

Circular RNAs in coronary heart disease: From molecular mechanism to promising clinical application (Review)

ZENGGUANG FAN¹, XINGXING YUAN² and YE YUAN¹

¹Department of Cardiology, Affiliated Hospital of Jiangxi University of Chinese Medicine, Nanchang, Jiangxi 330006, P.R. China;

²Department of Gastroenterology, Heilongjiang Academy of Traditional Chinese Medicine, Harbin, Heilongjiang 150006, P.R. China

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Abstract. Coronary heart disease (CHD) remains a leading cause of morbidity and mortality worldwide, posing a substantial public health burden. Despite advancements in treatment, the complex etiology of CHD necessitates ongoing exploration of novel diagnostic markers and therapeutic targets. Circular RNAs (circRNAs), a distinct class of non-coding RNAs with a covalently closed loop structure, have emerged as significant regulators in various diseases, including CHD. Their high stability, tissue-specific expression and evolutionary conservation underscore their potential as biomarkers and therapeutic agents in CHD. This review discusses the current knowledge on circRNAs in the context of CHD and explores the molecular mechanisms by which circRNAs influence the pathophysiology of CHD, including cardiomyocyte death, endothelial injury, vascular dysfunction and inflammation. It also summarizes the emerging evidence highlighting the differential expression of circRNAs in patients with CHD and

their potential utilities as non-invasive diagnostic and prognostic biomarkers and therapeutic targets for this disease.

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1. Introduction

Coronary heart disease (CHD), a leading cause of morbidity and mortality globally, represents a significant public health challenge (1). CHD is primarily driven by atherosclerosis, an inflammatory process characterized by the accumulation of lipids, inflammatory cells and fibrous elements within the arterial wall, which leads to the formation of atherosclerotic plaques and further compromises blood flow and oxygen delivery to the myocardium, contributing to severe outcomes such as myocardial infarction and heart failure (2). The underlying mechanisms of CHD are multifactorial, involving dyslipidemia, endothelial dysfunction, oxidative stress and chronic inflammation (3). These factors collectively contribute to the initiation and progression of atherosclerosis, highlighting the need for comprehensive approaches to understand and manage the disease. Furthermore, the heterogeneity of the disease, coupled with the complex interplay of genetic, environmental and lifestyle factors, complicates the identification of precise diagnostic markers and effective therapeutic targets (4).

Currently, circular RNAs (circRNAs) have emerged as a pivotal class of non-coding RNAs, attracting substantial attention in the field of cardiovascular research (5). Unlike linear RNAs, circRNAs are characterized by their covalently closed loop structure, which confers remarkable stability and resistance to exonuclease-mediated degradation (6). This unique structure not only enables circRNAs to function as microRNA (miRNA) sponges, which contain miRNA binding sites and regulate gene expression by sequestering miRNAs, but also allows them to interact with RNA-binding proteins (RBPs),

Correspondence to: Professor Ye Yuan, Department of Cardiology, Affiliated Hospital of Jiangxi University of Chinese Medicine, 445 Bayi Avenue, Nanchang, Jiangxi 330006, P.R. China
E-mail: yuanye901005@163.com

Abbreviations: CDKN1A, cyclin-dependent kinase suppressor 1; ceRNA, competitive endogenous RNA; CHD, coronary heart disease; ciRNA, circular intronic RNA; circRNA, circular RNA; EcircRNA, exonic circRNA; EiCiRNA, exon-intron circRNA; ELAVL1, human antigen R; FBXW7, F-box and WD-repeat domain-containing 7; FOXO1, forkhead box O1; HIPK, homeodomain-interacting protein kinase; HMGB1, high mobility group box 1; IL, interleukin; IRES, internal ribosome entry site fragments; LDL, low-density lipoprotein; miRNA, microRNA; m⁶A, N⁶-methyladenosine; NLRP3, NLR family pyrin domain containing 3; OGD/R, oxygen-glucose deprivation/reoxygenation; PDGF, platelet-derived growth factor; PDK1, 3-phosphoinositide-dependent protein kinase 1; RBP, RNA-binding protein; STIM1, stromal interacting molecule 1; TET, ten-eleven translocation; TNF, tumor necrosis factor; VSMC, vascular smooth muscle cell

Key words: coronary heart disease, circRNAs, miRNA sponge, pathophysiology, biomarker, therapy

participating in the regulation of gene expression (7). In CHD, emerging evidence suggests that circRNAs play critical roles in the regulation of vascular function, myocardial injury and inflammation (8-10). Several studies have identified differentially expressed circRNAs in patients with CHD, correlating with disease severity and clinical outcomes (11,12). These findings highlight the potential of circRNAs as non-invasive biomarkers for early diagnosis and prognosis of CHD. Furthermore, specific circRNA has been verified to participate in modulating key signaling pathways associated with atherosclerosis and myocardial angiogenesis, offering insights into novel therapeutic strategies (13,14).

This review aims to provide a comprehensive overview of the current understanding of circRNAs in CHD. It summarizes the molecular mechanisms by which circRNAs influence the pathophysiology of CHD, including their roles in cardiomyocyte death, endothelial injury, vascular dysfunction and inflammation. In addition, it explores the potential clinical applications of circRNAs as biomarkers and therapeutic targets, emphasizing the translational implications of circRNA research in improving patient outcomes.

2. Biogenesis and functions of circRNAs

CircRNAs are a unique class of non-coding RNAs found in various organisms, including plants and animals, as well as in certain plant and animal viruses, where they are linked to viral replication and survival (15). The stable structure contributes to their accumulation within cells and makes them play long-term regulatory roles (16). Irrespective of the size, a circRNA molecule may possess <100 nuclei and numerous bases, thereby rendering each element of the reverse shearing procedure deterministic (17). In general, circRNAs are comprised of 2-3 exons with a median size frequently exceeding 500 nucleotides, yet not surpassing 700 nucleotides (18). They exhibit a high degree of conservation across different species, with their expression typically being specific to certain cell types, tissues and stages of development (19). Hence, the presence in numerous species, abundance of information, tissue-specific nature and remarkable stability represent key attributes of circRNAs. Given these characteristics, circRNAs have the potential to serve as valuable indicators for specific disorders and novel targets for therapeutic interventions.

Biogenesis. The formation of circRNAs involves specific sequences and secondary structures within the precursor (pre)-mRNA, which facilitate the back-splicing process (20). Intronic complementary sequences and RBPs connect donor-splice and acceptor-splice sites by appropriate pairing of bases or interacting with definite motifs, playing crucial roles in circRNA biogenesis (21,22). RBPs such as Quaking and Muscleblind bind to flanking intronic sequences to bring splice sites into close proximity, promoting the back-splicing event (23,24). The resulting circRNAs can originate from three main sources: Exonic genes (exon-derived circRNA), intronic regions (intron-derived circRNA, such as pre-mRNA and pre-transfer RNA), or combinations of both exons and introns, leading to three primary types: Exonic circRNAs (EcircRNAs), circular intronic RNAs (ciRNAs) and exon-intron circRNAs (EciRNAs) (25-27). The majority of identified circRNAs are

derived from exonic regions, while ciRNAs and EciRNAs only constitute a small fraction within this category (28).

