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Review

The Regulatory Role of microRNAs in the Therapeutic Response to Statins: Narrative Review

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Abstract: Statins or 3-hydroxy-3-methylglutaryl coenzyme A inhibitors are a class of cholesterol-lowering drugs that are widely used in clinical practice for primary and secondary prevention of cardiovascular and cerebrovascular diseases associated with atherosclerosis. In recent years, there has been an increase in scientific and clinical interest in studying the relationship between statins and non-regulating ribonucleic acids circulating in the systemic bloodstream, known as circulating microRNAs. On the one hand, microRNAs play a crucial role in regulating the expression of genes associated with the therapeutic response to statins, including the expression of key isoenzymes of statin metabolism in the liver, as well as directly and indirectly regulate the metabolism of high-density lipoproteins (HDL), low-density lipoproteins (LDL) and very low-density lipoproteins (VLDL). On the other hand, statins can affect the expression levels of specific microRNAs circulating in the systemic bloodstream and affecting the epigenetic mechanisms regulating the expression of genes encoding key pathways of atherogenesis. This narrative review provides an update on the understanding of microRNAs' role as epigenetic regulators of interindividual differences in the therapeutic response to statins, as well as their potential as next-generation lipid-lowering medications in the long run. The influence of statins on altering the expression of microRNAs involved in various mechanisms of atherogenesis is also highlighted.

Keywords: *atherosclerosis, statin, epigenetic biomarker, efficacy, safety, personalized therapy*

1. INTRODUCTION

Statins or 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA reductase) inhibitors are a class of lipid-lowering drugs that are widely used in clinical practice for primary and secondary prevention of cardiovascular and cerebrovascular diseases associated with atherosclerosis [1]. Atherosclerosis is a poly-ethological disease, and atherogenesis is an evolutionarily complex multicomponent process accompanied by a cascade of diverse changes occurring at the level of tissue, cells, and biochemical pathways [2]. It is known that the therapeutic response to statins has interindividual variability, which explains the search for genetic and epigenetic biomarkers that allow personalized assessment of the expected effectiveness of lipid-lowering therapy and the risk of statin-induced adverse drug reactions (ADRs) [3]. In recent years, there has been an increase in scientific and clinical interest in studying the relationship between statins and non-regulating ribonucleic acids circulating in the systemic bloodstream, known as circulating microRNAs [2]. Preclinical studies of microRNAs (miR) in vitro and in vivo, as well as clinical studies of human microRNAs (Human Sapiens miR – hsa-miR) over the past decade, demonstrate their important role both in the development and progression of atherosclerosis and its therapy [4]. On the one hand, microRNAs play a crucial role in regulating the expression of genes associated with the therapeutic response to statins, including the expression of key isoenzymes of statin metabolism in the liver, as well as directly and indirectly regulate the metabolism of high-density lipoproteins (HDL), low-density lipoproteins (LDL) and very low-density lipoproteins (VLDL) [5,6]. On the other hand, statins can affect the expression levels of specific microRNAs circulating in the systemic bloodstream and affecting the epigenetic mechanisms regulating the expression of genes encoding key pathways of atherogenesis [7]. In general, this interaction can affect various cellular processes, including those related to lipid metabolism, systemic inflammation, endothelial dysfunction, and the state of the cardiovascular system. This explains the relevance of preclinical and clinical studies of the

role of microRNAs in atherogenesis and therapy of atherosclerosis using various approaches, including: (1) the search for microRNAs pathogenetically significant for arterial hypertension, dyslipidemia, diabetes mellitus and diseases acting as risk factors for atherosclerosis.; (2) assessment of the microRNA expression level in cells involved in the development of endothelial dysfunction, initiation and progression of atherosclerotic plaque (ASP) in patients with atherosclerosis and in an animal model; (3) analysis of associations of polymorphic variants in genes encoding key microRNAs involved in epigenetic control of atherogenesis; (4) Bioinformatic approaches to the identification of atherosclerosis-associated microRNAs [2].

