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THE ROLE OF MICRO-RNA IN ATHEROSCLEROSIS

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Summary.
Introduction. Micro-RNA (miRNA) are small ribonucleic acid (RNA) molecules that play a crucial role in regulating gene expression in eukaryotic cells. Currently, circulating microRNAs are considered promising biomarkers for diagnosis and potential therapeutic targets for treating cardiovascular diseases, including atherosclerosis.
Materials and Methods. A literature review of the last 10 years was conducted, using 30 bibliographic sources, including those from the "Nicolae Testemițanu" USMF Scientific Medical Library and electronic libraries such as PubMed, Elsevier, Cambridge Journals Online, Hinari, Medline, and MedScape.
Results. A number of studies have estimated the major role of miRNAs in the diagnosis and treatment of atherosclerosis. Hepatic overexpression of miR-30c significantly reduced atherosclerosis by decreasing cholesterol and ApoB-lipoprotein synthesis. Another study supports the conclusion that miR-30c-5p substantially protects human aortic endothelial cells from the cell death through pyroptosis. In one study, the administration of miR-23a-5p had a major impact on protection against atherosclerosis progression and improving plaque stability in dyslipidemic mice.
Conclusions. miRNAs play a major role in regulating molecular processes that contribute to the development and progression of atherosclerosis, including apoptosis, inflammation, and lipoprotein metabolism. Identifying specific microRNAs as biomarkers and therapeutic targets opens new perspectives for the development of more effective treatments and early diagnostic methods for atherosclerosis.
Keywords: micro-RNA, atherosclerosis, diagnosis, biomarkers, lipoproteins, treatment.

Rezumat. Rolul micro-ARN-ului în **ateroscleroză.**
Introducere. Micro-RNA (miRNA) sunt molecule mici de acid ribonucleic (RNA) care joacă un rol crucial în reglarea expresiei genice în celulele eucariote. În prezent, microRNA circulante sunt considerate biomarkeri promițători pentru diagnostic și potențiale ținte terapeutice pentru tratarea bolilor cardiovasculare, inclusiv ateroscleroza.
Materiale și **Metode.** S-a efectuat un reviu al literaturii din ultimii 10 ani, utilizând 30 de surse bibliografice, dintre care ale Bibliotecii Științifice Medicale ale USMF „Nicolae Testemițanu", date ale bibliotecilor electronice PubMed, Elsevier, Cambridge Journals Online, Hinari, Medline și MedScape.
Rezultate. Un șir de cercetări au estimat rolul major al miRNA în diagnosticul și tratamentul aterosclerozei. Supraexpresia hepatică a miR-30c a redus semnificativ ateroscleroza prin scăderea sintezei de colesterol și ApoB-lipoproteine. Alt studiu susține concluzia că miR-30c-5p protejează semnificativ celulele endoteliale aortice umane de moartea celulară prin piroptoză. Într-un studiu administrarea de miR-23a-5p a avut un impact semnificativ în protejarea împotriva progresiei aterosclerozei și îmbunătățirea stabilității plăcii la șoarecii cu dislipidemie.
Concluzii. miRNA joacă un rol crucial în reglarea proceselor moleculare care contribuie la dezvoltarea și progresia aterosclerozei, inclusiv apoptoza, inflamația, metabolismul lipoproteinelor. Identificarea microRNA specifice ca biomarkeri și ținte terapeutice deschide noi perspective pentru elaborarea unor tratamente mai eficiente și metode de diagnostic precoce în ateroscleroză.
Cuvinte-cheie: micro-RNA, ateroscleroza, diagnostic, biomarkeri, lipoproteine, tratament.

Резюме. Роль микро-РНК в атеросклерозе.
Введение. Микро-РНК (миРНК) – это небольшие молекулы рибонуклеиновой кислоты (РНК), которые играют важную роль в регуляции генной экспрессии в эукариотических клетках. В настоящее время циркулирующие микроРНК считаются перспективными биомаркерами для диагностики и потенциальными терапевтическими мишенями для лечения сердечно-сосудистых заболеваний, включая атеросклероз.
Материалы и методы. Был проведен обзор литературы за последние 10 лет, использовано 30 библиографических источников, включая библиотеку Научной медицинской библиотеки USMF «Николае Тестемицану» и электронные библиотеки, такие как PubMed, Elsevier, Cambridge Journals Online, Hinari, Medline и MedScape.

