International Journal of General Medicine

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

CircRNA Networks in CAD: Multi-Cellular Mechanisms and Clinical Potential

Huan Cheng[1], Xinyu Wu[2], Jingru Li[1], Luqiao Wang[1]

[1]Department of Cardiology, The First Affiliated Hospital of Kunming Medical University, Kunming, Yunnan, 650032, People's Republic of China; [2]Department of Cardiology, Zhumadian City Central Hospital, Zhumadian, Henan, 463000, People's Republic of China

Correspondence: Luqiao Wang, Department of Cardiology, the First Affiliated Hospital of Kunming Medical University, Kunming, Yunnan, 650032, People's Republic of China, Tel +86-15887099143, Email wlq8360@163.com

Abstract: Coronary artery disease (CAD), is a global cardiovascular disease that is characterized by myocardial ischemia and hypoxia caused by coronary artery occlusion. Circular RNAs (CircRNAs) is a particular kind of endogenous non-coding RNA, which can affect the occurrence and development of CAD. Concurrently, several circRNAs display stable persistence in CAD patients, attributable to their exceptional exonuclease resistance, thereby harboring the capacity to evolve into a biomarker for CAD diagnosis and prognosis. This article endeavors to clarify the pivotal role of circRNAs in the intricate pathophysiological processes underlying CAD patients or CAD disease models based on their unique biological characteristics and functionalities, and further discuss their prospects in clinical applications of CAD.

Keywords: anti-nuclease activity, endothelial cells, vascular smooth muscle cells; myocardial cells; cardiac fibroblasts, diagnostic biomarkers

Introduction

Coronary artery disease (CAD) remains one of the leading causes of global morbidity and mortality, characterized by myocardial ischemia and hypoxia resulting from the narrowing or occlusion of coronary arteries. Based on its distinct onset characteristics and treatment principles, it is categorized into six main types: stable angina, unstable angina, ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), sudden cardiac death, and ischemic cardiomyopathy.[1] Despite significant advances in therapeutic approaches, early diagnosis and improved prognosis remain the central challenges in CAD management. Although traditional biomarkers (eg, troponin, creatine kinase) are widely used for CAD diagnosis, they still exhibit limitations, including insufficient sensitivity and specificity, as well as the inability to dynamically assess plaque stability or disease progression.[2]

CircRNAs represent a class of endogenous non-coding RNAs characterized by their unique closed circular structure, capable of modulating gene expression in eukaryotic cells.[3] Their distinctive functional mechanisms include acting as miRNA sponges, binding to proteins, and participating in translation processes. Compared with other non-coding RNAs, circRNAs exhibit superior resistance to nuclease degradation, conferring enhanced cellular stability that renders them particularly suitable as long-acting regulatory molecules.[4]

In recent years, research on circRNAs in coronary artery disease (CAD) has gradually gained attention. At the mechanistic level, circRNAs have been identified as key regulators in CAD. Particularly in cardiovascular cells associated with CAD, circRNAs can precisely modulate critical pathophysiological processes—such as vascular endothelial function and phenotypic switching of smooth muscle cells—by acting as competing endogenous RNAs (ceRNAs) or directly interacting with proteins. Consequently, they influence atherosclerotic plaque stability, vascular remodeling, and inflammatory responses.[5–7] These findings not only deepen our understanding of CAD pathogenesis but also provide a theoretical foundation for developing circRNA-targeted therapies. Moreover, compared with healthy individuals, CAD patients exhibit significantly differential expression of circRNAs in peripheral blood. Owing to their

Received: 21 February 2025
Accepted: 26 May 2025
Published: 12 June 2025

superior stability and cell-type-specific expression patterns, circRNAs demonstrate unique advantages over conventional biomarkers (eg, troponin, creatine kinase isoenzymes) in the early diagnosis and disease stratification of CAD, suggesting their potential as alternative diagnostic biomarkers for CAD.[8]

Through established literature inclusion criteria, this review screened extensive publications to elucidate the molecular mechanisms and biological functions of circRNAs in CAD pathogenesis. These rigorous screening criteria represent a key innovative feature of our review. Compared to previous studies, this paper aims to comprehensively explore the molecular mechanisms of circRNAs in CAD from the pathophysiological perspective of cardiovascular cells, with particular emphasis on the functional characteristics conferred by their circular structure (such as miRNA sponge effects and protein decoy functions, among others). Based on these unique biological characteristics—the key advantages that distinguish circRNAs from traditional biomarkers—we further evaluate their clinical translational potential as novel diagnostic markers and RNA-based therapeutic targets, thereby providing a theoretical foundation for developing breakthrough diagnostic and therapeutic strategies for CAD.

Coronary Artery Disease

Coronary artery disease (CAD), as one of the most prevalent cardiovascular diseases worldwide, has a complex pathogenesis involving the interplay of endothelial dysfunction, lipid deposition, inflammatory responses, and the proliferation and migration of vascular smooth muscle cells (VSMCs). Atherosclerosis (AS) is the core pathological process of CAD, initiated by endothelial injury induced by various factors.[9] In this process, oxidative stress and inflammatory factors upregulate the expression of endothelial cell adhesion molecules (VCAM-1/ICAM-1), promoting monocyte infiltration and their differentiation into macrophages. These macrophages then engulf oxidized low-density lipoprotein (ox-LDL) to form foam cells, which constitute the early lipid core of atherosclerotic plaques.[10–12] As the lesion progresses, VSMCs proliferate and migrate into the intima, forming a fibrous cap to stabilize the plaque.[13] When the plaque ruptures, exposed prothrombotic substances can trigger thrombosis, leading to acute coronary occlusion and subsequently inducing myocardial infarction (MI).[14] Recent studies have revealed that ferroptosis plays a critical role in ischemic myocardial injury, and targeted regulation of glutathione peroxidase 4 (GPX4) may represent a potential therapeutic strategy.[15] Furthermore, although reperfusion therapy can restore blood flow, it may exacerbate oxidative stress and inflammatory responses, further contributing to myocardial ischemia-reperfusion injury (MI/RI). The underlying mechanisms include ROS burst-induced oxidative stress and NLRP3 inflammasome activation, which promotes IL-1β release and exacerbates inflammatory responses.[16] Current research focuses on targeting these related pathways to identify novel biomarkers and therapeutic targets for MI/RI, with certain molecules already demonstrating clinical translation potential. Current research hotspots also include the roles of non-coding RNAs (eg, lncRNA, circRNA, miRNA) and gut microbiota metabolites in CAD, offering novel avenues for disease diagnosis and therapeutic development.[7,17,18]

CircRNAs

As an emerging non-coding RNA, the biogenesis of circRNAs mainly relies on the reverse splicing of mRNA precursors, a splicing process different from conventional linear mRNA precursors.[19] During this process, an enclosed circular structure is formed when the downstream and upstream splice sites (connecting the 3'and 5' ends) unite.[20] This process is influenced by multiple factors, including RNA binding proteins (RBPs), cis-acting elements, and other non-coding RNAs.[21,22]

The essential role of circRNAs is becoming more and more clear with the continuous advancement of circRNA-related research. It mainly includes the following aspects: First of all, by influencing processes like DNA methylation or histone modification, circRNAs may control the expression of genes.[23–25] Secondly, circRNAs can bind to specific proteins, affecting their function and localization, thereby regulating intracellular signaling pathways.[26] Meanwhile, certain circRNAs have also been identified as functioning as protein scaffolds to participate in cellular biological processes. For example, Ding F et al demonstrated that circHIPK3 functions as a protein scaffold, facilitating the interaction between the E3 ubiquitin ligase β-TrCP and HuR within the cytoplasm. This interaction promotes the ubiquitination and subsequent degradation of HuR, which plays a role in mitigating heart aging.[27] Thirdly, some circRNAs (eg, circFGFR1, circSfl, and circZNF609, etc). m6A modification sites or internal ribosomal entry sites (IRES) can directly initiate translation processes and produce proteins or peptides, and this process is particularly

prominent during cellular stress,[28–31] they may directly affect the protein composition of cells in diseases. However, it is worth noting that compared to traditional mRNA translation efficiency, the translation of circRNAs is relatively inefficient.[32] Although previous studies have demonstrated the presence of circRNA-translated proteins in tissues or cells of human hearts and mice, these results still need further verification with stricter quality control and false discovery rate indicators,[33] the idea of circRNAs acting as an effective protein template remains controversial. Ultimately, by sponging miRNAs, circRNAs may prevent the expression of miRNAs, impacting critical processes like autophagy, apoptosis, and inflammation.[34] This functional mechanism, which is one of the crucial links in the onset and progression of CAD disease, will be emphasized and thoroughly explored in this work.

The degradation mechanism of circRNAs is relatively complex and needs more study to reveal its internal laws. The unique closed-loop structure of circRNAs gives them the ability to resist exonucleases (such as RNase R). However, through some specific pathways, we can still effectively regulate the circRNA degradation processes. Studies have shown that some endonucleases (such as RNase L and RNase H1) are essential for the degradation of circRNAs. RNase H1 has been reported to act on the R loop formed by circRNA ciankrd52 and DNA to trigger the degradation of ciankrd52.[35] Partial circRNAs can be extensively degraded by RNase L under the conditions of inflammation or infection.[36] In addition, certain specific binding proteins may also guide circRNA degradation, for example, Ago 2 promotes the degradation of specific circRNA by interacting with miR-671 and miR-1224.[37,38] At the same time, the m6A modification uncovers the degradation process of circRNA by engaging with YTHDF2 and HRSP12, as well as through the RNase P/MRP pathway.[39,40]

CircRNAs Regulate the Pathophysiological Processes of Cardiovascular Cells

We conducted a systematic literature search in PubMed using the following search strategy: ("Coronary Artery Disease" OR "CAD" OR "coronary atherosclerosis" OR "Myocardial Infarction" OR "Myocardial Ischemia reperfusion injury") AND ("RNA, Circular" OR "circRNA" OR "circular RNA") to identify relevant literature. The inclusion criteria for literature were: 1) publications between 2019–2024; 2) clinical studies or basic research (cellular or animal experiments) with definitive functional evidence; 3) cell lines including cardiomyocytes, vascular endothelial cells, vascular smooth muscle cells, and cardiac fibroblasts. After screening, a total of 107 CAD-related circRNAs were ultimately identified from 134 articles. The included literature provides reliable evidence for elucidating the molecular mechanisms of circRNAs in CAD. We conducted a systematic analysis of these research findings, with a focus on exploring the regulatory networks of circRNAs in different cardiovascular cell types and evaluating their potential for clinical translation.

Vascular Endothelial Cells

Endothelial dysfunction is a key initiating factor in CAD, and endothelial cells (ECs) play a crucial role in maintaining vascular health. They not only regulate vascular tension but also release contractile and thrombotic factors during injury.[41] Specific circRNAs, as sponges of miRNAs, can cause endothelial dysfunction and early atherosclerosis by reversing the inhibition of miRNAs on the expression of vasodilation-related mRNA. circROBO2 was demonstrated by Qinghu Ye et al to be greatly upregulated in cardiac microvascular endothelial cells (CMECs) induced by ox-LDL, and it could positively regulate TRIM14 through sponge miR-186-5p, thereby restraining angiogenesis and cell proliferation, promoting CMEC apoptosis, and contributing to the occurrence of coronary atherosclerosis.[42] In contrast, NGS and functional assays have demonstrated that circMBOAT2 promotes angiogenesis via the miR-495/NOTCH1 axis, exerting protective effects on vascular repair following MI/RI.[43] It can be seen that by modulating the pathophysiological processes of ECs, circRNAs have a significant impact on the progression and prognosis of CAD. Of course, in addition to the aforementioned circRNAs, more circRNAs have been revealed to play vital functions in the pathophysiological mechanisms of ECs through in vivo or in vitro experiments in recent years. The mechanistic studies of circRNAs summarized in Table 1 have all been validated through functional assays.

Table 1 Summary of circRNAs Related to the Pathophysiological Processes of Endothelial Cells in CAD

CircRNAs	Expression	Species	Cell lines	Mechanism	Pathophysiological Processes	Effection	Validation method	Ref
CircZBTB46	Up-regulated	Mice	HCAEC	hnRNPA2B1 /PTEN / AKT/mTOR	Apoptosis ↓ Proliferation ↑ Migration ↑	Promotes AS	Functional (in vitro/vivo)	[6]
Circ_100338	Down-regulated	-	HUVEC	miR-200a-3p /FUS	Proliferation ↑ Migration↑ Tube formation ↑	Inhibits MI/ RI	Functional (in vitro)	[44]
CircROBO2	Up-regulated	Human	CMEC	miR-186-5p /TRIM14	Apoptosis ↑ Tube formation ↓ Proliferation ↓	Promotes AS	Functional (in vitro)	[42]
Circ_0049979	Down-regulated	Mice	HUVEC	miR-653 /Cx43	Proliferation ↑ Migration↑ Tube formation ↑	Inhibits AS	Functional (in vitro/vivo)	[45]
Circ_0004104	Up-regulated	Human	VEC	miR-100 /TNFAIP8	Proliferation ↓ Apoptosis ↑ Inflammation ↑	Promotes AS	Functional (in vitro)	[46]
Circ_0001445	Down-regulated	Human	HAEC	miR-208b-5p /ABCG1	Proliferation ↑ Migration↑ Inflammation ↓	Inhibits AS	Functional (in vitro)	[47]
CircFASTKD1	Up-regulated	Mice	HUVEC/ HCMEC	miR-106a /LATS1/2	Tube formation ↓ Migration↓	Promotes MI	Functional (in vitro/vivo)	[48]
CircHECW2	Up-regulated	Human	HCMEC	miR-942-5p/TLR4	Proliferation ↓ Tube formation ↓ Apoptosis ↑	Promotes AS	Functional (in vitro)	[49]
Circ_0030042	Down-regulated	Mice	HUVEC	Sponges eIF4A3	Autophagy ↓	Promotes AS	Functional (in vitro/vivo)	[50]
CircANRIL	Up-regulated	Rats	EC	-	Oxidative stress ↑ Inflammation ↑	Promotes AS	Functional (in vitro/vivo)	[51]
CircFndc3b	Down-regulated	Mice	HUVEC/ MCEC	FUS/VEGFA	Tube formation ↑ Migration ↑ Proliferation ↑	Inhibits MI	Microarray + Functional (in vivo)	[52]
CircMBOAT2	Up-regulated	Human	HUVEC	miR-495 /NOTCH1	Tube formation ↑ Migration ↑	Promotes ANG	NGS+ Functional (in vitro/vivo)	[43]
CircDLGAP4	Down-regulated	Mice	HUVEC	miR-143 /HECTD1	Apoptosis ↓ Migration ↓.	Inhibits MI/ RI	Functional (in vitro/vivo)	[53]
CircHIPK3	Down-regulated	Mice	HCAEC	miR-133a /CTGF	Tube formation ↑ Migration ↑ Proliferation ↑	Inhibits MI	Functional (in vitro)	[54]
CircWhsc1	Up-regulated	Mice/ Rats	NCEC	TRIM59 /STAT3 /cyclin B2	Proliferation ↑	Inhibits MI	Functional (in vitro/vivo)	[55]
CircERBB2IP	Up-regulated	Mice	CMEC	miR-145a-5p /Smad5	Tube formation ↑ Migration ↑ Proliferation ↑	Inhibits MI	Functional (in vitro/vivo)	[56]
Circ_0001785	Down-regulated	Human/ Mice	HUVEC	miR-513a-5p /TGFBR3	Proliferation ↑ Apoptosis ↓ Migration ↓	Inhibits AS	Functional (in vitro/vivo)	[57]
Circ_0001445	Down-regulated	-	HUVEC	SRSF1/β-cate	Tube formation ↑ Proliferation ↑ Apoptosis ↓ Migration ↓	Inhibits AS	Functional (in vitro)	[58]

(*Continued*)

Table 1 (Continued).