The generation of endogenous circRNAs is characterized by notable inefficiency, a phenomenon attributed to the elongation process of RNA polymerase II and tightly regulated by cis elements (29,30). Various types of circRNAs are produced through distinct mechanisms (Fig. 1), primarily involving exon cyclization to generate cytoplasmic circRNAs (31). The creation of exon circRNAs predominantly occurs via two mechanisms: Lariat-driven circularization and circularization driven by introns containing reverse complementary sequences (32). Lariat-driven circularization involves the direct linkage of the 5' and 3' ends of the pre-mRNA to form a circular structure (33). Furthermore, this process is associated with exon skipping, where certain exons are omitted to facilitate circular structure formation (34). In addition, intron pairing loops facilitate circRNA formation by promoting base complementary pairing between introns (35). Typically, introns excised from the pre-mRNA are debranched and degraded by exonucleases. However, intron RNA formation is sustained by the presence of 7 GU sequences and 11 C sequences at the intron 5' splice site within a lasso structure, preventing degradation and promoting circularization (36). The generation mechanism of exon-intron RNA mirrors that of EcircRNAs, with the distinction that the circular structure retains the intron component (14,16,37).

Owing to the advancing sophistication of contemporary biological information and RNA sequencing techniques, a substantial volume of transcriptional data has emerged, revealing the presence of circRNAs in various cell types within human organs (38). In the human heart, the percentage of expressed genes capable of generating circRNAs is 9% (17). It is evident that as human organs develop and certain diseases occur, the expression of circRNA undergoes changes (39). Research has demonstrated an elevation in circRNA expression levels in the developing heart (40,41). While the reason for this escalation remains elusive, several possible explanations have so far been proposed. For instance, a study utilizing cardiomyocytes derived from human-induced pluripotent stem cells revealed the dynamic regulation of circRNA expression under chronic and acute stress conditions (42). It should be noted that N-6 methylation (m6A) has the ability to impact circRNA biogenesis and cellular localization. Sites of m6A position in proximity to the start and stop codons of mRNAs can recruit the spliceosome and further facilitate back-splicing and circRNA generation, while specific nuclear reader proteins possess the capability to interact with m6A motifs, aiding in the export of circRNAs from the nucleus to the cytoplasm (43,44). Furthermore, various stimuli like high temperature or oxidative stress also affect circRNA levels (45). Therefore, the biogenesis, structure formation, post-transcriptional modifications and subcellular localization of circRNAs, which are intricately linked to their functional significance within the organism, deserve further investigation.

Despite their stability, circRNAs can still undergo degradation through various pathways, such as RNase L and Argonaute-dependent and independent mechanisms (46). CircRNAs also interact with RBPs, which can influence their stability. For instance, proteins like transcript factor II B-related factor 1 and KH-type splicing regulatory protein,

