

Review

Profile of Surrounding MicroRNAs in Low Density Lipoprotein Uptake

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Abstract: The atherosclerosis, a chronic and inflammatory disease that occurs when there are high levels of low-density lipoprotein (LDL) on plasma. This important risk factor for development of cardiovascular disease (CVD) is the main cause of death worldwide. MicroRNAs have recently emerged as potential biomarkers and therapeutic target for lipid metabolism disorders. In this review, we will provide profile of surrounding miRNAs that have demonstrated being regulators of PCSK9, LDLR and APOB100 genes. Recent work has identified the mir-148, mir-128, mir-27a/b, mir-185, mir-301, mir-130 as important regulators of this pathway because they decrease supply of LDL receptors through interaction with PCSK9. Inhibition of LDLR expression cause elevation of plasma LDL levels which induces atherosclerosis. While mir-30c, mir-122, mir-34 decrease MTTP, which promotes degradation of APOB100 preventing assembly and secretion of VLDL. We conclude that, when overexpressed, mir-148a, mir128 and mir-27a/b, mir-122 and mir-34 are related to decrease in LDLR, facilitating occurrence of atherosclerosis. While mir-30 has been linked to decreased atherosclerosis. Detection of miRNAs profile could be used in the future as a biomarker for disturbs linked to c-LDL uptake and in future anti-miRNAs therapies may be used in the treatment of atherosclerosis.

Keywords: surrounding microRNAs; low-density lipoprotein; atherosclerosis; APOB; PCSK9; LDLR

1. Introduction

According to World Health Organization (WHO) around 17 million people die worldwide each year in consequence of cardiovascular diseases, being atherosclerosis the main cause. Atherosclerosis is an inflammatory and chronic disease that occurs when there is an elevation in Low Density Lipoprotein (LDL) levels on plasma, and it is closely related to pathologies as coronaries syndrome, ischemic heart disease, cerebrovascular disease and peripheral vascular disease, all caused by obstruction arteries due to the accumulation of LDL [1].

The LDL contains in its membrane an apolipoprotein (APOB100) which acts as a ligand of LDL receptor (LDLR) in hepatic cells. Ligand-receptor interaction (LDLR and APOB-100) make LDL vesicles being removed of blood flow and absorbed by hepatocytes by endocytosis, decreasing the risk of Atheroclerosis [2]. Supply of LDLR on the cell surface is regulated by PCSK9 (Protein convertase subtilisina/kexina type 9) which bind to LDL receptors leading to its internalization and degradation by lisosomal vesicles, thus decreasing the supply of receptor and rising plasmatic LDL what contributes to the elevation of plasmatic LDL.

Studies have reported the importance of a small class of molecules known as microRNAs in regulation of cholesterol metabolism [3-5]. The microRNAs are non-coding single-stranded RNAs of proteins (22-24pb) very important in post transcriptional genetic regulation, it acts in modulation of gene expression and intercellular communication, thus, interfering in a variety of physiological functions among these the cholesterol metabolism [4,6]. Studies shown that microRNAs modulates various pathways for lipid uptake, besides regulating various functions in the endothelial cells (EC), In vascular smooth muscle cells (VSMC), in macrophages, differentiation and proliferation of cardiac cells, glucose metabolism, interfering in the progression of atherosclerosis and other cardiovascular diseases [3, 6-7]. The aim of this review is delineate a profile of circulating miRNAs that interfere with the uptake of LDL through the regulation of LDLR, APOB-100 and PCSK9 genes that can be used as potential biomarkers for the prognosis and treatment of atherosclerosis.

2. Biogenesis of miRNAs

Currently, more than 1.500 miRNAs have been described, previous studies have suggested that up to 60% of our genes can be regulated by miRNAs, and as a consequence, these small endogenous silencers act as regulators of a number of processes such as cell proliferation, development, angiogenesis and cholesterol metabolism [8-9].