CircRNAs	Expression	Species	Cell lines	Mechanism	Pathophysiological Processes	Effection	Validation method	Ref
Circ_0007623	Up-regulated	Mice	HUVEC	miR-297 /VEGFA	Tube formation ↑ Migration ↑ Proliferation ↑ Apoptosis ↓	Inhibits MI	Functional (in vitro/vivo)	[59]

Abbreviations: HCAEC, Human coronary artery endothelial cell; EC, Endothelial cell; CMEC, Cardiac microvascular endothelial cell; HUVEC, Human umbilical vein endothelial cell; VEC, Vascular endothelial cell; HAEC, Human aortic endothelial cell; HCMEC, Human cardiac microvascular endothelial cell; MCEC, Mouse cardiac endothelial cell; NCEC, Neonatal cardiac endothelial cell; AS, Atherosclerosis; MI/RI, Myocardial ischemia reperfusion injury; MI, myocardial infarction; ANG, Angiogenesis; CAD, Coronary artery disease; ↑, Promotes; ↓, Inhibits.

Vascular Smooth Muscle Cells

The changes that occur in vascular smooth muscle cells (VSMCs) structure and function are the cytopathological basis for the formation and progression of atherosclerotic plaque in CAD. Regulating the biological functions of VSMCs can effectively intervene in the evolution of CAD.[60] Based on the functionally validated circRNAs summarized in Table 2

Table 2 Summary of circRNAs Related to the Pathophysiological Processes of Vascular Smooth Muscle Cells in CAD

CircRNAs	Expression	Species	Cell lines	Mechanism	Pathophysiological processes	Effection	Validation method	Ref
CircZBTB46	Up-regulated	Mice	HCASMC	hnRNPA2B1/PTEN/AKT/mTOR	Apoptosis ↓ Proliferation ↑ Migration ↑	Promotes AS	Functional (in vitro/vivo)	[6]
Circ_0031891	Up-regulated	Human	HA-VSMC	miR-579-3p /HMGB1	Dedifferentiation ↑ Proliferation ↑ Migration ↑	Promotes AS	Functional (in vivo)	[61]
CircRUSC2	Up-regulated	-	HCASMC	miR-661 /SYK	Proliferation ↑ Migration ↑ Apoptosis ↓	Promotes AS	Functional (in vitro)	[62]
CircDHCR24	Up-regulated	-	HA-VSMC	miR-149-5p /MMP9	Proliferation ↑ Migration ↑	Promotes *RS*	Microarray + Functional (in vitro)	[63]
CircROBO2	Up-regulated	Human	HASMC	miR-149 /TRAF6 /NF-κB	Proliferation ↑ Migration ↑ Apoptosis ↓	Promotes AS	Microarray + Functional (in vitro)	[64]
Circ_0006251	Up-regulated	-	VSMC	miR-361-3p /TET3 /PPM1B	Proliferation ↑ Migration ↑ Apoptosis ↓	Promotes AS	Functional (in vitro)	[65]
CircMAP3K5	Down-regulated	Human/ Mice	HCASMC / MASMC	miR-22-3p /TET2	Dedifferentiation ↓ Proliferation ↓	Inhibits AS	NGS + Functional (in vivo)	[66]
CircLDLR	Down-regulated	Human	HA-VSMC	miR-26-5p /KDM6A	Apoptosis ↑ Proliferation ↓	Inhibits AS	Functional (in vitro)	[67]
CircZCEBPZOS	Down-regulated	Human/ Mice	VSMC	miR-1178-3p /PDPK1	Proliferation ↑ Migration ↑ Tube formation ↑	Inhibits MI	Functional (in vitro/vivo)	[68]
CircTEX14	Down-regulated	Human	HA-VSMC	miR-6509-3p /THAP1	Migration ↓ Proliferation ↓	Inhibits AS	Functional (in vitro)	[69]
Circ_0000280	Down-regulated	Human	HASMC	ELAVL1	Proliferation ↓	Inhibits AS	NGS + Functional (in vitro)	[70]
CircTOP1	Up-regulated	Mice	VSMC	PTBP1	Transdifferentiation ↑	Promotes CAC	NGS + Functional (in vitro/ vivo)	[71]

Abbreviations: HCASMC, Human coronary artery smooth muscle cell; HA-VSMC, Human aortic vascular smooth muscle cell; HASMC, Human aortic smooth muscle cell; VSMC, Vascular smooth muscle cell; MASMC, Mouse aortic smooth muscle cell; AS, Atherosclerosis; RS, Restenosis; MI, Myocardial infarction; CAC, Coronary artery calcification; CAD, Coronary artery disease; ↑, Promotes; ↓, Inhibits.

that have been assessed in VSMCs, current research has primarily identified two functionally opposing categories of circRNAs at the VSMC level. Hsa_circ_0031891, circRUSC2, circDHCR24, circROBO2, and circ_0006251 have been confirmed to be significantly upregulated in VSMCs, These circRNAs serve as sponges for miRNA, modulating the expression of downstream genes and promoting the proliferation and migration of VSMCs, thereby accelerating the progression of AS.[61–65] On the other hand, the expression of circMAP3K5, circLDLR, circZCEBPZOS and circTEX14 in VSMCs showed a downregulation trend. The overexpression of these circRNAs could significantly inhibit the proliferation, migration and dedifferentiation process of VSMCs, thus slowing down the progression of AS.[66–69] It is worth noting that the currently revealed regulation mechanism of CircZBTB46 in the proliferation, migration and apoptosis of VSMCs is achieved through AK/mTOR signaling pathway mediating hnRNPA2B1 ubiquitination and degradation, while the impact of hsa_circ_0000280 on VSMC proliferation in CAD is reliant on the regulation of ELAVL1 expression, none of these processes are dependent on circRNA-miRNA-mRNA network.[6,70]

Cardiomyocytes

Myocardial infarction (MI) is a typical manifestation of CAD, and its resulting MI/RI is important for the progression and prognosis of CAD. Under CAD-related pathological conditions (such as I/R injury), circRNAs can regulate the proliferation, differentiation, apoptosis, and inflammation of cardiomyocytes (CMs), and playing a role in myocardial protection, remodeling, and angiogenesis in the progression of CAD. Current studies have identified numerous circRNAs that play pivotal roles in MI and MI/RI within CMs. As summarized in Table 3, a total of 95 relevant circRNAs have

Table 3 Summary of circRNAs Associated with the Pathophysiological Processes of Cardiomyocytes in CAD

CircRNAs	Expression	Species	Cell Lines	Mechanism	Pathophysiological Processes	Effection	Validation Method	Ref
CircHIPK3	Up-regulated	-	HCM	miR-124-3p	Proliferation ↓ Apoptosis ↑	Promotes MI/RI	Functional (in vitro)	[72]
CircHIPK3	Up-regulated	Mice	CM	miR-20b-5p /ATG7	Apoptosis ↑ Autophagy ↑	Promotes MI/RI	Functional (in vitro)	[73]
CircPAN3	Down-regulated	Mice	HCM	miR-421 /Pink1	Apoptosis ↓ Autophagy ↓	Inhibits MI/RI	Functional (in vitro/vivo)	[74]
CircPAN3	Down-regulated	Rats	HCM	miR-421 /Pink1	Pyroptosis ↓ Apoptosis ↓	Inhibits MI/RI	Functional (in vitro/vivo)	[75]
CircMAT2B	Up-regulated	-	H9C2	miR-133	Apoptosis ↑ Inflammation ↑	Promotes MI	Functional (in vitro)	[76]
Circ_0010729	Up-regulated	-	HCM	miR-370-3p /RUNX1	Apoptisis Proliferation ↓	Promotes MI/RI	Functional (in vitro)	[77]
CircFndc3b	Down-regulated	Human/ Mice	H9C2/ NRVM	FUS /VEGF-A	Apoptosis ↓	Inhibits MI	Microarray + Functional (in vivo)	[52]
CircHIPK3	Up-regulated	Mice	CM	Notch1	Proliferation ↑ Apoptosis ↓	Inhibits MI	Functional (in vitro)	[54]
CircSamd4	Up-regulated	Mice	CM	-	Proliferation ↑ Apoptosis ↓	Inhibits MI	Functional (in vivo)	[78]
CircRNA Pum1_0014	Up-regulated	-	H9C2	miR-146a-5p /NF2/VEGF/PAK1	Apoptosis ↓	Inhibits MI	Functional (in vitro)	[79]
CircIGF1R	Up-regulated	Mice	hiPSC-CM	DDX5	Proliferation ↑ Apoptosis ↓ Fibrosis ↓	Inhibits MI	NGS + Functional (in vivo)	[80]
Circ_0073932	Up-regulated	Rat	H9C2	miR-493-3p /FAF1 / JNK	Apoptosis ↑ Inflammation ↑	Promotes MI/RI	Functional (in vitro/vivo)	[81]

(*Continued*)

Table 3 (Continued).

CircRNAs	Expression	Species	Cell Lines	Mechanism	Pathophysiological Processes	Effection	Validation Method	Ref
Circ_0020887	Up-regulated	Human	AC16	miR-370-3p /CYP1B1	Apoptosis ↑ Oxidative stress ↑ Inflammation ↑	Promotes MI	Functional (in vitro)	[82]
CircStt3b	Down-regulated	Mice	HL-1	miR-15a-5p /GPX4	Apoptosis ↓ Inflammation ↓ Ferroptosis ↓	Inhibits MI	NGS + Functional (in vitro/vivo)	[83]
CircHMGA2	Up-regulated	Mice	HCM	NLRP3	Ferroptosis ↑ Apoptosis ↑ Pyroptosis ↑ Apoptosis ↑ Proliferation ↓	Promotes MI/RI	Functional (in vitro/vivo)	[84]
CircUSP39	Up-regulated	-	AC16	miR-362-3p /TRAF3	Apoptosis ↑ Oxidative stress ↑ Inflammation ↑	Promotes MI/RI	Functional (in vitro)	[85]
circHDAC9	Up-regulated	Mice	HCM	miR-671-5p /SOX4	Apoptosis ↑ Oxidative stress ↑ Inflammation ↑	Promotes MI/RI	Functional (in vitro/vivo)	[86]
CircCHSY1	Up-regulated	Mice	NRCM /hESC-CM	miR-24-3p /HO1	Mitochondrial homeostasis ↑	Inhibits MI/RI	Functional (in vitro/vivo)	[87]
Circ_010567	Up-regulated	-	H9C2	miR-141 /DAPK1	Apoptosis ↑	Promotes MI	Functional (in vitro)	[88]
CircTtc3	Up-regulated	Rats	CM	miR-15b-5p /Arl2	Apoptosis ↓	Inhibits MI	Functional (in vitro/vivo)	[89]
CircNFIX	Up-regulated	Mice	CM	miR-214 /Gsk3β	Tube formation↓ Apoptosis ↑ Proliferation ↓	Promotes MI	Functional (in vivo)	[90]
CircACAP2	Up-regulated	Human	AC16	miR-532	Apoptosis ↑	Promotes MI	Functional (in vitro)	[91]
CircNFIX	Up-regulated	Rats	H9C2	miR-125b-5p /TLR4	Apoptosis ↑ Proliferation ↓	Promotes MI	Functional (in vitro/vivo)	[92]
CircROBO2	Up-regulated	Mice	CM	miR-1184 /TRADD	Apoptosis ↓	Promotes MI	Functional (in vitro/vivo)	[93]
CircMFACR	Up-regulated	Human/ Mice	AC16	miR-125b	Apoptosis ↑	Promotes MI	Functional (in vitro/vivo)	[94]
CircCNEACR	Down-regulated	Mice	CM	HDAC7 /Foxa2 /RIPK3	Necrosis ↓	Inhibits MI/RI	Microarray + Functional (in vitro/vivo)	[95]
CircCDYL	Down-regulated	Mice	CM	miR-4793-5p /APP	Proliferation ↑	Inhibits MI	Functional (in vivo)	[96]
Circ_0000064	Down-regulated	Rats	CM	-	Autophagy ↓ Apoptosis ↓	Inhibits MI/RI	Functional (in vivo)	[97]
Circ_0060745	Up-regulated	Mice	CM	-	Apoptosis ↑	Promotes MI	Functional (in vivo)	[98]
CircSAMD4A	Up-regulated	Mice	H9C2	miR-138-5p	Apoptosis ↑ Inflammation ↑	Promotes MI/RI	Functional (in vitro/vivo)	[99]
CircHelz	Up-regulated	Mice	NMVC	miR-133a-3p /NLRP3	Inflammation ↑ Pyroptosis ↑	Promotes MI	Functional (in vitro/vivo)	[100]
CircJARID2	Up-regulated	-	H9C2	miR-9-5p /BNIP3	Apoptosis ↑ Inflammation ↑ Proliferation ↓	Promotes MI	Functional (in vitro)	[101]
CircTLK1	Up-regulated	Mice	HCM	miR-214 /RIPK1	Apoptosis ↑	Promotes MI/RI	Functional (in vivo)	[102]

(*Continued*)

Table 3 (Continued).

