





Decoding the Interplay of Genes and MicroRNAs in Cardiovascular Disease

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Abstract

Cardiovascular disease (CVD) is a leading cause of death worldwide, and it has been found to have a strong genetic component. In recent years, there has been much interest in the role of microRNAs (miRNAs) in CVD. miRNAs are small non-coding RNAs that regulate gene expression post-transcriptionally by binding to the 3' untranslated region (UTR) of target mRNAs. Many studies have shown that miRNAs play a crucial role in various physiological processes, including the regulation of cellular functions involved in the development of CVD.

Several miRNAs have been identified that are involved in the pathogenesis of CVD, and some of them are associated with specific cardiovascular risk factors, such as hypertension or diabetes. It has been suggested that targeting specific miRNAs or combinations of miRNAs could serve as a novel therapeutic approach for CVD.

Moreover, studies have also shown that certain genes are involved in CVD risk and progression leading to different clinical manifestations like coronary artery disease, heart failure, and valvular disease. Some of these genes are involved in lipid metabolism, inflammation, and cell proliferation and differentiation, and their expression is regulated by miRNAs.

In conclusion, a complex interaction between genes and miRNAs contributes to CVD pathogenesis, and further research is required to fully understand the mechanisms involved. Nevertheless, the identification of specific miRNAs that are involved in CVD provides potential targets for future therapeutics.

Keywords: MicroRNA, CVD, Genes

1. Introduction

Cardiovascular disease (CVD) is a multifactorial disorder that encompasses various pathological conditions that affect the heart and blood vessels, including coronary artery disease, heart failure, and valvular disease. It is a leading cause of morbidity and mortality worldwide, accounting for over 17 million deaths annually. The development and progression of CVD are influenced by a wide range of factors, including lifestyle, environmental factors, genetics, and epigenetics [1, 2]. Over the years, extensive research has identified several regulators that contribute to CVD pathophysiology, including genes and microRNAs (miRNAs) [3].

miRNAs are small non-coding RNAs that play critical roles in the regulation of gene expression by targeting messenger RNA (mRNA) transcripts for degradation or translational inhibition. Dysregulation of miRNA expression has been implicated in various aspects of

CVD, including angiogenesis, inflammation, oxidative stress, and apoptosis [4].

Recent studies have revealed the critical roles of miRNAs in CVD pathophysiology and have shown that miRNAs are involved in many aspects of CVD development and progression for instance, miR-21 promotes angiogenesis and vascular repair, while miR-34a inhibition reduces atherosclerosis and endothelial dysfunction in mouse models of CVD. MiR-126 plays a protective role in endothelial function and angiogenesis, while miR-155 plays a role in inflammation and immune cell activation in CVD. These findings have led to increased interest in the potential use of miRNAs as therapeutic targets for CVD [5, 6].

Understanding the dynamic interactions between miRNAs and genes could deepen our knowledge of CVD pathophysiology and enhance our diagnostic capabilities, leading to the development of novel therapeutic strategies. For example, miRNAs have been identified as potential

targets for CVD therapy, and several miRNA-based therapies have progressed to clinical trials. Additionally, miRNAs have shown promise as biomarkers for CVD diagnosis and prognosis [4]. The current understanding of various miRNAs and genes regulated by them that are involved in CVD pathophysiology is constantly evolving. Several studies have identified multiple miRNAs and genes that are implicated in CVD development and progression. For instance, miR-145 regulates smooth muscle cell function and is implicated in the development of atherosclerosis, while miR-33a inhibition reduces atherosclerotic plaque formation and improves cholesterol metabolism in preclinical studies. Moreover, miR-208a regulates cardiac hypertrophy and fibrosis and has been identified as a potential therapeutic target for heart failure and other CVDs [5].

The role of these regulatory elements in the context of different CVD subtypes such as coronary artery disease, heart failure, and valvular disease is also being investigated. For instance, miR-34a inhibition has been shown to reduce atherosclerosis and endothelial dysfunction in mouse models of coronary artery disease, while miR-208a has been implicated in cardiac hypertrophy and fibrosis in heart failure patients. Understanding the specific roles of microRNAs in different subtypes of CVD could lead to the development of subtype-specific therapies that target the dysregulated pathways [7]. Despite the potential therapeutic applications of miRNAs in CVD, several limitations and challenges need to be addressed. One significant challenge is the delivery of miRNA-based therapies to target cells or tissues [8]. Issues of specificity, efficiency, and off-target effects remain a major challenge in the development of miRNA-based therapies. Moreover, there are concerns about the potential toxicity and off-target effects on other molecular pathways [9]. To overcome these challenges, several therapeutic approaches have been developed, including microRNA mimics, inhibition of specific microRNAs, nanoparticle-based delivery systems (Fig 1), and conjugated microRNA therapies [10]. Additionally, multi-targeted approaches that involve combining several microRNA mimics or inhibitors for enhanced efficacy are being explored [9].

Further research is needed to optimize the efficacy and safety of miRNA-based therapies for CVD. Advances in gene editing technologies may provide new ways to modulate miRNA expression for therapeutic applications. Additionally, the development of miRNA-based biomarkers for diagnostics and disease monitoring holds great promise [11].

miRNAs have emerged as critical regulators of CVD pathophysiology, and understanding their roles in different subtypes of CVD could lead to the development of novel therapeutic strategies. However, several challenges need to be addressed, and further research is needed to optimize the safety and efficacy of miRNA-based therapies for CVD. The potential applications of miRNAs in CVD diagnosis and therapy are vast, and their role as biomarkers for disease monitoring and prognosis is gaining importance. It is imperative to continue studying the complex interactions between miRNAs and genes in CVD to better understand the disease's pathophysiology and identify new therapeutic targets. With further research and development, miRNA-based therapies could provide a promising avenue for preventing and treating CVD [12].

