Interpretation of the molecular mechanism and therapeutic potential of microRNA-155 in cardiovascular and cerebrovascular diseases (Review)

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Abstract. MicroRNA-155 (miR-155), a highly conserved non-coding RNA, serves a pivotal role in the initiation and progression of cardiovascular and cerebrovascular diseases (CCVDs) through the modulation of target gene expression. miR-155 contributes to the pathogenesis of conditions such as atherosclerosis, myocardial infarction, heart failure, hypertension and stroke, with mechanisms involving the regulation of endothelial function, inflammatory responses, oxidative stress, apoptosis and fibrosis. These findings suggest its potential as a biomarker. The present review provides a comprehensive overview of the biogenesis, regulation and biological functions of miR-155, highlights its molecular mechanisms in CCVD progression, and examines current advances in therapeutic strategies targeting miR-155, offering insights into the pathological mechanisms and precision treatment approaches for CCVDs.

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Abbreviations: AAA, abdominal aortic aneurysm; ABCA1, ATP binding cassette transporter A1; AGTR1, angiotensin II receptor subtype 1; ANP, atrial natriuretic peptide; AS, atherosclerosis; AT1R, angiotensin II type I receptor; BACH1, BTB domain and CNC homolog 1; BDNF, brain-derived neurotrophic factor; BIC, B-cell integration cluster; CCVD, cardiovascular and cerebrovascular disease; ceRNA, competitive endogenous RNA; CVD, cardiovascular disease; CTRP12, C1q tumor necrosis factor related protein 12; Cx43, connexin 43; CYTOR, cytoskeleton regulator RNA; DUSP14, dual specificity phosphatase 14; EC, endothelial cell; EMV, endothelial microvesicle; eNOS, endothelial nitric oxide synthase; HIF-1α, hypoxia-inducible factor 1α; HF, heart failure; IA, intracranial aneurysm; iCMP, inflammatory cardiomyopathy; I/R, ischemia-reperfusion; IRI, ischemia-reperfusion injury; IS, ischemic stroke; JAK, Janus kinase; LIN28, lineage protein 28; LXRα, liver X receptor α; MCAO, middle cerebral artery occlusion; MI, myocardial infarction; miR-155, microRNA-155; MSC, mesenchymal stem cell; NLRP3, NLR family pyrin domain containing 3; NO, nitric oxide; OGD/R, oxygen glucose deprivation/reoxygenation; PDCD4, programmed cell death 4; ROS, reactive oxygen species; SIRT1, sirtuin 1; sGCβ1, soluble guanylate cyclase β1 subunit; SOCS1, suppressor of cytokine signaling 1; TLR, toll like receptor; VSMC, vascular smooth muscle cell

Key words: miR-155, CCVDs, molecular mechanism, target, treatment

Contents

1. Introduction

Cardiovascular and cerebrovascular diseases (CCVDs), encompassing ischemic and hemorrhagic conditions affecting the heart and brain, are primarily caused by adverse lifestyle factors such as smoking, physical inactivity, poor diet, hypertension, hyperlipidemia and inadequate glycemic control (1-4). These diseases have become the leading cause of death worldwide (5,6). Coronary heart disease is the predominant type of cardiovascular disease (CVD). Additionally, conditions such as heart failure (HF), myocardial hypertrophy and myocarditis also fall under the spectrum of CVDs (7). Cerebrovascular diseases include ischemic stroke (IS) and hemorrhagic stroke (6). In China, the burden of CCVDs is particularly severe. The 2022 China Cardiovascular Health and Disease Report (8) indicated that there were ~330 million patients with CVD, with CCVDs accounting for two out of

every five deaths. The incidence is rising, particularly among individuals aged 30-50 years (9,10). CCVDs continue to pose a global health challenge, contributing to high rates of morbidity and mortality, while placing substantial medical and financial strain on healthcare systems (9). Although pharmacological and surgical interventions can improve vascular conditions, they fall short in promoting tissue regeneration and restoring function in areas affected by CCVDs (11). Thus, identifying novel therapeutic targets is crucial for the effective management of these diseases.

MicroRNA-155 (miR-155/miRNA-155) is a highly conserved non-coding single-stranded RNA encoded by the B-cell integration cluster (BIC) gene located on chromosome 21 (12). As a key member of the miRNA family, miR-155 regulates post-transcriptional processes by binding to the 3'-untranslated region (3'-UTR) of target gene mRNAs through complementary base pairing (12). As a multifunctional regulatory molecule, miR-155 is involved in a wide range of biological processes, including immune responses, inflammation, cell proliferation and apoptosis, vascular homeostasis, and tumorigenesis (13-15). Dysregulation of miR-155 expression is closely associated with the onset and progression of various pathological conditions (such as brain injury, pulmonary fibrosis and fatty liver disease) (16-18).

miR-155 serves a role in the pathogenesis and progression of CCVDs, including atherosclerosis (AS), myocardial hypertrophy, myocardial infarction (MI), ischemia-reperfusion (I/R), HF, stroke and aneurysm (19-24). The mechanisms of action of miR-155 include the regulation of inflammation, immunity, angiogenesis and other key processes (25-28). Currently, miR-155 is considered to be a promising diagnostic marker and therapeutic target for CCVDs (29-32). The present review explores the biogenesis, regulation and function of miR-155, summarizes the molecular mechanisms by which miR-155 influences the progression of various CCVDs, and examines therapeutic strategies targeting miR-155, with the aim of contributing to the understanding of CCVD pathogenesis and advancing precision treatment approaches. Compared with previous studies, to the best of our knowledge, the present review is the first to systematically integrate the dual regulatory roles of miR-155 in both CVDs and cerebrovascular diseases, elucidating its contradictory functions in processes such as inflammation and autophagy through distinct target genes [for example, endothelial nitric oxide synthase (eNOS) and suppressor of cytokine signaling 1 (SOCS1)]. The present review also compiles data on miR-155 inhibitors (such as cobomarsen) from the oncology field, exploring their cross-disciplinary therapeutic potential, and proposes an innovative biomimetic nanocarrier strategy [such as vascular cell adhesion molecule-1 (VCAM-1) antibody-modified exosomes] to address existing technological gaps in prior research.

2. Generation and regulation of miR-155

Generation of miR-155. The majority of miRNAs are generated through two primary steps: First, in the nucleus, the primary transcript (pri-miRNA) is processed by RNA polymerase II and the double-stranded RNA-binding protein complex Drosha/DiGeorge syndrome critical region gene 8 (DGCR8) to produce the miRNA precursor (pre-miRNA). Second, in the cytoplasm, the pre-miRNA is further processed by the type III RNA nuclease and the transactivation-responsive RNA-binding protein complex Dicer/TAR RNA-binding protein to generate the mature miRNA form (33). The human miR-155 gene is located within the third exon of the BIC gene on chromosome 21. The mature sequence of miR-155 is highly conserved across evolution, specifically targeting the 3'-UTR of target gene mRNAs through its seed sequence (comprising nucleotides 2-8 at the 5' end), thereby mediating post-transcriptional gene silencing or mRNA degradation (34). Argonaute protein 2 binds to the miR-155 double-stranded complex, forming the core of the RNA-induced silencing complex and producing single-stranded DNA molecules (34). The precursor miRNA hairpin has two arms that can generate biologically active mature miRNAs. The miRNA derived from the 5' arm is referred to as miR-155-5p, while that from the 3' arm is referred to as miR-155-3p. Notably, miR-155-5p exhibits higher biological activity (34) (Fig. 1). Additionally, miR-155 is expressed not only in hematopoietic cells but also in a wide range of tissues, including reproductive tissues, fibroblasts, epithelial tissues and the central nervous system (35-37).

Regulation of miR-155. miR-155 is a highly conserved miRNA, and its expression is tightly regulated at multiple levels, including transcriptional regulation, post-transcriptional modifications and epigenetic control (38-40) (Fig. 2). The physiological expression of miR-155 is essential for immune homeostasis, while pathological dysregulation contributes to the progression of various diseases, including AS, stroke and hyperlipidemia (41-43).

Regulation of transcription levels. The transcription of miR-155 primarily relies on the synergistic action of cis-regulatory sequences and trans-regulatory elements in the promoter region (12,44). Activation of toll like receptors (TLRs) or cytokines (such as TNF-α and IFN-γ) within inflammatory signaling pathways induces miR-155 expression by activating transcription factors such as NF-κB and adaptor protein complex-1 (AP-1), which directly bind to the miR-155 promoter region (38,39). In B and T cells, antigen receptor (B cell receptor/T cell receptor) signaling activates downstream transcription factors (such as STAT3) through the PI3K/AKT or MAPK pathways, promoting miR-155 expression (36,45). Additionally, the transcriptional activity of the BIC gene can be dynamically regulated by DNA methylation and histone acetylation. For example, reduced methylation of the miR-155 promoter region in tumors is closely associated with its upregulation (46).

Post-transcriptional regulation mechanism. The maturation of miR-155 involves the cleavage of pri-miR-155 to pre-miR-155 and cytoplasmic transport of pre-miR-155, a process regulated by RNA binding proteins such as KH-type splicing regulatory protein (KSRP). KSRP binds to the stem-loop structure of pri-miR-155 and recruits the Drosha-DGCR8 complex to promote the processing of pri-miR-155 into pre-miR-155 (37). Lineage protein 28 (LIN28) family proteins (LIN28A/B), as RNA-binding proteins, can selectively block the maturation of miRNAs such as let-7 by inhibiting the processing of pri-miRNAs by Drosha/Dicer complexes (47). We hypothesized that LIN28 may regulate

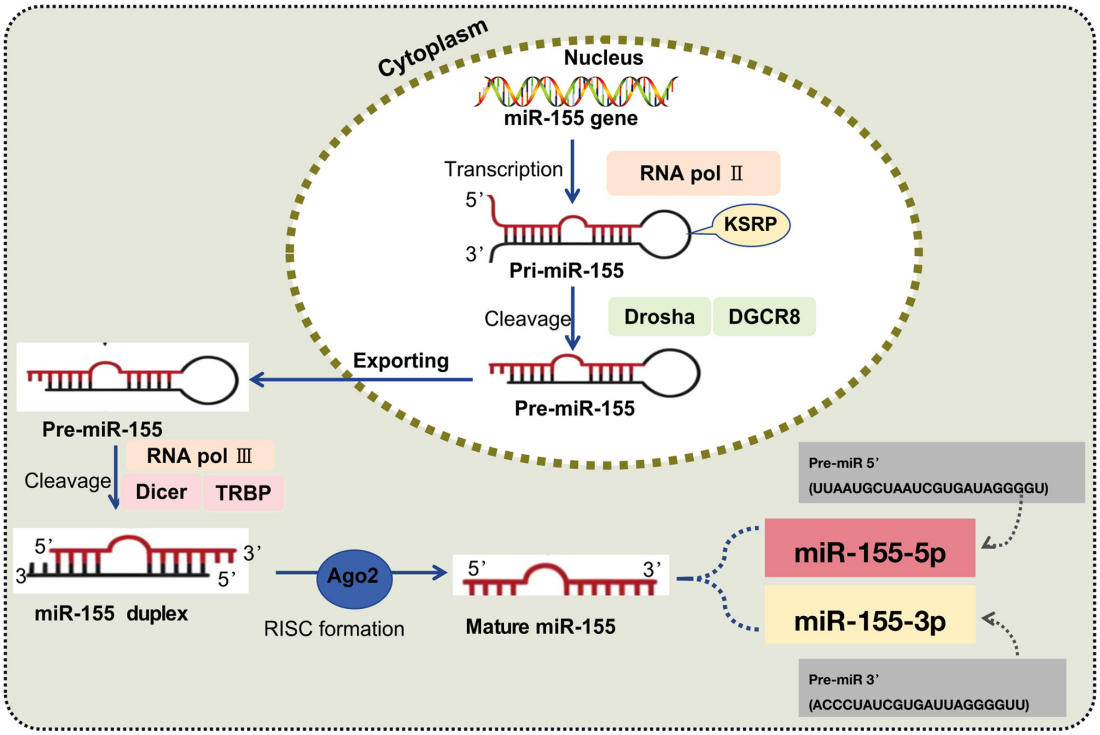

Figure 1. Generation process of miR-155. The generation of miR-155 begins in the nucleus, where the primary transcript (pri-miR-155) is processed by RNA pol II and the double-stranded RNA-binding protein complex (Drosha/DGCR8) to produce the miRNA precursor (pre-miR-155). During this process, KSRP binds to the stem-loop structure of pri-miR-155 and recruits the Drosha-DGCR8 complex to promote the processing of pri-miR-155 into pre-miR-155. In the cytoplasm, pre-miR-155 interacts with RNA pol III and the transactivation response RNA-binding protein complex (Dicer/TRBP) to form the mature miR-155. Ago2 binds to the miR-155 double-stranded complex, forming the core of the RISC and producing single-stranded DNA molecules. The two arms of the pre-miRNA hairpin, known as miR-155-5p and miR-155-3p, generate mature miRNAs with biological activity. Ago2, Argonaute protein 2; DGCR8, DiGeorge syndrome critical region gene 8; Dicer, Dicer1 ribonuclease III; Drosha, Drosha ribonuclease III; KSRP, KH-type splicing regulatory protein; miR/miRNA, microRNA; RISC, RNA-induced silencing complex; RNA pol II, RNA polymerase II; TRBP, trans-activation response element-binding protein.