The miRNAs are transcribed from intronic regions of genes encoding proteins or intergenic regions. This transcription is performed by RNA polymerase II, generating a long primary transcript (pri-miRNA) that are stacked and polyadenylated [10]. These transcripts are capable of folding into hairpin structures that are recognized by RNA binding proteins DGCR8 (DiGeorge syndrome critical region gene 8). DGCR8 carry the miRNAs to Drosha, an endonuclease that cleaves the duplex clusters of pri-miRNAs and transforms them into pre-miRNAs (70 nucleotides) [6,10]. Pre-miRNAs bind RNA-exporter proteins, such as exportin-5, and are transported rapidly into the cytoplasm [6].

Once in the cytoplasm, the pre-miRNA is processed by a complex of proteins called RNA-Induced Silencing Complex (RISC) formed by Dicer and Argonaute. Dicer is a double-stranded endonuclease that binds and cleaves the pre-miRNA in 21-23 bp segments forming mature miRNAs, which are brought by the RISC to the target mRNA to be paired with the promoter region (3'UTR) promoting gene silencing [10-11]. The perfect match between mRNA and miRNA causes degradation of the target mRNA, but these complementarities may also be imperfect when one or more bases are poorly paired, which represses the translation. This non-specificity causes a single miRNA to have several target mRNAs that can regulate the expression of several genes [12].

3. Surrounding miRNAs as potential biomarkers and therapeutic targets to CVDs

It was previously believed that miRNA expression was limited to intracellular endogenous activity. It is now known that miRNAs can be synthesized in specific cells and subsequently secreted into plasma, which facilitates the communication between cells of different tissues [13]. The small size of miRNA molecules, and the fact that they are transported into vesicles such as exosomes, microvesicles and lipoproteins, apoptotic bodies and protein complexes, are characteristics that protect these small molecules from the action of plasmatic RNases and make the microRNAs more stable than mRNAs and DNAs in plasma [14-15].

Studies show that numerous miRNAs have deregulated expression profiles that vary with pathology and degree of severity. Since then several studies have demonstrated the expression of surrounding miRNAs in CVDs, acute myocardial infarction, coronary diseases, dyslipidemia, obesity, diabetes, hypertension and metabolic syndrome. Thus, a new field of miRNA investigations was opened as potential biomarkers for the prognosis and therapeutic targets for the treatment of CVDs. As demonstrate in table 1 [4, 13, 16-18].

Tabela1. Surrounding microRNAs related to atherosclerotic process

MicroRNAs	Target gene	Pathology
Mir-148	LDLR, ABCA1	Obesity [19]
Mir-130B	LDLR, PPAR-g SREBP1	Metabolicsyndrome[20]
Mir-301b	LDLR, ABCA1, SREBP1,S1K1	Dyslipidemia [5]
Mir-128a/b	LDLR, ABCA1, SREBP1	Diabetes [21-22]
Mir-27a/b	LDLR,LPL, PCSK9,SREBP1, SREBP2, APOA1,APOB, APOE3	Oxidative stress [23]
Mir-122	MTTP	Dyslipidemia [24]
Mir-34	APOB, HNF4 ALFA	Endothelialdysfunction[25]
Mir-30c	MTTP, APOB	Hypertension [26-27]
Mir-544	APOB	Hypolipidemia [28]
Mir-1202	APOB	Hyperlipidemia [28]

4. Uptake of LDL (Low-density lipoprotein)

Uptake of LDL by hepatocytes occurs through the interaction of several genes, among them apolipoprotein B-100, a protein present in the membrane of LDL vesicles, which has the function of binding to LDLR, allowing the absorption and degradation of LDL by the liver. However, when there are no LDL receptors, metabolism of LDL does not occur and consequently there is an increase in plasma of c-LDL levels favoring the onset of atherosclerosis.

Availability of LDLR for cholesterol uptake occurs through two pathways, the first one is regulated according to the need for cholesterol that the liver cells present. This regulation occurs through the activation of the binding proteins to the sterol regulatory element (SREBPs). There are three isoforms of SREBP: SREBP1a, SREBP1c (encoded by the SREBF1 gene) and SREBP2 (encoded by the SREBF2 gene) [19, 29-30]. In intracellular medium the SREBP1 and SREBP2 are regulated by cholesterol levels. SREBP1 is responsible for transcription of genes involved in synthesis of fatty acids, phospholipids and triacylglycerols being regulated by insulin and oxysterols. SREBP2 are the main regulator of cholesterol biosynthesis [19, 29-30].