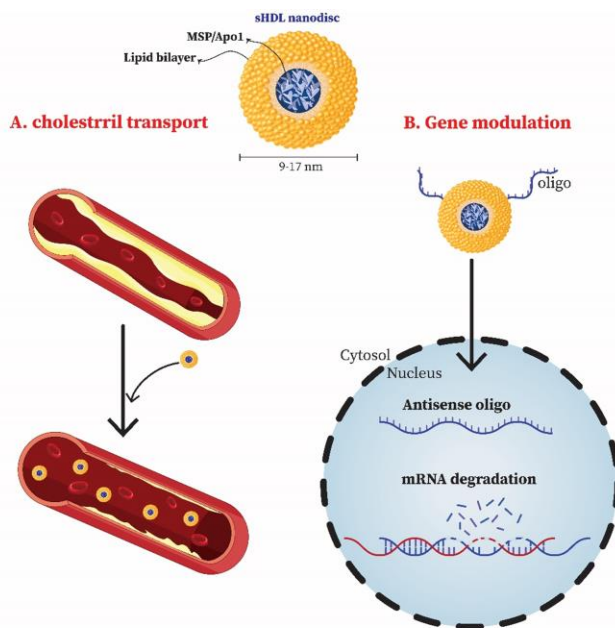


Figure 1. Application of Nano medicine in CVD treatment

Genes related to Lipid Metabolism

Lipid metabolism genes underpin the complex pathways that regulate lipid synthesis, transport, and degradation [13]. Multiple genetic variants can influence the production, storage, and metabolism of different lipid species, such as LDL, HDL, and triglycerides, with significant implications for CVD development [14, 15]. Dysregulated lipid metabolism, particularly high levels of LDL cholesterol, leads to the formation of atherosclerotic plaques that obstruct blood flow and can cause heart attacks and strokes [16, 17]. Genetic testing and counseling can help identify individuals with lipid metabolism disorders and increased CVD risk, enabling healthcare providers to tailor treatment plans to the individual's needs. In particular, genetic tests depicting cholesterol metabolism gene profiles can offer insight into identifying individuals at risk

for developing dysfunction in lipid metabolism, including CVD, earlier in their lives [18-21]. Advances in genomics have offered new opportunities for developing targeted interventions that address lipid metabolism and reduce CVD risk. [22] Emerging therapies, including RNA-based therapies and gene editing approaches, are aimed at targeting lipid metabolism genes like PCSK9 to lower LDL cholesterol levels and reduce the risk of CVDs [23, 24]. Such promising methods of gene therapy already show great promise in the treatment and prevention of CVDs [24].

In addition to LDL cholesterol, other lipid markers are associated with CVD risks, including triglycerides and HDL cholesterol [25, 26]. Multiple genes contribute to the regulation of these lipids, and genetic variations in these genes can impact the lipid profile and subsequent CVD risk [27, 28]. Genetic testing can identify individuals who possess these variations, as well as those with specific lipid metabolism defects such as familial hypercholesterolemia, enabling earlier intervention that can help mitigate their risk of developing CVDs [29, 30]. Developments in genomics present an opportunity in the field of precision medicine, where a patient's genetic makeup can be considered to target specific susceptibilities before they cause disease. Genetic profiling can help physicians develop personalized management strategies that may include lifestyle modifications, medication, or surgical interventions that optimize the health of each patient [31-33].

Overall, the application of genetic and genomic testing in the context of lipid metabolism can reveal personalized information about CVD risks, enable earlier interventions, and lead to a more targeted approach to therapy with the hope of preventing the development of CVDs. Through further research and innovation, genomics may play an increasingly vital role in identifying at-risk individuals, facilitating early detection, and improving treatments that ultimately save lives [34-37]. The genetic factors contributing to CVDs are diverse, and the links between lipid metabolism genes and CVDs are increasingly recognized. Advances in genomics have led to the discovery of novel associations between lipids, their metabolites, and CVD outcomes, enabling researchers to identify new therapeutic targets. Also, associations of certain lipid metabolism genes-linked CVDs can be influenced by lifestyle and diet factors, further underscoring the need for personalized intervention decisions [38, 39].

Gene therapy, an emerging field of medicine, provides a promising avenue for treating CVDs that stem from lipid metabolism dysregulation. By targeting key genes within lipid metabolism pathways, gene-editing methods, and RNA-based therapies can decrease the production of LDL cholesterol and other harmful lipids associated with CVD risks. Researchers have already designed gene therapy trials in animal studies and have initiated early human studies with promising results [40, 41].