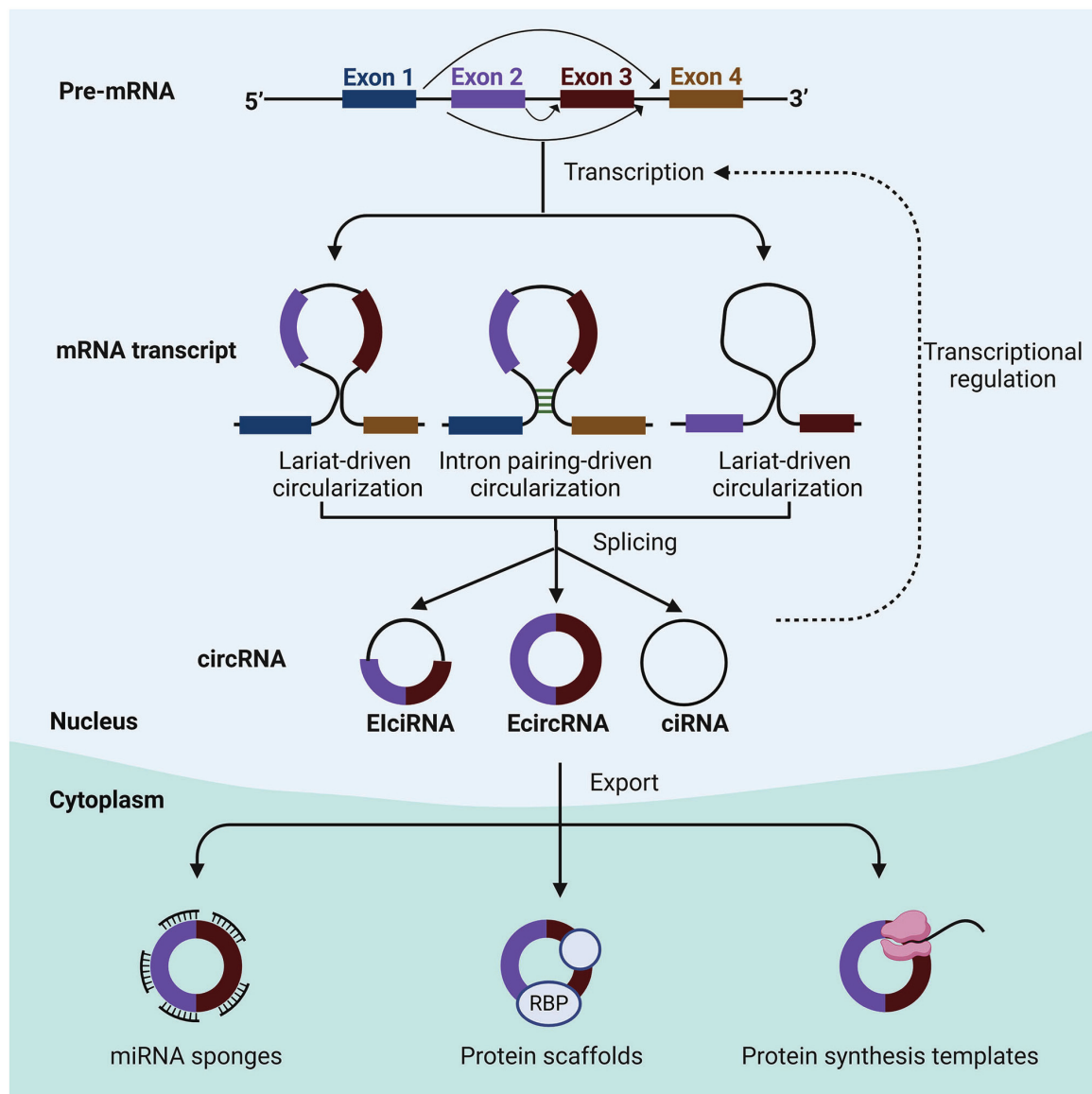


Figure 1. Biogenesis and function of circRNA. By the lariat-driven cyclization, exon splicing generates a lariat structure. The 5' splice donor site of exon 2 covalently links to the 3' splice acceptor of exon 3. EcircRNAs are formed after the removal of the intronic sequence. Likewise, the intron lariat forms the ciRNAs. Besides, by intron pairing-driven circularization, direct base-pairing of the introns flanking inverted repeats leads to the formation of a circular structure. The introns are removed to form ElciRNAs. CircRNAs can function as sponges to diminish miRNA function. They also regulate gene transcription. CircRNAs can function as decoys for proteins, like RBPs, to regulate their functions. They can act as translatable RNAs to encode peptides. ciRNA, circular intronic RNA; EcircRNA, circular exon RNA; ElciRNA, exonic circRNA; RBP, RNA-binding protein; miRNA, microRNA; circRNA, circular RNA.

which are regulated by signaling pathways such as PI3K, can mediate mRNA stability and potentially affect circRNA degradation (47). The m6A modifications on circRNAs further alter the interaction of circRNAs with RBPs, thereby influencing their stability and degradation pathways (48). Understanding the degradation pathways of circRNA can inform therapeutic strategies, particularly in diseases where circRNAs are dysregulated, such as CHD. Targeting specific degradation pathways could modulate circRNA levels and their associated biological effects.

Functions. In the last five years, investigations into circRNAs have facilitated a more thorough comprehension of RNA's functionality by researchers. The unique structural features of circRNAs confer specific biological functions upon them. Current research findings indicate that circRNAs exert a

significant effect across various developmental phases and pathophysiological states by functioning as miRNA sponges, engaging with RBPs, serving as modulators of transcription or translation, impacting pre-mRNA splicing and contributing to protein translation (Fig. 1) (22,27,49-51).

One of the most well-documented functions of circRNAs is their ability to act as miRNA sponges or competitive endogenous RNAs (ceRNAs) (37,52). CircRNAs include a quantity of miRNA response elements that decrease the expression abundance of miRNA by competitive binding to miRNA, hindering its complementary pairing with the 3'-UTR of the downstream target mRNA, thereby alleviating the suppressive effect of miRNAs on mRNA and subsequently enhancing mRNA expression (53,54). However, the majority of circRNAs lack a substantial number of miRNA binding sites and their expression levels are inferior to those of the corresponding

miRNAs (55). The first identified gene cerebellar degeneration-related protein 1 antisense RNA (CDR1as) is demonstrated to be responsible for the production of circRNA molecules. Circ-CDR1as possesses >70 specific target sites for miRNAs that effectively inhibit their functions, suggesting that circRNAs can serve as sponges for miRNAs (37).

Apart from miRNA sponges, circRNAs can also interact with RBPs and other regulatory proteins, regulating various cellular processes via affecting protein localization, stability and function (56,57). There are three prevalent manners of interaction. Primary among these is the role of circRNAs as sponges of proteins. Of note, it is reported that the introns encompassing circular forms of muscleblind (circ-MBL) are rich in MBL binding sites, which possess a specific affinity for MBL proteins, consequently leading to a reduction in the intracellular MBL protein levels (50). Another mode involves circRNAs acting as protein reservoirs. For instance, the abnormal presence of circ-forkhead box (FOX)O3 was verified to prompt cardiac fibroblast aging through interacting with various proteins linked to cellular stress responses, such as DNA binding inhibitor 1, E2F transcription factor 1, hypoxia inducible factor 1 and focal adhesion kinase, thereby sequestering these proteins from the cytoplasm (58). Furthermore, circRNAs can serve as scaffolds for proteins. Zeng *et al* (59) revealed that a circRNA derived from angiomin-1-like 1 associates with 3-phosphoinositol-dependent protein kinase 1 (PDK1) and AKT1 to facilitate the phosphorylation of PDK1-dependent AKT1, conferring protection to the heart. In addition, circRNAs have the ability to attract proteins to specific sites, which allows circRNAs to act as scaffolds or guides, facilitating the localization of proteins to distinct regions of the genome. For instance, circ-FECR1 recruits ten-eleven translocation (TET)1 protein to the promoter region of its host gene Friend leukemia integration 1, triggering the demethylation of CpG sites and promoting active transcription (60).

Although the majority of circRNAs predominantly localize in the cytoplasm where they are employed as protein scaffolds or miRNA sponges, a minority of ElciRNAs are situated in the nucleus and play crucial roles in transcriptional processes. For instance, circRNA eukaryotic translation initiation factor 3 subunit J and circRNA poly(A)-binding protein-interacting protein 2 are confirmed to activate the promoter and modulate the transcription of their host genes in a cis-regulatory manner through binding to U1 small ribonucleoprotein and RNA polymerase II transcription complexes (27). However, the underlying mechanism of ElciRNAs regulating gene transcription has remained largely elusive. In addition, ElciRNAs can affect gene expression by regulating the splicing of their linear counterparts. Furthermore, circRNAs that encompass the start codon of the host gene function as 'mRNA traps' to hinder the expression of the parental gene. By the circularization of an exon that contains an ATG translation start site, circ-homeodomain-interacting protein kinase (HIPK)2 and circ-HIPK3 are generated to repress the synthesis of the HIPK2 and HIPK3 proteins (61).

Due to the absence of essential components for cap-dependent translation, specifically the 5' cap and poly(A) tail, it is widely accepted that circRNAs are incapable of being translated into proteins. However, recent research has revealed

that circRNAs containing internal ribosome entry site fragments (IRES) and adenine-uracil-guanine codon sites may serve as templates for protein translation under particular conditions (62). For instance, circ-F-box and WD-repeat domain-containing 7 (FBXW7) has a region called the open reading frame that starts the translation process with the help of IRES, regardless of the 5'-cap structure, elevating the expression of FBXW7 (63). Additional mechanisms triggering circRNA translation include m6A-methylation initiation of translation and rolling circle adaptation (64,65). It is worth noting that while circRNAs possess a certain translational capacity, their translation efficiency is limited by the unique circular structure of circRNAs. The roles of translation products, such as proteins and peptides, generated from circRNAs remain elusive, necessitating additional investigation.

In conclusion, circRNAs represent a fascinating and rapidly evolving field of study with broad implications for understanding gene regulation and disease mechanisms. Their unique properties and diverse functions underscore their potential as biomarkers and therapeutic targets. Continued research into circRNAs will undoubtedly uncover more about their roles in various diseases such as CHD, paving the way for innovative diagnostic and therapeutic approaches.