Результаты. Ряд исследований оценил важную роль микроРНК в диагностике и лечении атеросклероза. Печеночная сверхэкспрессия miR-30c значительно снижала атеросклероз за счет уменьшения синтеза холестерина и аполипопротеина B (ApoB). Другое исследование подтверждает, что miR-30c-5p существенно защищает эндотелиальные клетки аорты человека от клеточной гибели посредством пироптоза. В одном исследовании введение miR-23a-5p оказало значительное влияние на защиту от прогрессирования атеросклероза и улучшение стабильности бляшек у дислипидемических мышей.

Выводы. МикроРНК играют важную роль в регуляции молекулярных процессов, которые способствуют развитию и прогрессированию атеросклероза, включая апоптоз, воспаление и метаболизм липопротеинов. Определение конкретных микроРНК в качестве биомаркеров и терапевтических мишеней открывает новые перспективы для разработки более эффективных методов лечения и ранней диагностики атеросклероза.

Ключевые слова: микро-РНК, атеросклероз, диагностика, биомаркеры, липопротеины, лечение.

Introduction.

Atherosclerosis is a chronic inflammatory disease of the arterial wall caused by endothelial injury and the subendothelial accumulation of lipids, extracellular matrix proteins, and calcium, especially in areas of disturbed blood flow, which ultimately forms the atherosclerotic plaque [1]. Several studies have shown that the plaque is characterized by an accumulation of immune cells, monocytes/macrophages, T lymphocytes, and dysfunctional endothelial cells undergoing endothelial-to-mesenchymal transition [2]. The formation of an atherosclerotic plaque in the coronary artery is the primary cause of stable coronary artery disease, and the subsequent rupture of the coronary atherosclerotic plaque, leading to coronary thrombosis, is the main reason for unstable angina and acute myocardial infarction [3].

Research over the last two decades has revealed that miRNAs play an essential role in regulating pathways that regulate lipid homeostasis. Therefore, they are significantly involved in the molecular mechanisms underlying the initiation and progression of the pathophysiological processes of coronary atherosclerotic plaques. Unbalanced levels of low-density lipoproteins (LDL) and high-density lipoproteins (HDL), both in cells and in circulation, are directly linked to various pathological processes in atherosclerotic diseases.

The importance of discovering new diagnostic and treatment methods for atherosclerosis is crucial, as it is a complex disorder and remains a major factor in morbidity and mortality to date.

Multiple treatment methods have been proposed to reduce the prevalence and incidence of atherosclerosis. One of these involves microRNAs—small ribonucleic acid (RNA) molecules that play an important role in regulating gene expression at the post-transcriptional level. The primary function of miRNAs is to control the translation of messenger RNA (mRNA) into proteins, thereby influencing protein production within the body's cells [1].

The discovery of new molecular mechanisms, including microRNA therapy or specific therapeutic targets, could open new directions in the development of drugs intended for the treatment of atherosclerosis. Continued research and innovation in this field are essential for medical progress and for improving the lives of patients with this condition.

Circulating miRNAs have been identified as potential biomarkers for cardiovascular diseases. Increasing evidence suggests that miRNAs are involved in the development and progression of atherosclerosis [4].

The aim of the work is to investigate and elucidate the role of microRNA as a biomarker in clinical diagnosis, as a potential therapeutic target and as a index to assess response to the treatment in atherosclerosis.

Material and methods.

The article was developed using the narrative synthesis method of specialized literature. To achieve the proposed goal, we analyzed literature published between 2014 and 2024. During the documentation process, the informational resources of the Scientific Medical Library of the "Nicolae Testemițanu" State University of Medicine and Pharmacy were consulted, as well as publications from specialized journals accessible through electronic databases such as PubMed, Medline, Medscape, Hinari, ScienceDirect, and UpToDate. Access to these resources was made through the Google search engine, using English key words such as micro-RNA, biomarkers, therapeutic target, cardiovascular diseases, and diagnosis. All information is analyzed only from publications in specialized scientific journals.

The criteria for including bibliographic sources were the relevance and accuracy of the information presented in the publications, the currency of the studies, and the publication years of the articles. For this topic, we used sources written in Romanian, Russian, and English.

Results.

