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Integrative Roles of MicroRNAs in Lipid Metabolism and Dyslipidemia.

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Abstract

Purpose of Review: The purpose of the review is to discuss recent advances in microRNA (miRNA) regulation of lipid metabolism and highlight the importance of miRNA-mediated gene regulation in dyslipidemia and fatty liver disease. This article reviews examples of miRNAs that bridge disparate metabolic pathways in the liver. For example, we highlight miRNAs that are regulated by the sterol-sensing pathway in the liver that in turn regulate cellular or systemic cholesterol, fatty acid, and glucose levels.

Recent Findings: The most widely-studied of these miRNAs are miR-33a/b; however, we recently reported that miRNAs in the miR-183/96/182 cluster are also likely regulated by hepatic cholesterol content and mediate the observed glucose-lowering effects of the bile acid sequestrant colesevelam through the sterol-sensing pathway. In addition, several other hepatic and adipose miRNAs have been recently demonstrated to be key regulators of cellular lipid synthesis, storage, and catabolism, as well as systemic lipid metabolism. Moreover, many of these miRNAs are altered in fatty liver disease and dyslipidemia.

Summary: miRNAs are not just fine-tuners of lipid metabolism, but critical regulatory factors in lipid homeostasis and health. Loss of these miRNA regulatory modules very likely contributes to the underlying metabolic defects observed in lipid disorders.

Keywords

microRNA; lipids; cholesterol; liver; adipose

Introduction:

The study of microRNAs (miRNA) is as vibrant as ever and many new functions for miRNAs in lipid-related mechanisms and disorders have been recently reported. Currently, miRbase.org (v22.1), the universal database of miRNAs, contains 1,917 human miRNAs; however, only 26% of these (505 miRNAs) are considered to be high confidence miRNAs[1]. Nevertheless, key biological functions have been reported for most of the broadly conserved

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mammalian miRNAs in humans, and many of these miRNAs regulate genes previously linked to lipid metabolism.

miRNAs are a class of small non-coding RNAs approximately 22 nucleotides (nt) in length which serve to post-transcriptionally regulate mRNA expression and stability through the RNA-Induced Silencing Complex (RISC)[2]. miRNAs are present in all tissues, and most, if not all, mammalian biological processes are regulated by miRNAs through either direct or indirect mechanisms[3]. miRNAs are transcribed by polymerase II as long pri-miRNAs that are processed in the nucleus by the RNAse III enzyme Drosha and its double-stranded RNA binding cofactor DiGeorge syndrome critical region 8 (DGCR8)[4]. This microprocessor complex cleaves the pri-miR structure into an approximately 60nt pre-miR, which is exported from the nucleus to the cytoplasm by exportin-5 [5]. In the cytoplasm, the pre-miRNA is further processed by the RNAse III endonuclease Dicer to generate a small double-stranded RNA duplex of approximately 22 nts in length containing a 2 nt 3' overhang[5]. The miRNA duplex is then loaded into the RISC through an ATP-dependent process facilitated by chaperones[6]. RISC structure and function are conferred by members of the Argonaute (AGO) family of proteins 1–4. Either strand of the miRNA duplex can be loaded into AGO-RISC pocket and recognize mRNAs and other transcripts through a critical seed region (bases 2–7) on the 5' end of the mature miRNA. Most miRNA target pairing occurs through imperfect matching conferred by Watson-Crick pairing between the miRNA seed region and sites within the 3' untranslated region (3' UTR) of the mRNA[7]. Most miRNA target sites are found in the 3' UTRs; however, miRNAs can also bind and repress mRNAs through sites in the open reading frame and 5' UTR of the mRNA targets, although these sites occur less frequently. Due to the imperfect base pairing between miRNAs and target mRNAs, one miRNA can potentially silence hundreds of genes, and multiple miRNAs can target the same mRNA. miRNAs repress target mRNA expression by interfering with translational initiation, preventing elongation, and/or destabilizing the transcript through mRNA decay[4]. mRNA decay after miRNA recognition involves the recruitment of the glycine-tryptophan protein of 182kDa (GW182), which interacts with the polyadenylate-binding protein and promotes deadenylation of the mRNA transcript[8]. The current models and state-of-the-art of miRNA processing, mRNA target recognition, and miRNA targeting mechanisms were recently reviewed here[9].

