Review | Open Access

Vessel Plus

Zhao et al. Vessel Plus. 2026;10:55 DOI:10.20517/2574-1209.2026.28

The emerging role of circular RNAs in acute and chronic heart failure: mechanisms, biomarkers, and therapeutic potential

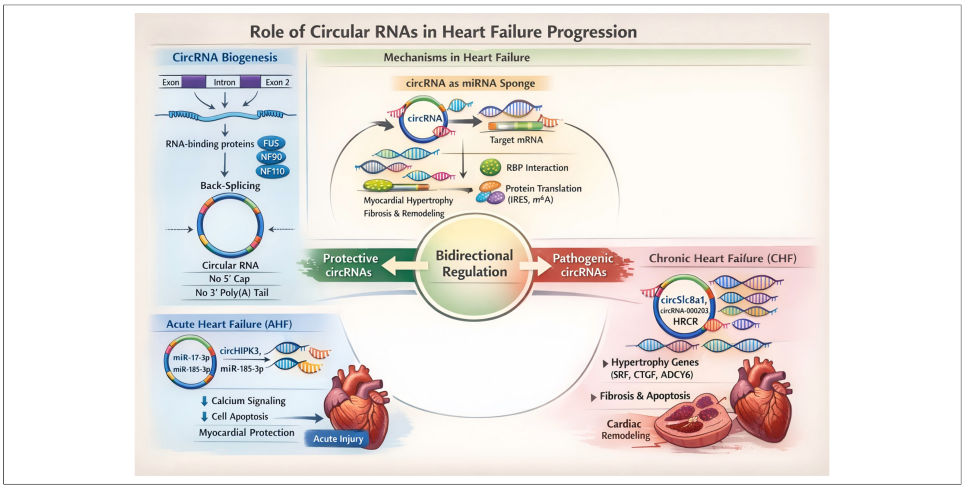
Xingwei Zhao[1], Shiliyang Liu[2], Yujie Su[2], Chunxiang Zhang[1,2]

Keywords:
circRNA, back-splice junction, miRNA sponges, heart failure, myocardial hypertrophy, cardiac remodeling, therapeutic targets

Citation: Zhao X, Liu S, Su Y, Zhang C. The emerging role of circular RNAs in acute and chronic heart failure: mechanisms, biomarkers, and therapeutic potential. *Vessel Plus.* 2026;10:55. https://dx.doi.org/10.20517/2574-1209.2026.28

Received: 27 Mar 2026 **First Decision:** 19 May 2026 **Revised:** 8 Sep 2026 **Accepted:** 8 Sep 2026 **Published:** 29 Sep 2026

Academic Editor: Jian Wu
Copy Editor: Fangling Lan
Production Editor: Fangling Lan



Abstract

Circular RNAs (circRNAs) are covalently closed non-coding RNAs with diverse regulatory functions, high stability, and tissue specificity. This review examines their biogenesis, molecular mechanisms, experimental evidence, biomarker potential, and therapeutic implications in acute heart failure and chronic heart failure. By functioning as microRNA sponges, interacting with RNA-binding proteins, acting as protein scaffolds, undergoing cap-independent translation, and participating in stress-response signaling, circRNAs may regulate heart failure progression. Representative circRNAs, including circHIPK3, circSIRT1, circSLC8A1, circRNA-00203, and HRCR, have been linked to cardiomyocyte injury, calcium homeostasis, apoptosis, hypertrophy, fibrosis, inflammation, and ventricular remodeling. Circulating and exosome-derived circRNAs may also serve as biomarkers for diagnosis, prognosis, and disease monitoring. However, clinical translation remains limited by challenges in detection and standardization, low transcript abundance, tissue and cell heterogeneity, delivery efficiency, off-target effects, immunogenicity, and insufficient validation in large clinical cohorts. Most available evidence comes from preclinical models of myocardial infarction, pressure overload, and cardiac remodeling; evidence in heart

[1]Key Laboratory of Medical Electrophysiology, Ministry of Education & Medical Electrophysiological Key Laboratory of Sichuan Province, Institute of Cardiovascular Research, Southwest Medical University, Southwest Medical University, Luzhou 646000, Sichuan, China.
[2]Nucleic Acid Medicine of Luzhou Key Laboratory, Southwest Medical University, Luzhou 646000, Sichuan, China.

Correspondence to: Prof. Chunxiang Zhang, Nucleic Acid Medicine of Luzhou Key Laboratory, Southwest Medical University, Luzhou 646000, Sichuan, China. E-mail: zhangchunxiangKZL@163.com

failure with preserved ejection fraction , heart failure with mildly reduced ejection fraction, and large human populations remains limited. Overall, circRNAs provide new insights into heart failure pathophysiology and represent promising candidates for biomarker development and targeted therapy, but rigorous clinical validation is required before routine application.

INTRODUCTION

Circular RNAs (circRNAs) are non-coding RNA molecules with a circular structure that distinguishes them from conventional linear mRNAs. Unlike mRNAs, which have 5' and 3' ends, circRNAs are formed through back-splicing, in which base pairing within inverted repeat elements, such as Alu sequences, brings a downstream splice donor site into proximity with an upstream splice acceptor site to form a covalently closed circular molecule[1]. Their complex biogenesis may also be influenced by specific RNA-binding proteins (RBPs), including fusion sarcoma protein (FUS), nuclear factor 90 (NF90), and NF110, which bind to intronic regions and promote circRNA formation[2]. For many years, circRNAs were considered "useless" transcripts arising from splicing errors. However, circRNA-specific identification algorithms and high-throughput RNA-seq have revealed their important roles in gene regulation and other cellular functions. circRNAs lack 5′ caps and 3′ poly(A) tails and are more resistant to RNA exonucleases, more stable, more conserved, and longer-lived than linear RNAs[3,4]. They may therefore serve as biomarkers and therapeutic targets in disease, particularly in heart failure initiation and progression, although further validation is required. Based on left ventricular ejection fraction, heart failure (HF) is classified as heart failure with reduced ejection fraction (HFrEF), heart failure with mildly reduced ejection fraction (HFmrEF), or heart failure with preserved ejection fraction (HFpEF). These three subtypes differ in clinical phenotype, ventricular structure, major pathophysiological mechanisms, and treatment response. HFrEF primarily involves ventricular systolic dysfunction, whereas HFpEF is typically associated with diastolic dysfunction, systemic inflammation, endothelial and microvascular dysfunction, metabolic comorbidities, and increased myocardial stiffness. However, the roles of circRNAs in HFpEF and HFmrEF remain incompletely understood, despite the partially overlapping pathophysiological features of these HF phenotypes.