MicroRNAs (miRNAs) represent a class of small RNA molecules, approximately 20-25 nucleotides in length, that play a crucial role in regulating gene expression. miRNAs function by binding to complementary messenger RNA (mRNA) molecules, thus causing their degradation or inhibiting their translation into proteins [5].

The biosynthesis of miRNA is a complex and important process in the regulation of cellular gene expression. Here is a detailed description of this process:

1. Transcription of miRNA: the process begins with the transcription of miRNA genes in the cell nucleus, resulting in the formation of the primary miRNA transcript (pri-miRNA).

2. Nuclear processing: this step leads to the formation of miRNA precursors (pre-miRNA).

3. Transport to the cytoplasm: this depends on a series of transport proteins, including exportin-5.

4. Cytoplasmic processing: the enzyme Dicer cuts the miRNA precursor, forming a mature miRNA double strand and its complementary sequence, known as anti-miRNA.

5. Integration into the RISC complex: the mature miRNA is then integrated into the RNA-induced silencing complex (RISC). Within this complex, miRNA serves as a guide, directing RISC to the mRNA molecules that need to be regulated.

6. Binding with mRNA: complementary binding occurs between miRNA and mRNA.

7. Targeting for degradation or repression: depending on the degree of matching between the miRNA and mRNA, RISC may either cause the degradation of the target mRNA or inhibit its translation. If the complementary sequences of miRNA and mRNA are nearly identical, it may lead to mRNA degradation. If the match is partial, mRNA may be subject to translation repression [6].

The biosynthesis of miRNA and gene expression regulation are illustrated in figure 1.

Thus, numerous studies in recent years demonstrate that circulating miRNAs can be used not only as potential biomarkers but also as therapeutic targets for atherosclerosis [8].

The synthesis and secretion of various lipoproteins into the blood are maintained by hepatocytes. Several miRNAs synthesized in the liver (miR-148a, miR-

