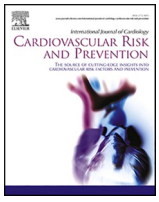
International Journal of Cardiology Cardiovascular Risk and Prevention 24 (2025) 200355

Contents lists available at ScienceDirect

International Journal of Cardiology Cardiovascular Risk and Prevention

journal homepage: www.journals.elsevier.com/international-journal-of-cardiology-cardiovascular-risk-and-prevention



The role of miR-155 in cardiovascular diseases: Potential diagnostic and therapeutic targets

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ARTICLE INFO

Handling editor: D Levy

Keywords:
MicroRNA
MiR-155
Cardiovascular diseases
Potential diagnostic
Therapeutic target

ABSTRACT

Cardiovascular diseases (CVDs), such as atherosclerotic cardiovascular diseases, heart failure (HF), and acute coronary syndrome, represent a significant threat to global health and impose considerable socioeconomic burdens. The intricate pathogenesis of CVD involves various regulatory mechanisms, among which microRNAs (miRNAs) have emerged as critical posttranscriptional regulators. In particular, miR-155 has demonstrated differential expression patterns across a spectrum of CVD and is implicated in the etiology and progression of arterial disorders. This systematic review synthesizes current evidence on the multifaceted roles of miR-155 in the modulation of genes and pathological processes associated with CVD. We delineate the potential of miR-155 as a diagnostic biomarker and therapeutic target, highlighting its significant regulatory influence on conditions such as atherosclerosis, aneurysm, hypertension, HF, myocardial hypertrophy, and oxidative stress. Our analysis underscores the transformative potential of miR-155 as a target for intervention in cardiovascular medicine, warranting further investigation into its clinical applicability.

1. Introduction

HF, hypertension, atrial fibrillation (AF), and coronary artery disease are prevalent CVD that lead to the highest morbidity and mortality rates worldwide [1,2], In China, these conditions are also among the primary causes of death and premature mortality [3,4]. Despite significant advancements in medical technology and the sciences, which have greatly improved the diagnosis, treatment, and prognosis of CVDs, these diseases still pose considerable health risks, accounting for approximately 30 % of global mortality [5]. Consequently, there is an ongoing need in clinical practice to explore novel biomarkers and strategies for the assessment, treatment, and monitoring of CVD [6]. From prokaryotes to eukaryotes, a class of small RNAs (sRNAs), approximately 18–30 nucleotides in length, plays diverse and crucial roles in various biological processes [7,8]. On the basis of their nucleotide length and structure, sRNAs are categorized into miRNAs, PIWI-interacting RNAs (piRNAs), small interfering RNAs (siRNAs), and tRNA-derived small RNAs (tsRNAs), among others [9,10]. Many of these sRNAs are vital regulatory factors that influence physiological processes such as growth, differentiation, development, and apoptosis by targeting and interfering with their binding messenger RNAs (mRNAs), thereby participating in immune system development and being closely associated with the maintenance of normal body functions and the occurrence of diseases [7,8]. Among them, miRNAs are endogenously encoded, single-stranded RNA molecules of approximately 22 nucleotides in length [11], Post-transcriptionally, they regulate gene expression by binding to specific target sequences in the 3′ untranslated region (UTR) of mRNAs [12,13]. With the development of nucleic acid and molecular biology techniques, an increasing number of miRNAs have been implicated in various diseases [11,14]. In recent years, research has increasingly linked miRNAs to CVD [14,15], Alterations in miRNA expression may affect abnormal processes such as proliferation, differentiation,

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https://doi.org/10.1016/j.ijcrp.2024.200355
Received 19 October 2024; Received in revised form 21 November 2024; Accepted 5 December 2024
Available online 6 December 2024

apoptosis, and senescence in cardiomyocytes and endothelial cells [16], Given the high sensitivity and specificity of miRNAs to CVD, they may serve as potential biomarkers for the early detection, diagnosis, treatment, and prognosis of CVDs in the future [14,17,18]. In recent years, miR-155 has garnered significant attention in the scientific community as a miRNA with diverse biological implications. Initially, discovered for its role in oncology [19,20], subsequent research has expanded our understanding of miR-155's involvement in a spectrum of diseases, notably Alzheimer's disease [21]. As the body of research on miR-155 continues to grow, its influence on CVDs has become increasingly apparent [22–24]. Accumulating evidence indicates that miR-155 exerts regulatory control over immune and inflammatory responses, and it is increasingly recognized for its substantial impact on the pathogenesis of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection [25,26], processes that are fundamental to the pathogenesis of cardiovascular conditions. Therefore, conducting a timely and exhaustive review of the advancements in miR-155 research within the field of CVDs is not only essential but also highly pertinent This review aims to provide a detailed examination of the physiological functions of miR-155 and elucidate its mechanisms of action in the context of various CVDs. Additionally, we explored the potential of miR-155 as a novel biomarker and therapeutic target, assessing its potential to revolutionize the prevention, diagnosis, treatment, and prognostic evaluation of CVDs.

2. Biogenesis of miRNA

MiRNAs, a class of small non-coding RNA molecules, are pivotal in the post-transcriptional regulation of gene expression, modulating cellular processes and gene silencing mechanisms [27]. The biogenesis of miRNAs is a sophisticated process that encompasses a series of intricate steps and relies on various cellular components, reflecting the complexity of post-transcriptional gene regulation [28]. The biogenesis of miRNAs commences with the transcription of miRNA genes by RNA polymerase II or III, yielding primary miRNAs (pri-miRNAs). These pri-miRNAs are lengthy, capped, and polyadenylated RNA molecules. Subsequently, within the nucleus, these pri-miRNAs are recognized and processed by a nuclease complex comprising Drosha and its cofactor, DGCR8 (DiGeorge syndrome critical region gene 8). This enzymatic activity results in the formation of precursor miRNAs (pre-miRNAs), which are key intermediates in the miRNA maturation pathway [29–31]. The pre-miRNA, approximately 70 nucleotides in length, adopts a hairpin-like structure [32]. This structural feature is crucial for its subsequent recognition and processing. The exportin-5 protein facilitates the translocation of pre-miRNA from the nucleus to the cytoplasm [33]. Within the cytoplasm, the RNAse III enzyme Dicer, in conjunction with its cofactor Transcription Activation Response RNA Binding Protein (TRBP), cleaves the pre-miRNA at the stem of the hairpin, yielding a miRNA duplex [34]. This duplex comprises a guide strand and a passenger strand, with the guide strand being selectively incorporated into the RNA-induced silencing complex (RISC) [35]. Upon integration into RISC, the miRNA guides the complex to target mRNAs with complementary sequences, leading to either translational repression or mRNA degradation, thereby exerting post-transcriptional gene regulation [36].

In conclusion, the intricate biogenesis and regulatory mechanisms of miRNAs underscore their pivotal role in the post-transcriptional control of gene expression. These findings not only highlight the fundamental importance of miRNAs in cellular homeostasis but also underscore their potential as therapeutic targets in a spectrum of diseases, particularly those with significant immune and inflammatory components. The capacity to modulate miRNA activity presents a promising frontier for the development of novel therapeutic strategies and diagnostic biomarkers, thereby warranting further investigation into their role in disease pathogenesis and treatment.