Most experimental evidence on circRNAs in heart failure currently comes from models of myocardial infarction, pressure overload, myocardial hypertrophy, and ventricular remodeling. This review therefore focuses on circRNA-mediated molecular mechanisms associated with ventricular dysfunction and remodeling, particularly those relevant to HFrEF-like pathological processes. In contrast, evidence on the roles of circRNAs in HFpEF and HFmrEF remains limited, warranting further investigation.

According to the "General Definition and Classification of Heart Failure" and current guidelines from the American Heart Association/American College of Cardiology/American Heart Failure Society (AHA/ACC/HFSA) and the European Society of Cardiology, HF is a clinical syndrome characterized by symptoms and/or signs caused by structural or functional cardiac abnormalities and supported by objective evidence, such as elevated natriuretic peptide levels or pulmonary and systemic edema.

Heart failure can manifest as acute heart failure (AHF) or chronic heart failure (CHF). AHF is a clinical state in which symptoms and signs develop rapidly or worsen substantially, requiring urgent assessment and treatment. Although AHF and CHF differ considerably in clinical presentation and disease progression, both involve complex molecular pathological mechanisms, including inflammation, cardiomyocyte injury, fibrosis, myocardial hypertrophy, and ventricular remodeling. HF represents a major public health burden worldwide, affecting more than 64 million individuals, with prevalence increasing markedly with age. In Europe and North America, its estimated prevalence in adults is approximately 1%-2%, rising to more than 10% among individuals older than 70 years. Population-based studies in China have also shown an

increasing prevalence of HF, largely driven by population aging and the growing burden of hypertension, coronary artery disease, diabetes, and obesity. Despite therapeutic advances, HF remains associated with high mortality and frequent hospitalization, particularly in patients with advanced disease or acute decompensation. These epidemiological data highlight the need for improved molecular biomarkers and therapeutic targets[5-8]. In AHF, severe myocardial stress or ischemic injury causes cardiomyocyte necrosis or apoptosis, rapidly developing ventricular dysfunction, and sudden clinical deterioration requiring immediate intervention[9]. In CHF, myocardial enlargement, stiffening due to fibrosis and calcification, and thickening (hypertrophy) ultimately worsen HF symptoms under excessive cardiac workload or abnormal stress[10].

circRNAs play critical roles in both acute and chronic HF processes. In AHF, they can influence miRNA-protein interactions and regulate cardiomyocyte injury repair and inflammatory responses[11]. They also function as “sponges” by binding miRNAs and thereby regulating the expression of miRNA targets, reducing cardiomyocyte apoptosis and even necrosis. For example, hsa-circRNAs modulate cardioprotective genes by competing for miR-133a binding and may help protect against AMI injury[12]. In CHF, their roles are more complex: under chronic overload, circRNAs may regulate multiple signaling pathways involved in cardiomyocyte remodeling[13], particularly those affecting hypertrophy, fibrosis, and apoptosis[14]. Studies have shown that circRNAs interact with RBPs to affect cardiomyocyte metabolism and structure, thereby influencing cardiac remodeling pathways[15]. Some circRNAs can interact with RBPs such as NF90 and FUS, enhancing cardiomyocyte adaptation to mechanical stress and slowing HF progression[16].

At the molecular level, circRNAs regulate HF progression through several pathways. First, they inhibit miRNA activity through the “miRNA sponge” mechanism, relieving suppression of target genes involved in cardiac remodeling[17]. They also regulate G protein-coupled receptor , PI3K/Akt, and MAPK/ERK signaling pathways to influence myocyte hypertrophy and apoptosis[18]. Thus, circRNAs may be key regulators of HF onset and progression, as well as potential therapeutic targets requiring further validation. Advances in circRNA research have revealed their roles in regulating key target mRNAs at the transcriptional and translational levels, providing new perspectives on early HF diagnosis and treatment. Identifying specific circRNAs in patients with HF and combining these findings with gene-editing technology may offer avenues for personalized treatment. circRNAs therefore retain substantial research value and potential applications in HF. Their specific regulatory roles at different stages of HF development are summarized in Figure 1.

This review progresses from the basic biological characteristics of circRNAs to disease-related evidence and clinical applications. It first summarizes circRNA biogenesis and molecular functions, then discusses experimental evidence in AHF and CHF. Finally, it examines potential clinical applications, current methodological limitations, and future research directions.

LITERATURE SEARCH STRATEGY

This narrative review systematically collected relevant literature on the roles of circRNAs in AHF and CHF from PubMed, Web of Science, and Scopus. The search covered literature published through June 2025 and used the following keywords and their combinations: "circRNA", "circular RNA", "heart failure", "acute heart failure", "chronic heart failure", "cardiac hypertrophy", "cardiac remodeling", "fibrosis", "miRNA sponge", and "RNA-binding protein". Eligible publications included original research papers, review articles, and mechanistic studies published in English. Priority was given to literature providing evidence on circRNA biogenesis, molecular mechanisms, and experimental investigations of cardiovascular function. Additional relevant studies were identified by manually screening the reference lists of key publications. The included literature was systematically integrated and analyzed to summarize current knowledge of the biological functions and potential therapeutic value of circRNAs in heart failure.