CircRNAs	Expression	Species	Cell Lines	Mechanism	Pathophysiological Processes	Effection	Validation Method	Ref
CircMARC2	Up-regulated	-	AC16	miR-335-5p /TRPM7	Apoptosis ↑ Inflammation ↑	Promotes MI/RI	Functional (in vitro)	[103]
CircHECTD1	Up-regulated	Rats	H9C2	miR-138-5p /ROCK2	Apoptosis ↑ Inflammation ↑	Promotes MI/RI	Functional (in vitro/vivo)	[104]
Circ_003593	Up-regulated	Rats	H9C2	NLRP3	Apoptosis ↑ Proliferation ↓	Promotes MI/RI	Functional (in vitro/vivo)	[105]
Circ_0010729	Up-regulated	-	AC16	miR-27a-3p /TRAF5	Apoptosis ↑	Promotes ICM	Functional (in vitro)	[106]
Circ_0010729	Up-regulated	-	HCM	miR-1184 /RIPK1	Apoptosis ↑ Oxidative stress ↑ Inflammation ↑	Promotes MI/RI	Functional (in vitro/vivo)	[107]
CircSNRK	Down-regulated	Rats	CM	miR-33 /SNRK	Apoptosis↓	Inhibits MI	NGS + Functional (in vivo)	[108]
Circ_0023461	Up-regulated	Human	AC16	miR-370-3p /PDE4D	Apoptosis ↑ Oxidative stress ↑ Inflammation ↑ Migration ↓ Proliferation ↓	Promotes MI	Functional (in vitro)	[109]
CircRNA1615	Down-regulated	Mice	HL-1	miR-152-3p /LRP6	Ferroptosis ↓	Inhibits MI	Functional (in vitro/vivo)	[110]
Circ_0091761	Up-regulated	-	H9C2	miR-335-3p /ACSL4	Proliferation ↓ Ferroptosis ↑	Promotes MI	Functional (in vitro)	[111]
Circ_0007059	Up-regulated	Mice	CM	miR-378 miR-383	Apoptosis ↑ Inflammation ↑	Promotes MI	Microarray + Functional (in vitro/vivo)	[112]
Circ_0002612	Down-regulated	Mice	CM	miR-30a-5p /Ppargc1a/ NLRP3	Apoptosis↓ Proliferation ↑	Inhibits MI/RI	Functional (in vitro/vivo)	[113]
CircACAP2	Up-regulated	Mice	H9C2	miR-29	Apoptosis↑	Promotes MI	Functional (in vitro/vivo)	[114]
CircDENND4C	Up-regulated	-	H9C2	miR-320	Apoptosis↑	Promotes IHD	Functional (in vitro)	[115]
CircFoxo3	Down-regulated	Rats	H9C2	KAT7 /HMGB1	Autophagy ↓	Inhibits MI/RI	Functional (in vitro/vivo)	[116]
CircHIPK3	Up-regulated	Mice	CM	miR-29a /VEGFA	Tube formation ↑ Proliferation ↑ Migration ↑	Inhibits MI	Functional (in vitro/vivo)	[117]
Circ_0001206	Down-regulated	Mice	H9C2	miR-665	Apoptosis↓	Inhibits MI	Functional (in vitro)	[118]
CircLRP6$^{2-2}$	Down-regulated	-	H9C2	HnRNPM /FGF9	Apoptosis↓	Inhibits MII	Functional (in vitro/vivo)	[119]
CircZNF512	Up-regulated	Mice	CM	miR-181d-5p /EGR1	Autophagy↓ Apoptosis↑	Promotes MI/RI	Functional (in vitro/vivo)	[120]
CircFbxl5	Up-regulated	Mice	NMVM	miR-146a /MED1	Apoptosis↑	Promotes MI/RI	Functional (in vitro/vivo)	[121]
CircZNF609	Up-regulated	Mice	NRCM	-	Apoptosis↑	Promotes MI/RI	Functional (in vitro/vivo)	[122]
CircARAP1	Up-regulated	Mice	CM	miR-379-5p /KLF9	Apoptosis↑	Promotes MI/RI	Functional (in vitro/vivo)	[123]
CircSNRK	Down-regulated	Rats	CM	miR-103-3p /SNRK	Apoptosis ↓ Tube formation ↑ Proliferation ↑	Inhibits MI	Functional (in vitro/vivo)	[124]
CircFEACR	Down-regulated	Mice	CM	NAMPT	Ferroptosis ↓	Inhibits MI/RI	NGS + Functional (in vitro/ vivo)	[125]
Circ_010567	Up-regulated	Rats	CM	-	Apoptosis↑	Promotes MF	Functional (in vivo)	[126]
CircMACF1	Down-regulated	Mice	CM	miR-500b-5p /EMP1	Apoptosis ↓	Inhibits MI	Functional (in vitro/vivo)	[127]

(*Continued*)

Table 3 (Continued).

CircRNAs	Expression	Species	Cell Lines	Mechanism	Pathophysiological Processes	Effection	Validation Method	Ref
CircPostn	Up-regulated	Human/ Mice	AC16	miR-96-5p /BNIP3	Apoptosis↑	Promotes MI	Functional (in vitro/vivo)	[128]
Circ_0002113	Up-regulated	Rats	H9C2	miR-188-3p /RUNX1	Apoptosis↑	Promotes MI	Functional (in vitro/vivo)	[129]
CircHSPG2	Up-regulated	-	AC16	miR-25-3p /PAWR	Proliferation ↓ Apoptosis ↓	Promotes MI	Functional (in vitro)	[130]
Circ_0068655	Up-regulated	-	HCM	miR-498 /PAWR	Apoptosis ↑ Migration ↓	Promotes MI	Functional (in vitro)	[131]
CircNNT	Up-regulated	Human/ Mice	CM	miR-33a-5p /USP46	Pyroptosis ↑	Promotes MI/RI	Functional (in vitro/vivo)	[132]
CircSLC8A1	Up-regulated	-	HL-1	miR-214-5p /TEAD1	Apoptosis ↑ Oxidative stress ↑ Inflammation ↑	Promotes MI	Functional (in vitro)	[133]
CircNFIX	Down-regulated	Mice	H9C2	-	Apoptosis ↑ Oxidative stress ↑	Promotes MI	Functional (in vitro/vivo)	[134]
CircTRRAP	Up-regulated	-	AC16	miR-214-3p /SOX6	Apoptosis ↑ Oxidative stress ↑ Proliferation ↓	Promotes MI/RI	Functional (in vitro)	[135]
CircDGKZ	Up-regulated	Rats	AC16	miR-345-5p /TLR4/NF-κB	Pyroptosis ↑ Autophagy ↓	Promotes MI/RI	Functional (in vitro/vivo)	[136]
CircPVT1	Up-regulated	Mice	CM	miR-125b miR-200a	Apoptosis ↑	Promotes MI	Microarray + Functional (in vitro/vivo)	[137]
CircRbms1	Up-regulated	Mice	H9C2	miR-742-3p /FOXO1	Invasion ↓ Migration ↓ Apoptosis ↑	Promotes MI	Functional (in vitro/vivo)	[138]
Circ_0124644	Up-regulated	Human	AC16	miR-590-3p /SOX4	Apoptosis ↑ Oxidative stress ↑	Promotes MI	Functional (in vitro)	[139]
Circ_0030235	Up-regulated	-	H9C2	miR-526b	Apoptosis ↑	Promotes MI	Functional (in vitro)	[140]
CircJA760602	Up-regulated	-	AC16	EGR1 E2F1	Apoptosis ↑	Promotes MI	Functional (in vitro)	[141]
CircSMG6	Up-regulated	Mice	HL-1	miR-138-5p /EGR1/ TLR4/TRIF	Apoptosis ↑ Neutrophil recruitment ↑	Promotes MI/RI	Functional (in vitro/vivo)	[142]
CircUBXN7	Down-regulated	Mice	H9C2	miR-622 /MCL1	Inflammation ↓ Apoptosis ↓	Inhibits MI	Functional (in vitro/vivo)	[143]
Circ_0049271	Up-regulated	Human	H9C2	miR-17-3p /FZD4	Apoptosis ↑ Oxidative stress ↑ Inflammation ↑ Proliferation ↓	Promotes MI	Functional (in vitro)	[144]
CircACR	Down-regulated	Mice	CM	Pink1 /FAM65B	Autophagy ↓	Inhibits MI/RI	Microarray + Functional (in vitro/vivo)	[145]
CircHSPG2	Up-regulated	Human	AC16	miR-1184 /MAP3K2	Apoptosis ↑ Oxidative stress ↑ Inflammation ↑	Promotes MI	Functional (in vitro)	[146]
CircUSP39	Up-regulated	-	AC16	miR-499b-5p /ACSL1	Apoptosis ↑	Promotes MI	Functional (in vitro)	[147]
Circ_0000848	Down-regulated	-	H9C2	ELAVL1 /SMAD7	Apoptosis ↓ Proliferation ↑	Inhibits MI	Functional (in vitro)	[148]
CircRbms1	Up-regulated	Mice	H9C2	miR-92a /BCL2L11	Apoptosis ↑ Oxidative stress ↑	Promotes MI/RI	Functional (in vitro/vivo)	[149]

(*Continued*)

Table 3 (Continued).

CircRNAs	Expression	Species	Cell Lines	Mechanism	Pathophysiological Processes	Effection	Validation Method	Ref
Circ_0001747	Down-regulated	-	HL-1	miR-199b-3p /MCL1	Inflammation ↓ Apoptosis ↓ Proliferation ↑	Inhibits MI	Functional (in vitro)	[150]
CircTRRAP	Up-regulated	Human	AC16	miR-761 /MAP3K2	Apoptosis ↑ Oxidative stress ↑ Inflammation ↑	Promotes MI	Functional (in vitro)	[151]
Circ_0031672	Up-regulated	Rats	H9C2	miR-21-5p /PDCD4	Apoptosis ↑	Promotes MI/RI	Functional (in vitro/vivo)	[152]
CircRbms1	Up-regulated	Mice	HCM	miR-2355-3p /MST1	Apoptosis ↑ Oxidative stress ↑ Inflammation ↑	Promotes MI/RI	Functional (in vitro/vivo)	[153]
Circ-RHOJ.1	Down-regulated	Rats	CM	miR-124-3p /NRG1	Inflammation ↓ Apoptosis ↓ Proliferation ↑	Inhibits MI/RI	Functional (in vitro/vivo)	[154]
CircMIRIAF	Up-regulated	Mice	AC16	miR-544 /WDR12	Oxidative stress ↑ Inflammation ↑	Promotes MI/RI	Microarray + Functional (in vitro/vivo)	[155]
Circ_0068566	Down-regulated	Mice	H9C2	miR-6322 /PARP2	Proliferation ↑ Apoptosis ↓ Oxidative stress ↓	Inhibits MI/RI	Functional (in vitro/vivo)	[156]
CircTRRAP	Up-regulated	-	AC16	miR-370-3p /PAWR	Apoptosis ↑ Oxidative stress ↑ Inflammation ↑	Promotes MI	Functional (in vitro)	[157]
CircDiaph3	Up-regulated	Mice	H9C2	miR-338-3p /SRSF1	Apoptosis ↑ Inflammation ↑	Promotes MI	Functional (in vitro/vivo)	[158]
Circ_0050908	Up-regulated	-	HCM	miR-324-5p /TRAF3	Apoptosis ↑ Oxidative stress ↑ Inflammation ↑	Promotes MI/RI	Functional (in vitro)	[159]
CircBCL2L13	Up-regulated	Mice	CM	miR-1246 /PEG3	Apoptosis ↓ Oxidative stress ↓	Inhibits MI/RI	Functional (in vitro/vivo)	[160]
CircANKIB1	Down-regulated	-	H9C2	miR452-5p /SLC7A11	Apoptosis ↓ Ferroptosis ↓	Inhibits MI	Functional (in vitro)	[161]
Circ_0001379	Up-regulated	Mice	HL-1	miR-98-5p /SOX6	Apoptosis ↑ Inflammation ↑	Promotes MI	Functional (in vitro/vivo)	[162]
CircSWT1	Down-regulated	-	AC16	miR-192-5p /SOD2	Oxidative stress ↓ Apoptosis ↓	Inhibits MI	Functional (in vitro)	[163]
CircCBFB	Up-regulated	-	H9C2	miR-495-3p /VDAC1	Oxidative stress↑ Apoptosis ↑	Promotes MI/RI	Functional (in vitro)	[164]

Abbreviations: HCM, Human cardiomyocyte; CM, Cardiomyocyte; NRVM, Neonatal rat ventricular myocyte; hiPSC-CM, Human induced pluripotent stem cell-derived cardiomyocyte; NRCM, Neonatal rat cardiomyocyte; hESC-CM, Human embryonic stem cell-derived cardiomyocyte; NMVC, Neonatal mouse ventricular cardiomyocyte; NMVM, Neonatal mice ventricular myocyte; NRCM, Neonatal rat cardiomyocyte; MI/RI, Myocardial ischemia/reperfusion injury; MI, Myocardial infarction; ICM, Ischemic cardiomyopathy; IHD, Ischemic heart disease; MF: Myocardial fibrosis; ROS, Reaction oxygen; CAD, Coronary artery disease; ↑, Promotes; ↓, Inhibits.

been characterized, with 70 showing upregulation and 60 demonstrating downregulation. These circRNAs can be functionally categorized into two major classes: cardioprotective and injury-promoting circRNAs. It is worth noting that some circRNAs regulate the expression of downstream genes by simultaneously targeting multiple miRNAs in CMs, which influences the extent of CM damage. For instance, researchers have validated the mechanism of circPAN3 through both in vivo and in vitro experiments using dual-luciferase reporter assays and reverse transcription-polymerase chain reaction (RT-PCR). The cardioprotective circPAN3 exerts synergistic protective effects through a dual-target regulatory mechanism: it mitigates mitochondrial damage via the miR-421/Pink1 axis while simultaneously suppressing endoplasmic reticulum stress through the miR-29b-3p/SDF4 axis.[72,73] Conversely, the injury-accelerating circHIPK3 functions as

a classical multitarget regulator that aggravates MI/RI damage by concurrently sponging miR-124-3 and miR-20b-5p, among other miRNAs.[74,75] These findings not only elucidate the complex regulatory networks of circRNAs in myocardial injury but also provide potential therapeutic targets for developing novel diagnostic and treatment strategies.

Cardiac Fibroblasts

Preventing and improving myocardial fibrosis after MI has always been a major challenge in the diagnosis and treatment of CAD. The occurrence of this process is not only related to changes in the biological function of CMs but also depends on the regulation of the pathological and physiological mechanisms of cardiac fibroblasts (CFs). Table 4 summarizes the currently identified 8 functionally characterized circRNAs in CFs, including 5 fibrosis-promoting circRNAs and 3 anti-fibrotic circRNAs. For instance, Ji et al found that circNSD1 was associated with the proliferation and collagen deposition of CFs, and its downregulation could ameliorate myocardial fibrosis by regulating the miR-429-3p/SULF1/Wnt/β-catenin signaling pathway.[165] Furthermore, Y. Wang et al also revealed that circMACF1 may suppress TGF-β1-induced fibroblast activation, migration and proliferation by controlling the miR-16-5p/SMAD7 pathway.[166] However, research on the role of circRNAs in CFs remains limited to date. As summarized in Table 4, only a small number of circRNAs have been functionally characterized in CFs, among which three circRNAs (CircPAN3, CircMACF1, and CircLAS1L) have only been studied at the cellular level through in vitro experiments, lacking further validation in vivo. These findings nevertheless establish a molecular foundation for developing anti-fibrotic therapies targeting CFs-specific circRNAs.