The purpose of this narrative review is to update current knowledge about local and circulating microRNAs that can influence atherogenesis and participate in the epigenetic regulation of statin response.

2. MATERIALS AND METHODS

A search and analysis of publications for the period 2015–2025 was conducted in the PubMed, eLIBRARY.RU, and Google Scholar databases. The Introduction and Discussion include references to publications issued prior to 2020 that are of historical interest.

3. RESULTS

3.The effect of Circulating microRNAs on the Efficacy and Safety of Statins

3.1.1. Regulation of Statin Transport

Nearly all statins serve as substrates for the OATP1B1 transporter, which is encoded by the *SLCO1B1* gene belonging to the family of organic anion transporters. Taking inhibitors of this transport protein at the same time raises the concentration of statins in the blood plasma and increases their toxicity [8] (**Table 1**). Most of the previous studies have been devoted to the study of the relationship between the carriage of the *SLCO1B1* gene and the risk of statin-induced ADRs [9]. The results of these studies formed the basis of clinical recommendations for the treatment of simvastatin-induced myopathy based on the *SLCO1B1* genotype, published by the Clinical Pharmacogenetics Implementation Consortium (CPIC) [10].

The ATP-binding cassette transporter A1 (ABCA1) is necessary for the outflow of cholesterol from cells into HDL. Disruption of the regulation of microRNAs targeting this transporter can affect cholesterol homeostasis and contribute to the development of coronary heart disease (CHD), as demonstrated in the study by Torres-Paz Y.E. et al. (2024) [11]: A decrease in the level of hsa-miR-33a-5p and an increase in the level of ABCA1 were associated with a reduced risk of coronary heart disease, while atorvastatin increased the level of ABCA1 mRNA in patients with coronary heart disease. The authors confirmed the hypothesis that dysregulation of microRNAs in monocytes can affect the formation of atherosclerotic lesions by regulating the outflow of cholesterol.

El Saadany T. et al. (2019) was shown, that miR-206 exerts a suppressive effect on OATP1B1 expression by an epigenetic mechanism. Individuals with high hepatic levels of miR-206 appear to display lower level of OATP1B1 [12]. The role of this microRNA was confirmed in a study by Xu Y. et al. (2020) [13]. The study of Peng J.F. et al. [14] indicates that miR-511 may play an important role in the regulation of OATP1B1 expression by free fatty acids. miR-192 decreases [15], and miR-579-3p increases the expression of OATP1B3 in hepatocytes [16]. An absence or low expression of miR-210 correlated to high ABCC5 expression [17]. A decrease in the expression level of miR-let-7f leads to an increase in the expression of ABCC5 [18] (**Table 2**).

3.1.2. Regulation of Statin Metabolism in the Liver

Statins are metabolized by P-oxidation with the participation of cytochrome P450 (CYP) isoenzymes (**Table 3**), in particular CYP3A4 and CYP3A5, which are crucial for the metabolism of most statins [27]. Simvastatin and lovastatin are largely metabolized by CYP3A4 and CYP3A5, while atorvastatin is less so. Pitavastatin undergoes minimal metabolism in the liver due to the first stage (enterohepatic circulation), its main pathway of metabolism is lactonization/glucuronidation. For fluvastatin and rosuvastatin, the key isoenzymes are CYP2C9 and CYP2C19, which are less susceptible to interaction with CYP3A4 (for example, rosuvastatin is practically not metabolized by CYP3A4 and has a low potential for drug interaction). Some statins, such as pravastatin, which is metabolized by sulfation, do not interact with CYP isoenzymes and therefore patients taking these lipid-lowering drugs are less susceptible to drug interactions with inhibitors or inducers of CYP3A4 and CYP3A5.