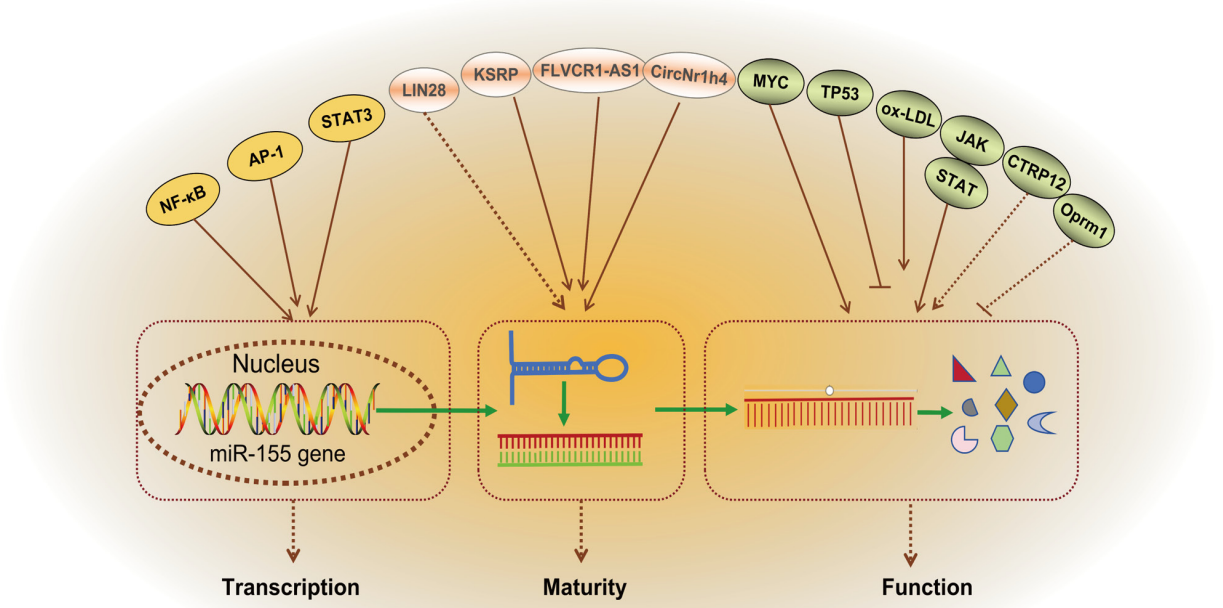

Figure 2. Regulatory process of miR-155 expression. At the transcriptional level, the expression of miR-155 is regulated by NF-κB, AP-1 and STAT3. The maturation process, involving cleavage and cytoplasmic transport from pri-miR-155 to pre-miR-155, is modulated by factors such as LIN28, KSRP, FLVCR1-AS1 and CircNr1h4. In pathological conditions, regulation by MYC, TP35, ox-LDL, JAK/STAT, CTRP12 and Oprm1 has been observed. AP-1, adaptor protein complex-1; CTRP12, C1q tumor necrosis factor related protein 12; FLVCR1-AS1, feline leukemia virus subgroup C receptor 1-antisense RNA 1; JAK, Janus kinase; KSRP, KH-type splicing regulatory protein; LIN28, lineage protein 28; miR, microRNA; Oprm1, opioid receptor Mu 1; ox-LDL, oxidized low-density lipoprotein.

miR-155 through a similar mechanism, although further research is needed to confirm this. Additionally, competitive endogenous RNAs (ceRNAs) can indirectly modulate the functional activity of miR-155 by sequestering it via the 'sponge effect'. For example, long non-coding RNAs (lncRNAs) such as feline leukemia virus subgroup C receptor 1-antisense RNA 1 can bind to miR-155, thereby reducing its inhibition of target genes (40). Lu *et al* (48) identified that circNr1h4 acted as a ceRNA interacting with miR-155-5p, subsequently influencing the pathological progression of renal damage in salt-sensitive hypertensive mouse models.

Abnormal regulation under pathological conditions. In disease environments, the expression of miR-155 is often dysregulated due to imbalanced regulatory networks (49). Specifically, the activation of cancer-related genes (such as MYC) or suppression of tumor-suppressor genes (such as TP53) within the tumor microenvironment can trigger persistently elevated levels of miR-155, enhancing cellular proliferation and metastasis (50-52). For instance, overexpression of the BIC gene increases miR-155 levels in diffuse large B-cell lymphoma (53). During chronic inflammatory conditions, sustained inflammatory stimuli [such as high levels of oxidized low-density lipoprotein (ox-LDL) in AS] maintain miR-155 expression, promoting eNOS production and exacerbating tissue damage through continuous activation of the NF-κB signaling pathway (54). Furthermore, in patients with rheumatoid arthritis, synovial fibroblasts aberrantly activate miR-155 via the Janus kinase (JAK)-STAT pathway, leading to the release of inflammatory mediators, including IL-6 and TNF-α (55). Wang *et al* (56) demonstrated that C1q tumor necrosis factor related protein 12 (CTRP12) could mitigate AS by enhancing reverse cholesterol transport and reducing vasculitis through the miR-155-5p/liver X receptor α (LXRα) pathway. However, it remains unclear whether CTRP12 directly regulates miR-155-5p (56). A study (57) utilizing cerebral I/R injury (IRI) mouse models has demonstrated that upregulated expression levels of lncRNA opioid receptor Mu 1 (Oprm1) alleviated cellular apoptosis induced by cerebral IRI via the Oprm1/miR-155/GATA binding protein 3 (GATA3) pathway. However, the direct regulatory relationship between Oprm1 and miR-155 remains undetermined (57).

3. Biological functions of miR-155

miR-155 is extensively involved in physiological and pathological processes, including immune regulation, inflammatory responses, tumorigenesis and metabolic homeostasis, by targeting the expression of downstream genes (36,38,53,54). miR-155 contributes to the development of CCVDs by regulating the expression of multiple molecules, some of which are shown in Fig. 3. miR-155 serves a critical role in both adaptive and innate immunity. One study has shown that in T cells, miR-155 targets and inhibits the protein expression of SOCS1, enhances STAT5 signaling, promotes the differentiation of T helper type 1 (Th1) and T helper type 17 (Th17) cells, and sustains the anti-infective immune response (36). In the regulation of inflammation, miR-155 is the only miRNA upregulated by macrophages in response to various inflammatory stimuli, including virus-related signals [such as the poly(I) synthetic analog of double-stranded RNA and interferons IFN-β/γ] and bacteria-related stimuli [for example, TLR ligands such as lipopolysaccharide, CpG DNA and Pam3Cys-Ser-(Lys) 4]. These stimuli activate miR-155 expression via myeloid differentiation primary response 88 (MYD88)- or Toll/IL-1 receptor domain-containing adaptor-inducing interferon-dependent TLR signaling pathways, while IFN-β/γ indirectly induces miR-155 expression through TNF-α autocrine signaling, involving TNFR1. miR-155 integrates the TLR, IFN and TNF-α signaling networks, activating transcription through the JNK/AP-1 pathway (38). miR-155 exhibits notable carcinogenic properties within the tumor microenvironment. The overexpression of miR-155 promotes tumor cell proliferation, invasion and angiogenesis by targeting and inhibiting tumor suppressor genes, such as tumor protein p53 inducible nuclear protein 1 (50,51) and SH2-containing inositol 5'-phosphatase 1 (58,59). miR-155 may also exert anticancer effects in certain solid tumors (for example, breast cancer, liver cancer and lymphoma) by inhibiting TGF-β signaling (60-63), highlighting its functional complexity.

4. Molecular mechanism of miR-155 in the pathogenesis of CCVDs

As a non-coding RNA molecule, miR-155 serves as a multidimensional regulator in the pathological processes of CCVDs. miR-155 participates in key mechanisms such as inflammation, endothelial dysfunction, oxidative stress and apoptosis by targeting the expression of downstream genes (64-68). This section will delve into the specific molecular mechanisms through which miR-155 influences the progression of CCVDs, including AS, HF, MI, hypertension, IRI, stroke and aneurysm (Tables I-III).

AS. AS represents a pathological condition characterized by inflammatory responses and lipid accumulation, serving a role in the progression of CCVDs (69). The pathogenesis of AS involves a prolonged immunological inflammatory process, initiated by various pro-inflammatory mediators interacting with multiple cell types, including endothelial cells (ECs), vascular smooth muscle cells (VSMCs) and monocytes/macrophages (25,54,70). miR-155, a versatile miRNA, is highly expressed in atherosclerotic plaques of both murine and human subjects (71), emerging as a critical molecular factor in controlling the initiation and progression of AS (Fig. 4).