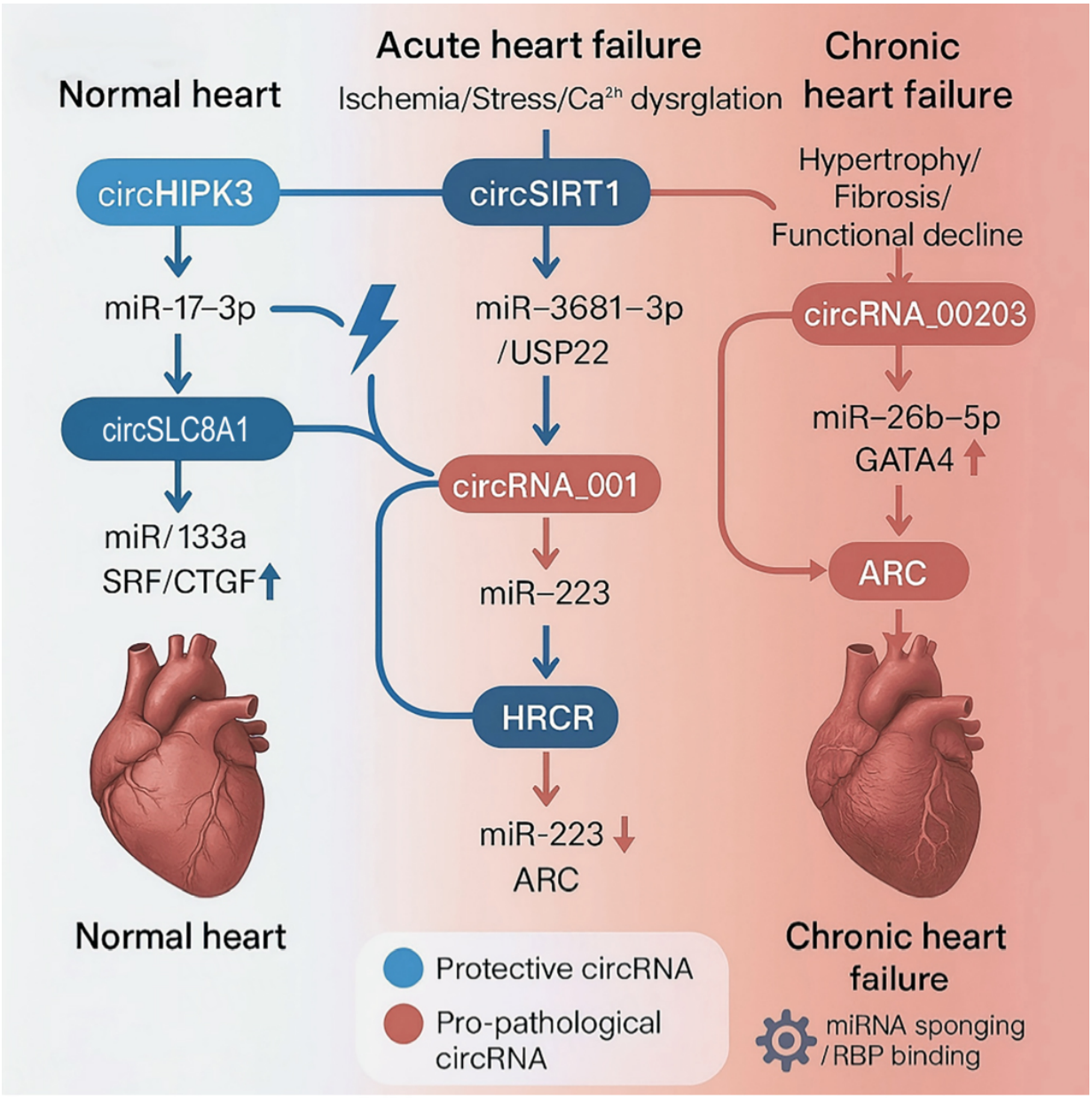


Figure 1. Dynamic roles of circRNAs during the progression of heart failure. CircRNAs regulate cardiac homeostasis under physiological conditions and participate in myocardial injury, remodeling, hypertrophy, and fibrosis during acute and chronic HF through interactions with miRNAs and RBPs. Blue arrows indicate protective effects, whereas red arrows indicate pathogenic effects.

BIOGENESIS AND MOLECULAR CHARACTERISTICS OF circRNAs

Back-splicing and classical splicing mechanisms

circRNA formation primarily relies on back-splicing, in which complementary sequences, such as Alu elements in flanking introns, bring a downstream exon's splice donor site into proximity with an upstream exon's splice acceptor site, forming a covalently closed circular RNA structure[19]. Unlike conventional linear mRNAs, circRNAs lack a 5′ cap and a 3′ poly(A) tail.

Back-splicing is not considered a classical splicing event because it still relies in part on the classical splicing mechanism, as shown in human cells where a classical splicing inhibitor or spliceosome mutation results in continued circRNA production (for example, using Isoginkgetin in HeLa cells)[20]. However, the absence of splicing factors such as U2 snRNP in Drosophila cells increases circRNA synthesis[21]. This suggests that,