Table 1. Primary and secondary proteins involved in statin transport (from [19,20,21], modified by authors)

Drug	Primary transport protein (uptake transporter)	Secondary transport protein
Atorvastatin	OATP1B1, OATP1B3	Efflux / Excretion: P-gp (ABCB1) and BCRP (ABCG2)
Fluvastatin	MRP1 (ABCC1), MRP5 (ABCC5)	Efflux / Excretion: P-gp (ABCB1) and BCRP (ABCG2)
Lovastatin	OATP1B1, MCT4	Efflux / Excretion: P-gp (ABCB1), BCRP (ABCG2), and MRP2 (ABCC2)
Simvastatin	OATP1B1	Efflux / Excretion: BCRP (ABCG2), MRP1 (ABCC1), and MRP2 (ABCC2)
Pitavastatin	OATP1B1, OATP2	Efflux / Excretion: BCRP (ABCG2)
Pravastatin	OATP1B1	Efflux / Excretion: BCRP (ABCG2), MRP2 (ABCC2), and BSEP (ABCB11)
Rosuvastatin	OATP1B1	Efflux / Excretion: BCRP (ABCG2)

Note: *ABCC1/ 5 - a protein belonging to the superfamily of transporters associated with the ATP-binding cassette (ABC); BCRP - breast cancer resistance protein; MCT4 - monocarboxylate transporter 4; MRP1/ 2 - canalicular multispecific organic anion transporter; P-gp – P glycoprotein; OATP1B1 / OATP1B3 - organic anion-transporting peptide 1B1/1B3) is a membrane transport protein that transports organic anions across the cell membrane.*

Table 2. The role of microRNAs in regulating the activity of major uptake transporter of statins

Transport protein	microRNA	References
OATP1B1	miR-206, miR-511, miR-613	[12,13,14]
OATP1B3	miR-192-3p, miR-579-3p	[15,16]
ABCC1	miR-9, miR-34a, miR-627-5p, miR-1268a, miR-1291	[22,23,24,25,26]
ABCC5	miR- let-7f, miR-210,	[17,18]

Note: *ABCC1/5 - a protein belonging to the superfamily of transporters associated with the ATP-binding cassette (ABC); OATP1B1/ OATP1B3 - organic anion-transporting peptide 1B1/1B3) is a membrane transport protein that transports organic anions across the cell membrane; miR – microRNA.*

Table 3. Primary and secondary enzymes involved in statin metabolism (from [19,20], modified by authors)

Drug	Primary enzyme	Secondary enzymes
Atorvastatin	Oxidation: CYP3A4	Oxidation: CYP3A5 and CYP2C8 (minimally) Glucuronidation: UGT1A1, UGT1A3, and UGT2B7
Fluvastatin	Oxidation: CYP2C9 (mainly) and CYP2C19	Oxidation: CYP3A4, CYP2C8, and CYP2D6
Lovastatin	Oxidation: CYP3A4	Oxidation: CYP3A
Simvastatin	Oxidation: CYP3A4	Oxidation: CYP2C8. Interconversion: active simvastatin acid can be converted back to the lactone form by UGT1A1 or UGT1A3
Pitavastatin	Glucuronidation: UGT1A1 and UGT2B7	Glucuronidation: UGT 1A3 and UGT2B6. Oxidation: CYP2C9 and CYP2C8 (minimally)
Pravastatin	Glucuronidation: UGT1A1 and UGT1A3	Oxidation: CYP3A4 (minimally)
Rosuvastatin	Oxidation: CYP2C9 (10%)	Oxidation: CYP3A4 (minimally)

Note: *CYP - cytochrome P450; UGT - UDP-glucuronyl transferase.*

Table 4. The role of microRNAs in regulating the activity of liver cytochrome P450 isoenzymes involved in statin metabolism

CYP	microRNA	References
CYP3A4	miR-1, miR-27a, miR-27b, miR-122–5p, miR-142, miR-206, miR-224–5p, miR-298, miR-532–3p, miR-577, miR-627, miR-628–3p, miR-641	[32,33]
CYP3A5	miR-142	[33]
CYP2C8	miR-103, miR-107	[34,35]
CYP2C9	miR-103, miR-107, miR-128–3p, and miR-130b	[32]
CYP2C19	miR-29a-3p, miR-103, and miR-107	[32]

