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\textsuperscript{n}, miR122, miR27a/b, miR378/378\textsuperscript{n}, miR-34a and miR-21.

Abbreviations: ABCA1, adenosine triphosphate-binding cassette transporter A1; ABCG1, adenosine triphosphate-binding cassette transporter G1; Ago2, argonaute 2; AMPK\textalpha, AMP-activated protein kinase \textalpha; 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\gamma, 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; LIPET, lipase hormone-sensitive; LNA, locked nucleic acids; LNPs, lipid-based nanoparticles; LPS, lipopolysaccharide; MEDI3, mediator complex subunit 13; MHV68, murine \gamma-herpesvirus 68; miRNAs or miRs, microRNAs; MTTP, microsomal TG transfer protein; NR1D1/REV-ERB\textalpha, transcriptional repressor nuclear receptor subfamily 1 group D member 1; NRs, nuclear receptors; PCK1, phosphoenolpyruvate carboxykinase 1; PDCD4, programmed cell death 4; PGC-1, peroxisone proliferator-activated receptor gamma coactivator; PLIN1, perilipin 1; PNA, peptide nucleic acid; PNPLA2, patatin-like phospholipase domain containing 2; PPARY, peroxisone proliferator-activated receptor gamma; pre-miRNAs, precursor-miRNAs; pri-miRNAs, primary-miRNAs; RTL1, retrotransposon-like 1; RXR\alpha, 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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1. Introduction

Gene regulation networks are the representation of multiple levels within a cell\(^1\). 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 miRNAs in major physiological and pathological processes. miRNAs are small non-coding RNAs involving in post-transcriptional regulation of gene expression by binding to the 3′-UTRs of the target mRNAs. Many miRNA targets are key regulators of lipid metabolism and disease in the liver, suggesting the functional involvement of miRNAs in this process. In this review, we provide new insight into the specific role of miRNAs in lipid metabolism.

2. microRNA regulation network

miRNAs are promising therapeutic strategies for metabolic diseases such as diabetes and atherosclerosis. They are modular components of complex gene regulatory networks, and can be involved in lipid homeostasis. A comprehensive understanding of miRNA regulation network is urgently needed. In this section, we review several key miRNA regulatory mechanisms, which provide new insights into the study of miRNA biogenesis, since their identification would aid the understanding of regulatory networks in which miRNAs play a crucial role\(^1\).

2.1. Epigenetic control of microRNA expression

Epigenetics is the study of heritable changes in gene expression that do not involve changes in the DNA sequence\(^2\). MiRNAs are encoded in intergenic regions of the genome and are transcribed by RNA polymerase II. Their expression can be regulated by DNA methylation, histone methylation, and other epigenetic modifications\(^3\). In this section, we will discuss the role of epigenetic modifications in the regulation of miRNA expression.

3. miRNA regulation of lipid metabolism

Lipid metabolism was reviewed in great detail elsewhere\(^4\). Dyslipidemia is strongly associated with metabolic syndrome, 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\(^1\). miR-127 is located in the intron of retrotransposon-like 1 (Rtl1), an imprinted mouse retrotransposon-like gene\(^5\). 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 space\(^6\). Their expression regulation involves epigenetic modification via DNA methylation and histone modification\(^7\). The miR-127 promoter represents an example of the complicated miRNAs transcriptional and epigenetic regulation\(^8\). 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 role\(^9\).

3.1. 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\(^10\). 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)\(^11\). miR-29a promoter activity was significantly increased by FXR through a likely FXR-responsive element\(^12\). 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.\(^13\) showed that all three members of the miR-29a family (a, b and c) were significantly down-regulated in mouse liver in both CCl\(_4\) and common bile-duct ligation (BDL) models. miR-199a-3p was also reported to be repressed by FXR\(^14\).

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\(^\sim\) mice\(^15\). Further study identified CREB, which controls hepatic lipid metabolism by repression of peroxisome proliferator-activated receptor gamma (PPAR\(\gamma\)) and induction of peroxisome proliferator-activated receptor gamma coactivator (PGC-1), is one of the targets of miR-433\(^16\). In addition, miR-433 expression is altered in the adipose tissue of patients with non-alcoholic fatty liver disease\(^17\).
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. A set of cholesterol biosynthesis genes was downregulated by an indirect mechanism, including 3-hydroxy-3-methylglutaryl-coenzyme A synthase 1 (HMGC S1), 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), and microsomal TG transfer protein (MTTP). The identification of SWI/SNF related matrix associated actin dependent regulator of chromatin subfamily d member 1 (Smard1) or reducing cholesterol ef-1 group D member 1 (NR1D1/REV-ERBα) 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-procession and energy homeostasis. The molecular mechanism of miR-122 could represent a novel way of regulation of the circadian rhythm and hepatic metabolism.

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.

3.3. miR-27a/27b

Retinoic X receptor alpha (RXRa) plays a central role in adipogenesis through forming a heterodimer with PPARγ and other nuclear receptors. Both miR-27a and miR-27b are demonstrated to target RXRa and regulate fat metabolism. Furthermore, PPARγ is a target of miR-27b 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 PPARγ and ABCA1. Overexpression of miR-27a accelerates adipolysis by releasing more glycerol and free fatty acids in the adipocytes 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, and PPARγ. miR-27a and miR-27b are embedded in the PGC-1β gene and counterbalance the metabolic actions of PGC-1β. 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 carmine O-acetyltransferase (CRAT), mediator complex subunit 13 (MED13), estrogen-related receptor gamma (ERRγ), GA binding protein transcription factor alpha subunit (GABPA), insulin-like growth factor 1 receptor (IGF1R), and ABCG1. miR-378 is also downregulated in 4-hydroxynonenal (HNE), one of several lipid oxidation products, treated cells. In addition, C/EBPα and C/EBPβ positively increase miR-378/378* transcriptional activity. 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 regulators.

3.4. miR-34a

miR-34a has multiple roles in the regulation of cell cycle, apoptosis, differentiation and migration because of its expressional control by p53. However, its induction by FXR raised the possibility of a new role of miR-34a in lipid metabolism. Sirtuin1 (SIRT1) was identified as one of the targets of miR-34a.
Hepatic overexpression of miR-34a increased acetylation of PGC-1α. On the other hand, miR-34a negatively regulates RXRα through binding to its 3′-UTR and decreases the induction of cytochrome P450 family 26 (CYP26) and cytochrome P450 family 3 subfamily A polypeptide 4 (CYP3A4). 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 loss.

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). In miR-21 knockout mice, a group of lipid metabolic genes was changed compared with wild-type mice. PPARα and insulin-like growth factor binding protein 3 (IGFBP3) were also targeted directly by miR-21. 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-κB pathway in lipopolysaccharide (LPS)-stimulated macrophages.

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 application. 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 cytotoxicity. The recently emerged lipid-based nanoparticles (LNPs) and LNP-DP1 provide more alternate ways for delivering siRNA and miRNA in vitro and in vivo.

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 communication. Future research works that integrate proteomics, systems biology and high-throughput technologies will help to develop better therapeutic strategies that target miRNAs.

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