3. Characteristics of miR-155

3.1. The architectural framework of miR-155

miR-155, a miRNA of significant interest, originates from the B-cell Integration Cluster (BIC) gene located on chromosome 21 [37,38]. The biogenesis of a mature miRNA typically begins in the nucleus, where RNA polymerase II transcribes the nuclear gene into the pri-miRNA. This pri-miRNA is subsequently cleaved by the RNase III enzyme into a hairpin structure, forming the pre-miRNA [38,39],The pre-miRNA is then transported to the cytoplasm via the exportin-5 protein, where it undergoes further processing by Dicer, yielding the miRNA duplex, specifically the mature strands miR-155-5p and miR-155-3p [40–42]. The regulation of miR-155 expression is a complex process involving multiple layers of control, including transcriptional regulation by various transcription factors that bind to its promoter region. For instance, the nuclear factor kappa-B (NF-κB) pathway is known to upregulate miR-155 expression in response to inflammatory signals [43]. Furthermore, the promoter region of the miR-155 gene encompasses multiple binding sites for transcription factors that can either activate or repress its transcription [44]. miR-155, a pivotal miRNA in immune responses and inflammation, is subject to regulation by a variety of transcription factors [45,46], exhibits a significant upregulation following T cell activation, which is essential for lymphocyte proliferation and differentiation [43]. This miRNA influences the lineage commitment of $CD4^+$ T cells by promoting their differentiation towards the Th17 phenotype and concurrently inhibiting the transition towards the Th2 phenotype. Moreover, miR-155 is highly expressed in regulatory T cells (Tregs), where it enhances the differentiation of $CD4^+$ T cells into Tregs and sustains their numbers and survival [47,48]. In $CD8^+$ T cells, the increased expression of miR-155 augments their antitumor activity by targeting SOCS-1 [49]. Furthermore, miR-155 can directly bind to the 3′ UTR of PD-L1 mRNA, downregulating PD-L1 expression and thereby influencing the modulation of immune checkpoints [50,51]. Within the context of neuroinflammation, miR-155 plays a pivotal role in modulating the activation of microglia and astrocytes, in addition to regulating the activity of peripheral immune cells [52,53]. Collectively, these discoveries elucidate the intricate network through which miR-155 orchestrates immune responses and inflammation, underscoring its critical function in both tumor immunity and neuroinflammatory conditions. Prior research indicates that from the two strands of a miRNA duplex, only one strand is typically activated and selectively integrated into the RISC during a process known as miRNA strand selection [54]; however, current studies recognize that both miR-155-5p and miR-155-3p are biologically functional miRNAs [55,56]. Moreover, an extensive body of research has implicated miR-155 as a small molecule RNA closely related to CVDs [57]. It exerts its effects not only in cardiovascular tissues such as the aorta and myocardium [58,59]; but also demonstrates regulatory activity in various cellular locations, including vascular endothelial cells, macrophages, and cardiac fibroblasts [60,61]. Additionally, miR-155 is involved in the regulation of myocardial fibrosis (MF) and has been studied in the context of cardiac development, myocardial hypertrophy, HF, aortic aneurysm, and atherosclerotic plaque formation [59,62,63].

3.2. Pathological roles of miR-155 in CVD

A burgeoning body of research indicates that miR-155 is a pivotal regulatory factor in the pathogenesis of CVD, exerting its influence through a multitude of pathophysiological mechanisms. These mechanisms encompass myocardial hypertrophy, fibrosis, angiogenesis, the modulation of calcium channel function, lipid aggregation, cholesterol transport, inflammatory responses, and the complex biology of endothelial and vascular smooth muscle cells. The intricate interplay between miR-155 expression and its regulatory functions in these contexts is currently a focal point of investigation, with accumulating evidence

underscoring its potential as a central mediator in the pathophysiology of CVD. This review provides an in-depth examination of the pathological mechanisms associated with miR-155 in CVD, as detailed in Table 1. The table elucidates its pivotal role as a regulatory factor in CVDs. The consistent upregulation of miR-155 in multiple pathological states implies its significant contribution to inflammatory responses, oxidative stress management, and the modulation of cardiac electrophysiological properties. The specific targeting of molecules like endothelial nitric oxide synthase (eNOS) in AF and ABCA1 in atherosclerosis further illustrates the broad-reaching influence of miR-155 on the molecular underpinnings of these diseases. Conversely, the observed downregulation of miR-155 in thoracic aorta aneurysm cases introduces a layer of complexity to our understanding of its role, suggesting that the function of miR-155 may be context-dependent and may vary across different cardiovascular conditions. This variability underscores the need for a nuanced approach to understanding miR-155's multifaceted impact on disease progression and underscores its potential as a therapeutic target, warranting further investigation into its mechanistic roles and the development of targeted interventions in CVD management. Furthermore, Fig. 1 offers a comprehensive summary of CVDs related to miR-155, showcasing the intricate network of molecular interactions influenced by this miRNA.

Table 1 delineates the intricate regulatory roles of miR-155 across a diverse array of CVDs and experimental models. As a miRNA of significant biological importance, miR-155 has emerged as a critical modulator in the pathogenesis of cardiovascular conditions, presenting itself as a potential biomarker and therapeutic target. The table is curated to systematically illustrate the directionality of miR-155 expression changes, the molecular targets influenced, the pathways affected, and the corresponding academic references that substantiate these relationships.

NM: Not Mentioned; eNOS: Endothelial Nitric Oxide Synthase; NO: Nitric Oxide; ABCA1: ATP-Binding Cassette Subfamily A Member 1; ABCG1: ATP-Binding Cassette Subfamily G Member 1; CTRP12: C-type Lectin Domain Family 12 Member; LXRα: Liver X Receptor Alpha; ROS: Reactive Oxygen Species; MIF: Macrophage migration inhibitory factor; HBP1: HEAT Repeat Containing Protein 1; c-Ski: Ski-related Novel Gene N; FoxO3a: Forkhead Box Protein 3A; BRCA1: Breast Cancer Type 1 Susceptibility Protein; PU.1 (an inhibitor of dendritic cell antigen presentation to T Cells; DIER-1: Differentiation Inhibiting Factor 1; TIMP-4: TIMP Metallopeptidase Inhibitor 4; CACNA1C: Calcium Voltage-Gated Channel Subunit Alpha1 C; ICa,L: L-type Calcium Current; P27: Cyclin-Dependent Kinase Inhibitor 1B; TNF-a: Tumor Necrosis Factor Alpha; CRP: C-Reactive Protein; IL-6: Interleukin 6; HUVECs: Human Umbilical Vein Endothelial Cells; RANK/RANKL: Receptor Activator of NF-κB/Receptor Activator of NF-κB Ligand; OPG: Osteoprotegerin; FOS: FBJ Murine Osteosarcoma Viral Oncogene Homolog; ZIC3: Zinc Fingers of the Cerebellum 3; KLF4: Kruppel-Like Factor 4.

4. miR-155's potential role as a biomarker and therapeutic target in CVD management

4.1. miR-155 and atherosclerosis

Atherosclerosis is not only a disease characterized by lipid accumulation but also a chronic inflammatory process [88], making it a major risk factor for CVDs. In atherosclerosis, the accumulation of lipids in the intimal space is closely related to local inflammation, and macrophages play a key role in this process by maintaining lipid balance in the vascular wall and coordinating inflammatory responses [89]. Recent studies have shown that miR-155 plays a crucial role in regulating the inflammatory response of macrophages and is part of a complex pathophysiological process involving multiple factors [90], and it is involved in the pathogenesis of atherosclerosis by modulating various signaling pathways (Fig. 2). Numerous studies have demonstrated that in mice fed a Western diet, the expression levels of miR-155 in the aorta are significantly elevated [90,91]. In recent years, research has underscored the critical role of miR-155 within the Renin-Angiotensin-Aldosterone System (RAAS) [74]. Anastasia et al. [73] have demonstrated that the RAAS plays a role in promoting the aggregation of inflammatory cells at

Table 1
MiR-155 expression and targets in pathophysiologic process of CVD.