Note: *CYP - cytochrome P450.*

P-oxidation as an enzymatic process mainly occurs in the liver and small intestine and is vital for the breakdown of statins into their metabolites. Changes in the functional activity of CYP isoenzymes are genetically determined and associated with genetic polymorphisms (single-nucleotide variants – SNVs), which may affect the effectiveness and risk of developing statin-induced ADRs [28]. In particular, carriage of CYP3A5*3 is associated with a high risk of statin-induced ADRs (homozygotes with a variable allele *3/*3 compared to homozygotes, but with a common allele *1/*1 + heterozygotes by common allele *1/*3 Odds ratio (OR) = 1.40, 95% confidence interval (CI) = 1.08–1.82), and for statin-induced myopathy, OR was 1.30 (95% CI: 0.96–1.75) [29].

In recent years, it has been shown that microRNAs can suppress the expression of non-coding RNAs, which, in turn, suppresses the expression of cytochrome P450 isoenzymes dependent on non-coding RNAs. In other cases, non-coding RNAs can enhance microRNA transcription by acting on their promoters or interacting with promoters of microRNA processing factors [30,31] (**Table 4**).

3.1.3. Studies of the Regulatory Role of microRNAs on Lipid Metabolism

Recent studies have shown that some microRNAs are involved in controlling the level of atherogenic LDL fractions and LDL cholesterol through post-transcriptional regulation of genes involved in VLDL secretion, cholesterol biosynthesis, and LDL receptor expression in the liver [36,37]. The role of microRNAs in the formation of early atherosclerotic lesions, as well as in rupture and erosion of ASP is known [38]. Certain circulating microRNAs (such as miR-30c, miR-33, miR-34, miR-122, miR-128-1, miR-144, miR-148a, miR-224, miR-483, and miR-520d) participate directly or indirectly in lipid exchange, regulating the metabolism of HDL, LDL, and VLDL [39].

Previously studied microRNAs for their effect on various links of atherogenesis (activation of endothelial cells and low-intensity inflammation, differentiation of monocytes, activation of macrophages, differentiation and activation of T cells, outflow of cholesterol, formation of foam cells, proliferation and migration of HMG, angiogenesis, remodeling of blood vessels, destabilization of ASP) are divided into atherogenic and anti-atherogenic [2]. Moreover, many microRNAs have a dual effect (both atherogenic and antiatherogenic), for example: miR-125b, miR126, miR-132, miR-146a, miR-155, miR-21, miR-17–92, miR-21, miR-221, miR-222, miR-24, miR-26a, miR-31, miR-378, miR-424, miR-663, miR-92a.

3.2. Effect Statins on microRNAs Expression

Studies over the past decade have demonstrated that the therapeutic effects of statins can be mediated by changes in the expression level of microRNAs involved in the epigenetic regulation of various links in atherogenesis [40,41,42], potentially affecting the synthesis and cleavage of cholesterol. However, the effect of various statins on the level of circulating microRNAs is variable: atorvastatin inhibits the expression of miR-29a-3p, miR-29b-3p, miR-33a-5p, miR-33b-5p, miR-300 and miR-454-3p in healthy volunteers, simvastatin has no effect on the expression of these microRNAs [43]. Later Cerda A. and co-authors. (2021) showed that atorvastatin-induced activation of miR-129, miR-143, miR-205, miR-381, and miR-495, along with atorvastatin-mediated inhibition of miR-29b and miR-33a, modulates the expression of target genes involved in lipogenesis and lipid metabolism [44]. Network analysis showed that atorvastatin-modulated microRNAs regulate key genes associated with changes in blood cholesterol levels, including ABCA1, HMGCR, INSIG1, LDLR, LPL, SCAP, and SREBF1 [43].

Statins are known to improve the function of the endothelium of blood vessels and reduce the local and systemic inflammatory response. These effects may be mediated, at least in part, by the modulation of certain microRNAs [45].

Preclinical studies of the effects of statins on the regulation of the expression level of microRNAs involved in atherogenesis are still few (**Table 5)** [44,46,47,48,49]. The design of these studies is variable. The authors have used various cell lines, but the results are promising.