ECs serve as the interface between the blood vessel wall and the bloodstream, facilitating the exchange of oxygen and nutrients between the blood and tissues (72). ECs serve a pivotal role in inflammation responses, thrombosis regulation and vascular tone modulation, directly influencing CVD progression (72). eNOS generates nitric oxide (NO), a crucial molecule for maintaining cardiovascular homeostasis. Aberrant eNOS expression is often linked to endothelial dysfunction and CVD (73,74). Sun *et al* (75) demonstrated that miR-155 directly targeted eNOS, where elevated miR-155 levels reduced eNOS expression and NO production in HUVECs, impairing acetylcholine-mediated endothelium-dependent vasodilation in human mammary arteries. miR-155 is co-expressed with the angiotensin II type I receptor (AT1R) in ECs and VSMCs. The molecular mechanism involves miR-155 binding specifically to the 3'-UTR of AT1R mRNA, inhibiting its translation,

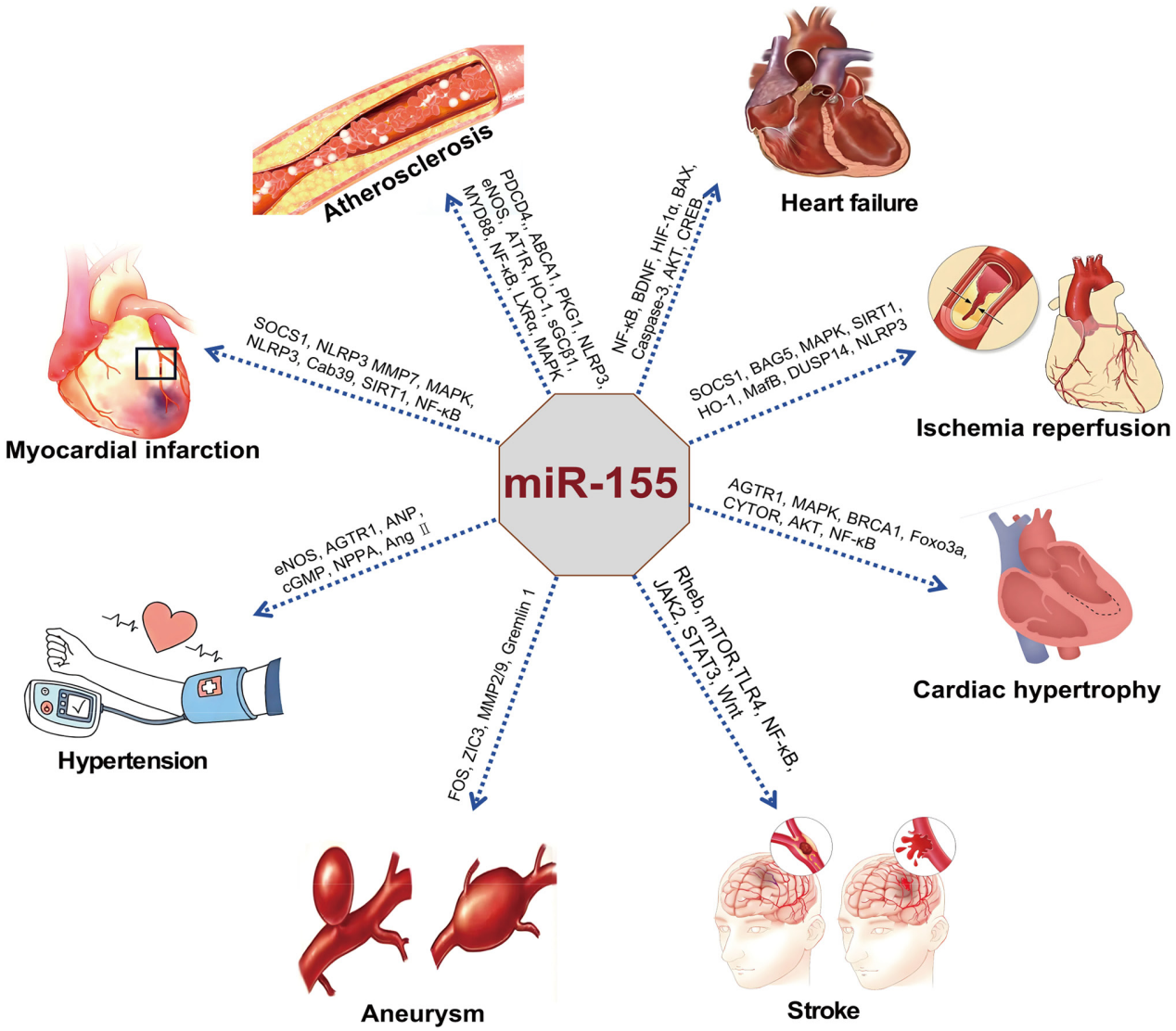

Figure 3. miR-155 participates in the development of cardiovascular and cerebrovascular diseases through interactions with multiple molecular pathways. ABCA1, ATP binding cassette transporter A1; AGTR1, angiotensin II receptor subtype 1; ANP, atrial natriuretic peptide; Ang II, angiotensin II; AT1R, angiotensin II type I receptor; BAG5, Bcl-2-associated athanogene 5; BDNF, brain-derived neurotrophic factor; Cab39, calcium binding protein 39; CREB, cAMP response element-binding protein; CYTOR, cytoskeleton regulator RNA; cGMP, cyclic 3',5'-guanosine monophosphate; DUSP14, dual specificity phosphatase 14; eNOS, endothelial nitric oxide synthase; FOS, FOS proto-oncogene; HIF-1α, hypoxia-inducible factor 1α; HO-1, heme oxygenase-1; JAK, Janus kinase; LXRα, liver X receptor α; miR-155, microRNA-155; MafB, V-Maf avian musculoaponeurotic fibrosarcoma oncogene homolog B; NPPA, natriuretic peptide A; MYD88, myeloid differentiation primary response 88; NLRP3, NLR family pyrin domain containing 3; NO, nitric oxide; PDCD4, programmed cell death 4; PKG1, protein kinase G1; Rheb, ras homolog enriched in brain; SIRT1, sirtuin 1; sGCβ1, soluble guanylate cyclase β1 subunit; SOCS1, suppressor of cytokine signaling 1; TLR4, toll like receptor 4; ZIC3, Zic family member 3.

and thus, mitigating the pathological effects of angiotensin II (Ang II) on HUVECs (76). This finding highlights the pivotal role of the miR-155-AT1R axis in vascular function regulation. EC apoptosis is a form of endothelial injury and is closely associated with the development of AS (73,74). Lee *et al* (77) demonstrated that G protein subunit α12 protected HUVECs from serum withdrawal-induced apoptosis by maintaining miR-155 expression. Additionally, another study demonstrated that overexpression of miR-155 inhibited palmitic acid-induced apoptosis, reactive oxygen species (ROS) production and inflammatory cytokine release in HUVECs by suppressing the Wnt signaling pathway (78). Endothelial autophagy, as a cytoprotective mechanism, maintains endothelial homeostasis by clearing damaged organelles and misfolded proteins, serving a critical role in preventing the onset and progression of AS (79,80). Under physiological conditions, ECs utilize autophagy to remove ox-LDL and ROS, thereby preventing lipid accumulation and inflammatory cytokine release (81). In HUVECs, ox-LDL induces autophagy and elevates miR-155 expression. Increased miR-155 levels promote autophagy, while reduced miR-155 expression suppresses autophagic activity in vascular ECs (82). Further research by Yin *et al* (83) indicated that elevated miR-155 levels enhanced ox-LDL-mediated autophagy in HUVECs by inhibiting the PI3K/AKT/mTOR signaling pathway. Metabolic abnormalities and genetic variations in homocysteine (Hcy) metabolism lead to hyperhomocysteinemia and endothelial dysfunction, which are both hallmark features of AS and key contributors to CVD (84). Research by Witucki and Jakubowski (85) demonstrated that metabolites of Hcy elevated the expression

Table I. Specific molecular mechanisms of miR-155 regulating atherosclerosis.

Disease	Mechanism	Effects on the disease	(Refs.)
Atherosclerosis	miR-155 ↑ → eNOS, NO ↓ → vasodilation ↑; miR-155 → AT1R ↓ → Ang II ↓ → EC migration ↓; miR-155 → Wnt ↓ → HUVEC apoptosis and inflammation, ROS↓; miR-155 ↑ →PI3K ↓ → AKT ↓ → mTOR ↓ → HUVEC autophagy ↑; miR-155 ↑ → TRAF6, NF-κB p5, HO-1 ↓ → inflammation ↓; miR-155 ↑ → HIF-1α ↓, E2F2 ↑ → angiogenesis ↑; miR-155 ↑ → AKT, BACH1, NoxA1-p47phox pathway ↓ → VSMC proliferation and migration ↓; ox-LDL → miR-155 ↑ → MYD88 ↓ → NF-κB ↓ → TNF, IL-6, IL-8 ↓ → inflammation ↓; CTRP12 → miR-155-5p ↓ → LXRα ↑ → ABCA1, ABCG1 ↑ → M2 type macrophages ↑ → inflammation ↓; miR-155 ↑ → MAP3K10, MAPK ↓ → inflammation ↓; miR-155 → CEH ↑ → macrophages transform into foam cells ↓	Alleviated	(41,56,75,76, 78,83,88,89,93, 94,9,99)
	TNF-α → miR-155-5p →NO↓→cGMP↓ →PKG1 ↓→VSMC vasodilation ↓; NF-κB → miR-155 → sGCβ1 ↓ → NO ↓ → VSMC vasodilation ↓; miR-155 → Bcl-6 ↓ → NF-κB ↑ → M1 type macrophages ↑ → inflammation ↑; miR-155 ↓ → SOCS1 ↓ → p-STAT, PDCD4 ↑ → IL-6, TNF-α ↑ → inflammation ↑; miR-155 ↓ → MEK ↑ → ERK ↑ → NF-κB ↑ → NLRP3 inflammasome ↑ → inflammation ↑	Aggravated	(26,54,91, 100,102)

ABCA1, ATP binding cassette transporter A1; ABCG1, ATP binding cassette transporter G1; Ang II, angiotensin II; AT1R, angiotensin II type I receptor; BACH1, BTB domain and CNC homolog 1; CEH, cholesteryl ester hydrolase; CTRP12, C1q tumor necrosis factor related protein 12; E2F2, E2F transcription factor 2; EC, endothelial cell; eNOS, endothelial nitric oxide synthase; HIF-1α, hypoxia-inducible factor 1α; HO-1, heme oxygenase-1; LXRα, liver X receptor α; miR-155, microRNA-155; MYD88, myeloid differentiation primary response 88; NLRP3, NLR family pyrin domain containing 3; NO, nitric oxide; NoxA1-p47phox, NADPH oxidase organizer 1-p47phox; ox-LDL, oxidized low-density lipoprotein; PDCD4, programmed cell death 4; PKG1, protein kinase G1; p-, phosphorylated; ROS, reactive oxygen species; sGCβ1, soluble guanylate cyclase β1 subunit; SOCS1, suppressor of cytokine signaling 1; TRAF6, TNF receptor associated factor 6; VSMC, vascular smooth muscle cell.

Table II. Specific molecular mechanisms of miR-155 regulating cardiovascular diseases.

Disease	Mechanism	Effects on the disease	(Refs.)
Myocarditis	miR-155 ↑ → NF-κB ↓ → inflammation ↓; miR-155 ↓ → Th17 ↓ → Treg ↑ → immune response ↑	Alleviated	(107,109)
	miR-155 ↓ → M1 type macrophages ↑ → inflammation ↑	Aggravated	(108)
Cardiac hypertrophy	miR-155 ↓ → AGTR1, calcium pathway ↓ → cardiac hypertrophy ↓; Rev → BRCA1 ↑ →miR-155 ↓ → FoxO3a ↑; miR-155 ↓ → CYTOR ↓ → IKKI ↑ → AKT, NF-κB ↓;	Alleviated	(115,120,121)
	miR-155 → MAPK ↑ → inflammation ↑	Aggravated	(117)
Myocardial infarction	miR-155 ↓ → M1 type macrophage, SOCS1 ↓ → NF-κB ↑ → NGF ↓; miR-155-5p ↓ → Cab39 ↓ → MAPK ↓ → MSC aging ↓; miR-155-5p ↓ → SIRT1 ↑ → NLRP3 ↓ → cardiomyocyte pyroptosis ↓; PS → miR-155-5p ↑ → HIF-1α, VEGF ↓ → angiogenesis ↑	Alleviated	(125,126, 130,131,135)
	miR-155-5p ↓ → SOCS1 ↑ → NF-κB ↓ → IL-1β, MMP7 ↓ → Cx43 degradation ↓	Aggravated	(128)
Myocardial ischemia-reperfusion	miR-155 ↓ → HIF-1α ↑ → MMP ↑ → myocardial injury ↓; miR-155 ↓ → BAG5 ↑, MAPK ↓ → JNK ↓ → cell proliferation ↑, apoptosis ↓; miR-155 ↓ → SHP2 ↑ → ERK1/2 ↓ → necroptosis ↓	Alleviated	(20,140,143)
	miR-155 ↓ → SOCS1 ↓ → ROS, inflammation ↑; miR-155-5p ↑ → JAK2 ↑ → STAT1 ↑ → inflammation ↑	Aggravated	(139,142)
Cerebral ischemia-reperfusion	miR-155 ↓ → Notch pathway ↑ → eNOS↓→ NO ↓; miR-155 ↓ → NRF2 ↑ → HO-1 ↑ → apoptosis ↓; miR-155 ↓ → MafB ↑ → IL-1β, IL-6, TNF-α ↓ → inflammation ↓; miR-155-5p ↓ → DUSP14 ↑ → TXNIP ↓ →NLRP3 ↓ → apoptosis ↓; Oprm1 ↑ → miR-155 ↓ → GATA3 ↑ → caspase-3 ↓ → apoptosis ↓; PARK7 ↑ → miR-155 ↓ → SHP1 ↑ → activation of astrocytes ↑	Alleviated	(57,65,144, 145,147,148)
	miR-155-5p ↑ → DUSP14 ↓ → NF-κB, MAPKs ↑	Aggravated	(146)
Heart failure	Sirt1 ↑ → NF-κB ↑ → miR-155 ↑ → BDNF ↑ → apoptosis ↓; miR-155 ↑ → HIF-1α ↓ → caspase-3, Bax ↓ → apoptosis ↓; Schisandrin A → miR-155 ↓ → AKT ↓ → CREB ↓ → apoptosis ↓	Alleviated	(153-155)