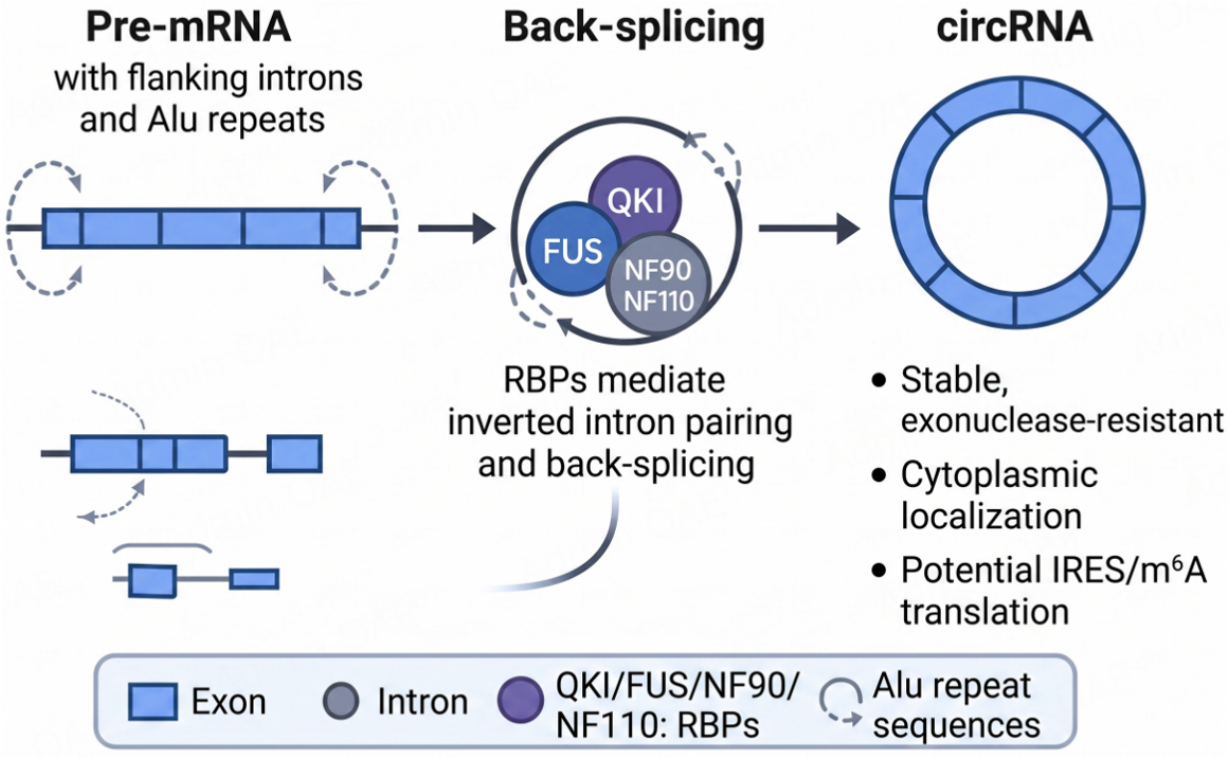


Figure 2. Biogenesis and molecular characteristics of circRNAs. circRNAs are formed through post-transcriptional splicing, in which complementary intronic sequences bind to RBPs, including QKI, FUS, and NF90/NF110, that promote exon ligation and circRNA formation. The resulting covalently closed circular structures lack a 5' cap and a 3' poly(A) tail, contributing to their stability and regulatory functions.

when pre-mRNA splicing is blocked, back-splicing can generate an alternative RNA product, thereby maintaining a balance between gene expression levels and splicing products.

RBPs and regulation of circRNA formation

RBPs play critical roles in circRNA formation. For example, FUS can promote back-splicing by recognizing and binding to intronic sequences flanking circularized exons, thereby facilitating RNA circularization[22]. Similarly, NF90 and NF110, proteins encoded by the interleukin enhancer-binding factor 3 (ILF3) gene, promote circRNA biogenesis by stabilizing complementary RNA pairing between flanking introns and facilitating back-splicing[23]. RBP dimerization also brings distant splice sites into proximity, further promoting circularization[24]. Beyond biogenesis, RBPs regulate circRNA stability and function. Conversely, circRNAs can act as molecular decoys or binding partners for RBPs, thereby modulating their activity[25].

Stability and structural characteristics of circRNAs

The circular structure confers high stability and conservation on circRNAs. Their lack of a 5' cap and a 3' poly(A) tail is associated with resistance to exonuclease degradation and substantially longer half-lives than those of linear RNAs[26]. These structural features support their high cellular abundance and stability under stress. circRNAs are predominantly generated by back-splicing.

circRNAs can be detected in both the nucleus and the cytoplasm, although most exonic circRNAs are predominantly cytoplasmic[27]. Their expression profiles vary significantly across tissues and developmental stages[28]. For example, the human brain and heart exhibit the highest circRNA abundance. In addition, circRNA expression is strongly correlated with host-gene function[29]. In summary, circRNA production involves back-splicing and canonical splicing mechanisms regulated by RBPs. Their circular structure contributes to their stability, and they are conserved in humans and other species. As alternative RNA structures, circRNAs may play important roles in gene regulation and pathological processes, including cardiovascular disease. Their biogenesis and molecular characteristics are illustrated in Figure 2.

MOLECULAR FUNCTIONS OF circRNAs

circRNAs modulate gene expression and intracellular signal transduction through several mechanisms. These include acting as miRNA sponges through the ceRNA mechanism, interacting with proteins, and undergoing translation mediated by internal ribosome entry sites (IRESs) and m^{6}A modification.

First, circRNAs may function as miRNA sponges that compete with miRNAs for binding to miRNA response elements (MREs), inhibiting miRNA binding to target mRNAs and relieving suppression of downstream gene expression. This is defined as the ceRNA mechanism[30]. For example, CDR1as (ciRS-7), shown in Figure 1, contains more than 70 miR-7 binding sites and regulates the expression of miR-7 target genes[31]. These findings support an important role for circRNAs in post-transcriptional regulation.

Second, circRNAs interact with RBPs to participate in diverse cellular processes[32]. Some circRNAs act as "decoys" or "reservoirs" that regulate RBP activity, whereas RBPs contribute to circRNA formation and stability. For example, FUS and NF90/NF110 facilitate circRNA circularization by binding to intronic regions, while cir-CCND1 binds to HuR to upregulate CCND1 expression[33]. Thus, circRNAs can function as effectors, receptors, or signaling intermediates and participate in post-transcriptional regulation.

In addition to their roles in post-transcriptional regulation and RNA interactions, some circRNAs have translational capacity. For example, circ-ZNF609 was the first circRNA confirmed to encode proteins in eukaryotic cells. Legnini *et al.* (Mol Cell, 2017) reported that circ-ZNF609 undergoes translation despite lacking a 5' cap and a 3'-poly(A) tail because it contains an IRES that enables cap-independent translation initiation, producing a 30 kDa protein. This translational activity increased markedly under heat shock stress and was associated with regulation of myocyte proliferation and differentiation[34]. Despite the absence of a cap at the 5' end and a tail at the 3' end, internal IRES or N6-methyladenosine (m^{6}A) sites can trigger circRNA translation[35,36]. IRES-dependent translation allows circRNAs to initiate translation during stress or hypoxia, while m^{6}A modification promotes circRNA translation initiation, with translational efficiency regulated by METTL3/4 methyltransferases and fat mass and obesity-associated protein (FTO) demethylase[37]. These findings broaden the potential roles of circRNAs in cellular function and disease.

Overall, circRNAs regulate gene expression through three main mechanisms: miRNA sequestration, interactions with RBPs, and cap-independent translation. Their major molecular functions and regulatory mechanisms are summarized in Figure 3. These functions provide a molecular basis for circRNA involvement in cardiovascular disease onset and progression. Beyond their classical roles as miRNA sponges and protein-binding molecules, circRNAs can regulate the assembly or activity of protein-associated signaling complexes. For example, circIGF1R directly interacts with DDX5 and activates β-catenin signaling, promoting cardiomyocyte proliferation and cardiac repair after ischemic injury[38]. circRNAs may also participate in epigenetic regulation through interactions with chromatin-modifying factors and RNA methylation-related mechanisms, including factors associated with m^{6}A. These non-classical mechanisms broaden circRNA-mediated gene regulation and may play important roles in cardiac remodeling and heart failure progression.