Clinical studies of the effects of statins on changes in the expression level of microRNAs involved in atherogenesis are conducted in different countries. The sample size varied from 15 [50] to 24 patients with hypercholesterolemia observed in lipidological clinics [51]. We have not found any available clinical studies for fluvastatin and lovastatin. MicroRNA signatures have been most studied in patients taking atorvastatin [43,50,51,52,53]. The daily dose of atorvastatin ranged from 10 to 20 mg /day, and the duration of treatment ranged from 1 to 3 months (**Table 6**).

Table 5. Preclinical studies of the effect of statins on the level of microRNA expression

Drug	Subject of the study, method of administration	Effect	References
Atorvastatin	HepG2 cells. Treatment with atorvastatin (0.1–10 μM) for 24 hours	Overexpression of miR-129, miR-143, miR-205, miR-381 and miR-495. Inhibition of miR-29b and miR-33 expression suppression. MicroRNA-mediated effect: modulation of the expression of target genes involved in lipogenesis and lipid metabolism (could further promote the protective effect of atorvastatin)	[44]
Fluvastatin	HEKn cells and the HaCaT cells	Fluvastatin attenuated IL-6 and IL-8 production induced by IL-17A via the miR-146a/ERK pathway	[46]
Lovastatin	HUVEC. Treatment with lovastatin (10 μM for 0.5 to 24 hours)	Lovastatin inhibited oxidative stress induced by multiple oxidants including ox-LDL, H_2O_2, TNFα, homocysteine thiolactone, and high glucose, which were reversed by inhibition of miR-29b in HUVECs.	[47]
Simvastatin	HepG2 cells. Treatment with atorvastatin (0.1–10 μM for 24 hours)	Hypo-expression of miR-33a (could further promote the protective effect of simvastatin)	[44]
Pitavastatin	LPS-stimulated H9c2 cells. Intraperitoneal injection of LPS in mice	Overexpression miR-106b-5p (could further promote the protective effect of pitavastatin)	[48]
Pravastatin	ND	ND	ND
Rosuvastatin	EC-specific-*Bach1* of knockout mice	Rosuvastatin inhibited BACH1 expression by upregulating microRNA let-7a in ECs, and decreased Bach1 expression in the vascular endothelium of hyperlipidemic mice.	[49]

Note: *BACH1 - BTB and CNC homology 1 (transcription regulator protein); EC - endothelial cell; ERK - extracellular signal-regulated kinase; HaCaT - spontaneously transformed aneuploid immortal keratinocyte cell line from adult human skin; H9c2 - subclone of the original clonal cell line derived from embryonic BD1X rat heart tissue; HEKn - human primary keratinocytes (cells); HepG2 - hepatoblastoma-derived cell line; HUVECs - human umbilical vein endothelial cells; IL – interleukin; LDL - low-density lipoproteins; LPS - lipopolysaccharides; miR – microRNA; ND – no data; TNFα - tumor necrosis factor alpha.*

Table 6. Clinical studies of the effect of statins on the level of microRNA expression

Drug	Subject of the study, method of administration	Effect	References
Atorvastatin	20 patients with hypercholesterolemia. Oral administration of 10 mg / day for 1 month	Overexpression of hsa-miR-29a-3p, hsa-miR-29b-3p, hsa-miR-300, hsa-miR-33a-5p, hsa-miR-33b-5p and hsa-miR-454-3p.	[43]
	20 patients with hypercholesterolemia. Oral administration of 20 mg / day for 1 month	Overexpression of hsa-miR-24-3p, hsa-miR-590 and hsa-miR-33b-5p	[52]
	15 patients with hypercholesterolemia. Oral administration of 10 mg / day for 12 weeks (3 months)	Overexpression hsa-miR-483-5p, hsa-miR-4667-5p, hsa-miR-1244, hsa-miR-3921, hsa-miR-455-5p, hsa-miR-3609 and hsa-miR-4428. Hypo-expression of hsa-miR-3128, hsa-miR-27a-5p and hsa-miR-4454	[50]
	20 patients with hypercholesterolemia. Oral administration at a dose of 20 mg / day for 4 weeks (1 month)	Overexpression of hsa-miR-20a-5p	[53]
Fluvastatin	ND	ND	ND
Lovastatin	ND	ND	ND
Simvastatin	20 patients with hypercholesterolemia. Oral administration of simvastatin (10 mg / day) for 1 month	No effect on microRNA expression	[43]