AGTR1, angiotensin II receptor subtype 1; BAG5, Bcl-2-associated athanogene 5; BDNF, brain-derived neurotrophic factor; CREB, cAMP response element-binding protein; Cab39, calcium-binding protein 39; Cx43, connexin 43; CYTOR, cytoskeleton regulator RNA; DUSP14, dual specificity phosphatase 14; eNOS, endothelial nitric oxide synthase; GATA3, GATA binding factor 3; HIF-1α, hypoxia-inducible factor 1α; HO-1, heme oxygenase-1; JAK, Janus kinase; MafB, V-Maf avian musculoaponeurotic fibrosarcoma oncogene homolog B; miR-155, microRNA-155; MSC, mesenchymal stem cell; NGF, nerve growth factor; NLRP3, NLR family pyrin domain containing 3; NO, nitric oxide; Nrf2, nuclear factor erythroid 2-related factor 2; Oprm1, lncRNA opioid receptor Mu 1; PARK7, parkinsonism associated deglycase; PS, phosphatidylserine; Rev, resveratrol; ROS, reactive oxygen species; SHP, Src homology 2 domain-containing protein tyrosine phosphatase; SIRT1, sirtuin 1; SOCS1, suppressor of cytokine signaling 1; Th17, T helper 17 cell; Treg, regulatory T cell; TXNIP, thioredoxin interacting protein.

Table III. Specific molecular mechanisms of miR-155 regulating hypertension, stroke and arterial aneurysm.

Disease	Mechanism	Effects on the disease	(Refs.)
Hypertension	amlodipine → miR-155 ↓ → RANK ↓ → RANKL ↓ → OPG ↑ → inflammation and endothelial dysfunction ↓; miR-155 ↓ → p27, α-SMA ↑ → intimal-medial thickness ↓; miR-155 ↑ → Cav1.2, AGTR1 ↓ → Ang II ↓ → vasoconstriction, ROS ↓; miR-155 + miR-425 → ANP, cGMP ↑ → NPPA ↓ → blood pressure ↓	Alleviated	(68,160, 163,164)
	miR-155 ↑ → eNOS, NO ↓ → endothelial dysfunction ↑	Aggravated	(75)
Stroke	miR-155 ↓ → Rheb ↑ → mTOR ↑ → p-S6K ↑ → apoptosis ↓; miR-155 ↑ → Wnt ↓ → β-catenin ↓ → Th1 ↓ → Treg ↑; OIP5-AS1 ↑ → miR-155-5p ↓ → IRF2BP2 ↑ → ROS and inflammation ↓	Alleviated	(169,172, 174)
	miR-155 ↑ → TLR4 ↑ → NF-κB ↑ → inflammation ↑	Aggravated	(170)
Arterial aneurysm	miR-155 ↓ → MMP2, MMP9 ↓ → ECM ↓	Alleviated	(24)
	miR-155-5p ↑ → FOS, ZIC3 ↓ → VSMC survival ↓; miR-155-5p ↑ → Gremlin 1 ↓ → VSMC proliferation and migration ↑	Aggravated	(178,179)

AGTR1, angiotensin II receptor subtype 1; Ang II, angiotensin II; ANP, atrial natriuretic peptide; α-SMA, α-smooth muscle actin; Cav1.2, calcium voltage-gated channel subunit α1 2; eNOS, endothelial nitric oxide synthase; ECM, extracellular matrix; FOS, FOS proto-oncogene; IRF2BP2, interferon regulatory factor 2 binding protein 2; miR, microRNA; NO, nitric oxide; NPPA, natriuretic peptide A; OIP5, Opa-interacting protein 5; OPG, osteoprotegerin; p-S6K, phosphorylated ribosomal protein S6 kinase; RANK, receptor activator of nuclear factor κ-B; RANKL, receptor activator of nuclear factor κ-B ligand; Rheb, ras homolog enriched in brain; ROS, reactive oxygen species; TLR, toll like receptor; VSMC, vascular smooth muscle cell; Th1, T helper 1 cell; Treg, regulatory T cell; ZIC3, Zic family member 3.

Figure 4. Molecular mechanisms of miR-155 in the development of atherosclerosis. The left panel illustrates the pathways through which miR-155 inhibits atherosclerosis. miR-155 suppresses PI3K, thereby inhibiting AKT and attenuating the activation of mTOR. Simultaneously, it inhibits AT1R, reducing the effects of Ang II and thereby inhibiting the progression of atherosclerosis. Additionally, miR-155 inhibits MYD88, leading to decreased NF-κB activity, and reduced production of TNF-α and IL-6/8. miR-155 also suppresses LXRα, downregulating the expression of ABCA1 and ABCG1, which impairs cholesterol reverse transport. These combined effects collectively inhibit the onset and development of atherosclerosis. The right panel depicts the pathways through which miR-155 promotes the progression of atherosclerosis. miR-155 inhibits sGCβ1, resulting in reduced NO production. miR-155 also suppresses Bcl-6, leading to increased NF-κB activity and subsequent activation of the NLRP3 inflammasome. Furthermore, miR-155 inhibits SOCS1, thereby relieving its suppression of p-STAT and PDCD4, which promotes the release of pro-inflammatory cytokines such as TNF-α and IL-6, ultimately exacerbating the progression of atherosclerosis. ABCA1, ATP binding cassette transporter A1; ABCG1, ATP binding cassette transporter G1; Ang II, angiotensin II; AT1R, angiotensin II type I receptor; LXRα, liver X receptor α; miR-155, microRNA-155; MYD88, myeloid differentiation primary response 88; NLRP3, NLR family pyrin domain containing 3; NO, nitric oxide; p-, phosphorylated; PDCD4, programmed cell death 4; sGCβ1, soluble guanylate cyclase β1 subunit; SOCS1, suppressor of cytokine signaling 1.

levels of miR-21, miR-155, miR-216 and miR-320c, which in turn reduced autophagy in human ECs, a process critical for maintaining vascular homeostasis. The stress-responsive enzyme heme oxygenase-1 (HO-1) protects cells under stress conditions and promotes endothelial anti-inflammatory and vasodilatory responses (86). Pulkkinen *et al* (87) showed that miR-155 exerted a protective effect on endothelial inflammation by reducing the translation of BTB domain and CNC homolog 1 (BACH1), which induced HO-1 expression in ECs. Another study demonstrated that both *Abelmoschus esculentus* and metformin ameliorated endothelial inflammation induced by a high-fat diet in rats through enhanced miR-155 expression, primarily by inhibiting TNF receptor associated factor 6 and NF-κB p65 activation (88). Yang *et al* (89) found that miR-155 not only regulated hypoxia-inducible factor 1α (HIF-1α) expression under hypoxic conditions but also enhanced the angiogenic potential of ECs by targeting E2F transcription factor 2. Promoting angiogenesis is a key feature of healthy ECs.

VSMCs serve a critical role in maintaining vascular function (90). A study revealed that TNF downregulated protein kinase G1 via NF-κB-dependent miR-155-5p biosynthesis, impairing the maintenance of the NO/cGMP-mediated

VSMC contractile phenotype and vasodilation (91). The NF-κB/miR-155-5p/protein kinase G axis may contribute to atherosclerotic intimal hyperplasia (91). Another study found that miR-155, induced by NF-κB, disrupted the contractile phenotype of VSMCs and inhibited NO-mediated vasodilation by downregulating soluble guanylate cyclase β1 subunit (sGCβ1) expression, leading to functional impairment of VSMCs (26). Overexpression of miR-155-5p reduces AKT1 levels by inhibiting AKT1 phosphorylation, suppressing VSMC proliferation and migration (92), as well as reducing VSMC apoptosis (71). Furthermore, overexpression of miR-155-5p alleviates oxidative stress and migration of VSMCs by inhibiting BACH1 expression (93). Notably, miR-155 has been reported to downregulate the NADPH oxidase activator 1-phagocyte oxidase protein 47-related signaling pathway in apolipoprotein E (ApoE)$^{-/-}$ mice, inhibiting VSMC migration and excessive proliferation, thereby attenuating AS progression in these mice (94).

The inflammatory process driven by macrophages serves a critical role in AS (54). ox-LDL induces distinct miR-155 expression within atherosclerotic lesions and macrophages (41,54). Huang *et al* (41) demonstrated an increase in miR-155 expression under high ox-LDL level conditions, where elevated miR-155 levels suppressed TNF, IL-6 and IL-8 production by inhibiting MYD88-dependent NF-κB pathway activation. Further investigation demonstrated that miR-155 accumulated in ox-LDL-stimulated EC-derived extracellular vesicles (EVs), which were subsequently transferred to human monocyte THP1 cells (41). These vesicles promoted monocyte activation by shifting the monocyte/macrophage balance from the anti-inflammatory M2 phenotype to the pro-inflammatory M1 phenotype (95). These studies highlighted that miR-155 serves a role in negatively regulating the inflammatory response induced by ox-LDL across various signaling pathways (41,95). CTRP12 is a conserved homolog of adiponectin, which may participate in the development of CVDs by promoting endothelial injury or the inflammatory response (23). Wang *et al* (56) demonstrated that CTRP12 reduced miR-155-5p levels, leading to increased expression of its target gene LXRα. This elevation enhanced ATP binding cassette transporter A1 (ABCA1) and ATP binding cassette transporter G1-mediated cholesterol efflux, promoting macrophage differentiation towards the M2 phenotype, suppressing inflammation and alleviating AS (56). However, one study has suggested that miR-155 may also facilitate AS development (54). Specifically, during AS progression, miR-155 enhances NF-κB pathway activation by downregulating Bcl-6 expression, thereby promoting NLRP3 activation. Bcl-6 expression amplifies the pro-inflammatory transformation of monocytes/macrophages, accelerates lipid accumulation in plaques, and contributes to the formation of an inflammatory microenvironment (54). This illustrates the multifaceted role of miR-155.

The accumulation of foam cells is a key pathological feature of AS (96). One study has shown that miR-155 inhibited foam cell formation in macrophages by promoting cholesteryl ester hydrolase expression (97). Li *et al* (98) identified elevated miR-155 levels in both plasma and atherosclerotic plaques of patients with AS. In AS animal models, the specific molecular mechanism involved TNF-α inflammatory signaling triggering NF-κB pathway activation, thereby promoting upregulation of miR-155 expression. Elevated miR-155 levels reduced chronic inflammation via a negative feedback mechanism and operated through the miR-155-calcium regulated heat stable protein 1-TNF-α signaling cascade, exerting a protective effect during foam cell formation associated with AS (98).