EXPERIMENTAL EVIDENCE OF CIRCRNAS IN HEART FAILURE

circRNAs were previously considered little more than by-products of pre-mRNA splicing. In recent years, however, they have been identified as regulators of HF pathogenesis and progression. They play important roles in AHF and CHF by regulating miRNAs, participating in signal transduction, and maintaining cellular homeostasis, potentially providing new molecular targets for HF diagnosis and therapy. Ventricular dysfunction in HF is not caused by a single form of nonspecific cardiomyocyte injury but by heterogeneous

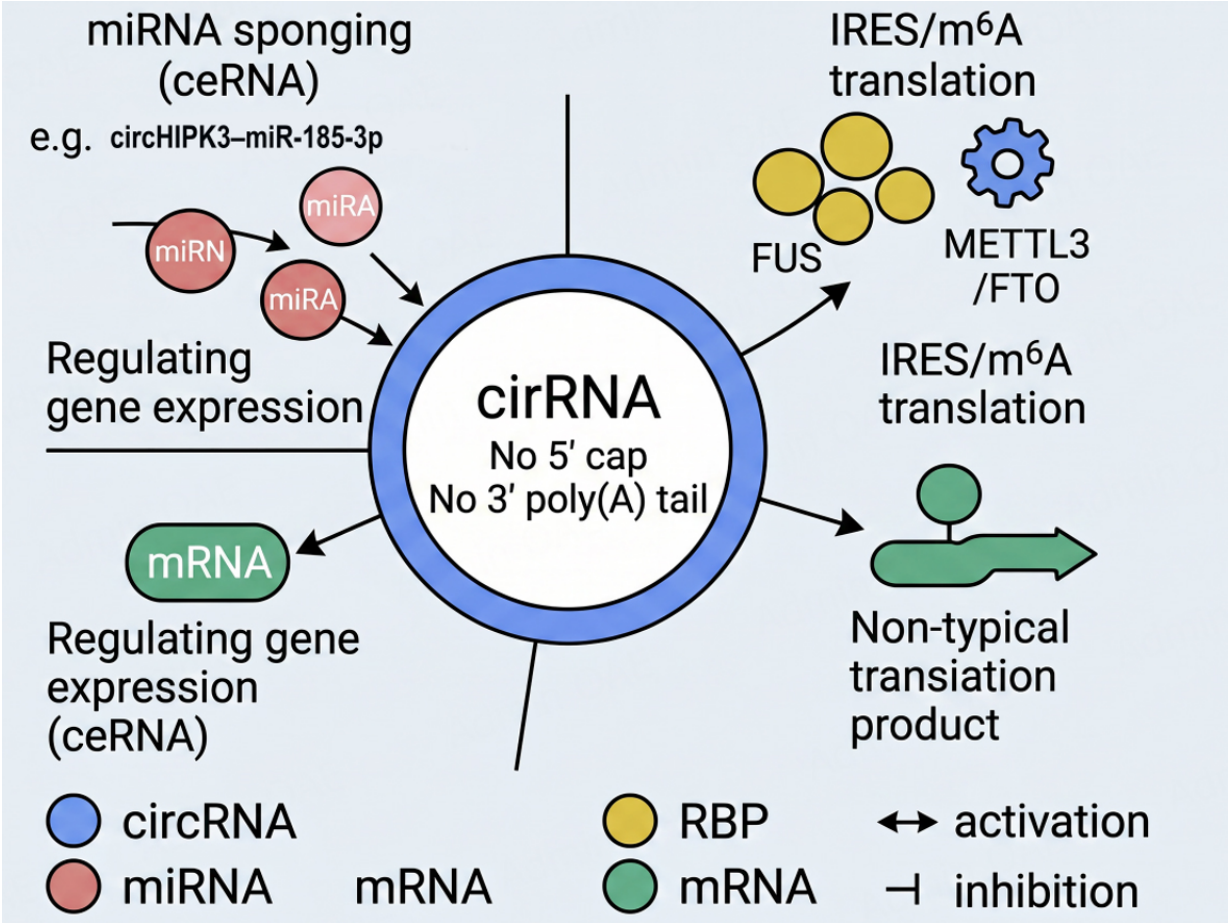


Figure 3. Major molecular mechanisms of circRNA function. circRNAs primarily regulate gene expression through three mechanisms: miRNA sequestration, interactions with RBPs, and cap-independent translation. These regulatory processes play crucial roles in maintaining cardiovascular homeostasis and promoting HF onset and progression.

pathological stimuli. Ischemic injury, such as acute myocardial infarction (MI), involves insufficient oxygen supply, mitochondrial dysfunction, oxidative stress, necrosis, apoptosis, inflammation, and scar formation. In contrast, pressure overload caused by hypertension or aortic valve stenosis primarily leads to concentric myocardial hypertrophy, activation of mechanical signaling pathways, fibroblast proliferation, extracellular matrix deposition, and subsequent deterioration of diastolic and systolic function. Volume overload, as occurs with valvular regurgitation or certain congenital heart diseases, more commonly manifests as eccentric ventricular remodeling, dilation, increased wall stress, and abnormalities in cytoskeletal and metabolic signaling. Although these conditions share downstream features, including inflammation, fibrosis, abnormal calcium handling, and ventricular remodeling, their upstream etiologies and temporal patterns of circRNA regulation may differ substantially. circRNA function must therefore be assessed in the context of the specific HF etiology and experimental model. Non-ischemic myocardial injury also contributes to HF onset and progression. Myocarditis caused by viral infection, autoimmunity, or other immune-mediated mechanisms can induce inflammatory cell infiltration, cytokine activation, cardiomyocyte necrosis or apoptosis, and subsequent fibrotic remodeling. Toxic cardiomyopathy, including anthracycline-induced injury, is typically associated with increased oxidative stress, mitochondrial damage, activation of DNA damage responses, impaired autophagy, and cardiomyocyte loss. These processes differ from ischemic injury and pressure overload but converge on common signaling pathways that lead to ventricular dysfunction. Current circRNA research in HF focuses mainly on ischemic and pressure overload models; studies of myocarditis and drug-induced cardiomyopathy remain relatively scarce. Future research should determine