These transcription factors, when inactive, remain attached to the nuclear envelope and to the membranes of the endoplasmic reticulum. In cells with low levels of sterols, SREBP2s are targeted to the golgi complex where they are processed to their mature nuclear form. They are then translocated to the nucleus where the DNA sequences responsible for the synthesis of enzymes involved in the biosynthesis of stereoisomers such as hydroxy-3-methylglutaryl CoA reductase (HMGCR), low density lipoprotein receptor (LDLR) and Proproteinconvertasesubtilisin/kexin type 9 (PCSK9). Elevation of the stereoisomers levels inhibits the maturation of SREBP2 and consequently the inhibition of the synthesis of the same in a feedback system [19, 29, 31].

The second pathway that regulates the availability of LDLR occurs through PCSK9, a serine protein that is expressed and secreted primarily in the liver, kidney and brain [32]. PCSK9 is synthesized as a soluble zymogen (proPCSK9) and requires autocatalysis for its activation and maturation [33]. Once activated, PCSK9 can follow two pathways for the degradation of LDLR. The

first, PCSK9 can bind to LDLR right after synthesis and direct to lysosomal vesicles [34]. In the second route, surrounding PCSK9 binds to low-density lipoprotein (LDLR) receptors present on the surface of hepatocytes, causing their internalization and degradation within lysosomal vesicles [33]. This affects availability of LDLR on the cell surface and consequently concentration of LDL in plasma [31, 35-36].

Normal functioning of LDL uptake pathway is important for maintenance of normal plasmatic cholesterol levels. Hypercholesterolemia occurs through the excess of plasma LDL, representing one of the most important risk factors for the development of atherosclerosis.

5. Role of miRNAs in the regulation of PCSK9 and LDLR

Recently, several miRNAs have been implicated in the regulation of lipid metabolism [37-38]. Several studies have shown that modulation of specific miRNAs can directly influence lipid metabolism through post-transcriptional control of key genes such as LDLR. Currently several miRNAs have been correlated with LDLR expression levels, among which are miR-27a/b, miR-148a, miR-128-1, miR-130b, miR-301b and miR-185 [19, 29, 39].

5.1. miR-148a, miR-130b and miR-301b

The miR-148a is located in an intergenic region of chromosome 7 and is predominantly expressed in liver. In a study by Wagschal *et al.* (2015) the expression of miR-148a and miR-130b was increased in the liver of rats fed with a high fat diet, suggesting an evolutionarily conserved binding to the function of lipid metabolism. miR-148a is targeted as a key regulator in hepatic cholesterol clearance modulating the expression of LDLR and ABCA1 of HDL. These studies emphasize the therapeutic potential of these miRNAs in the control of c-LDL levels in dyslipidemias [5, 19, 29].

Studies indicate that other microRNAs also participate in the regulation of LDLR such as miR-301b and miR-128-1. Wagschal *et al.*, (2015) emphasizes the role of miR-301b in controlling the expression of genes involved in hepatic lipogenesis with the salt-inducible kinase 1 (SIK1), gene responsible for activating SREBP1c. This regulation mechanism interferes with the supply of LDLRs in plasmatic membrane and consequently plasma c-LDL levels. It has been shown that in HepG2 cells transfected with miR-128-1, miR-301b, there was a decrease in the uptake of fluorescently labeled c-LDL (DiI-LDL) compared to non-transfected cells, suggesting that these miRNAs modulate the uptake of LDL-c.