3. Roles of circRNAs in CHD

CircRNAs have emerged as crucial players in the pathogenesis of CHD. Research has identified numerous circRNAs that are differentially expressed in patients with CHD compared to healthy controls, suggesting their crucial role in disease progression. For instance, hsa_circRNA11783-2 and hsa_circ_0000563 have been found to influence the initiation and progression of CHD, with hsa_circ_0000563 affecting the pathological process via targeting hub genes like ribosomal protein subunit 3 and subunit 1 (66,67). Hsa_circ_0000563 has been verified to participate in the atherosclerotic changes in human coronary artery segments with severe atherosclerotic stenosis (68). Furthermore, the combination of hsa_circ_0001879 and hsa_circ_0004104 can discriminate patients with CHD from healthy controls; in addition, upregulation of hsa_circ_0004104 causes dysregulation of atherosclerosis-related genes in macrophages, indicating that hsa_circ_0004104 is involved in inflammatory response during atherosclerosis (69). Similarly, it has been demonstrated that the combination of smoking and high hsa_circ_0008507 expression results in the occurrence and development of CHD (70). In addition, the exosome-derived circRNA hsa_circ_0005540 has been identified as a potential diagnostic biomarker for CHD, with its expression levels being associated with disease severity and progression (71). The ceRNA networks involving circRNA-miRNA have been shown to regulate key cellular and molecular biological processes, which are implicated in CHD pathophysiology (72,73). Indeed, hsa_circ_0066439, hsa_circ_0081241 and hsa_circ_0122984 were found to regulate multiple signaling pathways to participate in the acute myocardial infarction through hsa-miR-1254 and hsa-miR-328-5p (74). Furthermore, 9 circRNAs (hsa_circ_0089378, hsa_circ_0083357, hsa_circ_0082824, hsa_circ_0068942, hsa_circ_0057576, hsa_circ_0054537, hsa_circ_0051172, hsa_circ_0032970 and hsa_circ_0006323)

were identified to promote the expression of transient receptor potential melastatin-3, a calcium-permeable ion channel, by inhibiting hsa-miR-130a-3p in patients with CHD (75). However, these circRNAs were investigated by observational studies or bioinformatics, while molecular mechanistic evaluations warrant further investigation. Overall, the growing body of evidence highlights the multifaceted roles of circRNAs in CHD, from their involvement in cell proliferation and apoptosis to inflammation, providing new avenues for the diagnosis and treatment of this disease.

Of note, circRNAs have distinct cell-type-specific roles in cardiomyocytes, endothelial cells and vascular smooth muscle cells (VSMCs), contributing to CHD progression. In cardiomyocytes, circRNAs are involved in regulating cell apoptosis and hypertrophic responses, both of which are critical in the development of CHD (76). Furthermore, circRNAs in endothelial cells are key players in angiogenesis regulation, endothelial dysfunction and endothelial barrier inflammation (77). In addition to influencing the proliferation and migration of VSMCs, circRNAs regulate their phenotypic switch between contractile and synthetic phenotypes in response to vascular injury, affecting plaque formation and vascular stiffening (78).

Cardiomyocyte death. Cardiomyocyte death has a pivotal role in the progression of CHD by initiating and exacerbating a cascade of pathological events that compromise cardiac function. Various forms of cell death, including apoptosis, autophagy, necroptosis, pyroptosis and ferroptosis, are implicated in the deterioration of cardiomyocytes during CHD (79,80). The loss of cardiomyocytes weakens the contractile power of the heart, leading to impaired cardiac output and heart failure (81). This cell death is often triggered by ischemic events such as myocardial infarction, where the lack of oxygen and nutrients causes extensive cardiomyocyte damage and death (82). The failing cardiomyocyte is characterized by a complex interplay of abnormal signaling pathways, oxidative stress, impaired mitochondrial function and altered gene expression, all of which contribute to the vicious cycle of cardiac dysfunction and cell death (83). The irreversible loss of cardiomyocytes leads to fibrosis and scar formation, which exacerbate heart failure and limit the heart's ability to recover from injury (84). Thus, understanding the mechanisms of cardiomyocyte death is essential for developing targeted therapies to protect cardiomyocytes, reduce heart damage and improve clinical outcomes in CHD.

CircRNAs are involved in cardiomyocyte death through various mechanisms, primarily by acting as miRNA sponges, thereby influencing gene expression and cellular processes. For instance, circ-HIPK2 has been shown to interact with miR-485-5p to upregulate the expression of autophagy-related protein 101, which facilitates autophagy to accelerate cardiomyocyte apoptosis in H₂O₂-induced myocardial oxidative injury (8). Similarly, circ_0030235 is upregulated in oxygen-glucose deprivation/reoxygenation (OGD/R)-induced H9c2 cells, a widely used rat cardiomyoblast cell line that can be induced to exhibit certain properties of cardiac muscle cells, and aggravates mitochondrial dysfunction and oxidative damage in cardiomyocytes by targeting miR-526b and thus inactivating the PI3K/AKT and MEK/ERK pathways (85). These findings indicate that circRNAs exert a promoting

effect on cardiomyocyte death and disease progression. In addition, overexpression of circRNA-differentially expressed in normal cells and neoplasia domain containing 4 C (DENND4C) has been observed in OGD/R-stimulated H9c2 cells, and further mechanistic evaluation revealed that circ-DENND4C attenuates OGD/R-induced cardiomyocyte death by downregulation of miR-320 through activating the ERK and mTOR pathways (86). Consistent with this result, circ-LRP6²⁻² is confirmed to protect cardiomyocytes from hypoxia-induced apoptosis. This circRNA is downregulated in cardiomyocytes exposed to hypoxia, while its overexpression represses cell apoptosis. Mechanically, under hypoxia, circ-LRP6²⁻² recruits heterogeneous nuclear ribonucleoprotein M and further enhances the expression of fibroblast growth factor 9, facilitating hypoxia-adaption and viability of cardiomyocytes (87). Thus, circRNAs also exhibit protective effects on cardiomyocytes and delay disease progression. Overall, the multifaceted roles of circRNAs in cardiomyocyte death, through their interactions with miRNAs and other molecular targets, provide a comprehensive understanding of their contribution to cardiovascular pathophysiology and potential clinical applications.

Therefore, circRNAs have been implicated in regulating cardiomyocyte death by affecting processes such as cell proliferation and autophagy, further impacting the progression of CHD (Table I). Despite advances in therapeutic approaches, the limited regenerative capacity of adult cardiomyocytes poses a significant challenge in restoring heart function after extensive cell loss (88). In this regard, targeting specific circRNAs may improve cardiac outcomes, highlighting the potential to mitigate cardiomyocyte death. Understanding the molecular mechanisms by which circRNAs participate in different forms of cell death is essential for developing effective treatments to prevent cardiomyocyte loss and improve the prognosis for patients with CHD.