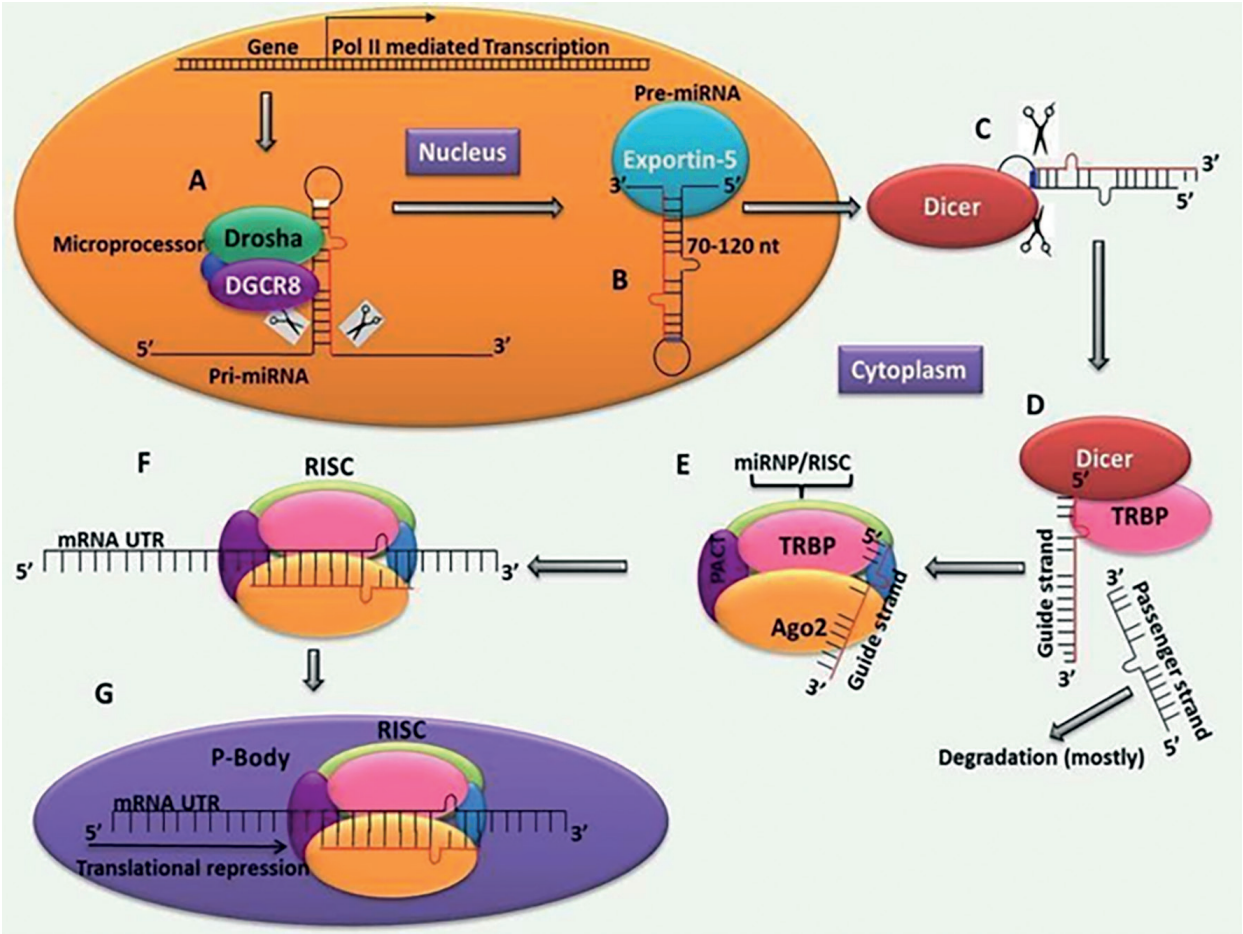

Figure 1. miRNA Biogenesis [7].

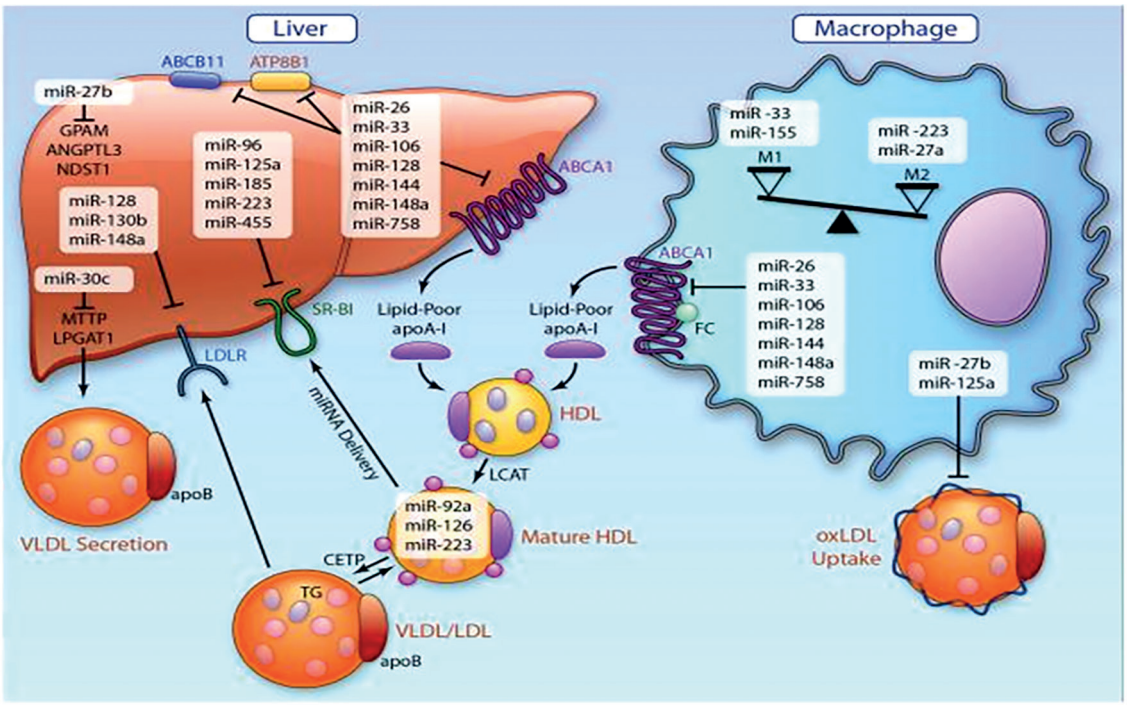

Figure 2. microRNA orchestration of cholesterol homeostasis and macrophage activation in atherosclerosis [9].