Table 1. Representative circRNAs implicated in experimental models relevant to acute and chronic heart failure

circRNA	HF subtype	Target/mechanism	Experimental model	Functional effect	Translational potential	References
circHIPK3	AHF/CHF	miR-17-3p/ADCY6; miR-185-3p/CaSR	MI and pressure overload models	Promotes cardiac hypertrophy and remodeling; regulates calcium handling in a context-dependent manner	Moderate	[35,37]
circSIRT1	AHF	miR-3681-3p/miR-5195-3p/SIRT1	Ang II and ischemia models	Anti-apoptotic and anti-hypertrophic	High	[38]
circSLC8A1	CHF	miR-133a/SRF/CTGF/ADCY6	TAC model	Promotes hypertrophy and remodeling	High	[39,41]
circRNA-00203	CHF	miR-26b-5p/miR-140-3p/GATA4	Ang II model	Promotes fibrosis and hypertrophy	Moderate	[42]
HRCR	CHF	miR-223/ARC	Hypertrophy model	Cardioprotective	High	[43]

Note: Most evidence summarized in this table is derived from experimental animal or cell models (e.g., myocardial infarction, TAC, Ang II-induced hypertrophy) and has not yet been extensively validated in large clinical cohorts or across all HF phenotypes.

whether specific circRNA expression profiles distinguish ischemia, pressure overload, volume overload, inflammation, and toxic cardiomyopathy. Although many circRNAs have been associated with HF, they differ substantially in biological function, experimental evidence, and clinical translational potential. Table 1 summarizes representative circRNAs associated with AHF and CHF according to their molecular targets, experimental models, regulatory mechanisms, and functional effects.

Experimental evidence in acute heart failure

AHF is a clinical syndrome characterized by the new onset or rapid worsening of the symptoms and signs of heart failure, requiring urgent clinical assessment and treatment[5,6,39]. AHF may occur as de novo HF or as acute decompensation of pre-existing chronic HF and can be precipitated by acute coronary syndrome, arrhythmias, uncontrolled hypertension, infection, acute mechanical causes, and other cardiovascular or systemic insults[5,6,39]. Its pathophysiology is heterogeneous and involves complex interactions among cardiac dysfunction, altered loading conditions, congestion, neurohormonal activation, inflammation, oxidative stress, and subsequent cellular and organ injury[5,39].

Growing evidence indicates that circRNAs participate in the pathological processes described above and may influence AHF onset, progression, and clinical course by regulating associated molecular networks. For example, circHIPK3 levels increase during acute MI, and this circRNA regulates intracellular Ca^{2+} levels through the miR-17-3p/ADCY6 axis, influencing cardiomyocyte contractility[40]. circHIPK3 overexpression increases ADCY6 expression, exacerbating cardiac remodeling and dysfunction, whereas circHIPK3 inhibition can alleviate injury-associated myocardial dysfunction caused by cimpAIRM1 and cimpAIRM2 and restore myocardial contractility[40,41]. circHIPK3 also sponges miR-185-3p to regulate CaSR expression, promoting pressure overload-induced cardiac hypertrophy and ventricular remodeling. Silencing circHIPK3 alleviates hypertrophy and improves cardiac function, suggesting that it may represent a therapeutic target rather than a cardioprotective factor[42]. Experimental studies implicate circHIPK3 in myocardial injury, abnormal calcium handling, and pathological remodeling during AHF, supporting its potential as a therapeutic target. In addition, circSIRT1 has shown cardioprotective effects in experimental models of cardiac stress. Wang *et al.* found that circSIRT1 expression was significantly downregulated under Ang II stimulation and ischemic conditions[43]. Mechanistically, circSIRT1 regulates the miR-3681-3p/miR-5195-3p/SIRT1 axis and recruits the deubiquitinating enzyme USP22 to stabilize SIRT1 protein, promoting autophagy and alleviating myocardial cell proliferation and injury. These findings suggest

that restoring circSIRT1 expression may offer a therapeutic strategy for AHF. This circRNA regulates SIRT1 expression through the miR-3681-3p/miR-5195-3p/SIRT1 pathway, which recruits the deubiquitinase USP22 to stabilize SIRT1 protein[43]. Experimental evidence suggests that circSIRT1 may confer cardioprotection under stress by modulating this axis, making it a potential target for early intervention in AHF.

Previous research suggests that circRNAs can regulate essential physiological processes, including Ca^{2+} signaling and myocardial remodeling following cardiac injury (PCI), and may serve as biomarkers and therapeutic targets for AHF. Further investigation of their roles in AHF may contribute to more effective therapeutic strategies and improved clinical outcomes.

Experimental evidence in chronic heart failure

CHF is a clinical syndrome resulting from structural and/or functional cardiac abnormalities, characterized by persistent or progressive symptoms and signs of HF[5,6,44]. Its progression involves sustained neurohormonal activation and maladaptive cardiac remodeling, including cardiomyocyte hypertrophy, myocardial fibrosis, alterations in ventricular structure and function, and metabolic dysregulation[5,6,44]. These processes can progressively impair cardiac function and contribute to the transition from compensated cardiac dysfunction to clinically overt or advanced HF[5,44]. Studies have found that myocardial-specific circSLC8A1 (also known as CircNCX1) is significantly upregulated in a transverse aortic constriction (TAC)-induced pressure overload hypertrophy model[45]. It sponges miR-133a, relieving inhibition of downstream target genes such as CTGF, SRF, and Adcy6; Adcy6, for example, can amplify hypertrophic signaling, promoting cardiomyocyte hypertrophy and ventricular remodeling[45,46]. Further experiments showed that circSLC8A1 knockdown can alleviate myocardial hypertrophy and slow HF progression, whereas its overexpression worsens cardiac dysfunction. Mechanistically, circSLC8A1 regulates the expression of serum response factor (SRF), connective tissue growth factor (CTGF), beta-1 adrenergic receptor (ADRB1), and adenylate cyclase 6 (ADCY6) by sponging miR-133a, leading to myocardial remodeling and cardiac dysfunction[47]. These findings elucidate the role of circSLC8A1 in CHF progression and highlight a potential therapeutic avenue requiring validation in human studies. circRNA-00203 was upregulated in an Ang II-induced myocardial hypertrophy model. It sponges miR-26b-5p and miR-140-3p, relieving inhibition of the transcription factor GATA4 and thereby promoting myocardial hypertrophy and fibrosis[48]. Experiments show that interfering with circRNA-00203 or overexpressing the associated miRNAs can significantly reverse its pathogenic effects, suggesting that circRNA-00203 is a candidate for further therapeutic investigation, although its clinical relevance remains unvalidated. In addition, circRNA HRCR has shown a protective role in CHF. By sponging miR-223 and reducing its interaction with the downstream anti-apoptotic gene ARC (Apoptosis Repressor with Caspase Recruitment Domain), HRCR reduces cardiomyocyte apoptosis and improves cardiac function[49]. Findings on HRCR illustrate the opposing roles of circRNAs in HF progression: some promote pathological changes, whereas others confer protection.