Endothelial cell injury. Endothelial cell injury is a critical factor in the development of CHD due to its multifaceted impacts on vascular function and integrity. The endothelium, which lines the inner walls of blood vessels, has a vital role in maintaining vascular tone, regulating hemostasis and controlling inflammation and thrombosis (89). When endothelial cells are damaged, several pathological processes are triggered. Firstly, endothelial injury enhances the permeability of the vascular intima, facilitating leukocyte adhesion and transmigration, which further exacerbates inflammation and promotes thrombus formation (90). Increased inflammatory mediators, such as cytokines and oxidized lipoproteins, lead to the overexpression of adhesion molecules, selectins and chemokines, which attract and retain leukocytes in the subendothelial space (91). This inflammatory cascade is compounded by oxidative stress, which not only damages endothelial cells directly but also disrupts the balance of pro- and anti-coagulant factors, shifting the endothelium towards a pro-thrombotic state (92,93). Furthermore, endothelial cell injury is linked to metabolic disturbances such as lipid metabolism disorders, which are significant risk factors for atherosclerosis. The damage to endothelial cells impairs their ability to regulate lipid levels, leading to the accumulation of lipids in the arterial walls and the formation of atherosclerotic

Table I. Role of circRNAs in the pathogenesis of coronary heart disease.

CircRNA	Expression	Experimental model	Targets	Effects	Impact on CHD	(Refs.)
Circ-HIPK2	Up	H ₂ O ₂ -stimulated cardiomyocytes	miR-485-5p/ ATG101	Facilitating cell autophagy and apoptosis	Pro-CHD	(8)
Circ_0030235	Up	OGD/R-induced H9c2 cells	miR-526b, PI3K/AKT, MEK/ERK	Promoting cell apoptosis and reducing cell viability	Pro-CHD	(85)
Circ-DENND4C	Up	OGD/R-induced H9c2 cells	miR-320, ERK, mTOR	Promoting cell injury	Anti-CHD	(86)
Hsa_circ_0007478	Up	Ox-LDL-stimulated macrophages	miR-765/ EFNA3	Increasing inflammation and foam cell formation	Pro-CHD	(10)
Hsa_circ_0000280	Down	Patients with CHD, PDGF-BB-induced VSMCs	ELAVL1, CDKN1A mRNA	Inhibiting cell proliferation and neointimal hyperplasia	Anti-CHD	(109)
Circ-LDLR	Down	Patients with CHD, transgenic VSMCs	miR-26- 5p/KDM6A	Inhibiting cell proliferation and promoting cell apoptosis	Anti-CHD	(110)
Circ-MAP3K5	Down	PDGF-BB-induced VSMCs	miR-22-3p/ TET2	Inhibiting cell proliferation and neointima formation	Anti-CHD	(111)
Circ-SATB2	Up	Transgenic VSMCs	miR-939/ STIM1	Inhibiting cell proliferation and migration	Pro-CHD	(112)
Hsa_circ_0031891	Up	Patients with CAD, PDGF-BB-induced VSMCs	miR-579- 3p/HMGB1	Boosting cell proliferation, migration and dedifferentiation	Pro-CHD	(113)
Circ_0006251	Up	PDGF-BB-induced VSMCs	miR-361-3p, TET3, PPM1B	Increasing cell proliferation	Pro-CHD	(114)
Hsa_circ_0030042	Down	Ox-LDL-stimulated HUVECs, high-fat-diet fed ApoE ^{-/-} mice	eIF4A3, FOXO1, Beclin-1	Decreasing autophagic cell death and maintaining plaque stability	Anti-CHD	(100)
Circ-CHFR	Up	Ox-LDL-stimulated HUVECs	miR-15b- 5p/GADD45G	Promoting cell apoptosis and inflammatory response	Pro-CHD	(121)
Circ_0004104	Up	Patients with CAD, ox-LDL-stimulated endothelial cells	miR-100/ TNFAIP8	Promoting cell apoptosis and inflammation	Pro-CHD	(122)
Hsa_circ_0000284	Down	Patients with CHD, TNF- α and H ₂ O ₂ -induced EA-hy926 cells	miR-338- 3p/ETS1	Affecting cell proliferation and apoptosis	Pro-CHD	(9)
Circ-LRP6 ²⁻²	Down	Hypoxia-treated cardiomyocyte	hnRNPM/ FGF-9	Inhibiting cell apoptosis	Anti-CHD	(87)
Circ_0001785	Down	Patients with CHD, high-fat-diet fed ApoE ^{-/-} mice	miR-513a- 5p/TGFBR3	Reducing endothelial cell injury and delaying atherosclerosis	Anti-CHD	(99)
Circ-MBOAT2	Up	Patients with CTO, mice with hindlimb ischemia	miR-495/ NOTCH1	Promoting angiogenesis and improving myocardial perfusion	Anti-CHD	(101)
Hsa_circ_0126672	Up	CHD patients	miR-145-5p, NOS1, RPS6KB1	Affecting atherosclerosis	Pro-CHD	(123)

Table I. Continued.

CircRNA	Expression	Experimental model	Targets	Effects	Impact on CHD	(Refs.)
Hsa_circ_0092576	Up	CHD patients	miR-145-5p, Apelin, JAK/STAT	Enhancing cell proliferation, inflammation and atherosclerosis	Pro-CHD	(124)

ATG, autophagy-related protein; CAD, coronary artery disease; CDKN1A, cyclin-dependent kinase suppressor 1; CHD, coronary heart disease; circRNA/circ, circular RNA; CTO, coronary chronic total occlusion; EFNA3, ephrinA3; ELAVL1, human antigen R; FBXW7, F-box and WD-repeat domain-containing 7; ETS1, E26 oncogene homolog 1; FGF9, fibroblast growth factor 9; FOXO1, forkhead box O1; GADD45G, growth arrest and DNA damage-inducible gene γ ; HIPK, homeodomain-interacting protein kinase; HMGB1, high mobility group box 1; hnRNPM, heterogeneous nuclear ribonucleoprotein M; HUVECs, human vascular endothelial cells; IL, interleukin; IRES, internal ribosome entry site fragments; KDM6A, lysine-specific demethylase 6A; LDL, low-density lipoprotein; MBOAT2, membrane-bound O-acyltransferase domain containing 2; miRNA/miR, microRNA; OGD/R, oxygen-glucose deprivation/reoxygenation; PBLs, peripheral blood leukocytes; PDGF, platelet-derived growth factor; PDK1, 3-phosphoinositol-dependent protein kinase 1; PPM1B, protein phosphatase 1B; RBPs, RNA-binding proteins; RPS6KB1, ribosomal protein S6 kinase β 1; STIM1, stromal interacting molecule 1; TET, ten-eleven translocation; TGFBR3, transforming growth factor β receptor 3; TNFAIP8, TNF- α -induced protein 8; TNF, tumor necrosis factor; VSMC, vascular smooth muscle cell.

plaques (94). Mechanical, chemical and biological stresses, including hypertension, hyperglycemia and infections, exacerbate endothelial dysfunction by inducing cell senescence, autophagy dysregulation and mitochondrial stress (95,96). Autophagy, a process crucial for cellular homeostasis, is often impaired in endothelial cells during aging and disease, further contributing to endothelial dysfunction (97). The persistent endothelial activation and injury, coupled with diminished repair capacity, create a vicious cycle that perpetuates vascular inflammation, thrombosis and atherosclerosis, ultimately leading to the development and progression of CHD (98).