Potential Clinical Applications of circRNAs in CAD

Diagnostic Biomarkers

The natural resistance of circRNAs to exonuclease is a significant feature that distinguishes it from linear RNA.[172] This resistance can bring stability to circRNAs, enabling their long-term regulation of gene expression in CAD and contributing to their specific expression in specific tissues. Certain circRNAs express differently in CAD patients than in healthy controls, and this expression difference may have already appeared in the early stages of CAD. The exonuclease resistance of circRNAs makes it relatively stable in the blood of CAD patients. providing an opportunity for circRNAs as a biomarker for early diagnosis of CAD. Non-invasive or minimally invasive detection of CAD can be

Table 4 Summary of circRNAs Related to the Pathophysiological Processes of Cardiac Fibroblasts in CAD

CircRNAs	Expression	Species	Cell lines	Mechanism	Pathophysiological processes	Effection	Validation method	Ref
Circ_0060745	Up-regulated	Mice	CF	-	Inflammation ↑	Promotes MI	Functional (in vitro/vivo)	[98]
CircPAN3	Up-regulated	Rats	CF	miR-221 /FoxO3 /ATG7	Migration ↑ Autophagy ↑ Proliferation ↑	Promotes MF	Functional (in vivo)	[167]
CircUbe3a	Up-regulated	Mice	CF	miR-138-5p /RhoC	Migration ↑ Proliferation ↑	Promotes MF	Functional (in vitro/vivo)	[168]
CircHelz	Up-regulated	Mice	CF	-	Proliferation ↑ Differentiation ↑.	Promotes MF	Functional (in vitro/vivo)	[169]
CircMACF1	Down-regulated	Human	CF	miR-16-5p /SMAD7	Migration ↓ Proliferation ↓	Inhibits MF	Functional (in vitro)	[166]
CircCELF1	Down-regulated	Mice	CF	miR-636 FTO/DKK2	Migration ↑ Apoptosis ↓	Inhibits MF	Functional (in vitro/vivo)	[170]
CircLAS1L	Down-regulated	Human	CF	miR-125b /SFRP5	Apoptosis ↑ Migration ↓ Proliferation ↓	Inhibits MF	Functional (in vitro)	[171]
CircNSD1	Up-regulated	Mice	CF	miR-429-3p /SULF1/ Wnt/β-catenin	Proliferation ↑ Collagen deposition ↑	Promotes MF	Functional (in vitro/vivo)	[165]

Abbreviations: CF, Cardiac fibroblast; MI, Myocardial infarction; MF, Myocardial fibrosis; CAD, Coronary artery disease; ↑, Promotes; ↓, Inhibits.

achieved by analyzing the expression levels of circRNAs in the blood, serum, plasma or other body fluids of CAD patients.[173,174] Compared to traditional biomarkers, this detection method may be able to reflect the presence of CAD earlier. The association between these circRNAs' sensitivity and specificity is shown by the receiver operating characteristic (ROC) curve, with values of the area under the curve (AUC) between 0.1 and 1, which can be used directly to assess the diagnostic value of circRNAs. The greater the value, the higher the possibility for diagnosis.[175]

We established the following inclusion criteria for the circRNAs analyzed: 1) Publications between 2019–2024; 2) Significant differential expression between CAD patients and healthy controls; 3) AUC greater than 0.70. Table 5

Table 5 Diagnostic Significance of circRNAs in CAD

CircRNAs	Expression	Samples	Function	ROC Curve Analysis			Ref
				Specificity	Sensitivity	AUC	
CircZNF609	Down-regulated	Samples of peripheral blood derived from 330 CAD patients and 209 healthy individuals.	Biomarker for diagnosis	0.804	0.615	0.761	[182]
Hsa_circ_0001879	Up-regulated	Samples of blood derived from 297 healthy individuals and 436 patients with CAD.	Biomarker for diagnosis	0.543	0.831	0.703	[176]
Hsa_circ_0004104	Up-regulated	Samples of blood derived from 297 people healthy individuals and 436 patients with CAD.	Biomarker for diagnosis	0.614	0.707	0.700	[176]
CircYOD1	Up-regulated	Samples of blood were derived from 316 healthy individuals and 1842 patients with CAD	Biomarker for diagnosis	0.824	-	0.824	[183]
Hsa_circ_0001445	Down-regulated	Samples of peripheral blood derived from 96 CHD patients and 126 healthy controls.	Biomarker for diagnosis	0.766	0.675	0.816	[184]
Hsa_circ_0005540	Up-regulated	Samples of plasma derived from 105 CAD patients and 86 healthy individuals.	Biomarker for diagnosis	0.765	0.810	0.853	[185]
CircLDB1	Up-regulated	Samples of peripheral blood were derived from 50 controls (included 24 females and 26 males) and 50 individuals with CAD (included 22 females and 28 males).	Biomarker for diagnosis	0.767	0.835	0.900	[177]
CircPPARA	Up-regulated	Samples of peripheral blood were derived from 50 patients with AMI and 50 controls.	Biomarker for diagnosis	-	-	0.876	[179]
CircPRDM5	Down-regulated	Samples of serum were derived from 118 AMI patients, 63 AP patients and 60 healthy controls.	Biomarker for diagnosis	0.878	0.763	0.862	[186]
Circ-0020887	Up-regulated	Samples of plasma were derived from 64 patients with STEMI and 64 controls.	Biomarker for diagnosis	-	-	0.85	[187]
Circ_cSMARCA5	Down-regulated	Samples of peripheral blood derived from 100 patients without CAD and 100 AMI patients.	Biomarker for diagnosis	0.890	0.677	0.83	[188]
Circ_cZNF292	Up-regulated	Samples of blood were derived from 42 patients with AMI and 33 non-AMI patients.	Biomarker for diagnosis	-	-	0.747	[189]
Circ_0051386	Up-regulated	Samples of blood were derived from 254 patients with STEMI and 151 controls.	Biomarker for diagnosis	-	-	0.766	[190]
Circ_0013958	Up-regulated	Samples of blood were derived from 120 patients with AMI and 102 controls.	Biomarker for diagnosis	0.842	0.862	0.908	[178]
Circ-0009590	Up-regulated	Samples of plasma were derived from 64 patients with STEMI and 64 controls.	Biomarker for diagnosis	-	-	0.80	[187]
Hsa_circ_0001360	Up-regulated	Samples of blood were derived from 10 patients with CHD and 10 healthy controls.	Biomarker for diagnosis	-	-	0.860	[180]
Hsa_circ_0000038	Down-regulated	Samples of blood were derived from 10 patients with CHD and 10 healthy controls.	Biomarker for diagnosis	-	-	0.870	[180]
Hsa_circ_0001946	Up-regulated	Samples of peripheral blood were derived from 120 patients with CHD and 120 healthy controls.	Biomarker for diagnosis	0.867	0.833	0.897	[181]

Abbreviations: CAD, coronary artery disease; AMI, acute myocardial infarction; STEMI, ST-segment elevation myocardial infarction; AP, angina pectoris; ROC, receiver operating characteristic; AUC, area under the curve.

includes a total of 18 circRNAs that demonstrate potential as diagnostic biomarkers for CAD. However, through analysis of existing studies, we identified significant heterogeneity in the diagnostic performance of these circRNAs. For instance, while hsa_circ_0001879 (AUC=0.703) and hsa_circ_0004104 (AUC=0.700) from the same study demonstrated moderate diagnostic accuracy,[176] circLDB1 (AUC=0.900) and circ_0013958 (AUC=0.908) exhibited superior diagnostic value,[177,178] these discrepancies may originate from variations in study population characteristics (eg, disease severity, comorbidities) or methodological differences in detection approaches. Moreover, certain circRNAs (eg, circPPARA, hsa_circ_0000038, and hsa_circ_0001946) demonstrated considerable diagnostic potential (AUC > 0.800), yet their clinical applicability may be constrained by the current lack of reported sensitivity and specificity data,[179–181] this limitation underscores the necessity for standardized reporting of ROC curve parameters in future investigations.

Assessment of the Severity and Prognosis of CAD

The expression levels of specific circRNAs in the blood of patients with CAD may be correlated with the severity and prognosis of CAD. Analyzing circRNA expression profiles at different stages of progression can provide a potential basis for the clinical evaluation of CAD severity in patients.[191] In a CAD study related to the Chinese population, circNIPSNAP3A was found to have higher expression levels in the serum of the atherosclerosis group and CAD group with higher disease severity than the general CAD group, suggesting that circNIPSNAP3A is related to the severity of CAD.[192] Besides, another study found that the expression of circRNAs in the peripheral blood of CAD patients was approximately three times higher than in healthy individuals, having an AUC value of 0.931, diagnostic sensitivity of 75.71%, specificity of 100%, ROC curve results exhibited that circRNAs in peripheral blood can function as a biomarker for predicting major adverse cardiovascular events (MACE) in patients with acute coronary syndrome.[193]

Therapeutic Targets and Drug Development

A study has shown that targeted regulation of circMAT2B in the MI model can improve myocardial function by upregulating miR-133 to inhibit inflammatory responses harmful to CMs,[76] targeted inhibition of circ_0004104 expression in ECs can promote cell proliferation and inhibit apoptosis, so as to slow down the progression of coronary atherosclerosis.[46] This prompts us that circRNA or the miRNAs and mRNAs regulated by it may become new targets for the treatment of CAD,[194] new drugs can be developed targeting these targets to regulate circRNA synthesis and degradation, achieving the goal of treating CAD. However, although sevoflurane and Gypenoside A have been verified in vitro and in vivo experiments to effectively protect CMs from ischemia-reperfusion injury by regulating the specific circRNA-miRNA-mRNA axis, these preliminary results still require in-depth clinical studies to verify its effectiveness.[75,77] In the future, there is still great potential for the research and development of drugs targeting circRNA in the field of CAD therapy.

Conclusions and Perspectives

CAD is widespread in the world, and its high incidence rate and mortality have been widely concerned by the world. The role of circRNAs in CAD is a rapidly developing research field, which has shown great potential in disease mechanisms, diagnosis, prognosis assessment, and treatment interventions. Although many studies have demonstrated the diversity of biological functions of circRNAs, in recent years, researchers more focused on how circRNAs through miRNA sponge effect, protein interaction or directly regulate downstream gene expression to affect the pathophysiology of cardiovascular cells, thus potentially impacting on the initiation, progression and prognosis of CAD.

As shown in Table 6, compared with existing published studies, this paper employed specific screening criteria to analyze 148 studies published between 2019 and 2024, thereby covering a broader time span. We comprehensively summarized 107 CAD-associated circRNAs whose functional mechanisms have been experimentally validated through in vivo or in vitro studies, along with 18 circRNAs exhibiting diagnostic biomarker potential. The quantity of circRNAs identified in our review significantly surpasses that reported in previous similar reviews. More importantly, based on the biological characteristics and functions of circRNAs, we innovatively conducted a multi-cellular dimensional integrated analysis and established a comprehensive regulatory network encompassing endothelial cells (ECs), vascular smooth muscle cells (VSMCs), cardiomyocytes (CMs), and cardiac fibroblasts (CFs). Our findings reveal that several circRNAs -

Table 6 Some Novelties of This Study Compared to Previously Published Studies

Ref	Years	Included literature (Year Range)	Number of circRNAs	Cell Lines	Mechanism Depth	Diseases	Clinical Application Potential
Our study	2025	2019–2024	107 (Mechanism) 18 (Diagnosis)	EC VSMC CM CF	ceRNA multi-cellular /multi-mechanism synergistic effect	AS MI MI/RI IHD	Diagnostic biomarkers; Therapeutic targets
[60]	2020	2016–2019	15 (Mechanism) 4 (Diagnosis)	-	ceRNA	AS MI MI/RI IHF	Diagnostic biomarkers
[195]	2021	2017–2020	14 (Mechanism) 7 (Diagnosis)	THP-1 VSMC RAW264.7	ceRNA	-	Diagnostic biomarkers
[196]	2023	2019–2023	31 (Mechanism)	EC VSMC THP-1	ceRNA	AS	Diagnostic biomarkers; Therapeutic targets
[197]	2022	2015–2021	17 (Mechanism) 12 (Diagnosis)	EC pericyte cells exosomes	ceRNA	-	Diagnostic biomarkers

Abbreviations: EC, Endothelial cell; VSMC, Vascular smooth muscle cell; CM, Cardiomyocyte; CF, Cardiac fibroblast; AS, Atherosclerosis; MI, Myocardial infarction; MI/RI, Myocardial ischemia/reperfusion injury; IHD, Ischemic heart disease; IHF, Ischemic heart failure; ceRNA, Competing endogenous RNA.

including CircHIPK3, CircPAN3, and CircROBO2 - can coordinately regulate the pathological progression of CAD across different cell types. For instance, circROBO2 was found to be highly expressed in CAD-associated ECs, VSMCs, and CMs simultaneously, where it regulates apoptosis and proliferation in these cell types through specific ceRNA networks.[42,64,93] Such coordinated multi-cellular regulation substantially advances beyond conventional research paradigms that were confined to single-cell-type investigations. Furthermore, the same target gene can also be influenced by different circRNAs to mediate the progression of CAD. For instance, circ_0068655, circHSPG2, and circTRRAP can jointly modulate the expression of PAWR in CMs through sponge miR-498, miR-25-3p, and miR-370-3p, respectively, thereby affecting apoptosis, proliferation, migration, inflammation, and oxidative stress in CMs. Therefore, certain circRNAs may play more pivotal roles in CAD progression, as they not only regulate multiple pathological processes across different cell types but also participate in intricate regulatory networks within individual cell types. These circRNAs exemplify a distinctive "multi-mechanism and multi-cellular" synergistic mode of action in CAD, warranting prioritized investigation to fully explore their clinical translation potential. Figure 1 summarizes the regulatory network of these circRNA in CAD-associated cardiovascular cells. Notably, beyond the classical ceRNA mechanism, circRNAs may also participate in CAD pathophysiology through non-coding-dependent pathways such as direct regulation of downstream target genes, translation into functional peptides, and protein-protein interactions - all of which merit in-depth exploration in future research.

With the continuous development of the molecular mechanism research of circRNAs, its potential clinical application value in CAD has gradually emerged. Capitalizing on the superior stability of circRNAs compared to conventional CAD diagnostic biomarkers, our review identified 18 circRNAs with significant diagnostic value, all rigorously validated in independent clinical cohorts (AUC > 0.70). Notably, CircLDB1 and Circ_0013958 demonstrated exceptional diagnostic performance (AUC > 0.900), further highlighting the potential of circRNAs as clinical surrogate biomarkers for CAD. However, it should be emphasized that current findings primarily rely on expression profiling and diagnostic efficacy analyses in clinical samples, while their functional mechanisms require further experimental validation through functional studies. These results nevertheless provide crucial clinical evidence supporting the continued exploration of circRNA biomarkers for CAD.