Disease or model	Tissue or cell	Regulation of miR-155 decrease ↓ increase ↑	Target molecule	Target pathway	Reference
Swine model of atrial fibrillation	myocardial tissue	↑	eNOS	eNOS/NO	[64]
Inflammation in transgenic Mouse model of Bmal1	myeloid cells	↑	Bmal1	NF-κB	[65]
Mouse model of atherosclerosis	endothelial cell	↑	Bmal1	NM	[66]
Mice model of atherosclerosis	THP-1 monocytes	↑	ABCA1, ABCG1	CTRP12/LXRa	[67]
Mice model of atherosclerosis	macrophages	↑	HBP1	MIF-ROS	[68]
Inflammation in Mice model	macrophages	↑	IL-6, IL-1β	ArgII	[69]
hypertrophic myocardium in a mice model	cardiomyocytes	↑	FoxO3a	BRCA1	[70,71]
Mice model of atherosclerosis	thoracic aorta	↑	ROS IL-6 TNF-a	RAAS/AngII	[72–74]
Atrial fibrillation in miR-155 knockout mice	atrial cardiomyocytes	↑	CACNA1C	ICa,L	[75]
Rat hypertension model	Vascular smooth muscle cell	↑	P27	NM	[76]
Endothelium-Dependent Vasorelaxation model	HUVECs	↑	eNOS	TNF-a/NO	[77]
spontaneously hypertensive rats	HUVECs	↑	TNF-a, IL-6	RANK/RANKL /OPG	[78]
Mice model of abdominal aortic aneurysms	body tissue and serum	↑	IL-6, IL-1β, TNF-a	NF-κB	[79,80]
The H2O2 and NaAsO2 Induced VSMC injury model	vascular smooth muscle cells	↑	FOS, ZIC3	NF-κB/p65	[81]
Patients with White coat hypertension	Plasma in hypertensive patients	↑	CRP, IL-6	NM	[82]
Patients with Thoracic aorta aneurysm	aortic tissue	↓	KLF4	NM	[83]
Patients with diabetic cardiomyopathy	plasma or serum in patients	↑	c-Ski	TGF-β1/Smad	[84,85]
Patients with acute myocarditis	right ventricular	↑	PU.1	NM	[86]
Patients with atrial fibrillation	left atrial appendage tissue	↑	DIER-1, TIMP-4, CACNA1C	NM	[87]

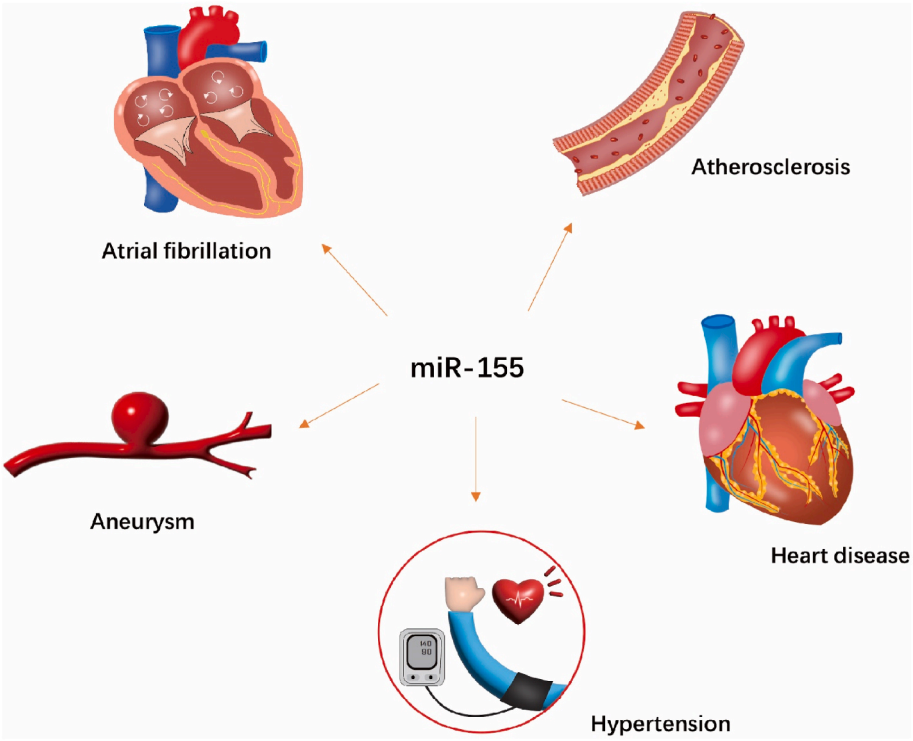

Fig. 1. Interplay of miR-155 with CVDs. This illustration highlights the interconnected roles of miR-155 in various CVD. This schematic highlights the potential regulatory effects of miR-155 across a spectrum of CVD, suggesting its broad implications in pathophysiological mechanisms.

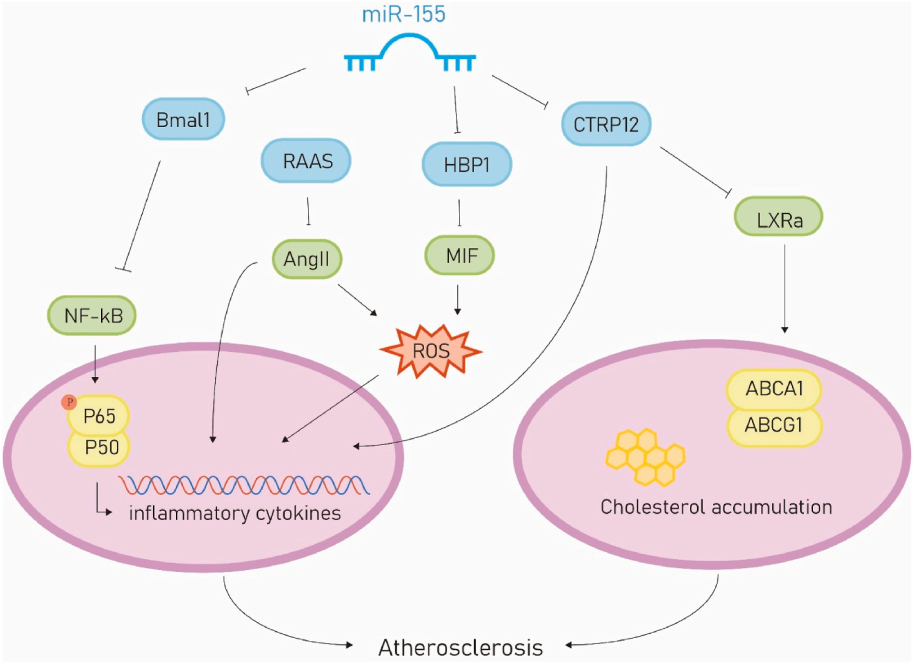

Fig. 2. Schematic Overview of miR-155 in Atherosclerotic Pathogenesis. This figure underscores the multifaceted role of miR-155 in orchestrating the complex interplay between inflammatory mediators, lipid metabolism regulators, and the subsequent development of atherosclerotic plaques. By delineating the signaling pathways modulated by miR-155, this illustration provides a view of its regulatory influence on atherogenesis, highlighting potential therapeutic targets and biomarkers.

plaque sites. Specifically, the activation of Angiotensin II within this system stimulates the release of inflammatory mediators and the generation of reactive oxygen species (ROS), while concurrently reducing the production of nitric oxide (NO), which collectively contribute to the formation of atherosclerotic plaques. It is suggested that by inhibiting the activation of the RAAS, the progression of disease could potentially be slowed. Some research has found that miR-155, along with Brain and Muscle ARNT-Like Protein-1 (Bmal1), plays an important role in the immune response of mice [65,92], although the specific interactions between them have not yet been fully elucidated. Recent research by