Table 1. Common Genes related to Lipid Metabolism

Genes	Functions	Role in Lipid Metabolism	Associations with CVD	Symptoms of CVD	Ref
APOB	Encodes for apolipoprotein B	Regulates lipid metabolism and transport	Elevated levels linked to increased risk of CVD	Chest pain, shortness of breath, fatigue	[42, 43]
CETP	Encodes for cholesterol ester transfer protein	Transfers cholesterol esters between lipoproteins	Mutations associated with lower risk of CVD	Palpitations, dizziness	[44, 45]
LDLR	Encodes for LDL receptor	Regulates clearance of LDL particles	Mutations can lead to dyslipidemia and increased risk of CVD	Chest pain, shortness of breath	[46, 47]
LPL	Encodes for lipoprotein lipase	Hydrolyzes triglycerides in circulating lipoproteins	Deficiency in LPL linked to hypertriglyceridemia and CVD risk	Fatigue, shortness of breath, leg swelling	[48, 49]
ABCA1	Encodes for ATP-binding cassette transporter A1	Facilitates cholesterol efflux from cells to HDL particles	Mutations associated with reduced HDL-C levels and increased risk of CVD	Chest pain, shortness of breath, fatigue	[50, 51]
PLTP	Encodes for phospholipid transfer protein	Facilitates transfer of phospholipids between lipoproteins	Elevated PLTP levels associated with increased risk of CVD	Dizziness, fatigue, shortness of breath	[52, 53]

Table 1 includes additional columns with associations with CVD, and common symptoms of CVD. However, it's important to note that not all individuals with these genetic variations experience the same symptoms or have the same risk for CVD.

MicroRNAs related to Lipid Metabolism

MicroRNAs (miRNAs) are small non-coding RNAs that regulate gene expression by binding to target mRNAs. Dysregulation of miRNAs has been implicated in various diseases, including cardiovascular disease (CVD). CVD is a group of disorders that affect the heart and blood vessels and is a leading cause of mortality worldwide. Dyslipidemia is a hallmark of CVD and is characterized by abnormal lipid metabolism. miRNAs have been shown to play an important role in the regulation of lipid metabolism and dyslipidemia [54-56]. MiR-33 and miR-122 are two miRNAs that have been shown to be involved in lipid metabolism in the liver. MiR-33 regulates cholesterol efflux and fatty acid oxidation, while miR-122 regulates hepatic lipid metabolism. MiR-33 has been proposed as a therapeutic target for dyslipidemia and CVD.

MiR-33 inhibition has been shown to increase HDL cholesterol levels and reduce atherosclerosis in animal models. In contrast, miR-122 inhibition has been shown to increase hepatic steatosis and promote NAFLD (non-alcoholic fatty liver disease) [57-60]. MiR-208a is a cardiac-specific miRNA that has been shown to regulate lipid metabolism in the heart. MiR-208a inhibition has been shown to increase cardiac fatty acid oxidation and improve cardiac function in animal models of heart failure [61-64]. MiR-223 is another miRNA that has been implicated in lipid metabolism and atherosclerosis. MiR-223 regulates macrophage and foam cell formation and may play a role in the development of atherosclerotic plaques [65-67]. MiR-29 has been shown to regulate collagen deposition in the heart. MiR-29 inhibition has been shown to increase collagen deposition and fibrosis in animal models of heart failure [68, 69]. MiR-126 is an endothelial-specific miRNA that has been shown to regulate angiogenesis and vascular function. MiR-126 plays an important role in the regulation of endothelial nitric oxide synthase (eNOS) and may protect against atherosclerosis [70, 71]. MiR-132 and miR-212 are two miRNAs that are involved in endothelial dysfunction and atherosclerosis. MiR-132 and miR-212 inhibition have been shown to improve endothelial function and reduce atherosclerosis in animal models [72-75]. MiR-145 is a smooth muscle cell-specific miRNA that has been shown to regulate smooth muscle cell differentiation and migration. MiR-145 may play a role in the development of intimal hyperplasia and restenosis following angioplasty [76, 77]. MiR-21 is an anti-apoptotic miRNA that has been shown to be upregulated in atherosclerotic plaques. MiR-21 inhibition has been shown to reduce plaque size and improve vascular function in animal models of atherosclerosis [78-81]. MiR-155 is an inflammatory miRNA that has been implicated in atherosclerosis. MiR-155 regulates macrophage activation and may promote the formation of atherosclerotic plaques [79, 82-84]. MiR-33 and miR-122 are potential therapeutic targets for dyslipidemia and CVD. MiR-208a and miR-212/132 may be therapeutic targets for heart failure and atherosclerosis. MiR-126 and miR-21 may be therapeutic targets for vascular dysfunction and atherosclerosis. MiR-145 may be a therapeutic target for restenosis following angioplasty [85-88].

Table 2. definitions of MicroRNAs related to Lipid Metabolism

miRNA	Role in Lipid Metabolism and Cardiovascular Disease	Potential Therapeutic Target	Ref
miR-33	Regulates cholesterol efflux and fatty acid oxidation; proposed target for dyslipidemia and CVD	Yes	[89-91]
miR-122	Regulates hepatic lipid metabolism; inhibition may promote NAFLD	Yes	[90, 92]
miR-208a	Regulates lipid metabolism in the heart; inhibition may improve cardiac function in heart failure	Yes	[93, 94]
miR-223	Regulates macrophage and foam cell formation; may play a role in atherosclerotic plaque development	No	[95-97]
miR-29	Regulates collagen deposition in the heart; inhibition may increase fibrosis in heart failure	No	[98-100]
miR-126	Regulates angiogenesis and vascular function; may protect against atherosclerosis	Yes	[101, 102]
miR-132	Involved in endothelial dysfunction and atherosclerosis; inhibition may improve endothelial function	Yes	[103-105]
miR-212	Involved in endothelial dysfunction and atherosclerosis; inhibition may improve endothelial function	Yes	[104, 106, 107]
miR-145	Regulates smooth muscle cell differentiation and migration; may play a role in restenosis following angioplasty	Yes	[108, 109]
miR-21	Anti-apoptotic miRNA upregulated in atherosclerotic plaques; inhibition may reduce plaque size and improve vascular function	Yes	[110, 111]
miR-155	Inflammatory miRNA implicated in atherosclerosis; regulates macrophage activation and may promote plaque formation	No	[112-114]