Vascular inflammation is a key contributor to the development of AS (69). Wu *et al* (25) demonstrated that miR-155 overexpression suppressed TNF-α-induced endothelial inflammatory responses by reducing the expression of NF-κB p65 and adhesion molecules (such as intercellular adhesion molecule-1 and VCAM-1), thereby decreasing monocyte-EC adhesion. Conversely, miR-155 inhibition enhanced p65 levels and endothelial inflammation, while p65 knockdown using small interfering RNA reversed this effect. Their study further revealed that TNF-α induced miR-155 expression, and this induction was attenuated by endogenous p65 deficiency, suggesting miR-155 may act as a negative feedback regulator to mitigate excessive inflammation triggered by TNF-α (25). Zhu *et al* (99) found that miR-155 expression was elevated in both AS mouse models and patients with coronary artery disease (CAD) compared with healthy controls. Operating within a negative feedback loop, miR-155 suppresses inflammatory cytokine production, with its expression decreasing as the condition progresses (99). Additionally, miR-155 has been shown to mediate inflammatory responses and the MAPK pathway by targeting MAP3K10 (99). Ye *et al* (100) revealed that miR-155 served dual roles in AS mouse models: It directly inhibited SOCS1 expression, while increasing phosphorylated-STAT and programmed cell death 4 (PDCD4) levels, as well as increasing the production of inflammatory mediators such as IL-6 and TNF-α. Suppression of miR-155 reduced these molecular levels of PDCD4, STAT, IL-6 and TNF-α. Therefore, it is suggested that miR-155 mediates inflammatory cytokine production in AS through the SOCS1-STAT3-PDCD4 axis (100). Furthermore, miR-155 knockout reduces CD4$^+$ T cell-induced EC apoptosis and promotes VSMC proliferation (101). By suppressing miR-155 expression, inflammation related to CD4$^+$T cells is diminished through decreased lymphocyte proliferation and altered differentiation patterns (101). Additionally, miR-155 has been shown to activate NLR family pyrin domain containing 3 (NLRP3) inflammasomes by regulating the MEK/ERK/NF-κB pathway, contributing to atherosclerotic plaque formation in ApoE$^{-/-}$ mice (102). These findings suggest that miR-155 holds promise as both a biomarker for AS and a potential target for therapeutic interventions.

Cardiomyopathy. miR-155 is a critical regulator involved in cardiac inflammation and hypertrophic responses (103-106). Bao and Lin (107) observed a marked increase in miR-155 levels in the myocardial tissue of mice with Coxsackievirus B3-induced myocarditis. Functional experiments *in vitro* showed that miR-155 mitigated myocardial damage by inhibiting the NF-κB pathway (107). Macrophage infiltration is a hallmark of viral myocarditis, and Zhang *et al* (108) found that silencing of miR-155 reduced viral myocarditis-induced cardiac damage and dysfunction by promoting macrophage M2 phenotype polarization. Additionally, inhibition of miR-155 improved experimental autoimmune myocarditis in mice by enhancing the Th17/regulatory T cell (Treg) immune response (109). These findings suggest that miR-155

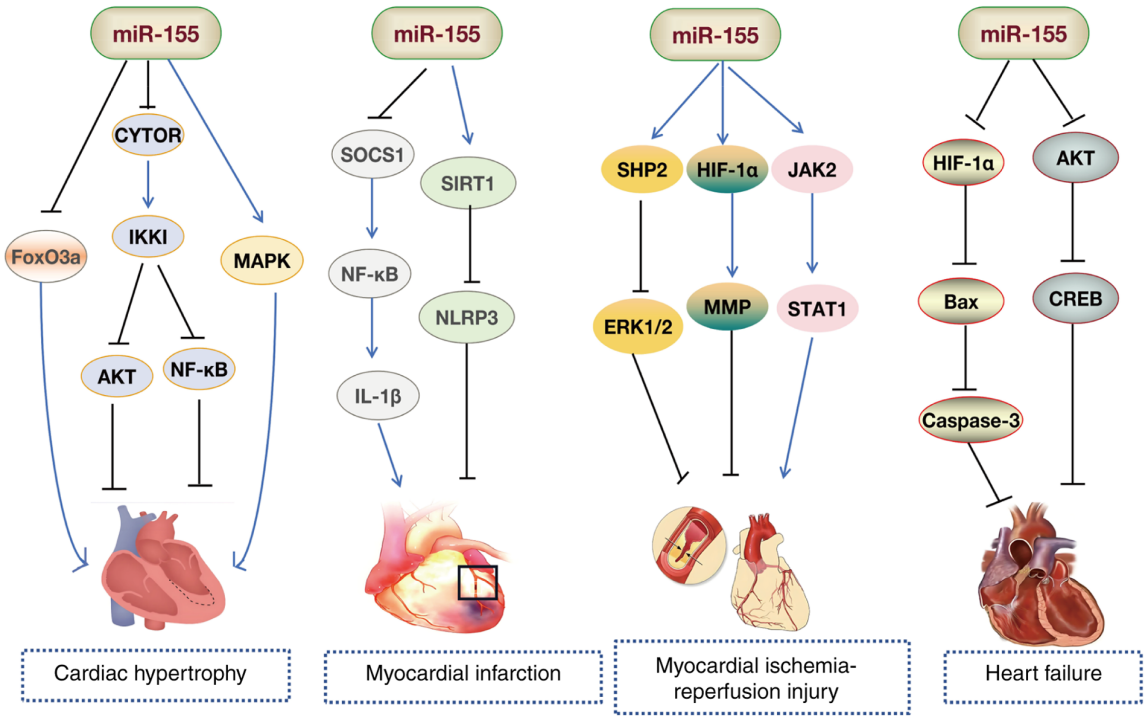

Figure 5. Molecular mechanisms of miR-155 in the development of cardiac hypertrophy, myocardial infarction, myocardial ischemia-reperfusion injury and heart failure. The left panel corresponds to cardiac hypertrophy, where miR-155 suppresses cardiac hypertrophy by inhibiting the protein expression of CYTOR, thereby promoting the activation of IKKI protein, which subsequently inhibits the protein activation of downstream AKT and NF-κB. miR-155 also promotes the development of cardiac hypertrophy by enhancing MAPK expression and inhibiting the expression of FoxO3a. The middle left panel corresponds to myocardial infarction, where miR-155 regulates SOCS1 and SIRT1. Low levels of miR-155 can inhibit SOCS1 expression. NF-κB upregulated by the inhibition of SOCS1 further regulates IL-1β, ultimately leading to myocardial infarction. SIRT1 inhibits NLRP3 expression and thereby improves myocardial infarction. Additionally, the middle right panel corresponds to myocardial ischemia-reperfusion injury, where miR-155 regulates SHP2, HIF-1α and JAK2. Elevated SHP expression inhibits ERK1/2 activation, thereby ameliorating ischemia-reperfusion injury. Concurrently, increased HIF-1α levels promote MMP expression, which likewise attenuates ischemic damage. Conversely, upregulation of JAK2 enhances STAT1 expression, consequently exacerbating the progression of ischemia-reperfusion injury. The right panel corresponds to heart failure, where miR-155 regulates HIF-1α and AKT, influencing Bax, Caspase-3 and CREB, ultimately leading to heart failure. CREB, cAMP response element-binding protein; CYTOR, cytoskeleton regulator RNA; HIF-1α, hypoxia-inducible factor 1α; JAK2, Janus kinase 2; miR-155, microRNA-155; NLRP3, NLR family pyrin domain containing 3; SHP2, SHP, Src homology 2 domain-containing protein tyrosine phosphatase; SIRT1, sirtuin 1; SOCS1, suppressor of cytokine signaling 1.

suppression could serve as an effective treatment for autoimmune myocarditis. Zhang *et al* (110) demonstrated that *Astragalus mongholicus* (Fisch.) Bge alleviated immune imbalances in peripheral Tregs in children with viral myocarditis by reducing miR-155 levels. Collectively, these studies (107-109) position miR-155 as a promising diagnostic biomarker and potential therapeutic target for cardiomyopathy.

Research has also indicated a decrease in miR-155 levels in animal and patient models of myocardial hypertrophy (111-113). Overexpression of miR-155 induces hypertrophy in H9C2 cardiomyocytes *in vitro* (114). Conversely, inhibition of miR-155 alleviates myocardial hypertrophy in H9C2 rat cardiomyocytes by downregulating angiotensin II receptor subtype 1 (AGTR1) and inhibiting the calcium signaling pathway activated by AGTR1 (115). Seok *et al* (116) found that the absence of miR-155 protected the heart from pathological cardiac hypertrophy, primarily by reducing jumonji and AT-rich interaction domain containing 2 expression. Another study revealed that EVs derived from hypertrophic cardiomyocytes activated the miR-155-mediated MAPK (ERK, JNK and p38) pathway, inducing macrophage inflammation and exacerbating myocardial cell damage (117). Studies have demonstrated that miR-155-overexpressing macrophages directly targeted and suppressed FoxO3a expression in cardiomyocytes of uremic mice via EVs, leading to reduced FoxO3a levels, which promoted cardiomyocyte pyroptosis, and exacerbated hypertrophy and fibrosis (118,119). Additionally, Fan *et al* (120) demonstrated that resveratrol, a polyphenol compound, alleviated cardiac hypertrophy and improved cardiac function by activating BRCA1 in cardiomyocytes. This mechanism involved BRCA1 activation, which suppressed miR-155 expression, thereby enhancing FoxO3a expression and reducing cardiac hypertrophy (120). Furthermore, Yuan *et al* (121) demonstrated that cytoskeleton regulator RNA (CYTOR) deletion decreased IKKI protein expression, while IKKI deficiency triggered cardiac hypertrophy via the AKT and NF-κB pathways. miR-155 suppression partially attenuated the effects of CYTOR. The authors proposed that CYTOR functions as a ceRNA for miR-155, counteracting miR-155-mediated inhibitor of nuclear factor κB kinase subunit ε suppression, thus offering protection against cardiac hypertrophy (121). These studies highlight the critical role of miR-155 in cardiac hypertrophy (117-121) (Fig. 5).

MI. MI is an acute cardiovascular event resulting from the rapid reduction or interruption of coronary blood flow, leading to ischemia, hypoxia and necrosis of myocardial cells. The primary cause is coronary atherosclerotic plaque rupture or

thrombosis (122). Plaque rupture often results from an imbalance between macrophage-mediated degradation and fibroblast repair functions (123). Wang *et al* (124) found that upregulated miR-155 was predominantly present in macrophages and fibroblasts in the damaged heart, while pri-miR-155 was exclusively expressed in macrophages. Mice deficient in miR-155 exhibited increased proliferation of cardiac fibroblasts and collagen production, along with reduced inflammation in the damaged heart (124). Notably, suppression of miR-155 reduces nerve growth factor expression by decreasing the phagocytic activity of M1 macrophages and the inflammation mediated by the SOCS1/NF-κB pathway, thereby mitigating sympathetic remodeling and ventricular arrhythmias induced by MI in mice (125,126). Pro-inflammatory macrophage-mediated degradation of connexin 43 (Cx43) serves a pivotal role in arrhythmia following MI (127). A study has demonstrated that miR-155 inhibited the downregulation of macrophage-mediated IL-1β and MMP7 expression via the SOCS1/NF-κB pathway, reducing Cx43 degradation after MI (128).