The miRNA interactome network for lipid disorders was recently reported based on text mining and many exciting results emerged from this study[10]. Approximately 150 distinct miRNAs were found to represent the 227 miRNA-lipid disease networks and the top 20 miRNA networks were further resolved[10]. These include experimentally validated regulatory modules of lipid genes for miR-33a/b, miR-223–3p, miR-375–3p, miR-144, miR-122, miR-103/107, miR-30c, miR-145, miR-146a, miR-29, and miRNAs in the miR-17–92 and miR-183/96/182 clusters. This study is a great resource for future studies investigating the mechanisms and consequences of miRNA-mediated lipid regulation. Here, we will discuss these key lipid miRNAs and their role in lipid diseases (Figure 1).

Sterol-sensing miRNAs bridge metabolic pathways

Like many genes that regulate cholesterol and lipid homeostasis, the expression of specific miRNAs is sensitive to cellular cholesterol levels. Although a comprehensive study of sterol-regulated miRNAs in metabolic cell-types remains to be completed, specific examples of miRNAs that harbor sterol-response elements in their promoters or host gene promoters have been identified. miR-33, the most widely-studied miRNA in lipid metabolism, was discovered through a screen of cholesterol-induced miRNAs in macrophages[11]. miR-33a and miR-33b are co-transcribed with host genes *SREBF2* and *SREBF1*, respectively[12]. While humans have two copies of miR-33 (miR-33a and miR-33b), rodents only have one copy, miR-33a, as miR-33b cannot be expressed due to a deletion in its encoding sequence in *Srebf1*. Cells respond to elevated cellular cholesterol (and other sterol) levels through a series of biological processes within the sterol-sensing pathway. Briefly, excess cellular cholesterol content causes a decrease in the transcription of genes that promote cellular cholesterol content, including critical cholesterol biosynthesis enzymes, cholesterol transporters, and lipoprotein uptake receptors[13]. When cellular cholesterol levels are low, cells respond by increasing cholesterol biosynthesis and lipoprotein uptake through increased transcriptional activity of sterol regulatory element-binding proteins (SREBPs) and activation of critical cholesterol-linked genes[14]. Part of this mechanism is the control of SREBP expression, which are the key transcription factors that control cellular cholesterol homeostasis. For example, when cellular cholesterol levels are low, *SREBF1* and *SREBF2* genes are turned on with miR-33b and miR-33a, which are harbored within the respective introns and co-transcribed with the host genes[11]. miR-33a/b directly targets and inhibits ATP-binding cassette transporter A1 (*ABCA1*), a key transporter of cellular cholesterol to lipid-poor apolipoprotein A-I and nascent high-density lipoproteins (HDL)[11]. miR-33 has been extensively investigated in most lipid pathways and miR-33a/b-5p has been reviewed exhaustively prior[15]. Nonetheless, recent studies have demonstrated new functions for miR-33 in lipid metabolism[16, 17]. One of the most exciting studies found that miR-33a/b-5p regulates key features of the NLR Family Pyrin Domain Containing 3 (NLRP3) inflammasome complex in macrophages, and thus, provides a further link between cellular cholesterol metabolism, immune cell activation, and vascular inflammation[18].