5.2. miR-27a/b

miR-27b is expressed in the liver and is recently related to the negative regulation of plasma cholesterol levels. Zang *et al.*, (2014) reports that miR-27a and miR-27b can influence metabolic pathways of efflux, influx, esterification and cholesterol hydrolysis by regulating several genes, including LDLR and PCSK9 (Vicks *et al.*, 2013). LDLR is one of miR-27a/b targets. A study with wild-type mice using AAV8 vectors showed that the elevation of miR-27b levels by 50-fold resulted in a reduction in ABCA1 expression by 50% and LDLR by 20%, however, there was no change in levels of Cholesterol or triglycerides [4, 15].

Alvarez *et al.*, (2015) found that overexpression of miR-27 in HepG2 cells caused a 40% decrease in the supply of LDLR, however, it was observed that interaction between miR-27 and PCSK9 increased in three-fold the expression of PCSK9.

Shirasaki *et al.* (2013) observed that miR-27a regulates lipid metabolism by inhibiting the expression of several genes, such as the SREBP1, SREBP2 transcription factors responsible for the activation of LDLR and PCSK9 transcription, as well as the inhibition of apolipoproteins expression ApoA1, ApoB100 and ApoE3. Thus, miR-27a regulates lipid metabolism by reducing lipid synthesis and lipid secretion of cells. To determine the effects of overexpression of miR-27b on surrounding lipids, Goedeke *et al.* (2015) fed wild-type rats with a lipid-rich diet and treated them with 5 mg/kg injections of anti-27b LNA oligonucleotides. Two weeks after treatment, rats showed increased

ABCA1 and LDLR expression by 10-20%, these results reinforce how miR-27b regulates the expression of important genes in lipid metabolism and may be a potential target for treatment of CVD.

LPL gene encodes the enzyme lipoprotein lipase, which aids the breakdown of lipoproteins, which normally carry fat molecules from the intestine into the bloodstream. Macrophage-derived lipoprotein lipase (LPL) plays a key role in accelerating lipid accumulation and secretion of proinflammatory cytokines in the atherosclerotic process. Xie et al. (2016) provides evidence that a novel anti-atherogenic role of miR-27 is closely related to the reduction of lipid accumulation and inflammatory response through the negative regulation of LPL gene expression, suggesting a potential strategy for the diagnosis and treatment of atherosclerosis [23].

5.3. miR-185

miR-185 is located on chromosome 22q11.2 and is considered an important regulator of carcinoma cells and neurological disorders [43]. However, more recent work on miR-185 has demonstrated its importance in the metabolism of atherosclerosis and CVDs.

Yu et al. (2016) found that miR-185 levels in patients with diabetes mellitus were significantly higher than those found in healthy controls, it was also demonstrated that there was no correlation between increased miR-185 levels and cardiac function.

miR-185 plays an important role in regulating various targets that play a role in cardiac hypertrophy, an adaptive mechanism of the heart, in response to increased activity or functional overload [44].

Overexpression of miR-185 causes decreased expression of hydroxy-3-methylglutaryl CoA reductase (HMGCR) and low-density lipoprotein (LDLR) receptor [37, 45]. Yang et al. (2014) evidenced that mice with elevated cholesterol had levels of miR-185 expression five times higher than the control group. Induced inhibition of miR-185 caused decreased expression of the SREBP-2, LDLR and PCSK9 genes and HMG-CoA reductase activity. In addition, miR-185 expression was found to be tightly regulated by SREBP-1c, through its binding to a single sterol response element in the miR-185 promoter.

6. Role of miRNAs in the regulation of apolipoprotein APOB

The APOB-100 are important components of the VLDL vesicles, and LDL, has the function of binding to LDL receptors for the absorption of plasma cholesterol by the liver, playing a key role in cholesterol metabolism [46]. After its synthesis, APOB-100 is translocated by the membrane of the endoplasmic reticulum (ER) to the addition of small molecules of lipids and also to avoid their degradation. It is in the RE that APOB100 binds to MTTP (Microsomal triglyceride transfer protein), which adds more phospholipids to APOB100 for the assembly and secretion of lipoproteins [39].

However, it is not yet known specifically which microRNAs are involved in the regulation of this pathway [28]. The microRNA is a major regulator of glucose metabolism, oxidative stress, arterial hypertension and processes such as adipogenesis, cardiac hypertrophy and ischemia, indicating that its expression may be essential for normal cardiac function and structure (Huang et al., 2016, Chen et al. 2016).