In summary, circRNAs play dual regulatory roles in CHF pathogenesis: circSLC8A1 and circRNA-00203 enhance myocardial hypertrophy and fibrosis, whereas HRCR confers protection by inhibiting apoptosis. These findings support further investigation of circRNAs as potential therapeutic targets, although further validation is required. Representative circRNA-mediated mechanisms in AHF and CHF are summarized in Figure 4.

Critical perspectives on circRNAs in heart failure

Although numerous studies have implicated circRNAs in the onset and progression of heart failure, their biological effects appear highly context-dependent. For example, circHIPK3 has been implicated in myocardial dysfunction and pathological cardiac remodeling through the miR-17-3p/ADCY6 and miR-185-3p/CaSR axes, and its effects may vary with the disease model and molecular context[40-42].

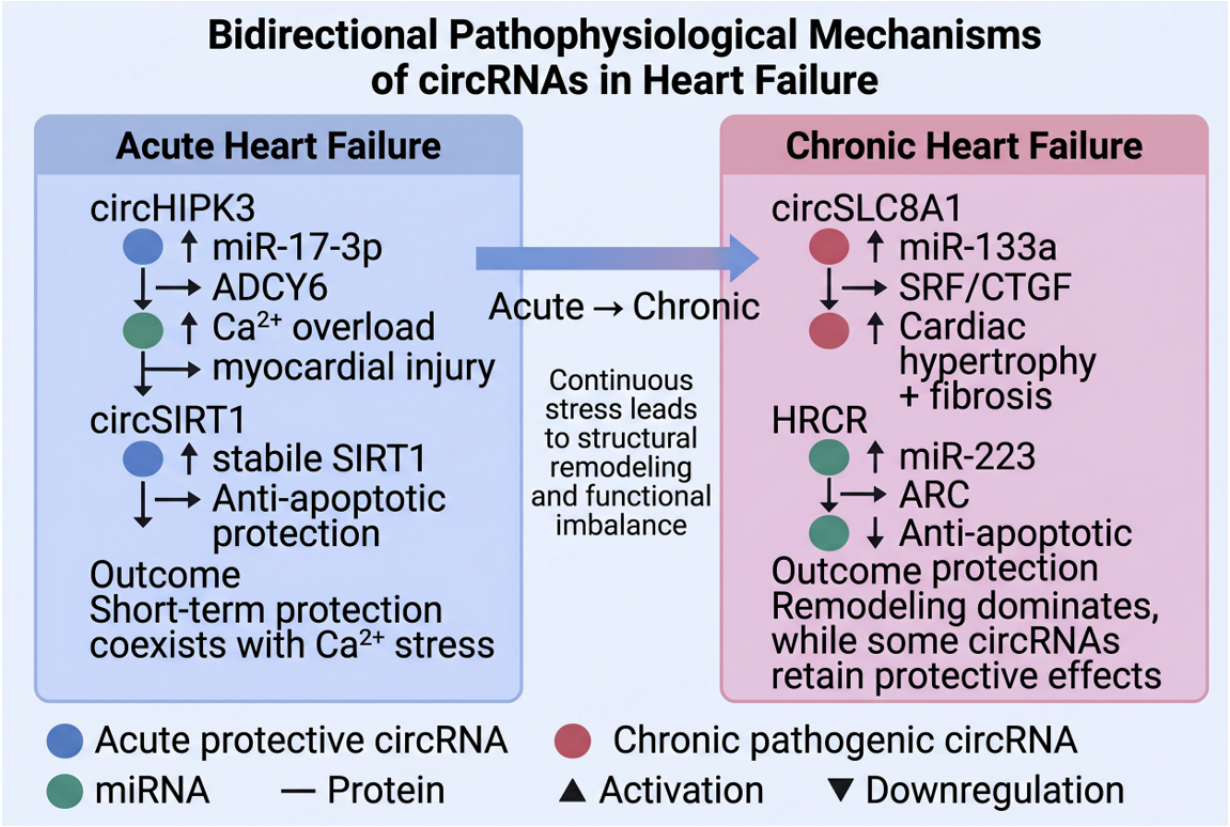


Figure 4. Regulatory roles of circRNAs in acute and chronic heart failure. Representative circRNAs can exert protective or pathogenic effects depending on the disease stage and molecular context. circHIPK3 and circSIRT1 are primarily associated with myocardial injury, calcium homeostasis, apoptosis, and stress responses in AHF, whereas circSLC8A1, circRNA-00203, and HRCR participate in hypertrophy, fibrosis, apoptosis, and ventricular remodeling in CHF.

circSLC8A1 has been associated with cardiomyocyte hypertrophy, ischemic myocardial injury, and adverse cardiac remodeling, particularly through interactions with miR-133a and its downstream targets[45-47]. Similarly, circRNA-00203 promotes cardiac hypertrophy by regulating the miR-26b-5p/miR-140-3p/GATA4 axis[48], whereas HRCR exerts cardioprotective effects by targeting miR-223 and attenuating pathological hypertrophy and cardiomyocyte apoptosis[49]. Collectively, these findings suggest that circRNAs are context-dependent regulators rather than molecules with uniformly beneficial or detrimental effects.