Certainly, the unique exonuclease resistance of circRNAs and their complex and variable regulatory mechanism in CAD not only endow it with the potential as a biomarker for early diagnosis and disease progression prediction of CAD

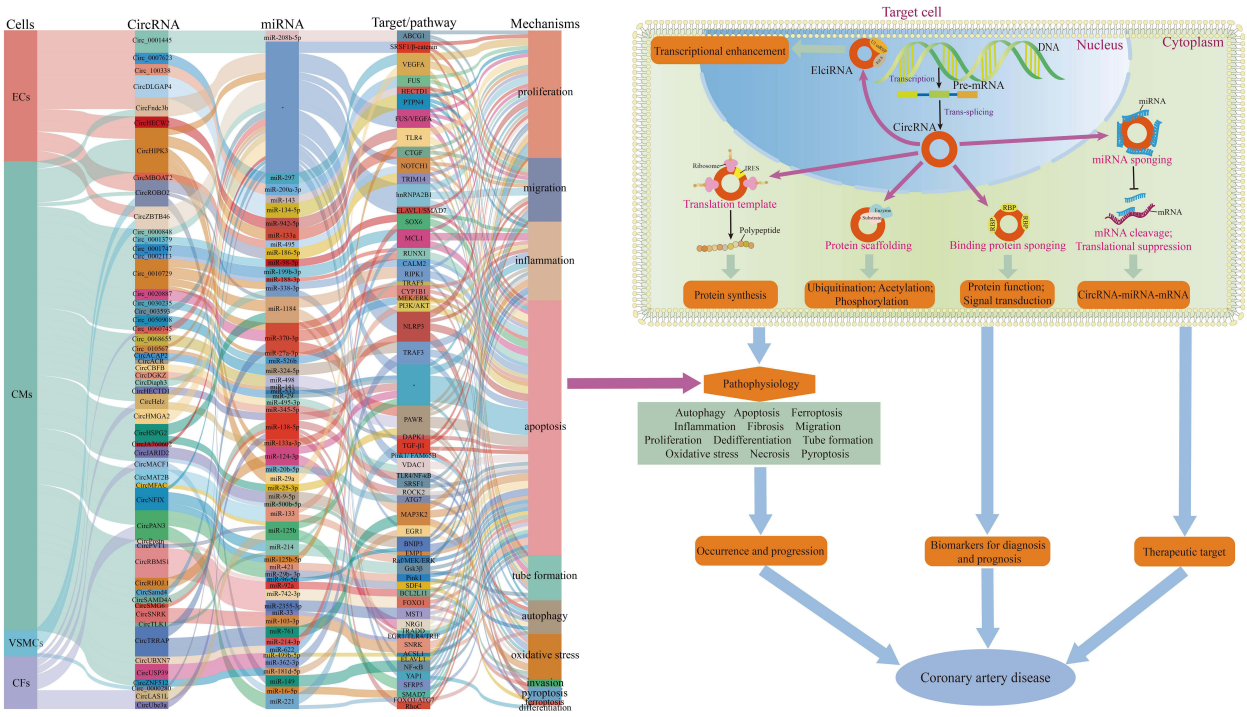

Figure 1 Functional networks of circRNAs in coronary artery disease from a multi-cellular and multi-mechanism perspective. CircRNAs regulate gene expression by enhancing the transcription of parental genes. CircRNAs serve as translation templates to promote protein synthesis. CircRNAs act as protein scaffolds to promote the interaction of enzymes with substrates, thereby regulating protein modifications. CircRNAs interact with RNA-binding proteins to regulate protein function and signal transduction. CircRNAs act as sponges for miRNAs, competitively binding to miRNAs and affecting their regulation of target mRNAs.

but also provide new targets and drug development directions for the treatment strategies of CAD. Unfortunately, most of the current studies still have some limitations, for example, the specific biological functions and mechanisms of action of circRNAs need to be further elucidated, and the exact details of its multiple regulatory mechanisms in the pathophysiology of CAD are still not clear enough. The detection method and standardized process of circRNAs have not been fully established.

Based on the above, circRNAs possess the ability to regulate the pathophysiological processes of CAD, which involves a "multi-cellular/multi-mechanism" synergistic mechanism. Although current studies have identified a large number of functionally well-defined circRNAs, clinical translation still requires overcoming numerous challenges. Future research should focus more on the following directions: Firstly, at the mechanistic level, it is essential to move beyond the singular perspective of the existing ceRNA mechanism and systematically explore how circRNAs participate in the pathological progression of CAD through non-coding-dependent pathways such as direct translation, protein interactions, or epigenetic regulation. Particular attention should be paid to key circRNAs like circHIPK3 and circROBO2, which exhibit "multi-cellular/multi-mechanism" synergistic effects, to uncover their central role in cross-cell-type regulatory networks. Secondly, in terms of clinical translation, efforts should be made to promote multicenter clinical validation of circRNAs with high diagnostic value, establish standardized detection protocols, and develop targeted intervention strategies for circRNAs that regulate critical genes. Finally, dynamic monitoring of circRNA changes throughout the entire course of CAD should be implemented to determine their potential as staging biomarkers and therapeutic nodes, ultimately achieving the comprehensive application of circRNAs in the precision diagnosis and treatment of CAD.

All in all, circRNAs are expected to become an important component of CAD precision medicine in the future and bringing new directions for the diagnosis and treatment of CAD, despite some remaining scientific and technological obstacles.

https://doi.org/10.2147/IJGM.S524189

AI Declaration

This review was conducted without the use of any artificial intelligence-assisted tools for data extraction or literature processing throughout its preparation.

Acknowledgement

We gratefully acknowledge all authors for their active contributions to this study. Their expertise and dedicated efforts were instrumental in completing this work. We also appreciate the editors and reviewers for their constructive feedback on this manuscript.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was supported by the National Natural Science Foundation of China (81860073 and 82360076), the Application foundation project of Yunnan Province (202001AT070039 and 202401AT070069), Special Foundation Projects of Joint Applied Basic Research of Yunnan Provincial Department of Science and Technology with Kunming Medical University (2019FE001(−138)), Young Talents of Yunnan Thousand Talents Plan (RLQN20200002), Yunnan Health Training Project of High-Level Talents (H-2018032), Young and middle-aged academic leaders and reserve candidates of Kunming Medical University(J13397031).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Regmi M, Siccardi MA. Coronary artery disease prevention. In: *StatPearls*. StatPearls Publishing Copyright © 2025, StatPearls Publishing LLC.; 2025.
2. Bodor GS. Biochemical markers of myocardial damage. *Ejifcc*. 2016;27(2):95–111.
3. Wesselhoeft RA, Kowalski PS, Anderson DG. Engineering circular RNA for potent and stable translation in eukaryotic cells. *Nat Commun*. 2018;9(1):2629. doi:10.1038/s41467-018-05096-6
4. Sun JY, Shi Y, Cai XY, et al. Potential diagnostic and therapeutic value of circular RNAs in cardiovascular diseases. *Cell Signal*. 2020;71:109604. doi:10.1016/j.cellsig.2020.109604
5. Zhang Z, Qian H, Wang L, et al. Construction of a circRNA-miRNA-mRNA regulatory network for coronary artery disease by bioinformatics analysis. *Cardiol Res Pract*. 2022;2022:4017082. doi:10.1155/2022/4017082
6. Fu Y, Jia Q, Ren M, et al. Circular RNA ZBTB46 depletion alleviates the progression of atherosclerosis by regulating the ubiquitination and degradation of hnRNPA2B1 via the AKT/mTOR pathway. *Immun Ageing*. 2023;20(1):66. doi:10.1186/s12979-023-00386-0
7. Li J, Wu X, Ma H, et al. New developments in non-exosomal and exosomal ncRNAs in coronary artery disease. *Epigenomics*. 2022;14 (21):1355–1372. doi:10.2217/epi-2022-0201
8. Zhou Q, Zhang Z, Bei Y, et al. Circular RNAs as novel biomarkers for cardiovascular diseases. *Adv Exp Med Biol*. 2018;1087:159–170.
9. Gao W, Liu H, Yuan J, et al. Exosomes derived from mature dendritic cells increase endothelial inflammation and atherosclerosis via membrane TNF-α mediated NF-κB pathway. *J Cell Mol Med*. 2016;20(12):2318–2327. doi:10.1111/jcmm.12923
10. Herrero-Fernandez B, Gomez-Bris R, Somovilla-Crespo B, et al. Immunobiology of Atherosclerosis: a Complex Net of Interactions. *Int J Mol Sci*. 2019;20(21). doi:10.3390/ijms20215293
11. Marchio P, Guerra-Ojeda S, Vila JM, et al. Targeting early atherosclerosis: a focus on oxidative stress and inflammation. *Oxid Med Cell Longev*. 2019;2019:8563845. doi:10.1155/2019/8563845
12. Medina-Leyte DJ, Zepeda-García O, Domínguez-Pérez M, et al. Endothelial dysfunction, inflammation and coronary artery disease: potential biomarkers and promising therapeutical approaches. *Int J Mol Sci*. 2021;22(8):3850. doi:10.3390/ijms22083850
13. Bentzon JF, Otsuka F, Virmani R, et al. Mechanisms of plaque formation and rupture. *Circ Res*. 2014;114(12):1852–1866. doi:10.1161/CIRCRESAHA.114.302721
14. Ueda Y, Kosugi S, Abe H, et al. Transient increase in blood thrombogenicity may be a critical mechanism for the occurrence of acute myocardial infarction. *J Cardiol*. 2021;77(3):224–230. doi:10.1016/j.jjcc.2020.08.007
15. Wang XD, Kang S. Ferroptosis in myocardial infarction: not a marker but a maker. *Open Biol*. 2021;11(4):200367. doi:10.1098/rsob.200367

16. Liu C, Li Z, Li B, et al. Relationship between ferroptosis and mitophagy in cardiac ischemia reperfusion injury: a mini-review. *PeerJ*. 2023;11:e14952. doi:10.7717/peerj.14952
17. Xue H, Chen X, Yu C, et al. Gut microbially produced indole-3-propionic acid inhibits atherosclerosis by promoting reverse cholesterol transport and its deficiency is causally related to atherosclerotic cardiovascular disease. *Circ Res*. 2022;131(5):404–420. doi:10.1161/CIRCRESAHA.122.321253
18. Huang B, Lai Z, Wang X, et al. Comprehensive analysis of non-coding RNA-mediated endothelial cell-specific regulatory circuits in coronary artery disease risk. *Front Genet*. 2025;16:1559798. doi:10.3389/fgene.2025.1559798
19. Li X, Yang L, Chen LL. The biogenesis, functions, and challenges of circular RNAs. *Mol Cell*. 2018;71(3):428–442. doi:10.1016/j.molcel.2018.06.034
20. Chen LL, Yang L. Regulation of circRNA biogenesis. *RNA Biol*. 2015;12(4):381–388. doi:10.1080/15476286.2015.1020271
21. Zang J, Lu D, Xu A. The interaction of circRNAs and RNA binding proteins: an important part of circRNA maintenance and function. *J Neurosci Res*. 2020;98(1):87–97. doi:10.1002/jnr.24356
22. Kristensen LS, Andersen MS, Stagsted LVW, et al. The biogenesis, biology and characterization of circular RNAs. *Nat Rev Genet*. 2019;20(11):675–691. doi:10.1038/s41576-019-0158-7
23. Zhang C, Cui H, Huang C, et al. Interactions of circRNAs with methylation: an important aspect of circRNA biogenesis and function (Review). *Mol Med Rep*. 2022;25(5). doi:10.3892/mmr.2022.12685
24. Fu Y, He S, Li C, et al. Detailed profiling of m6A modified circRNAs and synergistic effects of circRNA and environmental risk factors for coronary artery disease. *Eur J Pharmacol*. 2023;951:175761. doi:10.1016/j.ejphar.2023.175761
25. Bergonzini M, Loreni F, Lio A, et al. Panoramic on epigenetics in coronary artery disease and the approach of personalized medicine. *Biomedicines*. 2023;11(10):2864. doi:10.3390/biomedicines11102864
26. Zhou WY, Cai ZR, Liu J, et al. Circular RNA: metabolism, functions and interactions with proteins. *Mol Cancer*. 2020;19(1):172. doi:10.1186/s12943-020-01286-3
27. Ding F, Lu L, Wu C, et al. circHIPK3 prevents cardiac senescence by acting as a scaffold to recruit ubiquitin ligase to degrade HuR. *Theranostics*. 2022;12(17):7550–7566. doi:10.7150/thno.77630
28. Chen CK, Cheng R, Demeter J, et al. Structured elements drive extensive circular RNA translation. *Mol Cell*. 2021;81(20):4300–4318.e13. doi:10.1016/j.molcel.2021.07.042
29. Weigelt CM, Sehgal R, Tain LS, et al. An insulin-sensitive circular RNA that regulates lifespan in drosophila. *Mol Cell*. 2020;79(2):268–279.e5. doi:10.1016/j.molcel.2020.06.011
30. Legnini I, Di Timoteo G, Rossi F, et al. Circ-ZNF609 is a circular RNA that can be translated and functions in myogenesis. *Mol Cell*. 2017;66(1):22–37.e9. doi:10.1016/j.molcel.2017.02.017
31. Yang Y, Fan X, Mao M, et al. Extensive translation of circular RNAs driven by N(6)-methyladenosine. *Cell Res*. 2017;27(5):626–641. doi:10.1038/cr.2017.31
32. Pamudurti NR, Bartok O, Jens M, et al. Translation of CircRNAs. *Mol Cell*. 2017;66(1):9–21.e7. doi:10.1016/j.molcel.2017.02.021
33. Hansen TB. Signal and noise in circRNA translation. *Methods*. 2021;196:68–73. doi:10.1016/j.ymeth.2021.02.007
34. Chen KY, Liu Z, Lu JH, et al. The function of circular RNAs in myocardial ischemia-reperfusion injury: underlying mechanisms and therapeutic advancement. *Cardiovasc Drugs Ther*. 2024. doi:10.1007/s10557-024-07557-1
35. Li X, Zhang JL, Lei YN, et al. Linking circular intronic RNA degradation and function in transcription by RNase H1. *Sci China Life Sci*. 2021;64(11):1795–1809. doi:10.1007/s11427-021-1993-6
36. Zheng ZM. Circular RNAs and RNase L in PKR activation and virus infection. *Cell Biosci*. 2019;9:43. doi:10.1186/s13578-019-0307-x
37. Pan Z, Li GF, Sun ML, et al. MicroRNA-1224 splicing circularRNA-Filip1l in an Ago2-dependent manner regulates chronic inflammatory pain via targeting Ubr5. *J Neurosci*. 2019;39(11):2125–2143. doi:10.1523/JNEUROSCI.1631-18.2018
38. Piwecka M, Glažar P, Hernandez-Miranda LR, et al. Loss of a mammalian circular RNA locus causes miRNA deregulation and affects brain function. *Science*. 2017;357(6357). doi:10.1126/science.aam8526
39. Park OH, Ha H, Lee Y, et al. Endoribonucleolytic cleavage of m(6)A-containing RNAs by RNase P/MRP complex. *Mol Cell*. 2019;74(3):494–507.e8. doi:10.1016/j.molcel.2019.02.034
40. Zhang L, Hou C, Chen C, et al. The role of N(6)-methyladenosine (m(6)A) modification in the regulation of circRNAs. *Mol Cancer*. 2020;19(1):105. doi:10.1186/s12943-020-01224-3
41. Kozyk M, Strubchevska K, Marynenko T, et al. Effect of peptides from plasma of patients with coronary artery disease on the vascular endothelial cells. *Medicina*. 2023;59(2):238. doi:10.3390/medicina59020238
42. Ye Q, Ju C, Ye Z, et al. Circ_ROBO2/miR-186-5p/TRIM14 axis regulates oxidized low-density lipoprotein-induced cardiac microvascular endothelial cell injury. *Regen Ther*. 2022;20:138–146. doi:10.1016/j.reth.2022.04.005
43. Gao W, Li C, Yuan J, et al. Circ-MBOAT2 regulates angiogenesis via the miR-495/NOTCH1 axis and associates with myocardial perfusion in patients with coronary chronic total occlusion. *Int J Mol Sci*. 2024;25(2):793.
44. Chang H, Li ZB, Wu JY, et al. Circ-100338 induces angiogenesis after myocardial ischemia-reperfusion injury by sponging miR-200a-3p. *Eur Rev Med Pharmacol Sci*. 2020;24(11):6323–6332. doi:10.26355/eurrev_202006_21530
45. Sun M, Zhai S, Gao Y, et al. Circ_0049979 ameliorates myocardial infarction through improving Cx43-mediated endothelial functions. *Toxicol Appl Pharmacol*. 2024;492:117121. doi:10.1016/j.taap.2024.117121
46. Ji P, Song X, Lv Z. Knockdown of circ_0004104 alleviates oxidized low-density lipoprotein-induced vascular endothelial cell injury by regulating miR-100/TNFAIP8 axis. *J Cardiovasc Pharmacol*. 2021;78(2):269–279. doi:10.1097/FJC.0000000000001063
47. Yang Z, Liang X, Yang L. Circular RNA circ_0001445 alleviates the ox-LDL-induced endothelial injury in human primary aortic endothelial cells through regulating ABCG1 via acting as a sponge of miR-208b-5p. *Gen Thorac Cardiovasc Surg*. 2022;70(9):779–792. doi:10.1007/s11748-022-01799-2
48. Gao WQ, Hu XM, Zhang Q, et al. Downregulation of circFASTKD1 ameliorates myocardial infarction by promoting angiogenesis. *Aging*. 2020;13(3):3588–3604. doi:10.18632/aging.202305
49. Wei W, Tang M, Wang Q, et al. Circ_HECW2 regulates ox-LDL-induced dysfunction of cardiovascular endothelial cells by miR-942-5p/TLR4 axis. *Clin Hemorheol Microcirc*. 2025;89(1):1–14. doi:10.3233/CH-221550