Aging impairs the function of human mesenchymal stem cells (MSCs), reducing their therapeutic potential in MI (129). Hong *et al* (130) showed that inhibition of miR-155-5p suppressed MSC aging through the Cab39/AMPK signaling pathway. This suggests that miR-155-5p could be a novel target for restoring the vitality of bone marrow MSCs and enhancing their cardioprotective effects (130). Guo *et al* (21) also found that miR-155 levels dynamically increased in the hearts of mice with MI and in neonatal rat ventricular myocytes injured by hydrogen peroxide (H_2O_2). Downregulation of miR-155 promoted apoptosis induced by MI by targeting RNA binding protein Quaking (21). Hypoxia/reoxygenation (H/R)-induced cardiomyocyte apoptosis serves a critical role in MI pathogenesis. Inhibition of miR-155-5p can prevent NLRP3 inflammasome activation by targeting sirtuin 1 (SIRT1), thus reducing H/R-induced cardiomyocyte pyroptosis (131). lncRNA XIST promotes cardiac fibroblast proliferation and extracellular matrix (ECM) accumulation by acting as a sponge for miR-155-5p, thus facilitating MI formation (132). Another study demonstrated that in a mouse model of MI with dyslipidemia, the deletion of the miR-155 gene did not reduce infarct size or chronic HF but decreased the density of myofibroblasts in ischemic scars (133). An investigation into miR-155-based therapeutic strategies has revealed that rosuvastatin potentially reduces cardiovascular events and inflammatory markers (INF-γ, TNF-α and IL-6) in patients with acute coronary syndrome by suppressing the miR-155/Src homology 2-containing inositol 5-phosphatase 1 (SHIP-1) signaling cascade (134). Furthermore, combination of American ginseng with Danshen increased the serum levels of hepatocyte growth factor and basic fibroblast growth factor in acute MI rats, enhanced myocardial microvascular density and CD31 levels, and suppressed the miR-155-5p/HIF-1α/VEGF pathway, promoting angiogenesis, compared with those in the acute myocardial infarction model group (135). These findings highlight the potential of miR-155 as a target for the treatment of MI (Fig. 5).

I/R. IRI refers to the pathological phenomenon where tissue, such as cardiac or brain tissue, experiences restored blood flow after a period of ischemia, but this restoration exacerbates cell damage (136). This process is commonly observed in vascular recanalization therapies (such as thrombolysis and percutaneous coronary intervention surgery), cardiac or cerebrovascular surgeries, and organ transplantation following acute MI or IS (137,138). IRI poses a challenge in the field of CCVDs, highlighting the urgent need for the identification of novel therapeutic targets.

Myocardial I/R. miR-155 expression increases in myocardial tissue following IRI, which is associated with elevated levels of TNF-α, IL-1β, CD105 and caspase-3, as well as enhanced leukocyte infiltration (139). Knockout of miR-155 reduces inflammatory cell recruitment and decreases ROS production in white blood cells (139). Notably, miR-155 exacerbates the inflammatory response, leukocyte infiltration and tissue damage in IRI by regulating SOCS-1-dependent ROS production (139). Chen *et al* (20) found that inhibition of miR-155 reduced the MI area by specifically regulating HIF-1α, inhibited IRI-induced cardiomyocyte apoptosis, maintained MMP levels and alleviated myocardial injury in rats. Furthermore, inhibition of miR-155 led to targeted regulation of Bcl-2-associated athanogene 5 and MAPK/JNK signaling, reducing myocardial IRI and the size of MI (140). Another study found that, in IRI mice, miR-155 was expressed at high levels, while SIRT1 expression was low. The expression levels of SIRT1, confirmed to be a target gene of miR-155, were increased following sevoflurane treatment, which reduced miR-155 levels, improved cardiac function, reduced infarct size and inhibited myocardial cell apoptosis (141). Greco *et al* (142) observed that myocardial IRI-induced EVs exhibited pro-inflammatory features, exacerbating cardiac injury. The specific molecular mechanism involved these EVs transferring miR-155-5p to macrophages, thereby enhancing the inflammatory response via activation of the JAK2/STAT1 pathway (142). This suggests that targeting EVs could be a potential therapeutic approach for the management of IRI. An investigation has demonstrated that miR-155 deletion improved cardiac ultrasound measurements in IRI mice, with reductions in MI areas, myocardial fibrosis and cellular apoptosis (including reducing the expression levels of caspase-3, caspase-4 and caspase-11) (143). Investigation of the underlying mechanism revealed that decreased miR-155 expression increased SH2 domain-containing protein tyrosine phosphatase 2 levels and alleviated IRI-induced necroptosis by suppressing ERK1/2 pathway activation (143). These findings highlight the potential of miR-155 as a key therapeutic target in the treatment of myocardial IRI (Fig. 5).

Cerebral I/R. The elimination of the miR-155 gene protects against brain injury and hemorrhagic transformation induced by I/R (142). Multiple studies have corroborated these findings. Jiang *et al* (144) found that miR-155 deficiency reduced NO production and eNOS expression by activating the Notch pathway, thereby alleviating the damage caused by cerebral I/R in mice with middle cerebral artery occlusion (MCAO). Inhibition of miR-155 increases cell viability and reduces apoptosis by targeting the nuclear factor erythroid 2-related factor 2/HO-1 pathway, preventing neuronal damage induced by cerebral I/R (65). Furthermore, downregulation of miR-155 mitigates IRI by targeting V-Maf avian musculoaponeurotic fibrosarcoma oncogene homolog B, improving the neurological function and inhibiting inflammatory responses

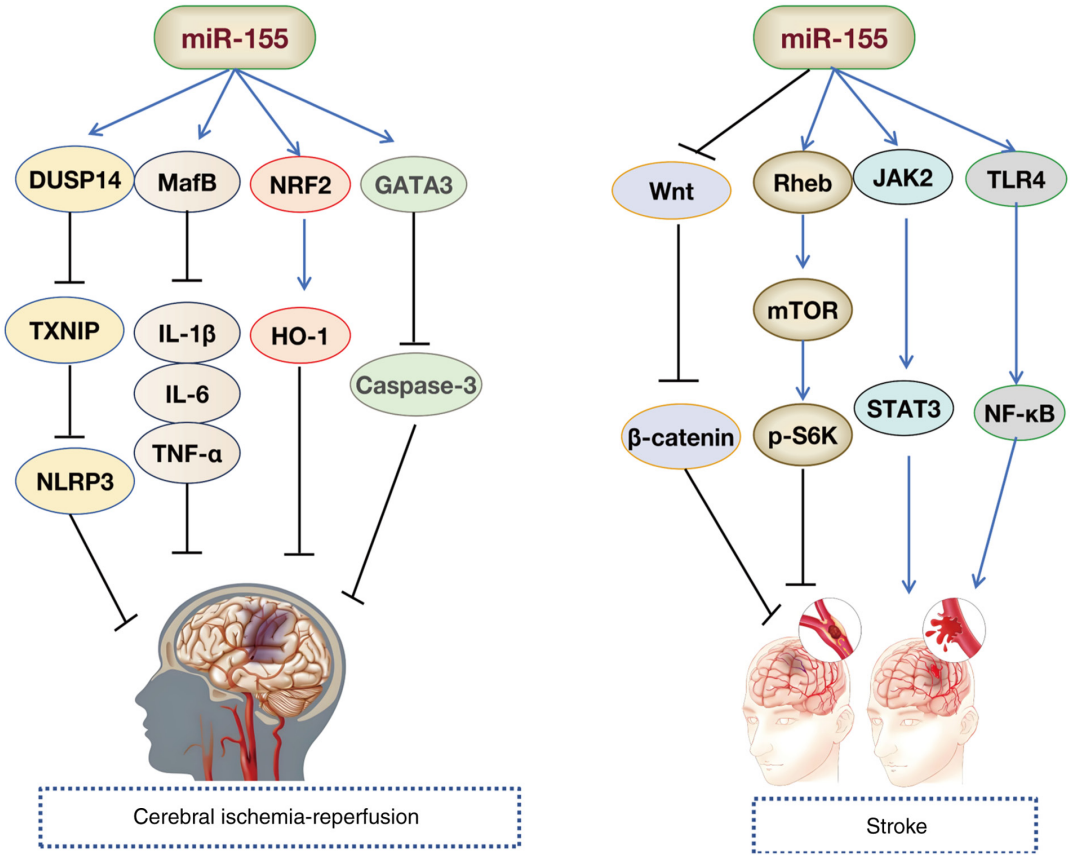

Figure 6. Molecular mechanisms of miR-155 in cerebral ischemia-reperfusion and stroke development. The left panel illustrates the regulatory pathways of miR-155 in cerebral ischemia-reperfusion. miR-155 targets DUSP14, MafB, NRF2 and GATA3: DUSP14 inhibits TXNIP, thereby influencing NLRP3; MafB suppresses pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α; NRF2 promotes HO-1 expression; and GATA3 inhibits Caspase-3, collectively participating in the regulation of cerebral ischemia-reperfusion. The right panel shows the pathways through which miR-155 mediates stroke progression. miR-155 regulates Wnt, Rheb, JAK2 and TLR4, respectively activating the β-catenin, mTOR-p-S6K, STAT3 and NF-κB pathways, thereby contributing to the pathogenesis of stroke. DUSP14, dual specificity phosphatase 14; GATA3, GATA binding protein 3; HO-1, heme oxygenase-1; JAK, Janus kinase; MafB, V-Maf avian musculoaponeurotic fibrosarcoma oncogene homolog B; miR-155, microRNA-155; NLRP3, NLR family pyrin domain containing 3; NRF2, nuclear factor erythroid 2-related factor 2; p-S6K, phosphorylated ribosomal protein S6 kinase; Rheb, Ras homolog enriched in brain; TLR4, toll like receptor 4; TXNIP, thioredoxin interacting protein.

[IL-1β, IL-6, TNF-α, inducible nitric oxide synthase (iNOS) and cyclooxygenase-2] (145). Another study also found that in MCAO/reperfusion mouse models and oxygen glucose deprivation/reoxygenation (OGD/R)-induced SH-SY5Y cells, miR-155-5p targeted dual specificity phosphatase 14 (DUSP14) by regulating the NF-κB and MAPK signaling pathways, thereby accelerating cerebral IRI (146). Suppression of miR-155-5p reduces cellular apoptosis and cerebral injury (146). Research by Shi *et al* (147) revealed that decreased miR-155-5p expression alleviated cerebral I/R-induced inflammation and cell death by modulating the DUSP14/thioredoxin interacting protein/NLRP3 signaling cascade. Notably, increased expression of lncRNA Oprm1 mitigates apoptosis following cerebral I/R damage via the Oprm1/miR-155/GATA3 regulatory axis (57). Furthermore, elevated Parkinson's disease protein 7 expression suppresses miR-155 levels, thereby enhancing SHP-1 expression and modulating astrocyte activation during cerebral IRI (148). These findings suggest potential therapeutic strategies for managing cerebral IRI (Fig. 6).