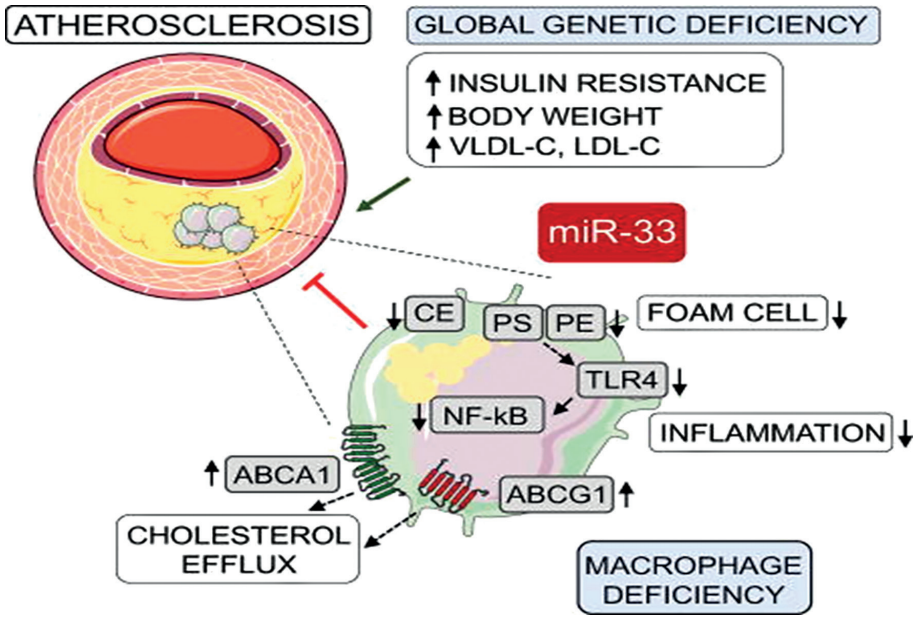

Figure 3. Effects of miR-33 inhibition in the process of atherosclerosis [15].

128-1, miR-130b, miR-122, miR-223, miR-27b, and miR-301b) have been well established as functional regulators of lipoprotein metabolism. Therefore, the imbalance of these miRNAs' homeostasis is critically involved in the onset of dyslipidemia and the development of atherosclerosis [9], as demonstrated in Figure 2.

In the same time, a study showed that hepatic overexpression of miR-30c significantly reduced atherosclerosis by decreasing cholesterol synthesis and ApoB lipoproteins in a hyperlipidemic mouse model, while miR-30c inhibition induced dyslipidemia and atherosclerosis. Therefore, increasing miR-30c levels in the liver could be important for the treatment of hyperlipidemia and atherosclerosis [10].

Several studies have reported an important role of miRNAs in both humans and animals in the development of atherosclerosis. It has been shown that miR-31, miR-181-b, miR-10a/b, miR-126, and miR-17-3p are directly involved in the development of endothelial dysfunction [5]. Additionally, it has been observed that miR-122 and miR-33a/b are

key regulators of cholesterol homeostasis, while the expression of miR-26a, miR-221, miR-155, miR-21, and miR-125a-5p was changed in patients with atherosclerotic plaques. In atherosclerosis, foam cells containing oxidized LDL become activated and can secrete various inflammatory cytokines, including those involved in angiogenesis. Several different miRNAs, such as miR-210, miR-222, miR-155, miR-27a/b, and miR-221, may accompany foam cells participating in angiogenesis [11].

A recent study observed that miR-30c-5p significantly protects human aortic endothelial cells from cell death by pyroptosis mediated by caspase-1 of atherosclerotic plaque macrophages associated with oxidized LDL cholesterol by reducing the expression of the Nod-like receptor protein (NLRP3) through the forkhead box O3 (FOXO3) signaling pathway. This may represent a new treatment approach in atherosclerosis [12].

In the study conducted by DiStefano et al. [13], it was found that angiopoietin-like protein 8 (ANGPTL8) is associated with reduced HDL cholesterol levels and may contribute to the development of dyslipidemia. By inhibiting miR-143-3p, a significant suppression of ANGPTL8 expression, an increase in HDL cholesterol content, and an effective prevention of dyslipidemia and atherosclerosis progression were achieved.