Further research is needed to fully elucidate the role of miRNAs in lipid metabolism and CVD. miRNA-based therapies have the potential to revolutionize the treatment of dyslipidemia and CVD. The use of miRNA mimics or inhibitors may be an effective approach to target dysregulated miRNAs. Nanoparticle-based delivery systems may be used to enhance the specificity and efficacy of miRNA-based therapies [115-119]. miRNA-based therapies may have fewer side effects than traditional drug therapies. miRNA-based therapies may be more personalized, as miRNA expression profiles can be used to identify patients who are likely to respond to treatment. Challenges to the development of miRNA-based therapies include the potential for off-target effects and the need for effective delivery systems [120, 121]. Advances in miRNA research have greatly expanded our understanding of the pathogenesis of dyslipidemia and CVD which is concluded in Table 2. miRNAs are promising targets for the development of new therapies for dyslipidemia and CVD. Further research is needed to fully realize the therapeutic potential of miRNAs in lipid metabolism and CVD.

Genes related to Inflammation

Inflammation is now considered to be a key component in the development of many chronic diseases, including CVD. Genetic factors have also been found to play a significant role in disease susceptibility, with numerous genes linked to inflammation identified as mediators in the development of CVD. Some examples include the NF- κ B and NLRP3 genes that regulate inflammation pathways, as well as other genes involved in lipoprotein metabolism that contribute to the development of atherosclerosis through the promotion of low-grade inflammation [122-124]. Genetic testing of cytokine and inflammation genes can help predict an individual's CVD risk, especially in cases where there is a family history or other known risk factors. Certain genetic polymorphisms can also modulate the effectiveness of anti-inflammatory drugs in CVD therapy, allowing for more personalized treatment plans [125-127]. Inflammatory markers can provide valuable insights into the onset and progression of CVDs, and the implementation of gene-based therapies targeted toward regulating inflammation may enhance the efficacy of contemporary CVD therapy approaches. For example, immunotherapy is an emerging avenue for personalized inflammation in CVD management and treatment [125-127]. However, it is important to note that gene-environment interactions may influence both inflammation

and CVD risk, especially in people with a family history of CVDs. Chronic infections by certain microbes, such as Chlamydia pneumonia and Helicobacter pylori, also contribute to CVD risk by promoting inflammatory pathways [125-127].

In conclusion, inflammation-related genes and their dysregulation have strong heritability components and are critically involved in the pathogenesis of CVDs and their role is stated in Table 3. Further research is needed to better understand the functional implications of inflammation-associated gene polymorphisms in CVDs and how these findings can be translated into personalized therapeutic interventions.

Topic	Description
Role of inflammation in chronic diseases	Inflammation is a key component in the development of many chronic diseases, including cardiovascular disease (CVD).
Genetic factors in disease susceptibility	Numerous genes linked to inflammation have been identified as mediators in the development of CVD, including genes involved in lipoprotein metabolism and inflammation pathways such as NF- κ B and NLRP3.
Genetic testing for CVD risk	Genetic testing of cytokine and inflammation genes can help predict an individual's CVD risk, especially in cases where there is a family history or other known risk factors.
Modulation of drug effectiveness through genetic polymorphisms	Certain genetic polymorphisms can modulate the effectiveness of anti-inflammatory drugs in CVD therapy, allowing for more personalized treatment plans.
Inflammatory markers in CVDs	Inflammatory markers can provide valuable insights into the onset and progression of CVDs.
Gene-based therapies for inflammation	The implementation of gene-based therapies targeted toward regulating inflammation may enhance the efficacy of contemporary CVD therapy approaches, such as immunotherapy.
Gene-environment interactions	Gene-environment interactions may influence both inflammation and CVD risk, especially in people with a family history of CVDs.
Chronic infections and inflammation	Chronic infections by certain microbes, such as Chlamydia pneumonia and Helicobacter pylori, also contribute to CVD risk by promoting inflammatory pathways.
Future research	Further research is needed to better understand the functional implications of inflammation-associated gene polymorphisms in CVDs and how these findings can be translated into personalized therapeutic interventions.

MicroRNAs related to Inflammation

MicroRNAs (miRNAs) are small non-coding RNA molecules that play a critical role in the regulation of gene expression [128, 129]. Dysregulated miRNA expression has been linked to the development and progression of cardiovascular diseases (CVDs), which are a group of conditions that affect the heart and blood vessels [130, 131]. Inflammation is a key component of CVD pathology and contributes to the development and progression of many forms of CVD. Inflammatory miRNAs have emerged as new targets for understanding and treating CVD [132].