Another critical miRNA, or cluster of miRNAs, to lipid metabolism is the miR-183/96/182 poly-cistronic cluster[19]. This miRNA cluster has previously been shown to be a transcriptional target of SREBPs and harbor sterol response elements in its promoter, thus this miRNA cluster is intricately linked to cellular cholesterol levels[20]. Therefore, it is not surprising that miR-182–5p expression was reported to be down-regulated in white adipose tissue, skeletal muscle, liver, pancreas, and blood from rats on a high-fat diet (HFD) which may have included increased cholesterol content in the diet[21]. For example, miR-182–5p expression would be predicted to be suppressed in cells with excess cholesterol gained through the HFD. In agreement, miR-182–5p levels were also found to be decreased in blood from non-human primates (NHP) that were fed a HFD[21]. Like miR-33a/b-5p, miRNAs in this cluster likely serves as a bridge between cellular cholesterol content and systemic energy control, e.g. glucose and triglyceride homeostasis. For example, miR-96–5p was recently found to target *FOXO1*, a critical regulator of insulin signaling, gluconeogenesis, and adipogenesis; critical processes in systemic energy and lipid

metabolism[22–24]. Recently, we reported that bile acid sequestrants, specifically the drug colesevelam (brand names Welchol, Cholestagel, or Lodalis), increased hepatic expression of the miR-183/96/182 cluster in rats and mice. Since this miRNA cluster is under regulation of SREBPs[20], and thus cellular cholesterol levels, the observed increase of this miRNA cluster in the liver is likely due to the transcriptional response of SREBPs to reduced hepatic cholesterol content due to the conversion and replenishment of bile acids lost to intestinal sequestration and reduced bile acid reuptake[25]. Colesevelam has previously been shown to promote *SREBP2* transcriptional activity to stimulate hepatic cholesterol biosynthesis in response to reduced cellular cholesterol levels due to the increased bile acid conversion from cholesterol[26, 27]. Collectively, colesevelam creates a cholesterol sink in the liver which increases hepatic uptake of circulating LDL particles to replenish hepatic cholesterol lost to bile secretion. As a consequence, colesevelam lowers circulating LDL-cholesterol levels, the primary risk factor for cardiovascular disease (CVD). Colesevelam is the most-effective drug in the bile acid sequestrant class for binding to bile acids and is indicated for primary hyperlipidemia; however, one remarkable pleiotropic effect of colesevelam is its glucose-lowering capacity. Therefore, it is prescribed to patients with type 2 diabetes mellitus to improve glycemic control[28–32]. We posit that miRNAs in the miR-183/96/182 cluster mediate, in part, colesevelam's glucose lowering effects, and thus, further links hepatic cholesterol metabolism and systemic lipid and glucose metabolism. Recently, we found that inhibition of miR-182–5p partially reversed the observed improvements in glucose tolerance observed with colesevelam in *db/db* mice, a model of diabetic dyslipidemia[25]. Paradoxically, the miR-183/96/182 cluster is also induced with statins[20], which contrary to colesevelam, has been reported to worsen glucose tolerance[33]. Therefore, it is possible that the hepatic gene regulatory networks that are altered with bile acid sequestrants are distinct from those altered with statins despite the likely shared utilization of the SREBP2 sterol-sensing pathway and transcriptional response. We recently demonstrated that miRNAs in the miR-183/96/182 directly target and suppress *Med1*, a gene that links nuclear receptor activity to Pol II transcription[25]. In addition to *Med1* and *Foxo1*, miRNAs in the miR-183/96/182 cluster also likely regulate Pyruvate Dehydrogenase Kinase 4 (*Pdk4*) another key gene in glucose and lipid metabolism[34]. It should be noted that colesevelam very likely alters the expression of other miRNAs in the liver, particularly miRNAs that are regulated by farnesoid X receptor (FXR). For example, normally 95% of bile acids are reabsorbed by the intestine and transported back to the liver through enterohepatic circulation and FXR is the primary sensor for endogenous bile acid feedback[35]. Colesevelam inhibits bile acid reabsorption and promotes their excretion, resulting in decreased FXR signaling[36]. One of these FXR-regulated miRNAs is likely miR-34a-5p. *Fxr* knockout mice were shown to have increased levels of miR-34a-5p[37], and *Cyp7a1* overexpressing mice were also reported to have increased levels of miR-33a-5p[38]. Therefore, it is possible that loss of *Fxr* or induction of *Cyp7a1* by colesevelam may also contribute to some of the observed effects of colesevelam in hepatic and systemic lipid homeostasis, as well as explain some of the discrepancies between statins and BAS drug classes on hepatic miRNA gene regulation and lipid metabolic outcomes. miRNA regulation of hepatic cholesterol metabolism is an important aspect of hepatic lipid homeostasis as many metabolic pathways are inter-connected through the sterol-sensing pathway. In addition to miR-33a/b and miRNAs in the miR-183/96/182 cluster, miR-29a/b/c was demonstrated to regulate