Administration of miR-23a-5p had a significant impact on protecting against the progression of atherosclerosis and improving plaque stability in dyslipidemic mice. This beneficial effect was achieved by reducing foam cell formation and positively influencing the expression levels of ATP-binding cassette subfamily A member 1 (ABCA1/G1) genes, whose proteins, ABCA1 and ABCG1, play important roles in cellular cholesterol efflux to HDL and its apolipoproteins. Furthermore, ABCA1 and ABCG1 influence the secretion of pro-inflammatory cytokines by regulating cholesterol content in the plasma membrane and intracellular compartments [14].

A study conducted by Price et al. [15] demonstrated that miR-33 inhibition with anti-miR-33 led to an increase in HDL levels and a reduction in inflammation and lipid accumulation, inhibiting macrophage transformation into foam cells and thereby greatly reducing atherosclerotic plaque progression in mice. The effects of miR-33 inhibition are shown in Figure 3.

Additionally, miR-155 overexpression can significantly inhibit foam cell formation by activating cholesterol hydrolase in macrophages, reducing intracellular lipid accumulation, and preventing atherosclerotic plaque formation. The amount of microRNA-155 was considerably elevated in patients with atherosclerosis compared to healthy individuals. At the same time, anti-miR-155 significantly reduced atherogenesis in mice by decreasing macrophage inflammatory response [16].

A study conducted by Sun et al. [17] demonstrated that the expression of miR-181b is significantly reduced in hyperlipidemic mice compared to the control group. Furthermore, the administration of miR-181b mimetic significantly reduced nuclear factor-kB (NF-κB) activity in endothelial cells and suppressed leukocyte recruitment, reducing the formation of atherosclerotic lesions in mice.

Additionally, the overexpression of miR-181b crucially inhibited thrombin-induced endothelial activation and reduced arterial thrombus formation by approximately 73%. Moreover, miR-181b significantly suppressed NF-κB-dependent proteins, including intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E-selectin. Therefore, miR-181b, with its anti-inflammatory properties, represents a potential target for preventing blood clot formation [18].

Changes in the quantities of endothelial-specific microRNAs–miR-126, miR-17, and miR-92a, along with vascular smooth muscle-specific miR-145 and inflammation-related miR-155—were inversely proportional to atherosclerotic plaque formation, while a positive correlation was observed with the necrotic and necrolipidic tissue content of the plaque, which were significantly reduced in patients with coronary artery disease (CAD). Thus, increasing the serum content of these microRNAs through systemic administration of mimetics reduced the progression of atherosclerotic plaques [19].

A recent study found that increased expression of miR-19b significantly reduced the progression of coronary atherosclerotic plaques in CAD by inhibiting endothelial cell activation and the formation of new vessels through decreased expression of signal transducer and activator of transcription 3 (STAT3) [20].

Recently, Liang et al. [21] observed a decrease in miR-124 expression in CAD patients and in mice with atherosclerosis. At the same time, the administration of miR-124 mimetic significantly reduced pro-inflammatory cytokines and inhibited macrophage apoptosis by suppressing p38. These findings suggest that increasing miR-124 expression could represent a promising treatment for patients with atherosclerosis and CAD. The anti-atherosclerotic mechanisms of microRNAs are summarized in Table 1.

Table 1.

Therapeutic role of microRNA in atherosclerosis [22].

miRNA	**Effects and targets**
miR-30c mimetic	Reduces hyperlipidemia and the development of atherosclerosis by decreasing lipid synthesis and apolipoprotein B secretion through the inhibition of microsomal transfer protein activity in mice.
miR-30c-5p mimetic	Significantly reduces atherosclerosis in human aortic endothelial cells by decreasing the inflammatory expression of the NLRP3 protein and FOXO3.
Anti-miR-143-3p	Increases HDL cholesterol levels and prevents the progression of dyslipidemia and atherosclerosis by suppressing the ANGPTL8 protein in liver cells.
Anti-miR-23a-5p	Significantly protects against atherosclerosis and improves plaque stability in mice by increasing the expression of ABCA1/G1.
Anti-miR-33	Increases HDL levels, improves cholesterol clearance, inhibits inflammation and the transformation of macrophages into foam cells, and significantly reduces the progression of atherosclerotic plaques in mice.
Anti-miR-155	Reduces the formation of atherosclerotic lesions in mice by decreasing the inflammatory response of macrophages and improves cholesterol clearance.