CircRNAs participate in regulating endothelial cell function in CHD through complex molecular mechanisms involving the sponging of miRNAs and subsequent modulation of mRNA targets. For instance, hsa_circ_0000284 is downregulated in patients with CHD and oxidative stress-induced EA-hy926 endothelial cells, and overexpression of hsa_circ_0000284 leads to impaired cell proliferation and increased apoptosis by sponging miR-338-3p, thereby repressing the expression of E26 transformation-specific sequence-1, a transcription factor involved in endothelial cell function (9). Another circRNA, circ_0001785, is decreased in the circulating peripheral blood of patients with CHD but increased within atherosclerotic plaque tissue. This circRNA is implicated in delaying atherogenesis by alleviating aortic endothelial cell injury and the formation of intraplaque neovascularization, via modulating the miR-513a-5p/TGFBR3 axis (99). In addition, hsa_circ_0030042 has been shown to suppress oxidized low-density lipoprotein (ox-LDL)-mediated abnormal autophagy of endothelial cells and maintain plaque stability in high-fat-diet fed apolipoprotein E^{-/-} mice by sponging the endogenous eukaryotic initiation factor 4A-III, which impedes its recruitment to beclin1 and FOXO1 mRNA (100). Furthermore, circRNA-0024103, which is highly expressed in patients with coronary chronic total occlusion, has been verified to accelerate tube formation and cell migration via the miR-495/Notch1 axis in endothelial cells. This circRNA also increased collateral formation of the ligated femoral artery in

mice after hindlimb ischemia, which is related to myocardial perfusion improvement after revascularization (101).

Collectively, these studies highlight the multifaceted roles of circRNAs in regulating endothelial cell function through intricate ceRNA networks, influencing key processes such as angiogenesis, cell proliferation and apoptosis, thereby offering novel insights into the pathogenesis and potential therapeutic strategies for CHD (Table I). Further studies are needed to unravel the detailed mechanisms by which circRNAs regulate endothelial cell function and contribute to CHD. Understanding these mechanisms will provide insights into potential therapeutic targets.

VSMC apoptosis. VSMC apoptosis is involved in the development and progression of CHD by affecting vascular remodeling, plaque stability and inflammatory responses (102). The balance between VSMC proliferation and apoptosis is crucial in the pathogenesis of atherosclerosis, a primary underlying cause of CHD (103). VSMCs with a synthetic phenotype are characterized by increased migration and proliferation to repair the damage (104). This phenotypic switching is regulated by a network of factors, including transcription factors, growth factors and non-coding RNAs, which contribute to vascular aging and atherosclerosis (104). Early atherosclerotic lesions are characterized by intense apoptosis of VSMCs, which decreases as the disease progresses, leading to intimal hyperplasia and plaque formation (105). Clonal expansion of VSMCs, initiated by a small fraction of cells that proliferate and migrate to form oligoclonal neointima, is a hallmark of early atherosclerotic lesions, suggesting that selective VSMC activation drives disease progression (106). Furthermore, VSMCs can transdifferentiate into mesenchymal and myeloid-like phenotypes, contributing to the progression of organ fibrosis and potentially affecting other vital organs beyond the vascular system (107). The dynamic variations in VSMC phenotypes shape the atherosclerotic plaque micro-environment, leading to heterogeneous clinical outcomes in CHD (108). Overall, the injury-induced phenotypic switching

and clonal expansion of VSMCs, along with the disequilibrium between cell proliferation and apoptosis, underscore the critical role of VSMCs in the pathogenesis of CHD, providing potential targets for therapeutic intervention.

Dysregulated circRNAs have been implicated in the phenotypes and function of VSMCs during CHD progression. For instance, hsa_circ_0000280 has been shown to inhibit VSMC proliferation and induce cell-cycle arrest by facilitating the interaction between human antigen R and cyclin-dependent kinase suppressor 1 mRNA, leading to cell cycle arrest at the G1/S checkpoint and reducing neointimal hyperplasia *in vivo* (109). Another circRNA, circ-LDLR, is downregulated in CHD tissues, and its upregulation represses proliferation and promotes apoptosis of VSMCs through the miR-26-5p/KDM6A axis (110). Furthermore, circ-MAP3K5 has been identified to exert antiproliferative effects on VSMCs, where circ-MAP3K5 acts as a master negative regulator of TET2-mediated VSMC differentiation by sequestering miR-22-3p and thus blocking the expression of TET2 (111). Thus, these findings indicate that circRNAs postpone CHD development via mitigating VSMC proliferation and differentiation. Furthermore, circ-SATB2 has been reported to promote the phenotypic switch of VSMCs from a contractile to a synthetic state through the miR-939/stromal interacting molecule 1 axis, which regulates VSMC phenotypic differentiation, proliferation, apoptosis and migration (112). In addition, hsa_circ_0031891 participates in atherosclerosis by promoting VSMC proliferation, migration and dedifferentiation through the miR-579-3p/high mobility group box 1 axis. Silencing hsa_circ_0031891 inhibits these processes, suggesting its role in the pathogenesis of atherosclerosis (113). Likewise, in platelet-derived growth factor subunit B-induced VSMCs, circ_0006251 is upregulated to facilitate VSMC proliferation and reduce their apoptosis by enhancing TET3 and protein phosphatase 1B expression through sponging miR-361-3p, thereby contributing to disease occurrence (114). Hence, circRNAs boost CHD progression by facilitating VSMC proliferation and differentiation.

Taken together, circRNAs are crucial regulators of VSMC phenotype and function in CHD, regulating cell proliferation, migration and phenotypic switching through complex molecular pathways, making them promising targets for future therapeutic strategies (Table I).

Inflammatory response. The inflammatory response is a complex biological process initiated by the immune system to protect the body against harmful stimuli such as pathogens, damaged cells or irritants (115). It involves the activation and recruitment of various immune cells, including macrophages, neutrophils and T cells, which release cytokines and other inflammatory mediators to eliminate the offending agents and promote tissue repair (116). However, chronic inflammation can have detrimental effects, particularly in the context of CHD. Inflammation has a pivotal role in the development and progression of CHD by contributing to endothelial dysfunction, atherosclerosis and plaque instability (117). Macrophages ingest ox-LDL, transforming into foam cells and forming the lipid-rich necrotic core of atheromas, while the secretion of cytokines and proteases by these cells further exacerbates the inflammatory process and weakens the fibrous cap, making plaques more

prone to rupture (118,119). The macrophage-mediated innate immune response is crucial in both the initiation and resolution of inflammation following myocardial infarction, influencing cardiac remodeling and heart failure development (120). Consequently, the inflammatory response is a double-edged sword in CHD, being essential for initial defense and tissue repair but potentially harmful when it becomes chronic.