Liang et al. [66] demonstrated that in a murine model of atherosclerosis, the expression of miR-155 is significantly increased while that of Bmal1 is decreased. The upregulation of miR-155 is associated with an enlargement of atherosclerotic plaques, increased apoptosis, and elevated levels of total cholesterol (TC) and triglycerides (TGs). Conversely, the suppression of miR-155 results in increased Bmal1 expression, suggesting a clear inverse relationship between these two molecules that may influence the progression of atherosclerosis. Furthermore, studies have indicated that C1q tumor necrosis factor-related protein 12 (CTRP12) is closely associated with CVDs [93]. Wang et al. [67] observed that the overexpression of CTRP12 in a murine model of atherosclerosis reduces miR-155-5p levels in the aortas of apoE−/− mice, leading to an upregulation of LXRα and enhancement of cholesterol efflux dependent on ABCA1 and ABCG1. This mechanism may mitigate the development of atherosclerosis. Additionally, elevated levels of reactive ROS significantly accelerate the pathological processes of oxidative stress and inflammation [94], thereby hastening the formation of atherosclerosis [95,96]. Research has shown that HMG box transcription protein 1 (HBP1), which acts as a transcriptional repressor [97], can reduce ROS production by inhibiting the expression of MIF [97,98], thus potentially slowing the progression of atherosclerosis. This transcriptional repressor has been found to be negatively regulated by miR-155 [68,99]. Tian et al. [68] demonstrated that overexpression of HBP1 can also decrease miR-155 levels in apoE−/− mice under high-fat diet conditions, suggesting that targeting the HBP1-MIF-ROS pathway may reduce miR-155 expression and consequently inhibit inflammatory responses, further impacting atherosclerosis. In terms of inflammation, studies have identified arginase 2 (Arg2) as a target of miR-155 [26],In models of inflammatory macrophages, the specific inhibition of the overexpressed miR-155-mediated suppression of Arg2 can maintain a higher level of Arg2 expression, thereby exerting an anti-inflammatory effect and reducing inflammatory responses [69]. This suggests that by targeting this pathway, the inflammatory response may be mitigated, potentially inhibiting the progression of atherosclerosis. Collectively, these findings suggest that miR-155 promotes the progression of atherosclerosis, and that its expression, along with that of related molecules, could be targeted to impede this process. Consequently, miR-155 holds promise as a potential diagnostic and therapeutic marker in atherosclerosis.

4.2. *miR-155 and heart failure and cardiomyopathy*

HF is a clinical syndrome caused by various cardiac structural or functional diseases that impair ventricular filling and/or ejection function, leading to inadequate cardiac output to meet the metabolic needs of tissues. It is characterized by symptoms such as respiratory distress, exercise intolerance, and fluid retention due to congestion in the pulmonary and/or systemic circulation [100,101]. Hypertension, myocarditis, AF, and myocardial interstitial fibrosis are among the many CVDs that can lead to HF [102]. In recent years, researchers have begun to elucidate the crucial role of miRNAs in cardiac hypertrophy and remodeling. Notably, miR-155 has been found to be upregulated in diabetic hearts and is known to promote MF by targeting signaling pathways within the heart [84]. Fig. 3 delineates a schematic overview of the molecular pathways governed by miR-155, which are pivotal to the pathophysiological mechanisms underlying the disease. Among the key players in MF is transforming TGF-β1, which potently induces cardiac fibroblast differentiation and plays a significant role in the fibrotic process [103]. Research by Wang et al. [85] revealed a synergistic relationship between miR-155 and TGF-β1, suggesting that the inhibition of miR-155 may suppress TGF-β1 expression and consequently mitigate MF. BRCA1, known as a tumor suppressor, has been recognized as a crucial modulator of cardiac function [73,74]. Under ischemic stress, the upregulation of BRCA1 can suppress the elevation of cardiac miR-155, potentially protecting against its detrimental effects on cardiac function. Studies by Fan et al. [46] have shown that resveratrol (REV)

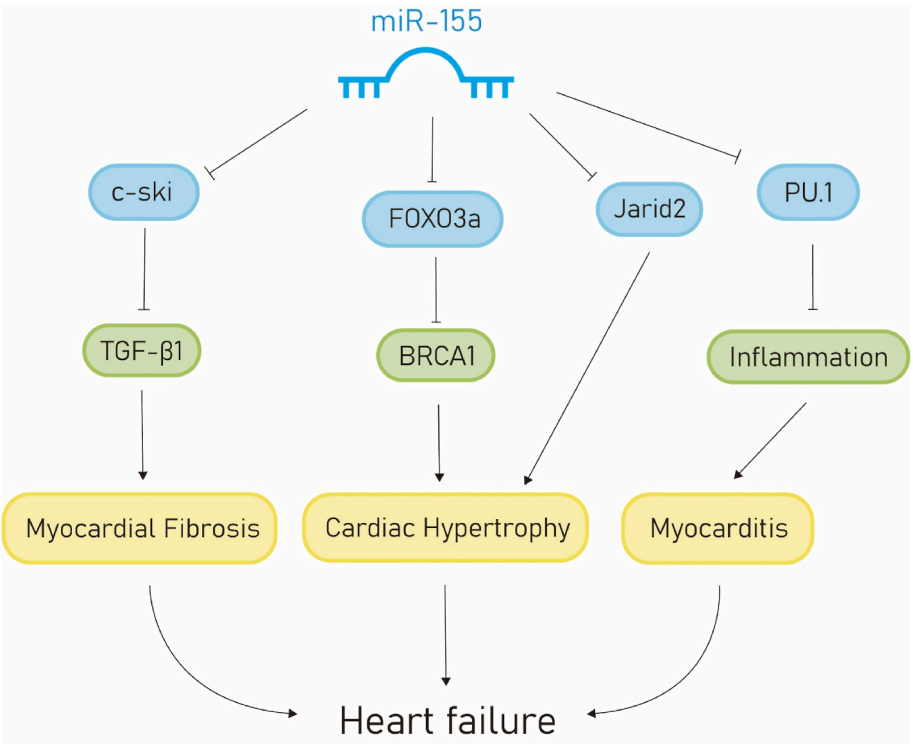

Fig. 3. Molecular Mechanisms of miR-155 in HF Pathogenesis. The figure illustrates the intricate relationships between miR-155 and its target molecules, providing a comprehensive view of how these interactions may contribute to the clinical manifestations of HF. By depicting the regulatory roles of miR-155 in the context of cardiac remodeling, inflammation, and fibrosis, serves as a valuable tool for researchers and clinicians alike, offering insights into potential therapeutic targets and biomarkers for the diagnosis and treatment of HF.