SREBF1/2 and SREBF Chaperone (*SCAP*), and thus lipid metabolism, through a SREBP feedback loop[39]. Like miR-33a-5p, miR-29c was also identified in a screen for miRNAs that are regulated (significantly decreased) by cellular cholesterol[11]. miR-29a-5p, the miRNA processing enzyme Dicer, and HMG Co-reductase (HMGCR) were also reported to form a novel axis that governs cholesterol accumulation in hepatocytes which contributes to fatty liver disease[40]. LDL-cholesterol is a causal factor in atherosclerosis and CVD and is secreted from the liver in the form of very low-density lipoproteins (VLDL). Apolipoprotein B (APOB), the key structural and functional protein of VLDL and LDL, is generally considered to be regulated at the protein level during VLDL assembly and biogenesis. Strikingly, miR-548p was recently reported to target and suppress *APOB* in hepatocytes which is a remarkable advancement[41]. Both miR-33a/b-5p and the miRNAs in the miR-183/96/182 cluster represent sterol-sensing responsive miRNAs that bridge cellular cholesterol metabolism and systemic lipid homeostasis, including glucose pathways. These miRNAs are not likely the only miRNAs that harbor SREs in their promoters and are transcriptional targets of SREBPs. Moreover, these miRNAs are not the only miRNAs that link cellular cholesterol metabolism to other metabolic networks that have been recently investigated. For example, miR-7–5p was found to be a hepatic peroxisome proliferator activated receptor-α (PPAR-α)-dependent miRNA that regulates SREBP signaling, as opposed to being regulated by SREBPs, through targeting and repression of endoplasmic reticulum lipid raft associated 2 (ERLIN2), which also provides a link between metabolic pathways in the liver[42].

miRNA regulation of hepatic lipid metabolism

The liver is one of, if not, the most important regulatory tissue in systemic lipid homeostasis and considerable advances in miRNA regulation of lipid-regulating genes in the liver have been made in the last few years. One of the most well-studied lipid-associated miRNAs in the liver is miR-34a-5p. Recently, miR-34a-5p has been reported to mediate the hepatic response to metabolic stress through regulation of HFN4A (hepatocyte nuclear factor 4 alpha), which is a critical hepatic transcription factor for lipid metabolism and lipoprotein secretion[43]. miR-34a antagonizes VLDL secretion and likely regulates plasma lipoprotein levels. miR-34a also suppresses NAFLD through targeting and suppression of PPARA[44]. Moreover, miR-34a, via PPAR-α, was recently found to contribute to systemic energy homeostasis through indirect regulation of FGF21, a key hormone in lipid metabolism[45]. The roles of miRNAs in post-transcriptional gene regulation underlying non-alcoholic fatty liver disease (NAFLD) and/or nonalcoholic steatophepatitis (NASH) was one of the more active areas of research for hepatic miRNAs in recent years. For example, miR-378–3p was reported to promote NASH in response high-fat diet (HFD) feeding through direct targeting of *Nrf1*[46]. miR-212–5p was also found to inhibit lipid accumulation in hepatocytes through suppression of fatty acid synthase (FAS) and stearoyl-CoA desaturase (SCD1), two critical fatty acid regulators in the liver[47]. Most interestingly, miR-194 likely is a key lipid-regulating miRNA in liver, as inhibition of miR-194 was reported to improve fatty liver disease through regulation of *FXR*[48]. Hepatic miRNAs were also found to contribute to alcohol-induced steatohepatitis, as miR-203–3p was found to target and repress *Lipin1*[49]. We have previously reported that miR-27b-3p is key regulatory hub for lipid metabolism and directly regulates critical lipid genes, including angiopoietin-like 3 (*ANGPTL3*), N-