CircRNAs have a vital role in the inflammatory response associated with the development of CHD. For instance, hsa_circ_0007478 has been found to be upregulated in ox-LDL-stimulated macrophages, and its expression exacerbates lipid metabolism imbalance and foam cell formation through the miR-765/EFNA3 axis, along with interleukin (IL)-1 β production and NLR family pyrin domain containing 3 inflammasome activation, a key player in cell pyroptosis and inflammation (10). Besides, in ox-LDL-stimulated endothelial cells and patients with CHD, circ-CHFR is upregulated to provoke atherosclerosis development by sponging miR-15b-5p, which in turn enhances the expression of GADD45G, thus triggering the secretion of atherosclerosis-associated cytokines, including IL-1 β , IL-6 and tumor necrosis factor (TNF)- α (121). Consistently, silencing of circ_0004104, which is upregulated in patients with CHD, mitigates ox-LDL-mediated inflammatory injury in endothelial cells by the miR-100/TNFAIP8 axis, highlighting the deleterious effect of circ_0004104 in CHD pathogenesis (122). Therefore, circRNAs can promote endothelial cell injury and atherosclerosis progression by enhancing inflammatory responses. Moreover, the construction of circRNA-related ceRNA networks has revealed that hsa_circ_0126672 is involved in regulating inflammation-related pathways, such as the JAK/STAT and Apelin signaling pathways, which are critical for atherosclerotic plaque progression and instability (123). By activating these signaling pathways, hsa_circ_0092576 induces vascular inflammation via the activation and proliferation of VSMCs, as well as mediates the accumulation of oxidized lipids and oxidative damage to endothelial cells, resulting in the development of atherosclerosis (124).

Therefore, circRNAs mediate the inflammatory response in CHD by regulating miRNA and mRNA interactions, influencing cell proliferation, oxidative stress and atherosclerosis, thereby contributing to disease development and progression (Table I). The circRNA-miRNA-mRNA regulatory network is crucial in controlling the inflammatory processes that contribute to atherosclerotic plaque formation and instability, highlighting the therapeutic potential of targeting these pathways. Hence, the complex interplay between circRNAs, miRNAs and mRNAs requires further elucidation to understand the precise mechanisms of action during CHD progression. Furthermore, the influence of environmental factors, such as smoking, on circRNA expression and their interaction with inflammatory response must be considered to develop personalized treatment strategies.

4. Applications of circRNAs for CHD

CircRNAs as biomarkers. CircRNAs have emerged as promising biomarkers for the diagnosis and treatment of cardiovascular disease due to their unique properties and regulatory roles in disease occurrence and development (20).

Compared with linear RNAs, such as miRNAs and long non-coding RNAs, they are covalently closed-loop structures without free 5' and 3' ends, which makes them highly resistant to exonucleases and more stable in bodily fluids, enhancing their reliability as biomarkers (125). CircRNAs are abundant and exhibit tissue-specific expression, making them ideal candidates for clinical applications (126). CircRNAs have been detected in considerable quantities in various bodily fluids, such as plasma, serum and saliva (71,127-129). Furthermore, they exhibit a half-life of 48 h in bodily fluids, a duration that surpasses that of linear RNA (130). In addition, circRNAs exhibit a broad distribution within cells, as well as in extracellular regions, and the extracellular amount of circRNAs is thought to reflect, at least in part, their intracellular abundance. When cells undergo stress or pathological conditions, transcriptional upregulation of intracellular circRNAs may lead to an increased release of circRNAs into the extracellular space. It is hypothesized that the expression levels of intracellular circRNAs could impact the concentrations of extracellular circRNAs, but the exact relationship between these two pools of circRNAs remains to be fully elucidated (131). These distinctive attributes of circRNA substantiate their potential suitability as biomarkers.

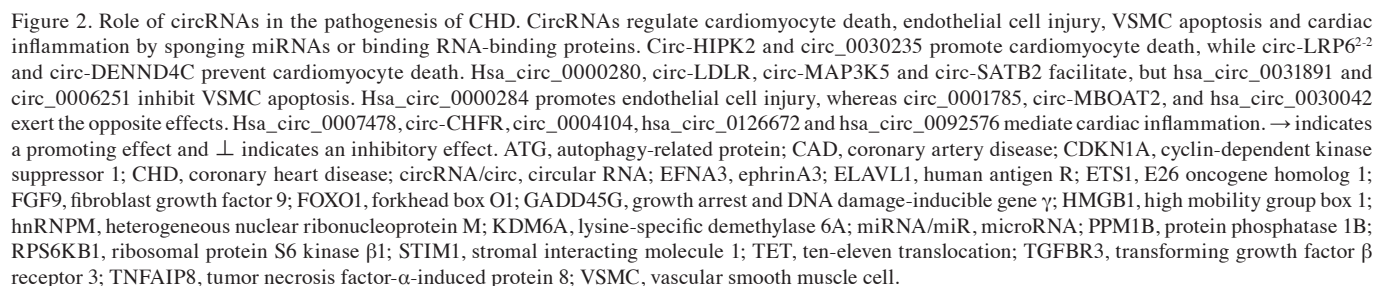
CircRNAs have emerged as promising biomarkers for the early detection and prognosis of CHD due to their unique properties and regulatory roles in gene expression. Numerous studies have highlighted their diagnostic value, with varying degrees of efficacy. A meta-analysis of 16 studies involving 3,962 subjects revealed that circRNAs have a pooled receiver operating characteristic curve of 0.80, with sensitivity and specificity values of 0.77 and 0.68, respectively, indicating their potential as reliable biomarkers for CHD diagnosis (132). Besides, several dysregulated circRNAs, such as circ-HECTD1, circ-ZBTB46 and hsa_circ_0001445, have been detected in the peripheral blood of patients with CHD and their expression level was shown to be associated with laboratory parameters, such as hemoglobin, triglycerides and cholesterol levels, suggesting their potential as diagnostic markers (73,133). High-throughput sequencing has confirmed differentially expressed circRNAs in the plasma of patients with CHD, such as hsa_circ_0069972, hsa_circ_0021509, circ-RPRD1A and circ-HERPUD2, which show significant upregulation and serve as new biomarkers for the diagnosis of coronary artery disease (134,135). Specifically, exosome-derived circRNAs have been identified as potential biomarkers for CHD, with certain circRNAs such as hsa_circ_0001445, hsa_circ_0001360 and hsa_circ_0000038 showing significant downregulation in patients with CHD (127,136). Furthermore, hsa_circ_0124644, hsa_circ_0001946, hsa_circ_0001785, hsa_circ_0000973, hsa_circ_0001741 and hsa_circ_0003922 in peripheral blood have shown their ability to discriminate between patients with CHD and healthy controls, with promising potential as diagnostic biomarkers for CHD (137-139). In addition, bioinformatics analyses have constructed circRNA-miRNA-mRNA regulatory networks, revealing the involvement of circRNAs such as circ-YOD1 in lipid metabolism and protein modification, further supporting their diagnostic and prognostic potential (140,141). Microarray data analysis has identified

differentially expressed circRNAs in patients with CHD with varying severity, with hsa_circ_0016868, hsa_circ_0001364, hsa_circ_0006731 and circ-ANRIL emerging as promising biomarkers for early CHD diagnosis (11,12,142).