Several miRNAs have been studied in the context of inflammation in CVD [129]. miR-155 is a pro-inflammatory miRNA that promotes inflammation by targeting the NF- κ B signaling pathway [133]. miR-146a/b, on the other hand, are anti-inflammatory miRNAs that suppress inflammation by targeting the same NF- κ B signaling pathway [134, 135]. miR-21 is another miRNA that promotes inflammation and is anti-apoptotic, meaning it prevents cell death, by targeting the PI3K/Akt signaling pathway [136, 137]. miR-34a, on the other hand, promotes apoptosis and senescence, which are processes that lead to cell death and aging, respectively, by targeting the p53 signaling pathway [138].

The potential of miRNAs to treat inflammation in CVD holds great promise for developing new approaches for the prevention and treatment of CVD. However, the use of miRNA-based therapies in CVD is still in the early stages, and more research is needed to identify safe and effective miRNA-targeted treatments. The discovery of new miRNAs involved in inflammation and CVDs may further advance the development of new treatments [139-141].

In summary, miRNAs play a critical role in the regulation of gene expression and have been linked to the development and progression of CVDs. Inflammatory miRNAs, such as miR-155, miR-146a/b, miR-21, and miR-34a, have been identified as new targets for understanding and treating inflammation in CVD. The potential of miRNA-based therapies in CVD holds great promise for developing new approaches for the prevention and treatment of CVD, but more research is needed to identify safe and effective miRNA-targeted treatments and the correct statement is gathered in Table 4.

miRNA	Role in Inflammation in CVD	Targeted Pathways	References
miR-155	Pro-inflammatory; promotes inflammation by targeting the NF- κ B signaling pathway	NF- κ B	[142, 143]
miR-146a/b	Anti-inflammatory; suppresses inflammation by targeting the NF- κ B signaling pathway	NF- κ B	[142, 144, 145]
miR-21	Pro-inflammatory; anti-apoptotic; prevents cell death by targeting the PI3K/Akt signaling pathway	PI3K/Akt	[142, 146, 147]
miR-34a	Promotes apoptosis and senescence by targeting the p53 signaling pathway	p53	[142, 148]

Genes Related to coagulation

Cardiovascular disease is a serious global health problem that can be influenced by genetic factors, including genes involved in the regulation of blood clotting [149]. Genetic mutations affecting coagulation in CVD are associated with an increased risk of the disease [150]. These mutations

can impact genes including Factor V Leiden, Prothrombin G20210A, GP Ib-IX-V complex, Von Willebrand factor (vWF), and the angiotensin-converting enzyme [151]. Factor V Leiden is one of the most common genetic mutations affecting coagulation, with individuals carrying this mutation having a higher risk of venous thromboembolism [152]. The Prothrombin G20210A mutation is also associated with an increased risk of blood clotting and is typically observed with an elevated prothrombin level [153]. The GP Ib-IX-V complex modulates platelet interaction with several proteins in the process of coagulation. Individuals carrying mutations in the GP Ib-IX-V complex may develop Bernard-Soulier syndrome, which leads to a bleeding disorder [154, 155]. Von Willebrand factor plays a crucial role in the formation of clots as it activates platelets and stabilizes fibrin that reinforces the blood clot [156]. Individuals carrying mutations in the vWF gene are more likely to have issues with bleeding and thrombotic disorders [157]. The angiotensin-converting enzyme (ACE) gene has also been associated with hypertension and increased risk of CVD-related mortality [158].

Research indicates that genetic variations that affect cytokine expression, inflammation, and lipid metabolism are also relevant to CVD [159]. Genetic polymorphisms in inflammatory genes such as TNF-alpha, IL-6, and IL-1 also increase the risk of CVD [160, 161]. Many lifestyle factors like smoking, diet, and physical activity can worsen the risk of CVD [162]. A family history of CVD may indicate an increased genetic risk for the disease. Genetic testing and counseling may help to identify individuals at risk for CVD [163]. This may also include testing for specific genetic mutations linked to CVD and its related conditions [164]. Targeted screening for genetic mutations could improve prevention efforts for those at risk and lead to better outcomes for individuals with CVD [165, 166].

When a genetic variant is identified, potential lifestyle risk factors can be addressed, and personalized treatment approaches can be implemented [167]. These approaches might include medication or lifestyle interventions, depending on the severity of the condition [168]. Bleeding disorders represent the other half of the spectrum, as individuals can experience excessive bleeding, hematomas, or increased bleeding after trauma [169]. Genetic testing for CVD is considered an important tool for stratifying risk and personalizing treatment strategies that lead to better patient outcomes [170].

Genotyping patients are becoming increasingly common and being integrated into clinical practice guidelines for CVD prevention [171]. Through targeted genotyping for coagulation-related genes, clinicians can readily identify patients who might benefit from therapy and adjust treatment based on this genetic information [172]. Current evidence suggests there is an association between genetic and environmental factors and the risk of thrombosis development leading to CVD [173]. Many controversies exist as the clinical significance of coagulation genetics findings is still under investigation, along with the cost-benefit analysis of genotyping for patients [174].

The recent focus is to include a comprehensive genetic examination in patients with vascular diseases to determine the underlying genetic constituency of thrombotic risk [175]. At-risk populations such as individuals with a family history of thrombosis, younger individuals with vascular diseases or thrombosis, and cryptogenic stroke patients can be potential candidates for genetic testing [176].

The information gained from genetic testing offers the possibility of therapy for individuals with genetic factors that contribute to the development of thrombophilia [177].