Deacetylase And N-Sulfotransferase 1 (*NDST1*), and Glycerol-3-phosphate acyltransferase 1 (*GPAM*)[50]. miR-27b-3p has also been reported to regulate *ABCA1* and low-density lipoprotein receptor (*LDLR*), which are essential for cholesterol and lipid efflux and lipoprotein uptake in the liver[51]. Recently, a group reported that miR-27a-3p also regulates hepatic lipids and fatty liver disease through regulation of *FAS* and *SCD1*[52]. Moreover, Ouimet *et al.* reported that oxysterol-binding protein-like 6 (OSBPL6) was found to be a target of both miR-27b-3p and miR-33a/b[53]. miR-122–5p is the most abundant miRNA in the liver and has been extensively studied in hepatic lipid metabolism. Recently, miR-122–5p was reported to antagonize lipid droplet formation through regulation of the transcription factor Yin Yang 1 (YY1) which may confer some of the previously identified links between miR-122–5p and hepatic lipid control[54]. Another key lipid miRNA in liver is miR-145–5p, and recently, statin treatments, e.g. Atorvastatin, were found to promote miR-145–5p expression in hepatocytes through activation of the PI3K/AKT pathway[55]. miR-145–5p has previously been found to regulate ABCA1 in the liver and pancreatic islets and like many of the miRNAs listed in this review bridge multiple metabolic pathways in the liver that contribute to hepatic and systemic lipid homeostasis[56]. miR-145 is also one of multiple miRNAs (listed here in this review) that regulate hepatic lipid metabolism but have been found to regulate lipid metabolism in other tissues and organs. For example, miR-33a/b-5p was also found to control lipid raft cholesterol content in the heart[57].

miRNA regulation of adipose lipid metabolism

In addition to the liver, adipose is another major tissue of systemic lipid regulation. miR-107,−5p which is was previously found to be a critical miRNA in glucose metabolism and insulin sensitivity[58], was found to inhibit cyclin dependent kinase 6 (CDK6) expression in adipocytes, which regulates adipogenesis and lipid storage[59]. In the last few years, multiple miRNAs have been found to be critical regulators of adipogenesis and lipid metabolism. Among the many studies, miR-204–5p was found to regulate adipocyte differentiation and adiposity[60], miR-199a-3p was demonstrated to regulate brown adipogenesis via mTOR[61], and miR-221–3p was shown to regulate angiopoietin-like 8 (ANGPTL8) in adipocytes[62]. Moreover, miR-34a-5p was found to be packaged and secreted from adipocytes in extracellular vesicles and was found to suppress anti-inflammatory phenotypes (M2-like) in adipose tissue macrophages through regulation of Kruppel-like factor 4 (KLF4), and this communication network likely promotes obesity-related adipose inflammation[63].

Conclusions:

In summary, numerous miRNAs have and continue to emerge as critical regulators in all facets of lipid biology. Despite the unfortunate designation as fine-tuners of gene expression, loss-of-function studies in both cells and animal models clearly reveal critical roles for miRNAs in cellular and animal phenotypes, metabolism, and disease. For example, one can quickly examine the list of specific miRNA-deficient mice (and other animal models) to easily grasp that miRNAs indeed play key roles in regulating gene expression in mammals[9]. In this review, we highlight key sterol-sensing miRNAs, such as miR-33 and the miR-183/96/182 cluster, that bridge the gap of metabolic pathways such as cellular

cholesterol metabolism, immune cell activation and glucose and triglyceride homeostasis. Furthermore, we discuss miRNAs that play a key role in hepatic and adipose lipid metabolism. Therefore, it is likely unwise to discount miRNAs due to any perceived lack of regulator strength. Here we show there is clearly nothing micro about the level of regulation miRNAs have on the expression of lipid metabolism genes.