Collectively, these findings suggest that circRNAs hold substantial promise as biomarkers for CHD, offering a new avenue for the early diagnosis, prognosis and personalized treatment of CHD, thereby addressing unmet clinical needs such as timely diagnosis and effective monitoring of treatment responses. However, circRNA-based biomarkers are still undergoing experimental evaluation in CHD. Further integration of circRNA profiling with advanced bioinformatics, high-throughput sequencing and molecular biology techniques will hold great promise for the identification and validation of differentially expressed circRNAs in patients with CHD, enabling the construction of circRNA-miRNA-mRNA regulatory networks that provide insight into disease mechanisms and potential therapeutic targets. However, circRNAs can be present at low concentrations and distinguishing them from linear RNA counterparts remains a technical challenge. Thus, developing more sensitive, reliable and high-throughput detection techniques is essential. Besides, circRNAs are highly heterogeneous and their expression can vary widely across different cell types and conditions. In this regard, identifying a panel of circRNAs rather than relying on a single circRNA marker may enhance the diagnostic power.

CircRNA-targeting therapeutic strategies. Current strategies for targeting circRNAs in the treatment of CHD are multifaceted, leveraging their unique properties and regulatory roles in cardiovascular diseases. By designing synthetic circRNAs or using antisense oligonucleotides to inhibit specific circRNAs, researchers aim to modulate these regulatory networks to achieve therapeutic effects. For instance, targeting proatherogenic circRNAs such as circ_0002984 and circ_0029589 could potentially mitigate atherosclerosis and its associated risks in patients with CHD (143). However, solutions to increasing the stability of the antisense oligonucleotide and its efficiency should be further developed. In addition, gene therapy techniques are being explored to either upregulate protective circRNAs or downregulate harmful ones, thereby restoring the balance of circRNA-miRNA-mRNA interactions crucial for cardiovascular health (144). Physical exercise has also been suggested as a non-pharmacological strategy to modulate circRNA expression, offering a low-cost and accessible means to alleviate CHD symptoms (145). Furthermore, the development of circRNA synthesis and engineering delivery systems holds promise for their application in therapeutics. These systems aim to enhance the stability, specificity and delivery efficiency of circRNA-based treatments, potentially overcoming current challenges in circRNA therapy (146). Thus, the integration of circRNAs into the therapeutic landscape of CHD represents a promising frontier, with ongoing research aimed at optimizing these strategies for clinical application.

CircRNAs can influence patient responses to conventional CHD treatments by modulating the molecular pathways involved in disease mechanisms and drug efficacy. Dysregulation of circRNAs has been linked to cholesterol homeostasis, which alters the effectiveness of statins, leading



Despite the promising potential of circRNAs as therapeutic targets, no clinical application or ongoing clinical trials has investigated circRNA-targeting therapeutic strategies in CHD, which face several challenges. One significant challenge is the accurate and sensitive detection of circRNAs, which is crucial for understanding their biological processes. Current

methodologies for circRNA identification, including purification and sequencing methods, have limitations in sensitivity and specificity, which can hinder the precise characterization of circRNAs involved in CHD. In addition, the regulatory roles of circRNAs in cardiovascular diseases are complex, involving interactions with miRNAs and mRNAs in regulatory networks that are not yet fully understood. This complexity necessitates advanced technologies for identifying, validating and analyzing circRNAs, which are still under development. Furthermore, the involvement of circRNAs in various pathophysiological processes, such as atherogenesis and myocardial infarction, adds another layer of complexity. Specific circRNAs have been identified with either atheroprotective or proatherogenic effects, but translating these findings into therapeutic applications requires a deeper understanding of their mechanisms and interactions within the circRNA-miRNA-mRNA regulatory axis. Thus, the continued exploration of circRNA functions and their interactions within the cardiovascular system will likely yield novel insights and more effective treatments for CHD.

5. Conclusions and future perspectives

CircRNAs represent a promising frontier in cardiovascular research, offering novel insights into the molecular mechanisms of CHD. They play crucial roles in various cellular processes pertinent to CHD, ranging from endothelial dysfunction to inflammation, by acting as miRNA sponges and further regulating gene expression and signaling pathways (Fig. 2). They exhibit distinct expression profiles in patients with CHD compared to healthy controls, positioning them as valuable biomarkers and therapeutic targets. However, translating circRNA research into clinical practice requires concerted efforts to overcome current challenges. First, advancements in high-throughput sequencing technologies and bioinformatics tools are essential for accurate circRNA detection and quantification. Standardized methods for circRNA isolation, sequencing and analysis will improve reproducibility and facilitate cross-study comparisons. Furthermore, extensive *in vivo* studies are required to elucidate the precise mechanisms by which circRNAs influence CHD pathophysiology. As numerous circRNAs serve as miRNA sponges or regulate transcription and splicing, uncovering their exact molecular functions in different cell types within the cardiovascular system is critical for therapeutic targeting. Integrating single-cell sequencing approaches could unravel cell-type-specific roles of circRNAs, offering a more precise understanding of their contributions to disease. In addition, large-scale clinical studies are needed to validate the diagnostic and prognostic utility of circRNAs identified in preliminary research. Integrating circRNA biomarkers into existing diagnostic frameworks could enhance early detection and risk stratification in patients with CHD. CircRNAs could be used to monitor treatment responses, particularly in therapies that target molecular pathways involved in lipid metabolism, vascular remodeling and inflammation. Furthermore, developing circRNA-based therapies involves designing molecules that can specifically modulate circRNA activity. Antisense oligonucleotides and small interfering RNAs targeting circRNAs hold promise but require optimization for efficient delivery and minimal off-target effects. Developing safe and effective delivery systems, such as lipid nanoparticles or viral vectors, will be crucial for translating circRNA-targeting therapies into clinical practice. Furthermore, addressing the potential immunogenicity of these delivery platforms is essential to ensure safety and minimize adverse reactions. Exploring the therapeutic potential of circRNAs in combination with existing treatments could offer synergistic benefits, improving patient outcomes in CHD.

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Authors' contributions

ZF and YY wrote the manuscript, XY revised the manuscript and YY designed the research. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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