50. Yu F, Zhang Y, Wang Z, et al. Hsa_circ_0030042 regulates abnormal autophagy and protects atherosclerotic plaque stability by targeting eIF4A3. *Theranostics*. 2021;11(11):5404–5417. doi:10.7150/thno.48389
51. Shi P, Ji H, Zhang H, et al. circANRIL reduces vascular endothelial injury, oxidative stress and inflammation in rats with coronary atherosclerosis. *Exp Ther Med*. 2020;20(3):2245–2251. doi:10.3892/etm.2020.8956
52. Garikipati VNS, Verma SK, Cheng Z, et al. Circular RNA CircFndc3b modulates cardiac repair after myocardial infarction via FUS/VEGF-A axis. *Nat Commun*. 2019;10(1):4317. doi:10.1038/s41467-019-11777-7
53. Chen L, Luo W, Zhang W, et al. circDLPAG4/HECTD1 mediates ischaemia/reperfusion injury in endothelial cells via ER stress. *RNA Biol*. 2020;17(2):240–253. doi:10.1080/15476286.2019.1676114
54. Si X, Zheng H, Wei G, et al. circRNA Hipk3 induces cardiac regeneration after myocardial infarction in mice by binding to notch1 and miR-133a. *Mol Ther Nucleic Acids*. 2020;21:636–655. doi:10.1016/j.omtn.2020.06.024
55. Wei G, Li C, Jia X, et al. Extracellular vesicle-derived CircWhsc1 promotes cardiomyocyte proliferation and heart repair by activating TRIM59/STAT3/Cyclin B2 pathway. *J Adv Res*. 2023;53:199–218. doi:10.1016/j.jare.2022.12.014
56. Long X, Qiu Z, Li C, et al. CircERBB2IP promotes post-infarction revascularization via the miR-145a-5p/Smad5 axis. *Mol Ther Nucleic Acids*. 2022;28:573–586. doi:10.1016/j.omtn.2022.04.006
57. Tong X, Dang X, Liu D, et al. Exosome-derived circ_0001785 delays atherogenesis through the ceRNA network mechanism of miR-513a-5p/TGFBR3. *J Nanobiotechnology*. 2023;21(1):362. doi:10.1186/s12951-023-02076-x
58. Liang G, Chen S, Xin S, et al. Overexpression of hsa_circ_0001445 reverses oxLDL-induced inhibition of HUVEC proliferation via SRSF1. *Mol Med Rep*. 2021;24(1). doi:10.3892/mmr.2021.12146
59. Zhang Q, Sun W, Han J, et al. The circular RNA hsa_circ_0007623 acts as a sponge of microRNA-297 and promotes cardiac repair. *Biochem Biophys Res Commun*. 2020;523(4):993–1000. doi:10.1016/j.bbrc.2019.12.116
60. Zhang S, Wang W, Wu X, et al. Regulatory roles of circular RNAs in coronary artery disease. *Mol Ther Nucleic Acids*. 2020;21:172–179. doi:10.1016/j.omtn.2020.05.024
61. Wang L, Li H, Zheng Z, et al. Hsa_circ_0031891 targets miR-579-3p to enhance HMGB1 expression and regulate PDGF-BB-induced human aortic vascular smooth muscle cell proliferation, migration, and dedifferentiation. *Naunyn Schmiedebergs Arch Pharmacol*. 2024;397(2):1093–1104. doi:10.1007/s00210-023-02663-7
62. Sun J, Zhang Z, Yang S. Circ_RUSC2 upregulates the expression of miR-661 target gene SYK and regulates the function of vascular smooth muscle cells. *Biochem Cell Biol*. 2019;97(6):709–714. doi:10.1139/bcb-2019-0031
63. Peng W, Li T, Pi S, et al. Suppression of circular RNA circDHCR24 alleviates aortic smooth muscle cell proliferation and migration by targeting miR-149-5p/MMP9 axis. *Biochem Biophys Res Commun*. 2020;529(3):753–759. doi:10.1016/j.bbrc.2020.06.067
64. Lin DS, Zhang CY, Li L, et al. Circ_ROBO2/miR-149 axis promotes the proliferation and migration of human aortic smooth muscle cells by activating NF-κB signaling. *Cytogenet Genome Res*. 2021;161(8–9):414–424. doi:10.1159/000517294
65. Zhong W, Wang L, Xiong L. Circ_0006251 mediates the proliferation and apoptosis of vascular smooth muscle cells in CAD via enhancing TET3 and PPM1B expression. *Cell Mol Biol*. 2023;69(8):34–39. doi:10.14715/cmb/2023.69.8.5
66. Zeng Z, Xia L, Fan S, et al. Circular RNA CircMAP3K5 acts as a MicroRNA-22-3p sponge to promote resolution of intimal hyperplasia via TET2-mediated smooth muscle cell differentiation. *Circulation*. 2021;143(4):354–371. doi:10.1161/CIRCULATIONAHA.120.049715
67. Dai H, Zhao N, Zheng Y. CircLDLR modulates the proliferation and apoptosis of vascular smooth muscle cells in coronary artery disease through miR-26-5p/KDM6A axis. *J Cardiovasc Pharmacol*. 2022;80(1):132–139. doi:10.1097/FJC.0000000000001275
68. Yu L, Liang Y, Zhang M, et al. Extracellular vesicle-derived circCEBPZOS attenuates postmyocardial infarction remodeling by promoting angiogenesis via the miR-1178-3p/PDPK1 axis. *Commun Biol*. 2023;6(1):133. doi:10.1038/s42003-023-04505-x
69. Kou L, Yang N, Dong B, et al. Circular RNA testis-expressed 14 overexpression induces apoptosis and suppresses migration of ox-LDL-stimulated vascular smooth muscle cells via regulating the microRNA 6509-3p/thanatos-associated domain-containing apoptosis-associated protein 1 axis. *Bioengineered*. 2022;13(5):13150–13161. doi:10.1080/21655979.2022.2070582
70. Wang Z, Wang H, Guo C, et al. Role of hsa_circ_0000280 in regulating vascular smooth muscle cell function and attenuating neointimal hyperplasia via ELAVL1. *Cell Mol Life Sci*. 2022;80(1):3. doi:10.1007/s00018-022-04602-w
71. Hu H, Shen S, Wu J, et al. CircTOP1 targeted regulation of PTBP1 expression promotes the progression of coronary artery calcification. *Exp Cell Res*. 2024;440(2):114147. doi:10.1016/j.yexcr.2024.114147
72. Bai M, Pan CL, Jiang GX, et al. CircHIPK3 aggravates myocardial ischemia-reperfusion injury by binding to miRNA-124-3p. *Eur Rev Med Pharmacol Sci*. 2019;23(22):10107–10114. doi:10.26355/eurrev_201911_19580
73. Qiu Z, Wang Y, Liu W, et al. CircHIPK3 regulates the autophagy and apoptosis of hypoxia/reoxygenation-stimulated cardiomyocytes via the miR-20b-5p/ATG7 axis. *Cell Death Discov*. 2021;7(1):64. doi:10.1038/s41420-021-00448-6
74. Zhang CL, Long TY, Bi SS, et al. CircPAN3 ameliorates myocardial ischaemia/reperfusion injury by targeting miR-421/Pink1 axis-mediated autophagy suppression. *Lab Invest*. 2021;101(1):89–103. doi:10.1038/s41374-020-00483-4
75. An L, Zhong Y, Tan J, et al. Sevoflurane exerts protection against myocardial ischemia-reperfusion injury and pyroptosis through the circular RNA PAN3/microRNA-29b-3p/stromal cell-derived factor 4 axis. *Int Immunopharmacol*. 2023;120:110219. doi:10.1016/j.intimp.2023.110219
76. Zhu Y, Zou C, Jia Y, et al. Knockdown of circular RNA circMAT2B reduces oxygen-glucose deprivation-induced inflammatory injury in H9c2 cells through up-regulating miR-133. *Cell Cycle*. 2020;19(20):2622–2630. doi:10.1080/15384101.2020.1814025
77. Ma H, Lu Y, Zhu D, et al. Gypenoside A protects human myocardial cells from ischemia/reperfusion injury via the circ_0010729/miR-370-3p/RUNX1 axis. *Biochemistry*. 2024;89(5):973–986. doi:10.1134/S000629792405016X
78. Zheng H, Huang S, Wei G, et al. CircRNA Samd4 induces cardiac repair after myocardial infarction by blocking mitochondria-derived ROS output. *Mol Ther*. 2022;30(11):3477–3498. doi:10.1016/j.ymthe.2022.06.016
79. Tang Y, Wang YX, Zhan YL, et al. Circular RNA Pum_0014 targets miR-146a-5p/NF2 axis to regulate VEGF/PAK1 pathway and reduce H2O2-induced cardiomyocyte apoptosis. *Altern Ther Health Med*. 2024;2024:AT9392.
80. Shan TK, Yang TT, Jing P, et al. Circular RNA IGF1R promotes cardiac repair via activating β-catenin signaling by interacting with DDX5 in mice after ischemic insults. *Research*. 2024;7:0451. doi:10.34133/research.0451
81. Su Y, Zhao L, Lei D, et al. Inhibition of circ_0073932 attenuates myocardial ischemia–reperfusion injury via miR-493-3p/FAF1/JNK. *Vitro Cell Dev Biol Anim*. 2024;60(6):628–643. doi:10.1007/s11626-024-00900-8