can reduce miR-155 expression in a murine model of cardiac hypertrophy by enhancing the expression of the BRCA1 signaling pathway, thereby inhibiting the prohypertrophic effects of miR-155. BRCA1, known as a tumor suppressor, has been recognized as a crucial modulator of cardiac function [104,105]. Under ischemic stress, the upregulation of BRCA1 can suppress the elevation of cardiac miR-155, potentially protecting against its detrimental effects on cardiac function. Studies by Fan et al. [70] have shown that REV can reduce miR-155 expression in a murine model of cardiac hypertrophy by enhancing the expression of the BRCA1 signaling pathway, thereby inhibiting the pro-hypertrophic effects of miR-155. Furthermore, FOXO3a can inhibit myocardial cell hypertrophy by transcriptionally targeting catalase [47]. The overexpression of miR-155 has been shown to decrease FOXO3a expression levels, whereas REV has been found to increase FOXO3a protein expression, thus participating in the antihypertrophic effect [46]. The overexpression of FOXO3a actively counters miR-155 expression, suggesting a new avenue for the prevention and treatment of myocardial hypertrophy. Furthermore, FOXO3a can inhibit myocardial cell hypertrophy by transcriptionally targeting catalase [71]. Seok HY et al. [62] have discovered that the absence of endogenous miR-155 enhances the expression of jumonji, AT rich interactive domain 2 (Jarid2), potentially reducing pathological cardiac hypertrophy through this key target. Ding et al. [106] suggested that miR-155-5p may serve as a novel biomarker for the diagnosis of early-stage HF, potentially complementing existing diagnostic criteria. Christian Besler et al. [107] reported higher myocardial endocardial miR-155 expression in inflammatory myocardial disease patients compared to noninflammatory dilated cardiomyopathy (DCM) patients, with miR-155 levels correlated with the number of inflammatory cells in the myocardial endocardium, although miR-155 levels were not associated with clinical outcomes in inflammatory myocardial disease (iCMP) patients. Danilo Obradovic et al. [108] found significantly higher plasma miR-155 concentrations in iCMP patients compared to DCM patients, suggesting that miR-155 may serve as a novel biomarker for diagnosing iCMP. Maarten F et al. [86] observed increased miR-155 expression during the acute phase in a murine model of Coxsackievirus B3-induced myocarditis, which may lead to adverse inflammatory responses to viral infection. Inhibiting miR-155 could potentially improve mortality and cardiac function following long-term treatment by reducing inflammatory responses. Concurrently, myocardial interstitial fibrosis plays a critical role in the pathological remodeling of cardiac structure and the progression of HF in patients [102]. However, the association between myocardial interstitial fibrosis and miR-155 remains to be fully elucidated and may represent a potential avenue for future research. Drawing from current research, we observe that miR-155 is closely associated with HF and myocardial diseases, and has been demonstrated to participate in the development and regulation of HF through multiple signaling pathways. It has also been shown to be involved in diseases such as MF and myocarditis. These findings suggest that miR-155 may serve as a novel biomarker, with potential significance in the onset, development, treatment, and prognosis of HF and cardiomyopathy, warranting further investigation.

4.3. *miR-155 and atrial fibrillation*

AF, the most common type of arrhythmia, can exacerbate HF [109]. AF represents a severe disorder of atrial electrical activity, characterized primarily by the loss of organized atrial electrical activity, which is replaced by rapid and disorganized fibrillation waves, resulting in an irregular and rapid heart rate [110,111]. Studies report an increased AF burden in patients with AF compared to those without the condition [112,113], Atrial fibrosis may be a terminal event in various forms of fibrillation. Recent studies have implicated miR-155 in the regulation of AF, which may be associated with atrial fibrosis [114]. Fig. 4 offers a schematic representation of the molecular interactions regulated by miR-155 within the context of AF. Not only have we observed a significant increase in miR-155 expression in patients with AF, but concurrently, the levels of miR-155, which are related to inflammation, were

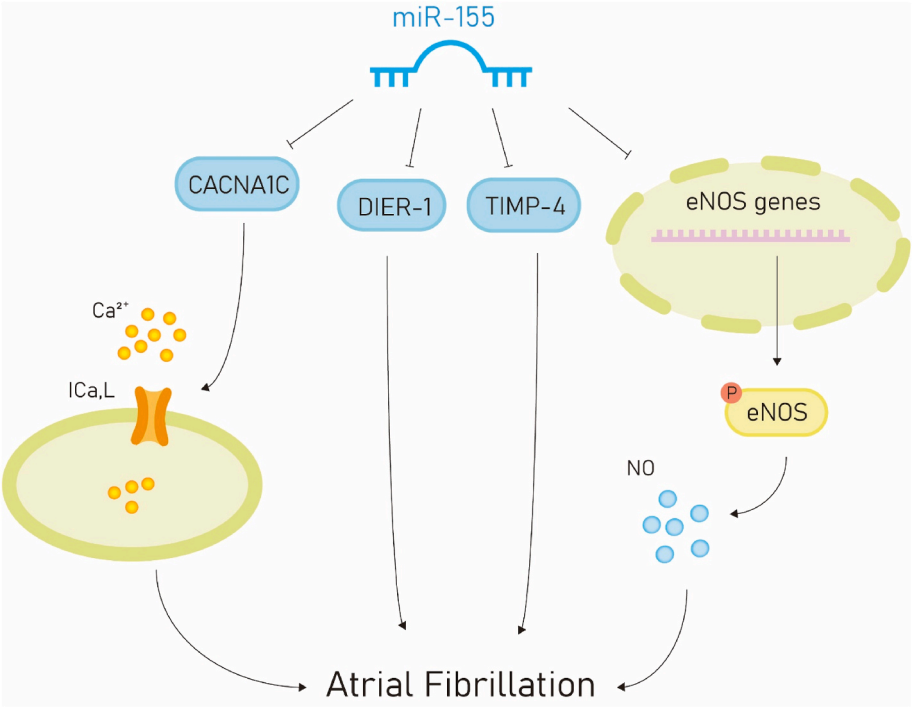

Fig. 4. Molecular Mechanisms of miR-155 in AF. This figure underscores the intricate relationships between miR-155 and pivotal molecular targets, including CACNA1C, eNOS genes, TIMP-4, and DIER-1. These interactions are crucial for the electrophysiological remodeling and structural alterations characteristic of AF. Furthermore, the figure elucidates the regulatory effects of miR-155 on calcium homeostasis, as evidenced by its association with ICa,L and the subsequent modulation of eNOS and NO synthesis.