HF. HF is a clinical syndrome characterized by a decline in the pumping function of the heart, leading to an inability to meet the metabolic needs of the body, with common symptoms including dyspnea, fatigue and fluid retention (149). The etiology of HF encompasses conditions such as hypertension, coronary heart disease and cardiomyopathy (150). The underlying pathological mechanisms involve myocardial remodeling, inflammation and fibrosis (151). Li *et al* (152) utilized bioinformatics and experimental validation to investigate the potential role of miR-155 in HF. The authors found that miR-155 may regulate the viability and apoptosis of H9c2 cardiomyocytes by targeting and modulating G protein-coupled receptor 18 (152). In the same year, another study reported that in established rat and cell models of HF, overexpression of Sirt1 upregulated NF-κB p65 and miR-155, promoting brain-derived neurotrophic factor (BDNF) expression and reducing cardiomyocyte apoptosis. The authors proposed that Sirt1 alleviated HF in rats via the NF-κB p65/miR-155/BDNF signaling cascade (153). Gao *et al* (154) found that schisandrin protected rat cardiomyocytes and prevented congestive HF by regulating miR-155 expression and mediating the AKT/cAMP response element-binding protein (CREB) signaling pathway. Another study revealed that miR-155 expression was downregulated in the myocardial tissue of mice with HF. Overexpression of miR-155 inhibited

myocardial cell apoptosis (via inhibition of Bax and downstream caspase-3) through HIF-1α, reducing cardiac function damage in HF mice (155). These studies (152-154) highlight the critical role of miR-155 in myocardial protection and suggest its potential for improving cardiac function through the regulation of specific molecules (for example, HIF-1α, AKT and CREB) (Fig. 5).

Hypertension. Elevated miR-155 levels in the circulation of hypertensive patients have been found to be positively associated with inflammatory markers, indicating their involvement in the pathological process of hypertension through immune regulation (68,156). Animal models have confirmed that miR-155 deficiency alleviates perivascular inflammation and reduces blood pressure (157). Yang *et al* (68) demonstrated that levamlodipine improved vascular inflammation and endothelial dysfunction by regulating miR-155 in hypertensive rats, thereby modulating the receptor activator of nuclear factor κ-B/receptor activator of nuclear factor κ-B ligand/osteoprotegerin pathway. Additionally, studies have shown that miR-155 regulates vascular tone and endothelial-dependent vasodilation by targeting the eNOS and vascular endothelial growth factor signaling pathways (75,158). Overexpression of miR-155 can inhibit eNOS activity, reducing NO production, promoting endothelial dysfunction and contributing to hypertension development (75). VSMCs are essential for maintaining vascular function, and inflammation-induced VSMC dysfunction can also lead to hypertension (159). Park *et al* (26) found that miR-155, induced by NF-κB, downregulated sGCβ1 expression, impaired the VSMC contractile phenotype and disrupted NO induced vasodilation, leading to VSMC functional damage. Another study revealed that in the tunica media (VSMCs) of hypertensive rats, miR-155 expression was elevated. Inhibition of miR-155 reduced systolic and diastolic blood pressure, increased expression of p27 and α-smooth muscle actin (α-SMA) in the tunica media, and decreased the thickness of the tunica media. These findings suggest that miR-155 has therapeutic potential for hypertension, with its expression levels being positively associated with vascular wall thickness (160).

Ang II is a key peptide hormone in the renin-angiotensin system, serving a critical role in regulating vasoconstriction and renal sodium reabsorption (161). The physiological and pathophysiological effects of Ang II are primarily mediated through AT1R (162). Zheng *et al* (157) found that overexpression of miR-155 in cells reduced Ang II-induced α-SMA expression, suggesting that miR-155 may regulate the differentiation of rat aortic adventitia fibroblasts and inhibit AT1R expression. Additionally, research has shown that vascular mineralocorticoid receptors promote vasoconstriction and increase blood pressure with age by modulating miR-155 (163). Specifically restoring miR-155 in aged mineralocorticoid receptor-intact mice reduces calcium voltage-gated channel subunit α1 2 and AgtR1 mRNA levels, alleviating L-type calcium channel-mediated and Ang II-induced vasoconstriction and oxidative stress (163). Atrial natriuretic peptide (ANP), secreted by primary atrial myocytes, lowers blood pressure by increasing cGMP levels, inducing vasodilation, diuresis and sodium excretion (164). Vandenwijngaert *et al* (165) found that compared with individual use of miR-425 or miR-155, the combination of miR-425 and miR-155 demonstrated greater suppression of natriuretic peptide A expression and cGMP production in cardiomyocytes. These studies showed that promoting the expression of miR-155 may represent an effective strategy for regulating blood pressure in hypertensive disorders (163-165).

Stroke. Stroke is the second leading cause of death worldwide, and IS is a major subtype (166). miR-155 serves a role in the progression of IS (167,168). With ongoing research, the molecular mechanisms of miR-155 in protecting against IS are becoming clearer (Fig. 6). Xing *et al* (169) used an *in vivo* rat model of MCAO and an *in vitro* oxygen-glucose deprivation cell model to simulate IS onset. The authors found that inhibition of miR-155 could protect against IS by promoting the phosphorylation of S6K through the Ras homolog enriched in brain/mTOR pathway (169). Ischemia induces autophagy via miR-155, contributing to nerve damage (170). Yang *et al* (170) revealed that miR-155-induced autophagy altered inflammatory responses and exacerbated ischemic brain injury by regulating the TLR4/NF-κB pathway in ischemic brain tissue. Another study indicated that miR-155 worsened cellular damage in IS by activating the TLR4/MYD88 signaling pathway (22). The study by Adly Sadik *et al* (171) demonstrated that miR-155 may promote inflammatory responses post-IS by activating the JAK2/STAT3 axis. A recent study found that miR-155 inhibited the activation of Wnt/β-catenin signaling, restored the Th17/Treg balance and prevented acute IS in mice (172). These findings highlight that miR-155 is involved in multiple signaling pathways and targets in IS. Knockdown of miR-155 expression and the use of specific inhibitors to block miR-155 targets may offer a novel approach for treating IS by interrupting signaling pathway transmission. Research has shown that geniposide and ginsenoside Rg1 protect against focal cerebral ischemia in MCAO model rats by inhibiting miR-155-5p in microglia following ischemic injury (173). Additionally, Opa-interacting protein 5-AS1 inhibits oxidative stress and inflammation by regulating the miR-155-5p/interferon regulatory factor 2 binding protein 2 axis, alleviating OGD/R-induced damage in HMC3 and SH-SY5Y cells, offering a novel targeted therapeutic molecule for IS treatment (174).

Arterial aneurysm. Arterial aneurysms are typically asymptomatic in their early stages, but as the aneurysm expands, the risk of rupture increases, which can lead to fatal bleeding (175). Based on anatomical location, aneurysms are classified into abdominal aortic aneurysms (AAAs), thoracic aortic aneurysms and intracranial aneurysms (IAs) (176). miR-155 promotes macrophage infiltration by upregulating pro-inflammatory factors such as TNF-α and IL-6, suggesting that miR-155 may contribute to the inflammatory process during aneurysm development (24,177). Zhang *et al* (24) found that inhibition of miR-155 prevented AAA formation by regulating macrophage inflammation. The development of AAA was linked to the proliferation and apoptosis of VSMCs. Their study also found that overexpression of miR-155 increased the levels of MMP-2, MMP-9, iNOS and monocyte chemoattractant protein-1 in $ApoE^{-/-}$ mouse models, stimulating VSMC proliferation and migration. Another study found that

miR-155-5p expression was increased in VSMCs damaged by H_2O_2 or $NaAsO_2$. Overexpression of miR-155-5p inhibited VSMC survival and promoted aneurysm formation by targeting FOS proto-oncogene (FOS) and Zic family member 3 (ZIC3) (178). These findings suggest that miR-155 could be a therapeutic target for AAA treatment. The degradation of the ECM in blood vessels is another key factor in aneurysm formation. miR-155 enhances the activity of MMP-2/9, accelerating the degradation of collagen and elastin (24). Inhibition of miR-155 can alleviate ECM damage and delay AAA progression (24). Yang *et al* (178) found that reduced miR-155 expression increased the incidence of IA rupture by upregulating MMP-2 expression, particularly in subjects with the SNP rs767649 genotype. This SNP in the miR-155 promoter reduces its transcriptional activity, suggesting a genetic predisposition to increased aneurysm risk (178). Additionally, another study found that miR-155-5p, derived from tumor-associated macrophages, can target IA formation and macrophage infiltration induced by Gremlin1 (179). These findings highlight miR-155-5p as a potential therapeutic target for IAs.

5. Biomarker potential of miR-155 in CCVDs

miR-155, a key regulatory miRNA, serves a pivotal role in the onset and progression of CCVDs by influencing pathological and physiological processes such as inflammation, oxidative stress and apoptosis (180-182). Research has shown that miR-155 is upregulated in the blood and tissues of patients with CCVDs such as MI (183) and stroke (171), indicating its potential as an effective marker for early diagnosis and prognosis evaluation.

Li *et al* (98) measured plasma miR-155 levels in 70 patients with AS and 55 normal controls. The results revealed higher miR-155 levels in patients with AS. Reverse transcription-quantitative PCR (RT-qPCR) analysis also showed markedly elevated miR-155 expression in 17 paired atherosclerotic lesions compared with normal veins from the same patients (98). Another study examined surface marker expression and miR-155 content in urinary EVs (uEVs) from patients diagnosed with unstable (n=12) and stable (n=12) CAD (184). Compared with uEVs from patients with stable CAD, uEVs from patients with unstable CAD exhibited increased miR-155 expression. Furthermore, miR-155 levels decreased during AS regression and increased during disease progression (184), suggesting its potential as an early diagnostic and prognostic biomarker.

In a clinical study of 89 patients with inflammatory cardiomyopathy (iCMP), Obradovic *et al* (185) observed elevated plasma miR-155 levels in patients with iCMP compared with those with dilated cardiomyopathy, suggesting miR-155 as a novel biomarker for iCMP diagnosis. Previous studies have indicated a marked increase in miR-155 expression in both myocardial tissue and blood after MI, which was strongly associated with inflammatory responses (IL-17A, IL-6 and TNF-α) and myocardial injury (183,186). Notably, Wang *et al* (187) found urinary miR-155 levels to be 30-fold higher in the MI group compared with healthy individuals, suggesting urinary miR-155 as a potential non-invasive diagnostic biomarker for MI.

miR-155 levels are elevated in the myocardium of patients with HF (188) and are positively associated with worsening heart function (32,105,189). However, Ikitimur *et al* (189) observed reduced serum miR-155 levels in 42 patients with systolic HF compared with 15 healthy controls, showing a notable positive association between miR-155 and left ventricular mass index. Conversely, a study by Ding *et al* (190), involving plasma samples from 62 healthy controls and 62 patients with HF, revealed higher miR-155-5p mRNA expression in patients with HF, suggesting miR-155-5p as a potential novel diagnostic biomarker for HF and related disorders. These contrasting findings highlight the functional complexity of miR-155 in cardiovascular pathophysiology.

In terms of cerebral stroke research, Zhang *et al* (31) recruited 93 patients with IS and 70 healthy controls, reporting elevated plasma endothelial microvesicle (EMV) and EMV-miR-155 levels during the acute and subacute phases of IS, with stable levels in the chronic phase. These elevations were positively associated with both infarct volume and National Institutes of Health Stroke Scale scores (31), suggesting plasma EMVs and their carried miRNA-155 as potential biomarkers for IS. Similarly, Adly Sadik *et al* (171) analyzed peripheral serum miR-155 expression in 46 patients with acute IS, revealing an 8.5-fold increase compared with healthy controls (171).

In terms of AAA research, Kin *et al* (191) collected tissue samples from AAA walls (n=13) during repair surgery and normal aortic walls (n=7) during valve replacement. Using high-throughput miRNA arrays for expression profiling, followed by qPCR validation of differentially expressed miRNAs, the authors revealed upregulation of miR-155 in AAA tissues (191). A complementary study comparing serum samples from 10 patients with AAA repair and 10 age- and sex-matched AAA-free controls revealed markedly elevated serum miR-155 levels in patients with AAA compared with controls (192). These collective findings highlight the need for further investigation into the pathogenic role of miR-155 in AAA development and its potential as a diagnostic biomarker.

miR-155 holds promise as a biomarker for CCVDs, serving a pivotal role in their pathogenesis and progression. Alterations in miR-155 expression are strongly associated with disease severity and clinical prognosis. Quantitative detection of miR-155 expression can facilitate earlier identification of disease risk, providing a foundation for timely clinical intervention and therapeutic management (171,184,185,189). Therefore, further exploration of the mechanistic pathways of miR-155, along with the development of miR-155-based diagnostic tools and therapeutic strategies targeting miR-155, presents substantial potential for breakthroughs in the prevention and treatment of these diseases.