82. Chen H, Cheng Z, Wang M, et al. Circ_0020887 silencing combats hypoxic-induced cardiomyocyte injury in an MiR-370-3p/CYP1B1-dependent manner. *Int Heart J*. 2024;65(2):308–317. doi:10.1536/ihj.23-325
83. Liu J, Wang Z, Lin A, et al. Exosomes from hypoxic pretreatment ADSCs ameliorate cardiac damage post-MI via activated circ-Stt3b/miR-15a-5p/GPX4 signaling and decreased ferroptosis. *Cardiovasc Toxicol*. 2024;24(11):1215–1225. doi:10.1007/s12012-024-09915-9
84. Feng P, Chu Y, Li J, et al. Effect and mechanism of circHMGA2 on ferroptosis and pyroptosis in myocardial ischemia-reperfusion model CircHMGA2 exacerbates MI/R injury. *Heliyon*. 2023;9(7):e17849. doi:10.1016/j.heliyon.2023.e17849
85. Wang J, Wang X, Cao M, et al. CircUSP39/miR-362-3p/TRAF3 axis mediates hypoxia/reoxygenation-induced cardiomyocyte oxidative stress, inflammation, and apoptosis. *Int Heart J*. 2023;64(2):263–273. doi:10.1536/ihj.22-232
86. Liu Q, Hu Y, Jie H, et al. CircHDAC9 regulates myocardial ischemia-reperfusion injury via miR-671-5p/SOX4 signaling axis. *Am J Med Sci*. 2024;367(1):49–60. doi:10.1016/j.amjms.2023.11.001
87. Tan J, Min J, Jiang Y, et al. CircCHSY1 protects hearts against ischaemia/reperfusion injury by enhancing heme oxygenase 1 expression via miR-24-3p. *Cardiovasc Res*. 2024;120(15):1924–1938. doi:10.1093/cvr/cvae162
88. Zhao Q, Li W, Pan W, et al. CircRNA 010567 plays a significant role in myocardial infarction via the regulation of the miRNA-141/DAPK1 axis. *J Thorac Dis*. 2021;13(4):2447–2459. doi:10.21037/jtd-21-212
89. Cai L, Qi B, Wu X, et al. Circular RNA Ttc3 regulates cardiac function after myocardial infarction by sponging miR-15b. *J Mol Cell Cardiol*. 2019;130:10–22. doi:10.1016/j.yjmcc.2019.03.007
90. Huang S, Li X, Zheng H, et al. Loss of super-enhancer-regulated circRNA Nfix induces cardiac regeneration after myocardial infarction in adult mice. *Circulation*. 2019;139(25):2857–2876. doi:10.1161/CIRCULATIONAHA.118.038361
91. Zhang J, Tang Y, Zhang J, et al. CircRNA ACAP2 is overexpressed in myocardial infarction and promotes the maturation of miR-532 to induce the apoptosis of cardiomyocyte. *J Cardiovasc Pharmacol*. 2021;78(2):247–252. doi:10.1097/FJC.0000000000001065
92. Wang X, Sun Q, Hu W. Carvedilol protects against the H2O2-induced cell damages in rat myoblasts by regulating the Circ_NFIX/miR-125b-5p/TLR4 signal axis. *J Cardiovasc Pharmacol*. 2021;78(4):604–614. doi:10.1097/FJC.0000000000001095
93. Chen TP, Zhang NJ, Wang HJ, et al. Knockdown of circROBO2 attenuates acute myocardial infarction through regulating the miR-1184/TRADD axis. *Mol Med*. 2021;27(1):21. doi:10.1186/s10020-021-00275-6
94. Wang S, Li L, Deng W, et al. CircRNA MFACR is upregulated in myocardial infarction and downregulates miR-125b to promote cardiomyocyte apoptosis induced by hypoxia. *J Cardiovasc Pharmacol*. 2021;78(6):802–808. doi:10.1097/FJC.0000000000001123
95. Gao XQ, Liu CY, Zhang YH, et al. The circRNA CNEACR regulates necroptosis of cardiomyocytes through Foxa2 suppression. *Cell Death Differ*. 2022;29(3):527–539. doi:10.1038/s41418-021-00872-2
96. Zhang M, Wang Z, Cheng Q, et al. Circular RNA (circRNA) CDYL induces myocardial regeneration by ceRNA after myocardial infarction. *Med Sci Monit*. 2020;26:e923188. doi:10.12659/MSM.923188
97. Jin P, Li LH, Shi Y, et al. Salidroside inhibits apoptosis and autophagy of cardiomyocyte by regulation of circular RNA hsa_circ_0000064 in cardiac ischemia-reperfusion injury. *Gene*. 2021;767:145075. doi:10.1016/j.gene.2020.145075
98. Zhai C, Qian G, Wu H, et al. Knockdown of circ_0060745 alleviates acute myocardial infarction by suppressing NF-κB activation. *J Cell Mol Med*. 2020;24(21):12401–12410. doi:10.1111/jcmm.15748
99. Hu X, Ma R, Cao J, et al. CircSAMD4A aggravates H/R-induced cardiomyocyte apoptosis and inflammatory response by sponging miR-138-5p. *J Cell Mol Med*. 2022;26(6):1776–1784. doi:10.1111/jcmm.16093
100. Bian Y, Pang P, Li X, et al. CircHelz activates NLRP3 inflammasome to promote myocardial injury by sponging miR-133a-3p in mouse ischemic heart. *J Mol Cell Cardiol*. 2021;158:128–139. doi:10.1016/j.yjmcc.2021.05.010
101. Cai X, Li B, Wang Y, et al. CircJARID2 regulates hypoxia-induced injury in h9c2 cells by affecting miR-9-5p-mediated BNIP3. *J Cardiovasc Pharmacol*. 2021;78(1):e77–e85. doi:10.1097/FJC.0000000000001033
102. Song YF, Zhao L, Wang BC, et al. The circular RNA TLK1 exacerbates myocardial ischemia/reperfusion injury via targeting miR-214/RIPK1 through TNF signaling pathway. *Free Radic Biol Med*. 2020;155:69–80. doi:10.1016/j.freeradbiomed.2020.05.013
103. Deng H, Cui M, Liu L, et al. CIRC-MARC2 SILENCING PROTECTS HUMAN CARDIOMYOCYTES FROM HYPOXIA/REOXYGENATION-INDUCED INJURY BY MODULATING MIR-335-5P/TRPM7 AXIS. *Shock*. 2024;61(5):675–684. doi:10.1097/SHK.0000000000002244
104. Yang YN, Luo YB, Xu G, et al. CircHECTD1 promoted MIRI -associated inflammation via inhibiting miR −138-5p and upregulating ROCK2. *Kaohsiung J Med Sci*. 2023;39(7):675–687. doi:10.1002/kjm2.12686
105. Xiao Y, Oumarou DB, Wang S, et al. Circular RNA involved in the protective effect of malva sylvestris L. on myocardial ischemic/re-perfused injury. *Front Pharmacol*. 2020;11:520486. doi:10.3389/fphar.2020.520486
106. Lei D, Wang Y, Zhang L, et al. Circ_0010729 regulates hypoxia-induced cardiomyocyte injuries by activating TRAF5 via sponging miR-27a-3p. *Life Sci*. 2020;262:118511. doi:10.1016/j.lfs.2020.118511
107. Wang L, Su H, Liu W. Hsa_circ_0010729 regulates H(2)O(2)-induced myocardial injury by regulating miR-1184/RIPK1 axis. *Transpl Immunol*. 2022;74:101653. doi:10.1016/j.trim.2022.101653
108. Wang ZY, Liu XX, Deng YF. Negative feedback of SNRK to circ-SNRK regulates cardiac function post-myocardial infarction. *Cell Death Differ*. 2022;29(4):709–721. doi:10.1038/s41418-021-00885-x
109. Ren K, Li B, Jiang L, et al. circ_0023461 silencing protects cardiomyocytes from hypoxia-induced dysfunction through targeting miR-370-3p/PDE4D signaling. *Oxid Med Cell Longev*. 2021;2021:8379962. doi:10.1155/2021/8379962
110. Li RL, Fan CH, Gong SY, et al. Effect and mechanism of LRP6 on cardiac myocyte ferroptosis in myocardial infarction. *Oxid Med Cell Longev*. 2021;2021:8963987. doi:10.1155/2021/8963987
111. Wei Q, Jiang M, Tang B, et al. Downregulation of circular RNA 00091761 protects against heart failure after myocardial infarction via microRNA-335-3p/ ASCL4 axis. *Acta Biochim Pol*. 2023;70(3):509–516. doi:10.18388/abp.2020_6404
112. Xu C, Jia Z, Cao X, et al. Hsa_circ_0007059 promotes apoptosis and inflammation in cardiomyocytes during ischemia by targeting microRNA-378 and microRNA-383. *Cell Cycle*. 2022;21(10):1003–1019. doi:10.1080/15384101.2022.2040122
113. Liu X, Dou B, Tang W, et al. Cardioprotective effects of circ_0002612 in myocardial ischemia/reperfusion injury correlate with disruption of miR-30a-5p-dependent Ppargc1a inhibition. *Int Immunopharmacol*. 2023;117:110006. doi:10.1016/j.intimp.2023.110006

114. Liu X, Wang M, Li Q, et al. CircRNA ACAP2 induces myocardial apoptosis after myocardial infarction by sponging miR-29. *Minerva Med*. 2022;113(1):128–134. doi:10.23736/S0026-4806.20.06600-8
115. Zhang J, Zhang T, Zhang W, et al. Circular RNA-DENND4C in H9c2 cells relieves OGD/R-induced injury by down regulation of microRNA-320. *Cell Cycle*. 2020;19(22):3074–3085. doi:10.1080/15384101.2020.1831253
116. Sun G, Shen JF, Wei XF, et al. Circular RNA Foxo3 relieves myocardial ischemia/reperfusion injury by suppressing autophagy via inhibiting HMGB1 by repressing KAT7 in myocardial infarction. *J Inflamm Res*. 2021;14:6397–6407. doi:10.2147/JIR.S339133
117. Wang Y, Zhao R, Shen C, et al. Exosomal CircHIPK3 released from hypoxia-induced cardiomyocytes regulates cardiac angiogenesis after myocardial infarction. *Oxid Med Cell Longev*. 2020;2020:8418407. doi:10.1155/2020/8418407
118. Wang D, Tian L, Wang Y, et al. Circ_0001206 regulates miR-665/CRKL axis to alleviate hypoxia/reoxygenation-induced cardiomyocyte injury in myocardial infarction. *ESC Heart Fail*. 2022;9(2):998–1007. doi:10.1002/ehf2.13725
119. Ding W, Ding L, Lu Y, et al. Circular RNA-circLRP6 protects cardiomyocyte from hypoxia-induced apoptosis by facilitating hnRNPM-mediated expression of FGF-9. *Febs J*. 2024;291(6):1246–1263. doi:10.1111/febs.17038
120. Huang C, Shu L, Zhang H, et al. Circ_ZNF512-mediated miR-181d-5p inhibition limits cardiomyocyte autophagy and promotes myocardial ischemia/reperfusion injury through an EGR1/mTORC1/TFEB-based mechanism. *J Med Chem*. 2022;65(3):1808–1821. doi:10.1021/acs.jmedchem.1c00745
121. Li D, You J, Mao C, et al. Circular RNA Fbxl5 regulates cardiomyocyte apoptosis during ischemia reperfusion injury via sponging microRNA-146a. *J Inflamm Res*. 2022;15:2539–2550. doi:10.2147/JIR.S360129
122. Wang L, Yu P, Wang J, et al. Downregulation of circ-ZNF609 promotes heart repair by modulating RNA N(6)-methyladenosine-modified yap expression. *Research*. 2022;2022:9825916. doi:10.34133/2022/9825916
123. Li X, Guo L, Wang J, et al. Pro-fibrotic and apoptotic activities of circARAP1 in myocardial ischemia-reperfusion injury. *Eur J Med Res*. 2023;28(1):84. doi:10.1186/s40001-023-01001-0
124. Zhu Y, Zhao P, Sun L, et al. Overexpression of circRNA SNRK targets miR-103-3p to reduce apoptosis and promote cardiac repair through GSK3β/β-catenin pathway in rats with myocardial infarction. *Cell Death Discov*. 2021;7(1):84. doi:10.1038/s41420-021-00467-3
125. Ju J, Li XM, Zhao XM, et al. Circular RNA FEACR inhibits ferroptosis and alleviates myocardial ischemia/reperfusion injury by interacting with NAMPT. *J Biomed Sci*. 2023;30(1):45. doi:10.1186/s12929-023-00927-1
126. Bai M, Pan CL, Jiang GX, et al. CircRNA 010567 improves myocardial infarction rats through inhibiting TGF-β1. *Eur Rev Med Pharmacol Sci*. 2020;24(1):369–375. doi:10.26355/eurrev_202001_19935
127. Zhao B, Li G, Peng J, et al. CircMACF1 attenuates acute myocardial infarction through miR-500b-5p-EMP1 axis. *J Cardiovasc Transl Res*. 2021;14(1):161–172. doi:10.1007/s12265-020-09976-5
128. Cheng N, Wang MY, Wu YB, et al. Circular RNA POSTN promotes myocardial infarction-induced myocardial injury and cardiac remodeling by regulating miR-96-5p/BNIP3 axis. *Front Cell Dev Biol*. 2020;8:618574. doi:10.3389/fcell.2020.618574
129. Tian T, Li F, Chen R, et al. Therapeutic potential of exosomes derived from circRNA_0002113 lacking mesenchymal stem cells in myocardial infarction. *Front Cell Dev Biol*. 2021;9:779524. doi:10.3389/fcell.2021.779524
130. Zhao Y, Wang S, Liu S, et al. CircHSPG2 absence weakens hypoxia-induced dysfunction in cardiomyocytes by targeting the miR-25-3p/PAWR axis. *Cardiovasc Diagn Ther*. 2022;12(5):589–602. doi:10.21037/cdt-22-197
131. Chai Q, Zheng M, Wang L, et al. Circ_0068655 promotes cardiomyocyte apoptosis via miR-498/PAWR axis. *Tissue Eng Regen Med*. 2020;17(5):659–670. doi:10.1007/s13770-020-00270-8
132. Ye X, Hang Y, Lu Y, et al. CircRNA circ-NNT mediates myocardial ischemia/reperfusion injury through activating pyroptosis by sponging miR-33a-5p and regulating USP46 expression. *Cell Death Discov*. 2021;7(1):370. doi:10.1038/s41420-021-00706-7
133. Lan Z, Wang T, Zhang L, et al. CircSLC8A1 exacerbates hypoxia-induced myocardial injury via interacting with MiR-214-5p to upregulate TEAD1 expression. *Int Heart J*. 2022;63(3):591–601. doi:10.1536/ihj.21-547
134. Cui X, Dong Y, Li M, et al. A circular RNA from NFIX facilitates oxidative stress-induced H9c2 cells apoptosis. *Vitro Cell Dev Biol Anim*. 2020;56(9):715–722. doi:10.1007/s11626-020-00476-z
135. Liu J, Dong W, Gao C, et al. Salvianolic acid B protects cardiomyocytes from ischemia/reperfusion injury by mediating circTRRAP/miR-214-3p/SOX6 axis. *Int Heart J*. 2022;63(6):1176–1186. doi:10.1536/ihj.22-102
136. Li S, Zhou Y, Li K, et al. Inhibition of circDGKZ ameliorates myocardial ischemia/reperfusion injury by targeting miR-345-5p/TLR4. *ESC Heart Fail*. 2024;11(5):2730–2741. doi:10.1002/ehf2.14809
137. Luo C, Ling GX, Lei BF, et al. Circular RNA PVT1 silencing prevents ischemia-reperfusion injury in rat by targeting microRNA-125b and microRNA-200a. *J Mol Cell Cardiol*. 2021;159:80–90. doi:10.1016/j.yjmcc.2021.05.019
138. Liu B, Guo K. CircRbms1 knockdown alleviates hypoxia-induced cardiomyocyte injury via regulating the miR-742-3p/FOXO1 axis. *Cell Mol Biol Lett*. 2022;27(1):31. doi:10.1186/s11658-022-00330-y
139. Tan J, Pan W, Chen H, et al. Circ_0124644 serves as a ceRNA for miR-590-3p to promote hypoxia-induced cardiomyocytes injury via regulating SOX4. *Front Genet*. 2021;12:667724. doi:10.3389/fgene.2021.667724
140. Zhang Y, Liu S, Ding L, et al. Circ_0030235 knockdown protects H9c2 cells against OGD/R-induced injury via regulation of miR-526b. *PeerJ*. 2021;9:e11482. doi:10.7717/peerj.11482
141. Li C, Wang J, Feng J, et al. Circ-JA760602 promotes the apoptosis of hypoxia-induced cardiomyocytes by transcriptionally suppressing BCL2. *Int J Dev Biol*. 2023;67(1):9–17. doi:10.1387/ijdb.220150jl
142. Huang C, Qu Y, Feng F, et al. Cardioprotective effect of circ_SMG6 knockdown against myocardial ischemia/reperfusion injury correlates with miR-138-5p-mediated EGR1/TLR4/TRIF inactivation. *Oxid Med Cell Longev*. 2022;2022:1927260. doi:10.1155/2022/1927260
143. Wang S, Cheng Z, Chen X, et al. CircUBXN7 mitigates H/R-induced cell apoptosis and inflammatory response through the miR-622-MCL1 axis. *Am J Transl Res*. 2021;13(8):8711–8727.
144. Liao H, Xiao C, Li W, et al. Silencing hsa_circ_0049271 attenuates hypoxia-reoxygenation (H/R)-induced myocardial cell injury via the miR-17-3p/FZD4 signaling axis. *Ann Transl Med*. 2023;11(2):99. doi:10.21037/atm-22-6331
145. Zhou LY, Zhai M, Huang Y, et al. The circular RNA ACR attenuates myocardial ischemia/reperfusion injury by suppressing autophagy via modulation of the Pink1/ FAM65B pathway. *Cell Death Differ*. 2019;26(7):1299–1315. doi:10.1038/s41418-018-0206-4