found to increase with C-reactive protein expression levels and the duration of AF. This increase may be related to target genes such as DIER-1, TIMP-4, and CACNA1C [87,115]. Owing to the close relationship between miR-155 and AF, assessing miR-155 may improve the prediction, prevention, and treatment of stroke in patients with AF [116,117]. A sub-study of the RE-LY trial suggested that troponin levels may serve as independent biomarkers of stroke risk associated with AF [118]. Elevated expression levels of miR-155 in atrial myocytes lead to electrical remodeling in AF, resulting in the downregulation of the target gene CACNA1C, which encodes the L-type calcium channel α1C subunit and reduces L-type Ca2+ current density in cardiomyocytes [75]. Therefore,the L-type calcium current (ICa,L), a voltage-gated ion channel situated on the cell membrane, is essential for the contraction of cardiomyocytes. Its regulation is particularly critical in the context of CVDs, where it plays a pivotal role in maintaining cardiac function. Given the established link between ICa,L and the modulation of myocardial contractility, future research should explore the therapeutic potential of modulating miR-155 expression. Targeting miR-155 could serve as a strategic intervention to alter the activity of calcium channels within cardiomyocytes. Such modulation may subsequently influence intracellular Ca2+ concentration, presenting a novel avenue for the regulation of AF and offering innovative therapeutic opportunities. Moreover, miRNAs serve as noninvasive diagnostic biomarkers, with numerous studies [119,120] indicating that the expression of various miRNAs in the serum and atrial tissue of patients with AF contributes to the pathogenesis of the condition by influencing atrial cell electrophysiological properties. Multiple clinical studies have corroborated the correlation between AF and a plethora of circulating miRNAs [121,122]. Post-catheter ablation surgery, the expression of specific miRNAs has been shown to determine the efficacy of the procedure and predict AF prognosis [123]. miR-155, which is closely associated with AF, not only influences the development of the condition but also exhibits reduced expression following radiofrequency ablation treatment [64]. These findings suggest that miR-155 plays a significant role in the evaluation of treatment outcomes and prognosis for AF patients. Additionally, NO has been identified to increase cardiac vagal activity and inhibit sympathetic activity, leading to uneven atrial contractions and, consequently, electrophysiological heterogeneity that triggers AF [124,125]. eNOS, a regulator of L-type calcium channels, effectively modulates myocardial cell contraction [126]. Research by Fatini et al. [127] has identified eNOS genes as susceptibility factors for AF. As a downstream target of miR-155, Inflammatory stimuli lead to an upregulation of miR-155 expression, consequently downregulating the expression of eNOS [128]. This finding implies that miR-155 may also regulate AF by affecting the expression levels of this gene. Studies in a porcine model of AF have found significantly increased expression levels of miR-155-5p, which were reduced following ablation treatment. Correspondingly, the levels of eNOS and NO in AF pigs also decreased, further confirming the involvement of miR-155-5p in the pathogenesis of AF by modulating the expression of eNOS and the production of NO [64]. The miR-155-eNOS-NO axis is, therefore, closely related to the development and progression of AF. Amassing research and clinical evidence underscore the intimate association between miR-155 expression levels and the pathogenesis of AF. This miRNA appears to exert a substantial influence on the electrophysiological remodeling observed in AF, a process critical to the disease's progression. Concurrently, Adly et al. [129] have reported a significant correlation between the relative expression levels of circulating miR-155 in stroke patients and atrial fibrillation, suggesting a potential role for miR-155 in the pathogenesis of atrial fibrillation in these patients. However, the specific mechanisms underlying this association require further investigation. Additionally, studies have revealed that, compared to patients with sinus rhythm, those with atrial fibrillation exhibit upregulated expression of STAT3 in atrial tissue, a key component of the JAK2/STAT3 signaling pathway, which plays a crucial role in atrial fibrosis and atrial remodeling [130]. Collectively, these findings not only highlight a close association between miR-155 expression levels and atrial fibrillation but also underscore the potential value of therapeutic strategies targeting miR-155 and its associated signaling pathways in post-stroke recovery. Despite the fact that AF is reliably diagnosed using electrocardiography (ECG), miR-155 offers promising avenues for enhancing preventive measures, therapeutic interventions, and prognostic assessments for patients afflicted with this arrhythmia.

4.4. miR-155 and hypertension

Hypertension, a pervasive chronic condition, is characterized by a persistent blood pressure elevation above the threshold of 140/90 mmHg. This complex pathophysiological state is subject to the intricate regulatory influence of key physiological systems, with the sympathetic nervous system (SNS) and the RAAS being the principal contributors [131,132]. The dysregulation of these systems is not only implicated in the direct elevation of blood pressure but also in downstream effects such as left ventricular overload, which may culminate in HF [133]. These interconnections firmly establish the inextricable link between hypertension and a spectrum of CVDs. An expanding corpus of evidence implicates miRNAs as potential contributors to the pathogenesis of hypertension, suggesting that their expression may be intricately linked to the mechanisms underlying the disorder or the ensuing target organ damage [134]. The presence of miRNAs in biofluids, coupled with their capacity to undergo expression alterations in response to elevated blood pressure, has propelled interest in their utility as potential biomarkers across the spectrum of hypertension phenotypes. The prospect of the use of miRNAs as noninvasive indicators of hypertension holds significant promise, given their diagnostic and prognostic potential. Notably, research by Xu et al. [76] has shed light on the potential therapeutic implications of miR-155 in hypertension. Their study in hypertensive rat models demonstrated that the administration of antagomiR-155, an inhibitor of miR-155, significantly reduced systolic and diastolic blood pressures. These findings suggest that the modulation of miR-155 expression could serve as a potential biomarker for the pathogenesis of hypertension or associated target organ damage. Further exploration of the relationship between miR-155 and hypertension revealed its intricate involvement in the disease's progression. Inflammation and oxidative stress are recognized as critical factors in the development of hypertension, and miR-155 appears to play a significant role in these processes [135,136]. By ameliorating redox and inflammatory status, vascular health can be improved, potentially impacting blood pressure regulation. C-reactive protein (CRP), a well-established biomarker of systemic inflammation, is an acute-phase protein produced by the liver in response to various stimuli, including tissue injury and inflammation. Elevated levels of CRP are commonly associated with an inflammatory state. miR-155, which is intimately linked to inflammatory responses, may modulate the expression of CRP and other inflammatory cytokines such as IL-6. The inhibition of miR-155 could, therefore, suppress the expression of these inflammatory mediators, potentially leading to a reduction in excessive blood pressure and offering a noninvasive diagnostic marker for white-coat hypertension (WCH) [82]. Furthermore, the vascular endothelium is intricately linked to the normal function of blood vessels and plays a crucial role in the maintenance of physiological blood pressure [137]. eNOS is pivotal in sustaining vascular tone and blood pressure regulation. However, under certain conditions, oxidative stress and inflammation can induce endothelial dysfunction, thereby diminishing the bioavailability of NO and affecting blood pressure homeostasis [138]. Hai-Xiang Sun et al. [77] demonstrated that miR-155 can modulate eNOS and endothelium-dependent vasorelaxation. The inhibition of miR-155 may facilitate vasodilation and alleviate vasoconstriction, potentially leading to improvements in hypertension, presenting a novel direction for the treatment of CVDs. Subsequent research has indicated that the expression of miR-155 not only impacts endothelial function but also may be involved in the pathogenesis of hypertension through additional mechanisms. For

instance, Jining Yang et al. [78] observed that in a rat model of spontaneous hypertension, S-amlodipine suppressed the expression of miR-155, affecting the activation of the RANK/RANKL/OPG system, and thereby inhibiting inflammation and preventing endothelial dysfunction, which contributed to lowering blood pressure. Moreover, Jennifer J et al. [139] highlighted that miR-155 might promote vasoconstriction in the aging vasculature by modulating the expression of L-type Cav1.2 calcium channels (LTCC) and Angiotensin II type 1 receptors (AgtR1), offering a new perspective for the treatment of age-related hypertension. In aged models with intact mineralocorticoid receptor (MRs), the specific restoration of miR-155 expression could induce a process leading to age-related hypertension. Future research might explore the use of MR antagonists to suppress miR-155 expression, thereby potentially mitigating age-related vascular degeneration and improving hypertension. The diagnostic criteria for hypertension are well-defined in current medical guidelines [140]; however, the standards for its control and prognostic assessment are subject to ongoing refinement. Fig. 5 illustrates the molecular interactions involving miR-155 in the context of hypertension. The involvement of miR-155 in the pathogenesis of hypertension presents a novel perspective for treatment and may revolutionize prognostic assessments. Future research endeavors will delve into the potential applications of miR-155 in hypertension therapy, potentially unveiling new strategies to enhance clinical outcomes. The regulation of miR-155 may also provide new targets for personalized hypertension treatment, particularly when the roles of inflammation and oxidative stress in the disease's pathogenesis are considered. In conclusion, the multifaceted role of miR-155 in the pathogenesis of hypertension, with its regulatory effects on endothelial function, inflammatory responses, and oxidative stress, offers new vistas for treatment and prognostic evaluation. Future studies will further elucidate the potential applications of miR-155 in hypertension management, potentially leading to innovative therapeutic approaches to improve patient outcomes.