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Key Points:

1. miRNAs are important regulators of all facets of lipid metabolism in multiple cell-types and tissues, including lipid synthesis, storage, circulation, and catabolism.
2. Sterol-sensing miRNAs in the miR-183/96/182 cluster bridge metabolic pathways, including hepatic cholesterol, fatty acid, and glucose metabolism.
3. miRNAs in the liver and adipose serve to control systemic energy homeostasis

Hepatic Lipid Metabolism, Lipoproteins, and NASH

miRNA	Target	Function
miR-182/96/183	*MED1, FOXO1, FBXW7, PDK4*	Decreases transcription of lipid-regulating and lipid synthesis genes.
miR-7-5p	*ERLIN2*	Decreases SREBP signaling and transcriptional activation
miR-27a/b	*FAS, SCD1, ABCA1, LDLR, ANGPTL3, GPAT, NDST1, PPARG, OSBPL6*	Reduces lipid accumulation, triglyceride synthesis, lipoprotein uptake, cholesterol and lipid efflux to HDL, and triglyceride catabolism.
miR-29a/b/c	*SCAP, SREBF, HMGCR*	Suppresses lipid synthesis, transcription of lipid-regulating genes, cholesterol biosynthesis, and cholesterol efflux and uptake
miR-33a/b-5p	*ABCA1, NDUFA5, OSBPL6*	Reduces cholesterol and lipid export to HDL, fatty acid oxidation, and mitochondrial dysfunction
miR-34a-5p	*HNF4A, PPARA, FGF21*	Regulated by FXR and decreases hepatic lipid levels and lipoprotein secretion.
miR-122-5p	*YY1*	Inhibits lipid droplets and triglyceride accumulation
miR-145-5p	*ABCA1*	Represses cholesterol and lipid efflux to lipoproteins
miR-190b-5p	*IGF1, ADAMTS9*	Increases lipid metabolism and reduces insulin sensitivity
miR-194-5p	*NR1H4* (LXR)	Promotes lipid droplet formation and fatty liver
miR-203-3p	*LIPIN1*	Reduces lipid accumulation
miR-212-5p	*FAS, SCD1*	Reduces lipid synthesis and metabolism
miR-378-3p	*NRF1*	Reduces fatty acid oxidation, hepatic lipid content, and NASH
miR-548p	*APOB*	Decreases LDL biogenesis

Adipose Tissue Lipid Metabolism

miRNA	Target	Function
miR-34a-5p	*KLF4*	Suppresses M2 polarization of adipose tissue macrophages
miR-107-5p	*CDK6*	Reduces lipid accumulation and triglyceride synthesis in adipocytes
miR-199-3p	*MTOR*	Reduces lipid accumulation and brown adipocyte thermogenesis
miR-204-5p	*BCL2, KLF3*	Increases pre-adipocyte differentiation and/or apoptosis, and triglyceride storage
miR-221-3p	*ANGPTL8*	Regulates lipid metabolism in adipocytes

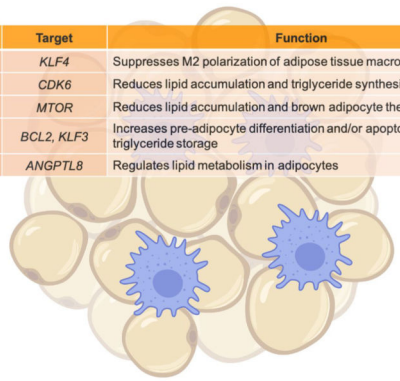

Figure 1. miRNA regulation of lipid metabolism in the liver and adipose.
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