146. Huang L, Guo B, Yan J, et al. CircHSPG2 knockdown attenuates hypoxia-induced apoptosis, inflammation, and oxidative stress in human AC16 cardiomyocytes by regulating the miR-1184/MAP3K2 axis. *Cell Stress Chaperones*. 2023;28(2):177–190. doi:10.1007/s12192-023-01328-x
147. Yan L, Qi H, Zhou W. Silencing of Hsa_circ_0055440 alleviates hypoxia-induced cardiomyocyte injury by regulating the MiR-499b-5p/ACSL1 axis. *Int Heart J*. 2023;64(2):274–282. doi:10.1536/ihj.22-473
148. Cao S, Li C, Li L, et al. Circular RNA hsa_circ_0000848 regulates cardiomyocyte proliferation and apoptosis under hypoxia via recruiting ELAVL1 and stabilizing SMAD7 mRNA. *Anatol J Cardiol*. 2022;26(3):189–197. doi:10.5152/AnatolJCardiol.2021.40067
149. Jin L, Zhang Y, Jiang Y, et al. Circular RNA Rbms1 inhibited the development of myocardial ischemia reperfusion injury by regulating miR-92a/BCL2L11 signaling pathway. *Bioengineered*. 2022;13(2):3082–3092. doi:10.1080/21655979.2022.2025696
150. Zhou D, Dai Z, Ren M, et al. Adipose-derived stem cells-derived exosomes with high amounts of Circ_0001747 alleviate hypoxia/reoxygenation-induced injury in myocardial cells by targeting MiR-199b-3p/MCL1 axis. *Int Heart J*. 2022;63(2):356–366. doi:10.1536/ihj.21-441
151. Xu W, Qian L, Yuan X, et al. Regulation of a novel CircTRRAP/miR-761/MAP3K2 CeRNA cascade in inflammation, apoptosis, and oxidative stress in human AC16 cardiomyocytes under hypoxia conditions. *Int Heart J*. 2023;64(3):442–452. doi:10.1536/ihj.22-624
152. Zhang J, Luo CJ, Xiong XQ, et al. MiR-21-5p-expressing bone marrow mesenchymal stem cells alleviate myocardial ischemia/reperfusion injury by regulating the circRNA_0031672/miR-21-5p/programmed cell death protein 4 pathway. *J Geriatr Cardiol*. 2021;18(12):1029–1043. doi:10.11909/j.issn.1671-5411.2021.12.004
153. Liang Y, Jie H, Liu Q, et al. Knockout of circRNA single stranded interacting protein 1 (circRBMS1) played a protective role in myocardial ischemia-reperfusion injury though inhibition of miR-2355-3p/Mammalian Sterile20-like kinase 1 (MST1) axis. *Bioengineered*. 2022;13(5):12726–12737. doi:10.1080/21655979.2022.2068896
154. Liu Y, Ke X, Guo W, et al. Circ-RHOJ.1 regulated myocardial cell proliferation and apoptosis via targeting the miR-124-3p/NRG-1 axis in myocardial ischemia/reperfusion injury. *Arch Med Sci*. 2022;18(3):732–745. doi:10.5114/aoms.2019.87205
155. Yin L, Li L, Gao M, et al. circMIRIAF aggravates myocardial ischemia-reperfusion injury via targeting miR-544/WDR12 axis. *Redox Biol*. 2024;73:103175. doi:10.1016/j.redox.2024.103175
156. Zhou HF, Xu LL, Xie B, et al. Hsa-circ-0068566 inhibited the development of myocardial ischemia reperfusion injury by regulating hsa-miR-6322/PARP2 signal pathway. *Eur Rev Med Pharmacol Sci*. 2020;24(12):6980–6993. doi:10.26355/eurrev_202006_21690
157. Zhang Y, Li Z, Wang J, et al. CircTRRAP knockdown has cardioprotective function in cardiomyocytes via the signal regulation of miR-370-3p/PAWR axis. *Cardiovasc Ther*. 2022;2022:7125602. doi:10.1155/2022/7125602
158. Lin L, Wang L, Li A, et al. CircDiaph3 aggravates H/R-induced cardiomyocyte apoptosis and inflammation through miR-338-3p/SRSF1 axis. *J Bioenerg Biomembr*. 2024;56(3):235–245. doi:10.1007/s10863-023-09992-5
159. Jin A, Zhang Q, Cheng H, et al. Circ_0050908 up-regulates TRAF3 by sponging miR-324-5p to aggravate myocardial ischemia-reperfusion injury. *Int Immunopharmacol*. 2022;108:108740. doi:10.1016/j.intimp.2022.108740
160. Wu H, Li H, Zhang Q, et al. CircBCL2L13 attenuates cardiomyocyte oxidative stress and apoptosis in cardiac ischemia–reperfusion injury via miR-1246/PEG3 signaling. *J Biochem Mol Toxicol*. 2024;38(4):e23711. doi:10.1002/jbt.23711
161. Li G, Tang X, Tang H. Circular RNA ANKIB1 alleviates hypoxia-induced cardiomyocyte injury by modulating miR-452-5p/SLC7A11 axis. *Adv Clin Exp Med*. 2024;33(3):261–272. doi:10.17219/acem/168242
162. Wang K, Wang H, Zhang Q, et al. Knockdown of CIRC_0001379 attenuates hypoxia/reoxygenation-induced cardiomyocyte apoptosis and inflammatory response bY MIR-98-5P/SOX6 AXIS. *Shock*. 2023;60(3):410–418. doi:10.1097/SHK.0000000000002178
163. Chen S, Sun L, Hao M, et al. Circ-SWT1 ameliorates H(2)O(2)-induced apoptosis, oxidative stress and endoplasmic reticulum stress in cardiomyocytes via miR-192-5p/SOD2 axis. *Cardiovasc Toxicol*. 2022;22(4):378–389. doi:10.1007/s12012-022-09720-2
164. Chen YE, Yang H, Pang HB, et al. Circ-CBFB exacerbates hypoxia/reoxygenation-triggered cardiomyocyte injury via regulating miR-495-3p in a VDAC1-dependent manner. *J Biochem Mol Toxicol*. 2022;36(11):e23189. doi:10.1002/jbt.23189
165. Ji DN, Jin SD, Jiang Y, et al. CircNSD1 promotes cardiac fibrosis through targeting the miR-429-3p/SULF1/Wnt/β-catenin signaling pathway. *Acta Pharmacol Sin*. 2024;45(10):2092–2106. doi:10.1038/s41401-024-01296-7
166. Wang Y, Liu Y, Fei A, et al. CircMACF1 alleviates myocardial fibrosis after acute myocardial infarction by suppressing cardiac fibroblast activation via the miR-16-5p/SMAD7 axis. *Medicine*. 2023;102(37):e35119. doi:10.1097/MD.0000000000035119
167. Li F, Long TY, Bi SS, et al. circPAN3 exerts a profibrotic role via sponging miR-221 through FoxO3/ATG7-activated autophagy in a rat model of myocardial infarction. *Life Sci*. 2020;257:118015. doi:10.1016/j.lfs.2020.118015
168. Wang Y, Li C, Zhao R, et al. CircUbe3a from M2 macrophage-derived small extracellular vesicles mediates myocardial fibrosis after acute myocardial infarction. *Theranostics*. 2021;11(13):6315–6333. doi:10.7150/thno.52843
169. Pang P, Si W, Wu H, et al. The circular RNA circHelz enhances cardiac fibrosis by facilitating the nuclear translocation of YAP1. *Transl Res*. 2023;257:30–42. doi:10.1016/j.trsl.2023.01.008
170. Li XX, Mu B, Li X, et al. circCELF1 inhibits myocardial fibrosis by regulating the expression of DKK2 through FTO/m(6)A and miR-636. *J Cardiovasc Transl Res*. 2022;15(5):998–1009. doi:10.1007/s12265-022-10209-0
171. Sun LY, Zhao JC, Ge XM, et al. Circ_LAS1L regulates cardiac fibroblast activation, growth, and migration through miR-125b/SFRP5 pathway. *Cell Biochem Funct*. 2020;38(4):443–450. doi:10.1002/cbf.3486
172. Xiao MS, Wilusz JE. An improved method for circular RNA purification using RNase R that efficiently removes linear RNAs containing G-quadruplexes or structured 3' ends. *Nucleic Acids Res*. 2019;47(16):8755–8769. doi:10.1093/nar/gkz576
173. Yang W, Sun L, Cao X, et al. Detection of circRNA biomarker for acute myocardial infarction based on system biological analysis of RNA expression. *Front Genet*. 2021;12:686116. doi:10.3389/fgene.2021.686116
174. Zhu W, Li X. Liquid biopsy in coronary heart disease. *Methods Mol Biol*. 2023;2695:279–293.
175. Nahm FS. Receiver operating characteristic curve: overview and practical use for clinicians. *Korean J Anesthesiol*. 2022;75(1):25–36. doi:10.4097/kja.21209
176. Wang L, Shen C, Wang Y, et al. Identification of circular RNA Hsa_circ_0001879 and Hsa_circ_0004104 as novel biomarkers for coronary artery disease. *Atherosclerosis*. 2019;286:88–96. doi:10.1016/j.atherosclerosis.2019.05.006
177. Sun YN, Liu B, Wang JJ, et al. Identification of aberrantly expressed circular RNAs in hyperlipidemia-induced retinal vascular dysfunction in mice. *Genomics*. 2021;113(1 Pt 2):593–600. doi:10.1016/j.ygeno.2020.09.055

178. Sun F, Zou S, Li X, et al. Abnormal expression of circ_0013958 in patients with acute myocardial infarction (AMI) and its influence on prognosis. *J Cardiothorac Surg*. 2024;19(1):517. doi:10.1186/s13019-024-03036-8
179. Huang S, Wu Z, Zhou Y. Hypoxia-induced circRNAs encoded by PPARA are highly expressed in human cardiomyocytes and are potential clinical biomarkers of acute myocardial infarction. *Eur J Med Res*. 2024;29(1):159. doi:10.1186/s40001-024-01753-3
180. Zhang W, Cui J, Li L, et al. Identification of plasma exosomes hsa_circ_0001360 and hsa_circ_0000038 as key biomarkers of coronary heart disease. *Cardiol Res Pract*. 2024;2024:5557143. doi:10.1155/2024/5557143
181. Huang S, Zeng Z, Sun Y, et al. Association study of hsa_circ_0001946, hsa-miR-7-5p and PARP1 in coronary atherosclerotic heart disease. *Int J Cardiol*. 2021;328:1–7. doi:10.1016/j.ijcard.2020.12.026
182. Liang B, Li M, Deng Q, et al. CircRNA ZNF609 in peripheral blood leukocytes acts as a protective factor and a potential biomarker for coronary artery disease. *Ann Transl Med*. 2020;8(12):741. doi:10.21037/atm-19-4728
183. Miao L, Yin RX, Zhang QH, et al. A novel circRNA-miRNA-mRNA network identifies circ-YOD1 as a biomarker for coronary artery disease. *Sci Rep*. 2019;9(1):18314. doi:10.1038/s41598-019-54603-2
184. Dinh P, Peng J, Tran T, et al. Identification of hsa_circ_0001445 of a novel circRNA-miRNA-mRNA regulatory network as potential biomarker for coronary heart disease. *Front Cardiovasc Med*. 2023;10:1104223. doi:10.3389/fcvm.2023.1104223
185. Wu WP, Pan YH, Cai MY, et al. Plasma-derived exosomal circular RNA hsa_circ_0005540 as a novel diagnostic biomarker for coronary artery disease. *Dis Markers*. 2020;2020:3178642. doi:10.1155/2020/3178642
186. Liu R, Hu L, Zhou Y, et al. Serum circPRDM5 as a novel diagnostic biomarker for acute myocardial infarction. *Gene*. 2024;899:148142. doi:10.1016/j.gene.2024.148142
187. Wang G, Wang C, Huang Z, et al. Exosomal circ-0020887 and circ-0009590 as novel biomarkers for the diagnosis and prediction of short-term adverse cardiovascular outcomes in STEMI patients. *Open Med*. 2023;18(1):20230807. doi:10.1515/med-2023-0807
188. Zhao JW, Yu HY, Zhang YZ, et al. Expression and clinical significance of circRNA cSMARCA5 in patients with acute myocardial infarction. *Zhonghua Yi Xue Za Zhi*. 2023;103(12):901–906. doi:10.3760/cma.j.cn112137-20220810-01722
189. Zhou Q, Boeckel JN, Yao J, et al. Diagnosis of acute myocardial infarction using a combination of circulating circular RNA cZNF292 and clinical information based on machine learning. *MedComm*. 2023;4(3):e299. doi:10.1002/mco2.299
190. Xu J, Wang Z, Ai Y, et al. Serum circRNA (Circ)_0051386 assists in the diagnosis of acute ST-segment elevation myocardial infarction and prediction of the occurrence of major adverse cardiovascular events after percutaneous coronary intervention. *Acta Cardiol*. 2024;79(2):215–223. doi:10.1080/00015385.2024.2324218
191. Hou C, Gu L, Guo Y, et al. Association between circular RNA expression content and severity of coronary atherosclerosis in human coronary artery. *J Clin Lab Anal*. 2020;34(12):e23552. doi:10.1002/jcla.23552
192. Wang X, Nie H, Su M, et al. Serum CircNIPSNAP3A is associated with metabolic disorders, atherosclerosis and severity of coronary artery disease in a Chinese population. *Tohoku J Exp Med*. 2024;263(2):123–131. doi:10.1620/tjem.2024.J023
193. Chen C, Zhao X, Xie X. Prognostic value of peripheral blood circular RNAs in patients with acute coronary syndrome. *J Thorac Dis*. 2022;14(4):1139–1145. doi:10.21037/jtd-22-253
194. He AT, Liu J, Li F, et al. Targeting circular RNAs as a therapeutic approach: current strategies and challenges. *Signal Transduct Target Ther*. 2021;6(1):185. doi:10.1038/s41392-021-00569-5
195. Ghafouri-Fard S, Gholipour M, Taheri M. The emerging role of long non-coding RNAs and circular RNAs in coronary artery disease. *Front Cardiovasc Med*. 2021;8:632393. doi:10.3389/fcvm.2021.632393
196. Dergunova LV, Vinogradina MA, Filippenkov IB, et al. Circular RNAs variously participate in coronary atherogenesis. *Curr Issues Mol Biol*. 2023;45(8):6682–6700. doi:10.3390/cimb45080422
197. Ma X, Chen X, Mo C, et al. The role of circRNAs in the regulation of myocardial angiogenesis in coronary heart disease. *Microvasc Res*. 2022;142:104362. doi:10.1016/j.mvr.2022.104362