Personalized medicine based on genetic and phenotypic data offers an avenue to tailor treatments to those patients with the highest risk [178]. In summary, identifying coagulation-related genetic mutations through genetic testing and counseling and making appropriate interventions can significantly lower the risk of CVD [179]. While it remains unclear which patients will benefit most from genetic testing for CVD, it is clear that this technology is rapidly advancing and will become more accessible to patients and healthcare providers in the coming years [180]. Through genomic screening and personalized approaches, clinicians will have a powerful tool that increases the chances of preventing and treating CVD [181]. Ultimately, this may lead to better health outcomes and a reduction of cardiovascular disease morbidity and mortality worldwide [180, 181]. Further research on understanding the role of genes in CVD-related phenotypes can help in developing better therapeutic practices and drug development [178].

MicroRNAs Related Coagulation

MicroRNAs are small non-coding RNA molecules that regulate gene expression, including those involved in coagulation and cardiovascular disease (CVD) [182]. Dysregulation of coagulation can contribute to CVD, and microRNAs have been shown to play a role in various aspects of coagulation, including platelet activation, thrombin formation, and fibrinolysis [183]. Specific microRNAs implicated in coagulation in CVD include miR-1, miR-7, miR-21, miR-23a/b, miR-24, miR-26a, miR-29a/c, miR-30d, miR-31, miR-34a, miR-92a, miR-93, miR-96, miR-99a, miR-100, miR-126, miR-143, miR-145, miR-155, miR-181b, miR-191, miR-195, miR-206, miR-223, miR-296-5p, miR-342-3p, miR-433, miR-497, miR-499, miR-505-5p, miR-508-3p, miR-532-5p, miR-574-5p, miR-590-3p, miR-605, and miR-664a-3p [182, 183].

These microRNAs have been found to regulate various coagulation-related genes, including those involved in platelet function, thrombin formation, and fibrinolysis [183].

These microRNAs have been found to regulate various coagulation-related genes, including those involved in platelet function, thrombin formation, and fibrinolysis [183]. Some microRNAs promote platelet activation and thrombosis, while others inhibit these processes [183, 184]. For example, miR-30a-5p has been shown to inhibit platelet aggregation and thrombosis by targeting the thromboxane A2 receptor [185]. MicroRNAs also play a role in the regulation of inflammation and other aspects of cardiovascular disease pathology [186, 187].

These microRNAs have been implicated in various aspects of coagulation in cardiovascular disease, including thrombosis and clotting disorders [188, 189].

For instance, miR-223 has been shown to regulate cell proliferation and apoptosis in lung adenocarcinoma cells via the regulation of FBXW7, a gene involved in coagulation [190]. Overall, microRNAs related to coagulation represent a promising area of research for the development of novel diagnostic and therapeutic approaches to CVD and other coagulation-related disorders [183, 184].

Mutations and Related Cardiovascular Diseases

Mutations in the genetic sequence can play a significant role in the development of cardiovascular disease (CVD), which encompasses a range of conditions affecting heart and blood vessels [191]. Alterations in genes responsible for lipid metabolism, such as LDLR, APOB, PCSK9, LIPA, and ANGPTL3, can lead to the PCSK9 onset of familial hypercholesterolemia and persistent elevation of LDL cholesterol levels, thereby accelerating the risk of CVD early in life [191] Fig 2. Additionally, mutations in genes regulating blood pressure and blood vessel endothelial function, such as ACE, AGT, NOS3, and FKBP5, are linked to an increased risk of CVD [192].

Mutations in the genes responsible for heart muscle structure, such as LMNA, MYBPC3, MYH7, TNNT2, BAG3, and ACTC1, can lead to hypertrophic, dilated, or restrictive cardiomyopathies and an increased likelihood of developing heart failure or arrhythmias, especially under conditions of exercise or stress [193].

Genetic mutations affecting other organs can also contribute to CVD risk, such as in the case of hereditary hemochromatosis (HFE gene mutation), amyloidosis (TTR gene mutation), Marfan syndrome (FBN1, TGFBR1, and TGFBR2 genes), cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) (COL4A1 and COL4A2 genes), and Alström syndrome (ALMS1 gene mutation) [194].

Finally, mutations in genes involved in the regulation of fatty acid metabolism and stress, such as FABP4 and HCN4, respectively, can also contribute to increased CVD risk [195]. Other genes that, when mutated, can lead to specific cardiac conditions include SCN5A, KCNQ1, KCNH2, RYR2, GJA5, GUCY1A3, KCNJ2, LMOD3, MYH6/MYL2, PCCA/PCCB, and PRKAG2 [196].

RNA Based Therapies as an Inhibitors in CVD

MicroRNAs that exhibit active participation in pathophysiological processes often display elevated expression levels under normal conditions, significant dysregulation during disease states, and a predisposition for being present in both cells and tissues. Some examples of these microRNAs, for instance, miR-21-5p, which is the most abundant microRNA in cardiac macrophages, experiences a seven-fold upregulation in the myocardium of the transverse aortic constriction (TAC) model of ventricular pressure overload [197]. Similarly, miR-29b-3p exhibits high expression levels in cardiac myocytes and undergoes approximately a three-fold upregulation following TAC [198].