6. Therapies targeting miR-155

In the field of precision medicine, innovative therapies based on miRNAs are gaining increasing attention, with miR-155 standing out due to its pivotal role in the pathological and physiological processes of CVDs (19,60,193). As a critical therapeutic candidate, miR-155 has garnered interest in biomedical research. While preclinical investigations of miR-155 extend across various disciplines beyond CCVDs, the mechanistic

insights gained have considerable translational implications for the advancement of vascular medicine (13,46,58). Notably, cobomarsen, a synthetic oligonucleotide inhibitor specifically targeting miR-155, has shown therapeutic promise in oncology. Its action, validated in hematologic malignancies, demonstrates particular efficacy in managing non-Hodgkin lymphoma and cutaneous T-cell lymphoma (in a xenograft NSG mouse model of the activated B-cell subtype of diffuse large B-cell lymphoma), with ongoing clinical trials confirming favorable pharmacodynamic profiles (194,195). These studies indicate that cobomarsen can inhibit tumor growth and regulate critical signaling pathways, such as the JAK/STAT, MAPK/ERK and PI3K/AKT pathways, to exert antitumor effects (194,195). In fibrosis research, local injection of miR-155 antagonists has been shown to inhibit the Wnt/β-catenin and AKT signaling pathways, thereby reducing skin collagen deposition and improving fibrosis (196). Experiments have revealed that this antagomiR-155 targets the regulation of casein kinase 1α and SHIP-1, blocking key fibrotic pathways (196). Additionally, systemic delivery of miR-155-5p inhibitors (antigomiR-155) has been shown to reduce lipid accumulation in macrophages and reduce atherosclerotic plaque burden in ApoE$^{-/-}$ mice (197). Another study involving intravenous injection of miR-155 inhibitors starting 48 h post-distal MCAO in mice demonstrated a reduction in C-C motif chemokine ligand 3 and C-C motif chemokine ligand 12 cytokine expression after 7 days, with notable increases in IL-10, IL-4, IL-6, macrophage inflammatory protein-1α, IL-5 and IL-17 levels after 14 days (27). These findings suggest that miR-155 inhibition in stroke models alters the temporal progression of cytokine expression, potentially influencing inflammation and tissue repair following cerebral ischemia (27). Furthermore, magnetic resonance imaging examination revealed that the miR-155 inhibitor group exhibited a 34% reduction in infarct volume compared with the control group after 21 days (14.43% in controls vs. 9.5% in the inhibitor group (42). These findings highlight the potential of miRNA-based therapies in targeting key pathogenic pathways in diseases. miR-155-based therapies, in particular, hold great promise for the treatment of CVDs. With ongoing research and technological advancements, this novel approach may offer new options for the treatment of patients with CVD.

7. Conclusion and future

miR-155, a highly conserved non-coding RNA, regulates target gene expression and serves a critical role in the pathological processes of various CCVDs, including AS, MI, HF, hypertension and stroke. miR-155 is involved in mechanisms such as endothelial dysfunction, inflammation, oxidative stress, apoptosis and fibrosis. Notably, miR-155 exhibits a dual nature, exerting both pro-inflammatory and anti-inflammatory effects, depending on the specific disease context and microenvironment. Additionally, miR-155 holds promise as a diagnostic biomarker for CCVDs and represents a potential target for gene therapy. For example, cobomarsen, an anti-miR-155 oligonucleotide, has shown therapeutic efficacy in a xenograft NSG mouse model of the activated B-cell subtype of diffuse large B-cell lymphoma (195).

However, current research on miR-155 faces several challenges. Firstly, the mechanistic complexity of miR-155 remains incompletely understood. For instance, in AS, overexpression of miR-155 inhibits palmitic acid-induced apoptosis, ROS production and pro-inflammatory cytokine release in HUVECs by suppressing the Wnt signaling pathway (78), thereby mitigating the progression of AS. However, studies have also demonstrated that overexpression of miR-155-5p reduces AKT1 levels and its phosphorylation, thereby inhibiting VSMC proliferation and migration (92) while decreasing VSMC apoptosis (71), which conversely promotes AS development. Across different diseases, miR-155 exhibits functional complexity. In AS, elevated miR-155 levels enhance ox-LDL-mediated autophagy in HUVECs by inhibiting the PI3K/AKT/mTOR signaling pathway (83), thereby alleviating inflammation during AS progression. Conversely, researchers have found that overexpression of miR-155-5p promotes aneurysm formation by targeting FOS and ZIC3 to inhibit VSMC survival (178). These discrepancies may stem from the multifunctionality of its upstream and downstream genes. While multiple mRNAs have been identified as direct targets of miR-155-5p, these targets could also be regulated by other miRNAs. Furthermore, alterations in miR-155-5p may induce expression changes in associated upstream genes, such as lncRNAs and circular RNAs, potentially contributing to its differential expression patterns in the same disease. This remains a key area for future research. Secondly, validation of miR-155 target genes remains insufficient. Numerous studies have demonstrated that miR-155 can regulate the expression levels of various molecules (for example, Oprm1 and CTRP12) (23,57), but have not yet confirmed whether miR-155 directly targets and modulates their expression, with the intermediate molecules between them remaining unclear. Thirdly, animal models, predominantly murine models (such as ApoE^{-} mice), have limitations due to species-specific differences from human diseases, and clinical data are still limited. Fourthly, most clinical studies related to miR-155 have small sample sizes, which compromises the stability and reliability of the findings and makes it difficult to comprehensively and accurately reflect the true role of miR-155 in relevant diseases or physiological processes. Additionally, small-scale studies may fail to adequately account for inter-individual variations, such as variations in age, sex, ethnicity, lifestyle and underlying medical conditions, which influence miR-155 expression and function, thereby limiting the generalizability and clinical applicability of the conclusions. Lastly, therapeutic strategies targeting miR-155 are in the early stages. While cobomarsen, a miR-155 inhibitor, shows efficacy in oncology, its safety, delivery efficiency and long-term effects in CCVDs require further validation.

The proposed solutions to address these challenges primarily include: First, utilizing single-cell sequencing and spatial transcriptomics to elucidate the cell type-specific functions of miR-155, complemented by the development of humanized animal models that better replicate human disease microenvironments. Second, employing multimodal experimental validation, such as dual-luciferase assays to confirm direct binding interactions, followed by RT-qPCR and western blot analyses of target genes (such as Oprm1 and CTRP12) after miR-155 overexpression or inhibition, with subsequent validation in both cellular and animal models. Third, implementing multicenter clinical studies incorporating organoid models to

assess therapeutic efficacy and safety. Finally, phase I/II trials should prioritize high-risk CCVD populations (for example, patients with familial hypercholesterolemia) (198), integrating dynamic monitoring technologies such as fluorescent reporter genes for real-time tracking of miR-155 activity, with dosage adjustments based on circulating miR-155 levels.

Systemic regulation targeting miR-155 requires careful consideration of several key issues. First, off-target effects present significant risks: miR-155 modulates hundreds of genes (such as eNOS, SOCS1 and Bcl-6), and systemic inhibition or overexpression may disrupt physiological functions in non-target tissues, potentially causing immune dysregulation. As a key regulator of Th1/Th17 cell differentiation, miR-155 suppression could compromise anti-infective immunity and increase susceptibility to infections (172,199). Paradoxically, inhibition of miR-155 could enhance VSMC proliferation, leading to vascular stenosis or restenosis and disrupting vascular homeostasis (200). Second, delivery systems lack specificity: Current technologies, such as lipid nanoparticles or viral vectors, struggle to precisely target diseased tissues, risking hepatorenal toxicity (201,202). Third, dose-dependent toxicity may arise: miR-155 exhibits nonlinear disease associations; insufficient levels may impair anti-inflammatory effects (41), while excessive expression could promote fibrosis [for example, cardiac fibrosis (203)]. Future research should integrate single-cell sequencing and CRISPR screening to clarify cell-specific miR-155 functions and develop tissue-targeted delivery systems (such as exosomal vectors) (92,177,180,204,205). Conventional carriers, such as lipid or viral vectors, face issues such as hepatic sequestration (causing hepatotoxicity) and poor vascular barrier penetration (for example, of the blood-brain barrier) (206,207). Innovative solutions include: i) Bioinspired nanocarriers, including engineering exosomes to encapsulate miR-155 inhibitors (such as antagomirs) for degradation protection, with surface-conjugated VCAM-1 antibodies for precise binding to inflamed endothelium; ii) biomimetic membrane coatings, such as macrophage membrane-wrapped nanoparticles [for example, poly(lactide-co-glycolide)-polyethylene glycol cores loaded with inhibitors] that leverage innate chemotaxis to migrate toward lesions (such as plaques and infarcted myocardium); and iii) preclinical validation in large animal models with dynamic monitoring (such as fluorescent reporters) for real-time dose adjustments (208-210).

Despite being in the early stages of development, miRNA-based therapies demonstrate substantial potential. As of August 2025, no miRNA drugs have received global approval, although ~100 candidates are actively being investigated across therapeutic areas, including oncology, rare diseases, CVDs, metabolic diseases and inflammatory conditions (211-213). Clinical progress remains measured, with only a few candidates advancing to clinical trials. Notably, obefazimod (targeting miR-124) for ulcerative colitis achieved a 16.4% clinical remission rate in phase III trials (NCT05507216; July 2025), with the ABTECT-1 subgroup reaching a clinical remission rate of 19.3% (214). This indicates that it is a highly promising miRNA drug candidate for the future treatment of ulcerative colitis. In CVDs, CDR132L (a miR-132 inhibitor) completed a phase II trial (NCT05350969), demonstrating myocardial functional recovery in HF (215). Other notable candidates include miravirsen (miR-122 inhibitor for hepatitis C virus; phase II; NCT01200420) (216), CWT-001 (miR-29a mimic for tendinopathy; phase II; NCT06192927) and TTX-MC138 (miR-10b inhibitor for breast/pancreatic cancers; phase I; NCT06260774). However, safety concerns have stalled some pipelines. For instance, a trial investigating MRX34 (miR-34a mimic; NCT01829971) was halted due to severe immune-related adverse events and is currently under reevaluation (217), highlighting the translational challenges. No miR-155-targeted therapies have currently entered clinical trials. However, these clinical studies (214-217) strongly support the general feasibility of miRNA-based therapeutics, providing robust evidence for miR-155 as a potential therapeutic target. With deepening insights into miRNA mechanisms, future development of miR-155-specific therapies may yield breakthroughs in treating CCVDs.

In conclusion, the integration of preclinical research with emerging breakthroughs in miRNA therapeutics across diverse medical fields positions miR-155 as a promising therapeutic candidate for CCVDs. This strategic approach may pave the way for novel therapeutic interventions in cerebrovascular disease. The expanding understanding of the multifunctional regulation of miR-155 in CCVD pathophysiology has enhanced the prospects for precision-targeted therapies, potentially driving paradigm shifts in vascular medicine. As knowledge of the dual regulatory roles of this miRNA in both vascular homeostasis and disease progression deepens, rationally designed miR-155 modulators may ultimately redefine therapeutic standards for complex cerebrovascular conditions.

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Authors' contributions

PW contributed to the conception and design, and critically revised the manuscript. XZ was responsible for conceptualization, validation and writing the original draft of the manuscript.

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Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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