Discussions.

Recent research regarding the role of miRNA in cardiovascular diseases has revealed that miRNAs play a key role in regulating the molecular processes that contribute to the development and progression of cardiac pathologies. The scientific studies estimate that these miRNAs, which are small RNA molecules, are involved in the regulating of gene expression and can affect the activity of important cells in the heart and blood vessels [6].

An essential aspect discussed in recent research is the influence of miRNAs on inflammatory processes in cardiovascular pathology. For instance, miR-155 and miR-146a are involved in regulating the inflammatory response in endothelial cells and macrophages. Other miRNAs, such as miR-1, miR-21, miR-133, and miR-208, play important roles in cellular regulation, apoptosis, proliferation, and inflammatory responses, all of which are associated with altered conditions leading to cardiovascular diseases. These findings suggest that miRNAs may control abnormal inflammation in the context of heart pathologies [19, 23].

It has also been observed that circulating miRNAs can serve as useful biomarkers for the diagnosis and prognosis of cardiovascular diseases. The expression profile of miRNAs in peripheral blood has been shown to be altered in various cardiovascular conditions, including atherosclerosis. This opens the way for the development of non-invasive diagnostic tests and monitoring of cardiovascular diseases based on miRNAs.

For example, an increased level of miR-143-3p leads to a reduction in HDL cholesterol levels, which causes the development of atherosclerosis. These discoveries provide promise in using miRNAs as non-invasive indicators for cardiac lesions and for assessing cardiovascular risk [13].

An important aspect of current discussions is the association of miRNAs with cardiovascular risk, as they are evaluated as potential biomarkers for present and future cardiovascular manifestations. Thus, the expression of miRNAs signals not only the presence of cardiovascular diseases but also their potential for future development.

On the other hand, clinical applicability and research activity remain an active area of exploration. How miRNAs can be used in early diagnosis, how they can be targeted in drug development, and how they can be implemented in treatment strategies are questions that require precise and current answers.

The prospects for the application of miRNAs are not limited to treating existing cardiovascular diseases but extend the approach to new frontiers of prevention and personalized medicine. With the help of genomic technologies and massive analyses, miRNAs can be identified as potential biomarkers that inform the risk of developing cardiovascular diseases, providing personalized prevention and early investigations.

For true progress, it is essential that research studies expand, pursuing the development of new non-invasive technologies and massive analyses. This aspect encompasses new visions belonging to personalized medicine, aimed at the developing of new diagnostic techniques, personalized treatments, and prevention strategies for patients with heart disease [24].

Recent discussions regarding the role of miRNAs in cardiovascular diseases underscore the complexity and versatility of these molecules in regulating pathological processes. An important aspect in this

direction is the continuation of scientific and clinical research, contributing to identifying new development tactics that will lead to changes in diagnostic and treatment strategies. Molecular prospects, along with technological advancements, offer hope for achieving positive outcomes in the field of heart failure, thus contributing to improving the quality of life and reducing the prevalence of this condition [25,26].

Conclusions.

1. miRNAs, as important regulatory factors, significantly influence cellular homeostasis. The process of biogenesis and the diverse mechanisms of action of miRNAs, such as inhibiting protein synthesis, controlling apoptosis, and regulating the cell cycle, highlight the complexity of their influence on essential cellular functions not only in heart failure but also in other cardiovascular multiple pathologies.

2. miRNAs are involved in pathological processes, such as inflammation, vascular remodeling, and myocardial dysfunction. A detailed analysis of how miRNAs exert their functions, such as preventing the association of ribosomes with messenger RNA or degrading it, is essential for identifying potential innovative therapeutic strategies.

3. The potential of miRNAs as biomarkers in the diagnosis of cardiovascular diseases, including atherosclerosis, is due to their ability to be detected in biological fluids, thereby facilitating the diagnosis and prognosis of these conditions.

4. Specific miRNAs represent promising therapeutic targets in the treatment of cardiovascular diseases. For example, anti-miR-23a-5p and anti-miR-33 could be used in the treatment of atherosclerosis. The development of therapeutic strategies focused on regulating these miRNAs could bring significant benefits to patients with cardiovascular conditions.

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