The expression of miR-21-5p exhibits a significant increase in the human heart that is experiencing failure. In addition, there is a notable increase in the expression of miR-92a-3p in endothelial cells and its dysregulation in mouse models of vascular and myocardial tissue injury [199]. In patients with cardiac inflammation or corresponding animal models, there is an upregulation of miR-155-5p expression in immune cells [200]. MicroRNA-based therapies for CVD involve the modulation of microRNA expression levels to

restore homeostasis or treat disease using a range of vectors, including viral vectors, nanoparticles, and conjugated molecules, which is stated in Table 5 [139]. One approach is the administration of microRNA mimics, which can restore or increase the expression of specific microRNAs associated with protective or therapeutic effects [139]. Another approach is the inhibition of specific microRNAs using antisense oligonucleotides or small molecule inhibitors, which can reduce the expression of a target microRNA in disease states [139]. Several microRNAs, such as miR-21, miR-34a, miR-126, miR-145, miR-155, and miR-33a, have been identified as the potential targets for therapy in CVD [139].

In animal models of CVD, miR-21 has been shown to promote angiogenesis and vascular repair, and miR-21 inhibitors have been developed for potential therapeutic use [201]. Inhibition of miR-34a has been shown to reduce atherosclerosis and endothelial dysfunction in mouse models of CVD [201].

miR-126 plays a protective role in endothelial function and angiogenesis, and miR-126 mimics have been developed for the potential treatment of CVD [202].

miR-145 is important in the regulation of smooth muscle cell function and has been implicated in the development of atherosclerosis [203]. miR-155 plays a role in inflammation and immune cell activation in CVD, and miR-155 inhibitors have been developed for potential therapeutic use [204].

In preclinical studies, inhibition of miR-33a has been shown to reduce atherosclerotic plaque formation and improve cholesterol metabolism [205].

miR-208a, which regulates cardiac hypertrophy and fibrosis, has also been identified as a potential therapeutic target for heart failure and other CVDs [206]. Several microRNA-based therapies have progressed to clinical trials for CVD, including miR-34a inhibitors and miR-92a mimics, with promising results [206].

Another potential therapeutic strategy is the use of microRNAs for the modulation of immune cell function in CVD, such as miR-146a [206] [207]. Nanoparticle-based delivery systems and conjugated microRNA therapies have been developed to increase the specificity and efficiency of microRNA delivery to targeted cells or tissues [208]. However, the delivery of microRNA-based therapies to target cells or tissues remains challenging due to issues of specificity, efficiency, and off-target effects [206]. Current limitations of microRNA-based therapies include issues of specificity, toxicity, and potential off-target effects on other molecular pathways [206]. Further research is needed to optimize the efficacy and safety of microRNA-based therapies for CVD [206]. Recent advances in gene editing technologies may provide new ways to modulate microRNA expression for therapeutic applications [206]. Integration of microRNA-based therapies with other treatment modalities, such as stem cell therapy or gene therapy, could provide synergistic effects for CVD, as seen in preclinical studies combining microRNA delivery with stem cell therapy [206]. Multi-targeted approaches, combining multiple microRNA mimics or inhibitors, may provide enhanced efficacy compared to single-targeted approaches [206]. The development of microRNA-based biomarkers for diagnostics and disease monitoring will lead to improved patient selection and treatment monitoring for microRNA-based therapies [206]. Regulatory approval of microRNA-based therapies will require rigorous scientific and regulatory review to ensure safety and efficacy and address ethical and legal considerations [206].

Table 5. MicroRNAs in Cardiovascular Disease Therapy: Mechanisms, Status, and Future Directions

MicroRNAs	Potential Targets for Therapy in CVD	Therapeutic Approaches	Description	Limitations and Future Directions
miR-21	Promotes angiogenesis and vascular repair; miR-21 inhibitors developed for potential therapeutic use	Inhibition of Specific microRNAs	Reduce the expression of a target microRNA in disease states	Delivery Challenges: Issues of specificity, efficiency, and off-target effects
miR-34a	Inhibition reduces atherosclerosis and endothelial dysfunction in mouse models of CVD; miR-34a inhibitors progressed to clinical trials	Inhibition of Specific microRNAs	Reduce the expression of a target microRNA in disease states	Current Limitations: Issues of specificity, toxicity, and potential off-target effects on other molecular pathways
miR-126	Plays a protective role in endothelial function and angiogenesis; miR-126 mimics developed for potential treatment of CVD	MicroRNA Mimics	Restore or increase the expression of specific microRNAs associated with protective or therapeutic effects	Further Research Needed: To optimize the efficacy and safety of microRNA-based therapies for CVD
miR-145	Regulates smooth muscle cell function and implicated in the development of atherosclerosis	-	-	Advances in Gene Editing Technologies: May provide new ways to modulate microRNA expression for therapeutic applications
miR-155	Plays a role in inflammation and immune cell activation in CVD; miR-155 inhibitors developed for potential therapeutic use	Inhibition of Specific microRNAs	Reduce the expression of a target microRNA in disease states	Development of microRNA-based Biomarkers: For diagnostics and disease monitoring
miR-33a	Inhibition shown to reduce atherosclerotic plaque formation and improve cholesterol metabolism in preclinical studies	-	-	Regulatory Approval: Requires rigorous scientific and regulatory review to ensure safety and efficacy and address ethical and legal considerations
miR-208a	Regulates cardiac hypertrophy and fibrosis; identified as a potential therapeutic target for heart failure and other CVD	-	-	Integration with Other Treatment Modalities: Combination with stem cell therapy or gene therapy for synergistic effects; Multi-Targeted Approaches: Combining multiple microRNA mimics or inhibitors for enhanced efficacy