The importance of miRNAs in the assembly and secretion of lipoproteins containing APOB is now known. However, it is not yet known specifically which miRNAs are involved in the regulation of this pathway (Basir et al., 2014). miR-30c is a major regulator of glucose metabolism, oxidative stress, arterial hypertension and processes such as adipogenesis, cardiac hypertrophy and ischemia, indicating that its expression may be essential for normal cardiac function and structure [47].

6.1. miR-30

One of the functions recently discovered, and therefore little described, is the role of miR-30 in the regulation of lipid metabolism. Previous studies have shown that overexpression of miR-30c

decreases hepatic MTTP synthesis. Soh et al. (2013) observed that inhibition of miR-30c in Huh7 hepatocytes increased MTTP expression. The secretion and function of APOB100 and lipoproteins remained unchanged, evidencing how miR-30c is an important regulator of plasma c-LDL levels. Overexpression of miR-30c mediated by lentivirus, decreased hepatic MTTP expression [26-27]. The absence of formation of MTTP-APOB complex promotes the degradation of APOB in the lumen of the endoplasmic reticulum, which causes compromise in the VLDL assembly [39]. It was observed that mice fed for three weeks on a high fat diet and exhibiting lentivirus-mediated overexpression of miR-30c, remained low c-LDL levels compared to controls. MiR-30c contributed to the decrease of atherosclerosis in APO^{-/-} mice, demonstrating that it is important for the regulation of hepatic and plasma lipid concentrations through the inhibition of lipid synthesis and secretion of lipoproteins containing APOB100 rich in triglycerides [26-27, 47]. Soh et al. (2013) suggest that miR-30 analogues can be used to treat hypercholesterolemia and atherosclerosis in patients who are intolerant to statins.

6.2. miR-122

The most abundant microRNA in the liver is miR-122, accounting for about 70% of all expressed miRNA, responsible for maintaining the hepatic cell phenotype [48]. miR-122 also plays an important role in the regulation of the MTTP and APOB100 pathways. Mice with deletion in the coding region of miR-122 remained with low plasma LDL levels, but developed hepatic steatosis [49]. Inhibition of miR-122 causes assembly impairment and lipoprotein secretion due to inhibition of various genes, such as MTTP which is important in preventing the degradation and lipidation of nascent APOB during the generation of VLDL in the liver [24]. In a study conducted by de Liu et al. (2013), the influence of miR-122 expression on the differentiation of pluripotent stem cells in sperm-like cells in vitro was investigated. The miR-122 interferes in the expression of lipoproteins like APOB and APOA causing the abnormal development of spermatozoa.

Several studies associate the inhibition of miR-122 expression in mice with the reduction of plasma cholesterol and triglyceride levels when compared to controls [50-51]. According to Zampetaki et al. (2012), this decrease in plasma c-LDL is a consequence of increased fatty acid oxidation and decreased hepatic cholesterol synthesis caused by the inhibition of miR-122 through the regulation of fatty acid oxidation related genes [49-50].

Gene expression studies emphasize the importance of miR-122 in the synthesis of VLDL by regulating genes such as MTTP, APOB, APOE, LDLR and SREBP1c, demonstrating miR-122 as a potential target for the treatment of lipid disorders [51-52].

6.3. miR-34

Another miRNA that has been reported in the regulation of APOB is miR-34 [25]. Recent studies have shown that this miRNA regulates lipid metabolism through genes such as HNF4 α , a hepatic hormone-nucleolar receptor that regulates APOB expression. The expression of miR-34 decreases the secretion of LDL, VLDL, which results in hepatic steatosis and decrease in plasma lipid levels. Thus the increase of miR-34a reduces the expression of HNF4 α in the liver by attenuating the development of atherosclerosis in APOE^{-/-} or LDLR^{-/-} mice. These data indicate that the miR-34a-HNF4 α pathway is activated under common metabolic stress conditions and may play a role in plasma lipoprotein metabolism and atherosclerosis protection [25, 53].