4.5. *miR-155 and aneurysm*

Aneurysms arise from degradation, destruction, and pathological changes within the arterial wall, leading to a loss of inherent elasticity and increased vulnerability [141]. The affected tissue continues to endure the pulsatile forces exerted by blood flow within the lumen, resulting in irregular dilatation and expansion of the arterial wall. such as miR-155, have emerged as critical regulators within this pathophysiological landscape. Fig. 6 offers a comprehensive schematic overview of the molecular mechanisms linking miR-155 to the development and progression of aortic aneurysms. Specifically, miR-155 has been shown to be expressed at elevated levels in patients with abdominal aortic aneurysms (AAA) and in murine models of AAA [79,142]. This upregulation of miR-155 may be correlated with the overexpression of inflammatory cytokines, such as IL-6, suggesting a potential role in the inflammatory processes contributing to aneurysm development. In addition to the initial pathogenic changes in arterial walls, the expression of matrix metalloproteinases (MMPs), specifically MMP2 and MMP9, is markedly elevated in aneurysms [143,144]. This overexpression leads to degradation of the vascular extracellular matrix, a key event in the pathogenesis of aneurysm formation. Our research, in concert with other studies, revealed a close association between miR-155 and inflammatory mediators, including macrophages [79]. Inflammatory cytokines and macrophages are known to upregulate the

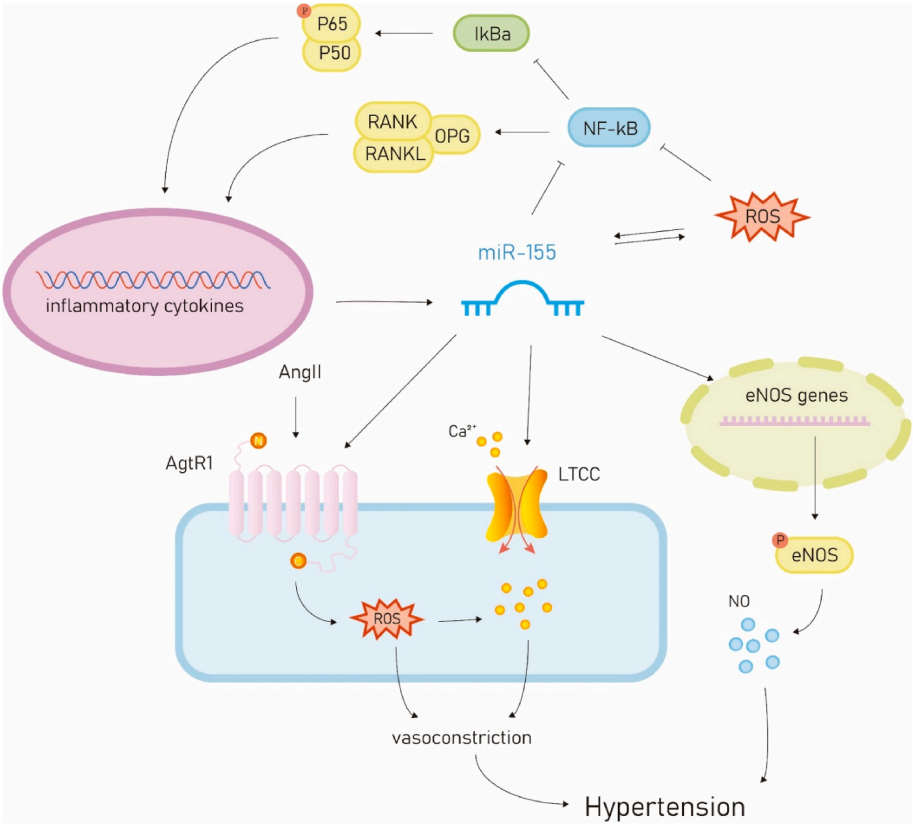

Fig. 5. Schematic Representation of miR-155 in the Molecular Etiology of Hypertension. This figure delineates the intricate molecular mechanisms by which miR-155 is implicated in the pathogenesis of hypertension. This schematic representation illustrates the complex interplay between miR-155 and key molecular targets, including NF-κB, RANK/RANKL/OPG signaling, and the regulation of reactive ROS. This visual representation highlights the modulation of AgTR1 and LTCC by miR-155, which are critical in the regulation of vascular tone and blood pressure. The interaction of miR-155 with eNOS and the subsequent production of NO are depicted, showcasing the miRNA 's role in vasodilation and blood pressure homeostasis.

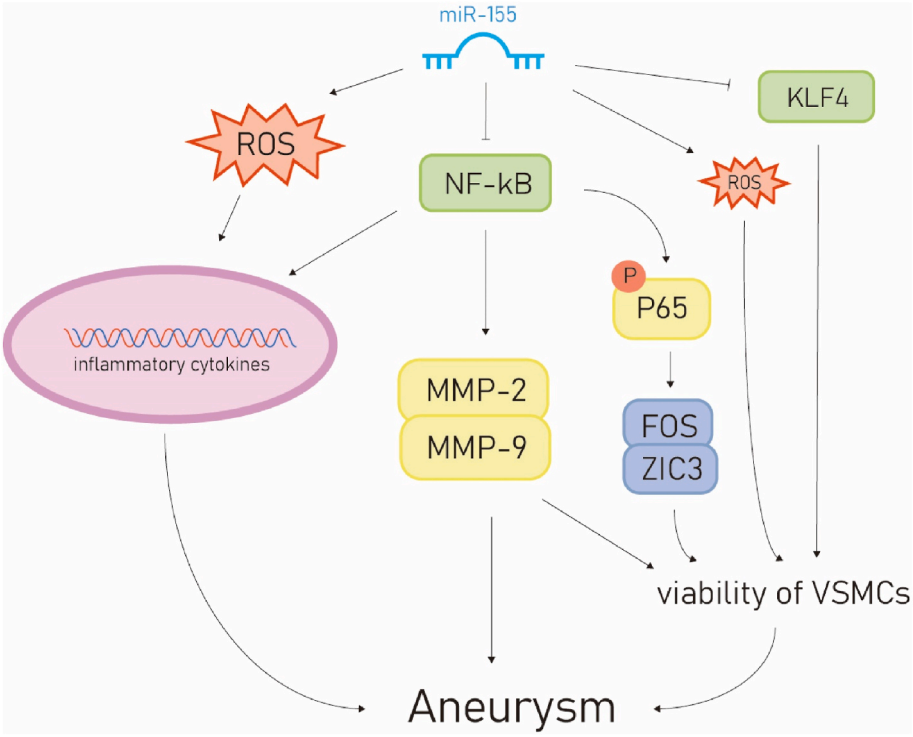

Fig. 6. Molecular Mechanisms of miR-155 in Aneurysm. Fig. 6 offers a schematic of the molecular interactions involving miR-155, which play a central role in the pathogenesis of aortic aneurysms. This visual synthesis highlights miR-155's regulatory influence on critical molecular targets such as KLF4, NF-κB, ROS, MMP-2, FOS, and ZIC3. These targets are essential in mediating the inflammatory and degenerative processes associated with aortic aneurysms.