Limitations of RNA-based therapies for CVD

Currently, the primary limitation inhibiting the widespread utilization of miRNA is the inefficiency in delivering them to clinical settings. Unbound miRNAs are inherently unstable and would undergo rapid degradation upon entry into the systemic circulation, before reaching the intended tissue. The development of secure and effective carriers remains the most significant challenge in the realm of *in vivo* miRNA delivery. Consequently, the successful transition of miRNA therapeutics into clinical practice ultimately hinges upon the creation of a suitable delivery system that can safeguard the integrity of these small RNA molecules against nuclease degradation and facilitate their efficient transportation to the desired target tissues or cells, all while minimizing any adverse effects [209].

The effective and efficient transportation of miRNA mimics or antagomirs to specific tissues remains a substantial obstacle for miRNA-based therapies. Noteworthy limitations linked with miRNA transportation include vulnerability to decomposition by nucleases, swift elimination from the bloodstream, immunotoxicity, and limited tissue permeability. The application of chemical modifications to miRNAs has considerably enhanced their durability and offered safeguards against nucleases [210].

Epigenetic modifications in CVD pathogenesis

Epigenetic modifications are heritable changes in the DNA that impact the expression and functionality of genes, while leaving the DNA sequence unaltered. One specific epigenetic process associated with human disease is DNA methylation, which is influenced by dietary factors. DNA methylation involves the addition of a 1-C molecule to cytosine groups within the DNA. When genes are methylated, they either do not undergo transcription or experience a reduced transcription rate. Hypomethylation of DNA can lead to increased expression of certain proto-oncogenes, which are genes involved in cell proliferation or metastasis, thereby increasing the risk of cancer. Similarly, hypermethylation and reduced expression of tumor suppressor genes (e.g., DNA repair genes) can also contribute to cancer development [211]. DNA methyltransferases (DNMTs), in conjunction with the methyl donor molecule S-adenosylmethionine (SAM), facilitate the process of DNA methylation. Aberrant DNA methylation has been implicated not only in the onset of human cancer but also in cardiovascular disease. Polyphenols, a category of phytochemicals that are consumed in considerable quantities in the human diet, have an impact on the risk of cancer and heart diseases like CVD [212].

Discussion

The relationship between related genes and microRNAs (miRNAs) in the pathogenesis of cardiovascular disease (CVD) is complex, and many studies have investigated the roles of specific miRNAs and genes in cardiovascular function and disease.

Evidence suggests that numerous genes are involved in CVD pathogenesis, and many are associated with specific CVD risk factors, such as hypertension or diabetes. These genes impact many crucial cellular processes, including lipid metabolism, inflammation, and cell proliferation and differentiation, with their expression often closely regulated by miRNAs. Hence, dysregulation of miRNAs plays a significant role in the development and progression of CVD.

MiRNAs have been identified as crucial regulators of gene expression involved in various pathological processes of CVD, such as angiogenesis, inflammation, and hypertension. The regulation and dysregulation of miRNAs expression levels affect the expression of genes involved in these processes, culminating in the manifestation of CVD.

Recent studies have shown that targeting specific miRNAs or combinations of miRNAs may help create novel therapeutic approaches to treat CVD. One such approach is through regulating the expression of genes and signaling pathways that play a role in CVD pathogenesis.

In addition to CVD management, miRNAs expression levels could also serve as biomarkers for CVD risk stratification, diagnosis, and monitoring of patients with CVD. Cardiologists and other medical professionals can use noninvasive measures such as blood tests to measure miRNA concentrations, allowing for quick and accurate clinical assessments of patients with CVD risk.

However, despite the wealth of information that has been generated in this field, the exact mechanisms by which miRNAs and related genes contribute to CVD pathogenesis remain largely unknown. Further research will be necessary to define these mechanisms and develop more effective therapeutic approaches against CVD.

Conclusion

In conclusion, microRNAs (miRNAs) and genes play a pivotal role in the pathogenesis of cardiovascular disease (CVD). miRNAs regulate many important physiological processes including promoting and inhibiting angiogenesis, controlling inflammation and lipid metabolism, and preventing undesirable myocardial hypertrophy and fibrosis. It has been found that the dysregulation of particular miRNAs is a major contributor to the pathogenesis of CVD, and targeting these miRNAs holds promise as a therapeutic approach. Moreover, genes related to CVD impact one's risk of developing this condition, and the expression of these genes is often closely regulated by miRNAs. Through a complex interaction between genes and miRNAs, CVD manifests through different subtypes such as coronary artery disease, heart failure, and valvular disease.

The detailed relationship between various genes and miRNAs involved in CVD is still emerging as research in the field continues. However, the identification of pathway targets regulated by microRNAs provides promising therapeutic targets for developing novel therapeutic interventions against CVD. Further research could

help widen the knowledge of the regulatory networks that influence CVD pathogenesis, and identify new and more effective therapeutic avenues for treating and preventing CVD.

Author's contributions

Mehrdad Gholamzad conceptualized and supervised. Amir Gholamzad, Melina Moulaeian, Mahsa Khatibi and Mohammadmatin Nourikhani contributed to the investigation, validation, writing original draft. Yalda Goudarzi contributed to the graphical design.

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