Pitavastatin	19 patients with hypercholesterolemia. Oral administration of 2 mg / day for 12 weeks	Overexpression of hsa-miR-483-5p, hsa-miR-4667-5p, hsa-miR-1244, hsa-miR-3921, hsa-miR-455-5p, hsa-miR-3609 and hsa-miR-4428. Hypo-expression of hsa-miR-3128, hsa-miR-27a-5p and hsa-miR-4454	[50]
Pravastatin	24 patients with hypercholesterolemia. Oral administration of 40 mg / day for 1 year	Overexpression of hsa-miR-30c	[51]
Rosuvastatin	22 patients with hypercholesterolemia. Oral administration of 40 mg / day for 1 year	Overexpression of hsa-miR-30c	[51]

Note: *ND – no data.*

3.3.Studies of microRNA-206 as Next-Generation Drugs for Lipid-Lowering Therapy

For patients with severe atherosclerosis, heart failure, or other terminal diseases, the benefits of statins are extremely limited. In addition, patients with statin-induced ADRs have limited access to lipid-lowering therapy, including liver damage, hyperglycemia, weight gain, headache, sleep disorders, muscle pain, and dizziness [54]. This explains the importance of finding new and effective therapeutic strategies for the treatment of atherosclerosis (**Table 7**). The discovery of microRNAs has provided new possibilities for the treatment of atherosclerosis [55]. MicroRNAs regulate gene expression by binding to 3'-untranslated regions (3'-HT) of messenger RNAs, and can affect many genes. During pathogenesis, a stable interactome was formed between microRNA expression and their targets to maintain physiological homeostasis in the human body [56,57].

Since hypercholesterolemia is often accompanied by hypertriglyceridemia, hepatosteatosis, and hyperglycemia, it is necessary to develop next-generation therapeutic drugs for the treatment of these interrelated metabolic disorders. Due to their unique properties described above, microRNAs are an ideal regulator for fine-tuning lipid and lipoprotein homeostasis by simultaneously modulating multiple signaling pathways. Given the relative ease of production of microRNA inhibitors and analogues, they may become new therapeutic agents for the treatment of atherosclerosis [58] (for examples, miR-19b [59], miR-27a [60], miR-27b [61], miR-29 [62], miR-33 [63], miR-33a-3p [64], miR-520c-3p [65]. The Table presented new research results on the effectiveness of microRNAs as drug traces for lipid-lowering therapy: miR-99a-5p [66], miR-140-5p [67], miR-148a [68], miR-181d-5p [69], miR-185 [70], miR-206 [71,72], miR-320b [73], miR-337-3p [74], miR-483-5p [75].

4. DISCUSSION

From the perspective of personalized medicine, the use of circulating microRNAs as epigenetic biomarkers of statin efficacy and safety is relevant and promising. Understanding how statins affect the signature (pattern) of circulating microRNAs in patients with atherosclerosis may lead to more personalized approaches to statin therapy (drug choice, dose, duration of administration, need and frequency of therapeutic drug monitoring of statins in the blood, need and frequency of monitoring of biochemical biomarkers of statin efficacy and safety) potentially optimizing lipid-lowering therapy based on the individual profile of circulating microRNAs in a particular patient [76,77,78,79]. Both the effect of statins on the expression level of circulating microRNAs and the effect of circulating microRNAs on the efficacy and safety of statins may vary from patient to patient with atherosclerosis, potentially explaining the interindividual differences in the efficacy and safety of this class of drugs.