levels of MMP2 and MMP9, which in turn, augment the risk of abdominal aortic aneurysm (AAA) rupture. Therefore, targeting miR-155, rpresents a potential therapeutic strategy to mitigate the inflammatory response and proteolytic activity associated with AAA. By modulating the activity of macrophages and the expression of MMPs, the progression of AAA may be inhibited, offering a promising avenue for intervention. Vascular smooth muscle cells (VSMCs) are integral to the vascular system, providing elastin and contributing significantly to the maintenance of vascular wall elasticity and structural stability [145]. An emerging body of research underscores the critical role of VSMCs in the development and progression of AAA [146,147]. Given the significance of VSMCs in vascular health, it is plausible that miR-155 may modulate their activity. Lei Zhao et al. [81] reported a significant upregulation of miR-155 in an induced VSMC injury model. The overexpression of miR-155 was found to target Fos and ZIC3, consequently diminishing the functionality of VSMCs. This finding suggests that the inhibition of miR-155 could potentially regulate the activity of VSMCs by affecting the expression of molecules such as Fos and ZIC3, thereby presenting a novel therapeutic target for AAA patients. Targeting miR-155 may offer a promising strategy to attenuate the pathophysiological processes underlying AAA, warranting further investigation into its clinical applicability. However, the variance in the expression of miR-155 across different aneurysm types highlights the complexity of its regulatory role in vascular pathologies. In the context of thoracic aortic aneurysm (TAA), an intriguing phenomenon occurs where there is a significant increase in the number of VSMCs expressing Kruppel-like factor 4 (KLF4), a transcription factor known to promote VSMC differentiation [148]. Concurrently, miR-155-5p exhibits notably low expression levels within TAA tissue [83]. This juxtaposition suggests a potential negative regulatory interplay between miR-155-5p and KLF4, which may be pivotal for the structural integrity of aortic wall. Further insights into the genetic predisposition to aneurysm formation are unveiled by the presence of single nucleotide polymorphisms (SNPs) within the regulatory regions of miR-155. Specifically, the SNP rs767649 within the promoter sequence of miR-155 has been associated with reduced expression levels of the miRNA. The diminished expression of miR-155, in turn, may lead to the upregulation of matrix metalloproteinase-2 (MMP-2), a key enzyme implicated in extracellular matrix degradation, thereby potentially increasing the risk of rupture in intracranial aneurysm (IA) [149]. Immune responses are recognized as integral to aneurysm development, with inflammation being a key mediator of aneurysm progression [150]. miR-155, known for its role in immune modulation, has been found to be upregulated in the context of AAA, potentially exacerbating inflammatory processes through its effects on immune cell function [142]. This highlights the multifaceted role of miR-155 in aneurysm pathogenesis, where it may contribute to the interplay between immune responses and the structural integrity of the vasculature. The diverse expression patterns of miR-155 in different aneurysm types underscore the need for a nuanced understanding of its regulatory mechanisms. The consistent theme, however, is the close association of miR-155 with the vascular elasticity and structural stability, as well as its influence on inflammatory and immune responses. These findings indicate that miR-155 may serve as a common regulatory node across various aneurysm phenotypes, reflecting a conserved role for this miRNA in vascular homeostasis. Given the current body of research, miR-155 is inextricably linked to aneurysm diseases, with evidence suggesting its involvement in multiple signaling pathways that contribute to disease progression and regulation [79,142,145]. Although the expression levels of miR-155 vary among different aneurysm types, the consensus is emerging that miR-155 holds significant potential as a novel biomarker for aneurysm development, progression, and prognosis. Future research endeavors should focus on elucidating the precise mechanisms by which miR-155 is regulated and exerts its effects in the vasculature. This knowledge may pave the way for targeted therapies aimed at modulating miR-155 levels, offering new hope for the prevention and treatment of aneurysm diseases.

4.6. miR-155-based therapeutics

Based on the emerging frontier of miRNA-based therapeutics in precision medicine, miR-155 has garnered particular attention due to its significant role in the pathophysiology of CVDs [151]. In this context, miR-155 has been identified as a key target, and although preclinical studies focusing on miR-155 may not exclusively pertain to the field of CVDs, the insights gleaned from these investigations could have profound implications for cardiovascular medicine. Cobomarsen, an inhibitor of miR-155, has demonstrated potential in the treatment of certain types of cancer, particularly in non-Hodgkin lymphoma and cutaneous T-cell lymphoma [152,153]. Research has shown that Cobomarsen can slow tumor growth, modulate survival signaling pathways, and has exhibited good tolerability and clinical activity in clinical trials, thereby confirming miR-155 as an important therapeutic target. This approach highlights the potential of miRNA-based therapies in targeting key pathways in disease pathogenesis. Although the translation of miR-155-based therapies from preclinical research to clinical practice in CVDs is still in its infancy, the success of therapies like cobomarsen in other diseases has proven the potential of miRNA-based intervention strategies. In summary, based on preclinical research and the advancements of miRNA-based therapies in other fields, the exploration of miR-155 as a therapeutic target for CVDs holds promise for the development of innovative treatment strategies. As our understanding of the role miR-155 plays in the pathophysiology of CVDs deepens, the potential of targeted therapies is also increasing, which could lead to revolutionary changes in cardiovascular medicine.

5. Conclusion and perspectives

The field of miRNA research has garnered significant attention and interest within the scientific community, with miR-155 standing out as a significant molecule of interest in cardiovascular medicine. The exploration of this tiny yet potent molecule has revealed its intricate interplay with a spectrum of CVDs, offering not only diagnostic insights but also potential therapeutic avenues. This systematic review has meticulously examined the role of miR-155 in the cardinal manifestations of HF, AF, hypertension, atherosclerosis, and aneurysms, underscoring its regulatory influence across the continuum of cardiovascular pathologies.

In the contemporary medical landscape, the diagnosis of CVD has been significantly enhanced by noninvasive diagnostic modalities such as electrocardiography and Doppler echocardiography. These methods have provided clinicians with the means to detect HF and AF with precision. However, the diagnosis of complex conditions such as coronary artery disease, atherosclerosis, and aneurysms still largely relies on invasive imaging techniques and coronary angiography. Within this context, the role of miR-155, while potentially redundant in diagnosis, shines in its therapeutic and preventive implications. Its expression levels may not alter the diagnostic landscape but offer profound significance in the mitigation and management of CVD, with its prognostic value being a fertile ground for future research. The intricate mechanisms by which miR-155 exerts its influence on cardiovascular health have not yet been fully characterized. The existing body of research hints at a complex network of interactions between miR-155 and a myriad of other molecular players within the cardiovascular system. This interplay is posited to be central to the pathogenesis of CVD, suggesting that a systems biology approach may be needed to elucidate the full extent of the regulatory role of miR-155. The elucidation of these mechanisms is expected to bring forth a more nuanced understanding of CVD, potentially leading to the development of miRNA-based therapeutics that could revolutionize patient care. In conclusion, the study of miR-155 has cast a spotlight on its potential as a biomarker and therapeutic target in cardiovascular medicine. Future research should be directed towards demystifying the molecular mechanisms underlying the influence of miR-155 on CVD, exploring its synergistic interactions with other small molecules, and assessing its prognostic significance. By surmounting these challenges, we may unlock new paradigms in the prevention, diagnosis, treatment, and prognosis of CVDs, and perhaps other pathologies, heralding a new epoch in medical science.

CRediT authorship contribution statement

Rui-Lin Zhang: Writing – review & editing, Writing – original draft, Software, Investigation, Data curation, Conceptualization. **Wei-Ming Wang:** Writing – review & editing, Investigation, Formal analysis. **Ji-Qiang Li:** Funding acquisition, Formal analysis. **Run-Wen Li:** Project administration, Formal analysis. **Jie Zhang:** Visualization, Project administration. **Ya Wu:** Writing – review & editing, Writing – original draft, Supervision, Resources, Conceptualization. **Yong Liu:** Writing – review & editing, Writing – original draft, Validation, Software, Conceptualization.

Conflicts of interest

There are no conflicts of interest.

Acknowledgements

This work was supported by the financial support from the National Natural Science Foundation of China (NO.82200432), the Natural Science Foundation of Sichuan Province of China (2024NSFSC0045), the Luzhou-Southwest Medical University cooperation project (NO.2023LZXNYDT013), the Foundation of Sichuan Provincial Medical Association (No. S23010), Southwest Medical University campus level research project (No. 2022QN070), Open Program of Nuclear Medicine and Molecular Imaging Key Laboratory of Sichuan Province (No. HYX22002), Doctoral Research Initiation Fund of Affiliated Hospital of Southwest Medical University.

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