6.4. miR-544 and miR-1202

Through bioinformatics analyzes, miR-544 and miR-1202 were identified as potential apoB regulators. Transfection of HepG2 cells with these miRNAs demonstrated that miR-544 decreases APOB mRNA expression. While in miR-1202 transfected cells there was an increase in APOB mRNA expression, these data demonstrate that specific miRNAs are involved in the expression of ApoB [28].

7. Other surrounding miRNAs and risk factors for atherosclerosis

Diabetes mellitus has been recognized as an important risk factor for atherosclerosis. Zampetaki et al. (2010) observed that high glucose concentration reduced the miR-126 content in endothelial apoptotic bodies. Similarly, studies have shown that in patients with pre-diabetes mellitus there was a reduction of miR-126. The miRNAs, miR-233, miR-24 and miR-92 are found in the plasma along the HDL vesicles. Zampetaki et al. (2010) shows that expression of miR-233 is deregulated in patients with diabetes mellitus and hypercholesterolemia. In patients with insulin resistance, overexpression of miR-233 in adipocytes was associated with decreased GLUT4, an insulin-regulated glucose transporter [3, 18]. The study by Wen et al. (2015) was performed with 121 patients, and indicated high levels of miR-233 in obese individuals when compared to control [54]. Thus, these articles suggest that miR-233 may be a biomarker and target of therapies for treating obesity, diabetes and hypercholesterolemia, important pathologies related to progression of atherosclerosis.

Accumulation of LDL in the artery wall and its subsequent oxidation (ox-LDL) leads to greater activation of the vascular wall. The work of Loyer et al. (2014) shows that in hypercholesterolemic mice with LDLR $-/-$ there was an increase in the expression of miR-92a in the bifurcations and ramifications of the arteries, areas prone to atheroma plaque formation due to ox-LDL. In addition, the expression of miR-92 was regulated by the oxidation of LDL. For Winther et al. (2014) the miR-92 inhibition is shown to be associated with reduced endothelial inflammation, in addition to preventing monocyte and macrophage adhesion during atherosclerotic plaque formation. Using PCR array, Niculescu et al. (2015) observed that miR-92a and miR-486 are surrounding miRNAs bound to HDL vesicles, most expressed in patients who present stable and unstable angina, acute myocardial infarction and heart failure. Author suggests that the miRNAs can be used as biomarkers of inflammation and endothelial dysfunction, since they can be detected in the plasma through the HDL vesicles.

8. Conclusion

In this review, we highlighted the role of miR-30c, miR-34 and miR-122 in decreasing plasma LDL-C by inhibiting secretion of lipoproteins containing APOB100. However, miR-34 and miR-122 were also related to the development of hepatic steatosis, a risk factor for cardiovascular diseases. While overexpression of miR-148a, miR-27a/b and miR-185 were associated with a decrease in the supply of LDLR, leading to the onset of hypercholesterolemic main cause of atherosclerosis. Detection of the expression profile of these mi-RNAS can be used as a biomarker for disorders linked to c-LDL uptake and future anti-miRNA therapies may be used in the treatment of atherosclerosis. Given the importance of these miRNAs, additional studies are needed to characterize other miRNAs in the pathway PCSK9-LDLR-APOB100 that may have contributed to the atherosclerotic disease.

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Abbreviations

miRNAs	microRNA
LDL	Low-density lipoprotein
DCV	Cardiovascular disease
PCSK9	Protein convertase subtilisina/kexina type 9
LDLR	Low-density lipoprotein Receptor

APOB	Apolipoprotein B
MTTP	Microsomal triglyceride transfer protein
EC	Endothelial cells
VSMC	Vascular smooth muscle cells
DGCR8	DiGeorge syndrome critical region gene 8
RISC	RNA-Induced Silencing Complex
SREBPs	Binding proteins to the sterol regulatory element
HMGCR	Hydroxy-3-methylglutaryl CoA reductase
ABCA1	ATP-binding cassette transporter A1
HDL	High-density lipoprotein
SIK1	Salt-inducible kinase 1

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