In addition, some microRNAs can potentially be used in the treatment of atherosclerosis and associated cardiovascular diseases, both to increase the effectiveness of statins and to reduce the risk and severity of statin-induced ADRs [80]. This encourages researchers to develop a new generation of hypolipidemic drugs based on microRNAs by regulating cholesterol and TG levels in blood plasma [81,82], stabilization of ASP [83] and prevention of arterial restenosis after invasive interventions [84].

Various microRNAs are becoming attractive therapeutic candidates for the treatment of atherosclerosis and associated diseases. For example, the review by Khan A.A. et al. (2022) [85] demonstrated the therapeutic potential of miR-19b, miR-20a, miR-21, miR-27, miR-29, miR-34a, miR-144, miR-148a and miR-199a.

Table 7. Studies of the effect of microRNA as drugs for lipid-lowering therapy

microRNA	Subject of the study, method of administration	Effect	References
miR-99a-5p	Human and mouse hepatocytes. Transfection of miR-99a-5p or anti-miR-99a-5p	In silico: miR-99a-5p overexpression potently inhibited PCSK9 expression, thereby up-regulating LDLR, functionally enhancing LDL-C uptake and increasing intracellular cholesterol levels in human, but not in mouse, cells. Conversely, anti-miR-99a-5p upregulates PCSK9, leading to a reduction in LDLR, attenuation of LDL-C uptake, and a decrease in the intracellular cholesterol levels of human hepatocytes	[66]
miR-140-5p	Human and mouse hepatocytes. Transfection of hsa-miR-140-5p and anti-miR-140-5p	In hepatocytes: overexpression of miR-140-5p dramatically reduces LDLR expression and reduces LDL-C uptake. Inhibition of miR-140-5p significantly increases LDLR expression and increases LDL-C uptake in human HepG2 cells and hepatocytes, but not in mouse Hepa1-6 cells. miR-140-5p is a negative regulator of LDLR expression in human hepatocytes	[67]
miR-148a	Huh7 cells. Transfection of a library of 1,719 distinct miRNA mimics and incubated with 30 μg DiI-LDL cholesterol/ml	In hepatocytes: miR-148a is a negative regulator of LDLR expression and activity, and define a novel SREBP1-mediated pathway by which miR-148a regulates LDL-C uptake. *In vivo*: inhibition of miR-148a increases hepatic LDLR expression and decreases plasma LDL-C.	[68]
miR-181d-5p	Mice. PCSK9 knockdown Huh7 cells. Transfection of AAV-miR-181d-5p	In hepatocytes: *PCSK9* to be a possible target gene of miR-181d-5p, which was confirmed by *in vitro* experiments. *In vivo:* miR-181d-5p could directly interact with both the *PCSK9* 3'-UTR and promoter to inhibit PCSK9 translation and transcription. miR-181d-5p targets the *PCSK9* 3'-UTR to inhibit PCSK9 expression and to reduce serum LDL-C	[69]
miR-185	HepG2 cells. Transfection of antisense inhibitor of miR-185	In hepatocytes: miR-185 controls cholesterol homeostasis as a key post-transcriptional LDLR modulator. *In vivo:* miR-185-inhibitor upregulated hepatic LDLR expression and correlated with a decrease in plasma cholesterol level and arterial plaque area in ApoE KO mice	[70]
miR-206	Mice. Transfection of MC-miR-206	In hepatocytes: inhibition of *de novo* lipogenesis, cholesterol synthesis, assembly and secretion, VLDL, gluconeogenesis. In macrophages: activation of expression of genes regulating cholesterol outflow. *In vivo*: regression of hypercholesterolemia, hypertriglyceridemia, hyperglycemia, and hepatosteatosis. It surpasses statins in its effectiveness in reducing hyperglycemia and blood cholesterol levels	[71,72]
miR-320b	Human mononuclear cells in peripheral blood. *Apoe* $^{-/-}$ mice. Transfection of AAV2-miR-320b	In human: miR-320b was highly expressed in coronary artery disease patients compared with that in the healthy controls. *In vitro*: miR-320b decreased HDL- and apoA1-mediated cholesterol efflux from macrophages partly by directly targeting the *ABCG1* and *EEPD1* genes and partly via suppressing the LXRα-ABCA1/G1 pathway. *In vivo*: AAV2-miR-320b attenuated cholesterol efflux from peritoneal macrophages, which showed reduced expression of ABCA1/G1 and EEPD1, and increased lipid LDL-C level, with a down-regulation of hepatic LDLR and ABCA1	[73]

