonstrated to target RXR α and regulate fat metabolism⁴⁷. Furthermore, PPAR γ is a target of miR-27b⁴⁸ and ABCA1 a target of miR-27a. Due to their sharing of the same seed region between miR-27a and miR-27b, it is reasonable to predict that both miRNAs could target PPAR γ and ABCA1. Overexpression of miR-27a accelerates adipolysis by releasing more glycerol and free fatty acids in the adipocytes⁴⁹ and represses lipid storage in cells. In addition, miR-27a inhibits the expression of many lipid metabolic genes, including fatty acid synthase (FASN), SREBP-1, SREBP-2, PPAR α and PPAR γ , as well as ApoA1, ApoB100 and ApoE3⁵⁰. Thus, miR-27 may regulate lipid metabolism by reducing lipid synthesis and increasing lipid secretion from cells.

3.4. miR-378/378*

miR-378 and miR-378* are embedded in the PGC-1 β gene and counterbalance the metabolic actions of PGC-1 β . A reduction of adipocyte size in miR-378/378* knockout mice indicates that both miRNAs are required for efficient hypertrophy and lipid uptake in white adipocytes. Several targets of miR-378/378* are found, including carnitine O-acetyltransferase (CRAT), mediator complex subunit 13 (MED13)⁵¹, estrogen-related receptor gamma (ERR γ), GA binding protein transcription factor alpha subunit (GABPA)⁵², insulin-like growth factor 1 receptor (IGF1R)⁵³, and ABCG1⁵⁴. miR-378 is also downregulated in 4-hydroxynonenal (HNE), one of several lipid oxidation products, treated cells⁵⁵. In addition, C/EBP α and C/EBP β positively increase miR-378/378* transcriptional activity^{56,57}. Furthermore, inhibition of miR-378 attenuates lipolysis and reduces the expression of lipase hormone-sensitive (LIPE), perilipin 1 (PLIN1) and patatin-like phospholipase domain containing 2 (PNPLA2), a set of genes encoding key lipolytic regulators⁵⁸.

3.5. miR-34a

miR-34a has multiple roles in the regulation of cell cycle, apoptosis, differentiation and migration because of its expressional control by p53^{59,60}. However, its induction by FXR raised the possibility of a new role of miR-34a in lipid metabolism⁶¹. Sirtuin1 (SIRT1) was identified as one of the targets of miR-34a.

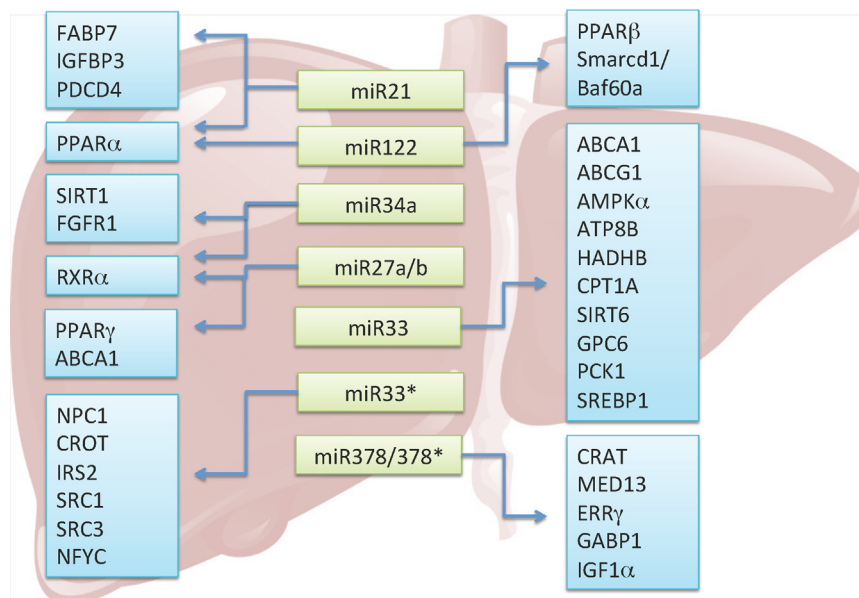


Figure 1 Regulatory role of miRNAs in lipid metabolism. Light green boxes highlight miRNAs involved in lipid metabolism. Blue boxes represent target genes of miRNAs. The miRNAs and their respective targets are linked by arrows.

Hepatic overexpression of miR-34a increased acetylation of PGC-1 α ⁶². On the other hand, miR-34a negatively regulates RXR α through binding to its 3'-UTR and decrease the induction of cytochrome P450 family 26 (CYP26) and cytochrome P450 family 3 subfamily A polypeptide 4 (CYP3A4)⁶³. Moreover, through targeting fibroblast growth factor receptor 1 (FGFR1), miR-34a contributes to attenuating fibroblast growth factor 21 (FGF21) signaling in obese mice. The expression of miR-34a was elevated in obesity, indicating its potential role in inhibiting fat browning and weight loss⁶⁴.

3.6. miR-21

The expression of miR-21 was decreased in liver from high-fat diet-fed mice compared to chow fed mice. Overexpression of miR-21 markedly blocked stearic acid (SA) induced intracellular lipid accumulation by targeting fatty acid-binding protein 7 (FABP7)⁶⁵. In miR-21 knockout mice, a group of lipid metabolic genes was changed compared with wild-type mice. PPAR α and insulin-like growth factor binding protein 3 (IGFBP3) were also targeted directly by miR-21^{66–68}. Further studies showed that miR-21 targeted programmed cell death 4 (PDCD4) to regulate lipid accumulation through the toll-like receptor 4 (TLR4) and NF- κ B pathway in lipopolysaccharide (LPS)-stimulated macrophages⁶⁸.

Additional miRNAs were also shown to regulate lipid metabolism. miR-758, miR-26, and miR-106b all targeted ABCA1. miR-370 targeted CPT1A and miR-24 targeted insulin induced gene 1 (INSIG1). Altogether these findings suggest that miRNAs play important roles in regulating lipid and lipoprotein homeostasis, which is summarized in Fig. 1.

4. Therapeutic potential of microRNAs

Although miRNAs represent a new class of potential targets for therapeutic intervention, there are obstacles to their clinical application, such as poor efficiency for cellular uptake. Lipofection of an antisense oligonucleotide based on a locked nucleic acids

(LNA)/2'-O-methylene mixmer or electroporation of a peptide nucleic acid (PNA) oligomer is effective at blocking miR-122 activity, highlighting the use of miRNA in future therapeutic application⁶⁹. A non-covalent peptide-based strategy was used for efficient delivery of miR-122 mimic or inhibitor, which appeared to be effective to alter cholesterol levels without cytotoxicity⁷⁰. The recently emerged lipid-based nanoparticles (LNPs) and LNP-DP1 provide more alternate ways for delivering siRNA and miRNA *in vitro* and *in vivo*⁷¹.

5. Conclusion and perspectives

A key role of miRNAs in lipoprotein and lipid metabolism is emerging. Because multiple genes can be targeted by one miRNA and one gene may be targeted by a group of miRNAs, the mRNA and miRNA regulatory network remains complicated. Recent evidence suggests that circulating extracellular miRNAs can also be biologically active in intercellular communication⁷². Future research works that integrate proteomics, systems biology and high-through technologies will help to develop better therapeutic strategies that target miRNAs.

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