miR-337-3p	GEO dataset and two hyperlipidemic models (knockdown of PCSK9- and *LDLR*$^{-/-}$ mouse). Transfection of AAV-miR-337-3p	*In vivo*: miR-337-3p could directly interact with both the PCSK9 3'UTR and promoter to inhibit PCSK9 translation and transcription. the result from DiI-LDL uptake assay under the knockdown of PCSK9 demonstrated that miR-337-3p promoting the absorption of LDL-C in HepG2 cells was dependent on PCSK9, and the result from *LDLR*$^{-/-}$ mouse model indicated that miR-337-3p regulating LDL-C was dependent on PCSK9/LDLR pathway	[74]
miR-483-5p	HepG2 cells. Hyperlipidemic mice (Ldlr-knockout). Transfection of AAV8 - *PCSK9*-3'-UTR	*In vivo*: hepatic miR-483 overexpression increased LDLR levels by targeting Pcsk9, with a significant reduction in plasma total cholesterol and LDL-C levels. The cholesterol-lowering effect of miR-483-5p was significant in mice receiving AAV8-PCSK9-3'-UTR but not *Ldlr*-knockout mice or mice receiving AAV8 PCSK9-3'-UTR (ΔBS) with the miR-483-5p targeting site deleted	[75]

Note: *AAV - adeno-associated virus; ABCG1 - ATP binding cassette subfamily G member 1; Apoe - apolipoprotein E; EEPD1 - endonuclease/exonuclease/phosphatase family domain containing 1; GEO - Gene Expression Omnibus; HDL - high-density lipoprotein; HepG2 - hepatoblastoma-derived cell line; Hepa1-6 - mouse hepatic cells; Huh7 - human hepatic cells; LDL-C - low-density lipoprotein cholesterol; LDLR - low density lipoprotein receptor; LXRα - liver X receptor α; MC - mini-circle system; miR – microRNA; PCSK9 - proprotein convertase subtilisin/kexin type 9.*

4. LIMITATIONS

The introduction of circulating microRNAs as epigenetic biomarkers of statin efficacy and safety into real clinical practice is currently limited by the following reasons: (1) the need to conduct additional preclinical studies to understand the specific pathways and mechanisms by which microRNAs are involved in the therapeutic response to statins; (2) the need to conduct clinical studies to assess the diagnostic and prognostic potentials of the signature (pattern) of circulating microRNAs as epigenetic biomarkers of an individual therapeutic response to statins [86] and identification of patients at high risk of statin-induced ADRs; (3) the need to conduct clinical trials of new-generation lipid-lowering drugs based on microRNAs in combination with statins (adjuvant therapy of hypercholesterolemia) or in monotherapy (alternative therapy of hypercholesterolemia) [87]; (4) the level of microRNA expression can be modified by a wide range of factors (taking statins, smoking, oxidative stress, hypoxia; while different types of cells react differently to these effects) and depends on the presence of concomitant pathology (diabetes mellitus, dyslipidemia, obesity) [2,88-90].

4. CONCLUSIONS

Thus, both the initiation and progression of atherosclerosis and the use of statins in atherosclerosis are characterized by the various effects of microRNAs and the dynamics of their expression in the patient's blood and tissues. However, to translate previously conducted preclinical and clinical studies into real-world clinical practice, it is important to conduct large, long-term "bridge" studies. Understanding the role of microRNAs in atherosclerosis is essential for the development of epigenetic biomarkers and new therapeutic targets for statins. Updating knowledge about the role of microRNAs in the development of atherosclerosis is also important for the development of next-generation targeted lipid-lowering drugs.

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