Another important challenge in circRNA research is insufficient clinical validation. Most evidence derives from in vitro experiments and animal models, with few large-scale human studies. Species-specific differences in circRNA expression may further affect the reproducibility and extrapolation of preclinical findings. Caution is therefore required when translating experimental observations into clinical applications. Among the circRNAs discussed in this review, circHIPK3, circSIRT1, circSLC8A1, circRNA-00203, and HRCR have been experimentally implicated in key pathological processes, including myocardial injury, hypertrophy, apoptosis, fibrosis, and cardiac remodeling[40-43,45-49]. These findings make them promising candidates for further translational investigation as potential biomarkers or therapeutic targets[41,46,50,51]. However, their clinical utility remains unestablished, and validation in well-designed, multicenter human studies is required before clinical application.

TRANSLATIONAL APPLICATIONS AND METHODOLOGICAL LIMITATIONS OF CIRCRNAS IN HEART FAILURE

Recent advances in sequencing technologies have substantially facilitated circRNA research. Long-read sequencing and full-length single-cell RNA sequencing have improved the characterization of full-length circRNA isoforms and their cell-type-specific expression patterns[52-54]. However, circRNA identification and quantification remain technically challenging because most approaches rely on detecting back-splice junctions (BSJs), and different computational pipelines and algorithms may generate inconsistent candidate sets[52-54]. Standardized sequencing protocols and bioinformatic workflows are therefore essential to improve reproducibility and comparability across studies.

Some circRNAs exhibit tissue-, cell-type-, and disease-stage-specific expression patterns[55,56]. These characteristics may facilitate the development of circRNA-based molecular signatures, although their diagnostic and therapeutic utility requires further validation[57].

The clinical feasibility of circRNA-based therapies also depends on delivery, safety, and regulatory considerations. Delivery platforms, including lipid nanoparticles, viral vectors, polymeric nanoparticles, and engineered extracellular vesicles or exosomes, need to achieve efficient, tissue-selective delivery while minimizing systemic exposure and unintended effects[58,59]. Potential immunogenicity and inflammatory responses require careful evaluation, particularly for exogenously produced circRNAs and repeated administration[58,59]. Moreover, the pharmacokinetic and pharmacodynamic properties of circRNA therapeutics, including biodistribution, intracellular persistence, degradation kinetics, and dose-response relationships, remain incompletely characterized[59,60]. Clinical translation will also require scalable production, rigorous quality control, systematic safety assessment, and validation in appropriate preclinical and clinical studies[59,60].

Despite their potential, most evidence on circRNAs in heart failure remains preclinical, with functional studies predominantly based on cultured cells and animal models and limited validation in large human cohorts[50,51,61-63]. Tissue- and cell-type-specific expression may further complicate target selection and therapeutic delivery[49,50]. Differences in study design, detection platforms, quantification methods, and bioinformatic pipelines also limit cross-study comparability and reproducibility[52-54]. Multicenter human studies, independent validation cohorts, and standardized analytical procedures are therefore needed before circRNA-based biomarkers or therapies can be incorporated into routine clinical management[50,51,58,59,61-63].

Methodological limitations in circRNA research

Despite rapid advances in circRNA profiling technologies, several methodological limitations should be considered when interpreting existing findings. First, circRNA identification primarily relies on accurate detection of BSJs, which can be influenced by sequencing depth, read length, library preparation strategies, and sequence-alignment or circRNA-calling algorithms[52-54]. RNase R treatment and ribosomal RNA depletion can facilitate circRNA enrichment but may introduce experimental biases and do not necessarily eliminate all linear RNA species[53,54]. Candidate circRNAs identified by RNA sequencing should therefore ideally undergo orthogonal experimental validation, including RT-PCR using divergent primers spanning the BSJ, Sanger sequencing of the junction, assessment of RNase R resistance, and RT-qPCR when appropriate[53,54].

Second, sequencing artifacts and false-positive predictions remain important concerns in circRNA research. Apparent BSJs may result from experimental artifacts, sequence homology, reverse-transcription template switching, or read-mapping errors[52-54]. The relatively low abundance of many circRNAs also makes their

detection sensitive to sequencing depth and analytical methods. Different circRNA-detection algorithms may consequently generate substantially different candidate sets, limiting reproducibility and comparability across studies[52-54].

Third, tissue and cellular heterogeneity poses an additional challenge in cardiovascular circRNA research. Myocardial tissue contains multiple cell populations, including cardiomyocytes, fibroblasts, endothelial cells, smooth muscle cells, and immune cells. Bulk RNA-sequencing data may therefore reflect changes in cellular composition as well as cell-intrinsic circRNA regulation. Integrating full-length single-cell RNA sequencing, spatial transcriptomic approaches, standardized bioinformatic workflows, and independent validation cohorts may improve the cellular resolution, reproducibility, and biological interpretability of future studies[52].

FUTURE RESEARCH DIRECTIONS

This review discusses the complex roles of circRNAs in acute and chronic HF and their mechanisms of cardiac regulation. Further analysis of circRNA regulatory networks involved in myocardial stress responses, calcium homeostasis, energy metabolism, and fibrosis is needed to clarify their roles in these processes. Future studies should examine dynamic circRNA expression across pathological stages, tissue specificity, and interactions with signaling pathways, using integrative technologies such as high-throughput omics and single-cell sequencing to construct circRNA regulatory networks. The high stability, strong evolutionary conservation, and tissue-specific expression of circRNAs suggest potential applications in HF diagnosis. Future research should explore shared circRNA regulatory mechanisms across pathological states and systematically evaluate their value as diagnostic biomarkers and potential therapeutic targets. These applications require validation through further basic research and large-scale clinical studies. Detailed characterization of circRNA-related molecular networks and their interactions may deepen understanding of HF pathogenesis and support precision medicine strategies based on molecular classification and individualized intervention. Functional characterization is also needed to investigate circRNA-related multi-disease molecular patterns. Developing circRNA-related gene-editing or RNA-targeting drug strategies and improving in vivo delivery efficiency or circRNA-specific expression may provide further evidence to support precision medicine, early diagnosis, and targeted HF therapies. Future studies should also evaluate circulating circRNAs and exosome-derived circRNAs as minimally invasive biomarkers for HF diagnosis and prognostic assessment. Integrating advanced sequencing, bioinformatic tools, gene-editing platforms, and RNA delivery systems is expected to accelerate clinical translation and support precise diagnosis, risk stratification, and individualized HF treatment.

CONCLUSION

circRNAs are increasingly recognized as key regulators of the onset and progression of HF. They play important roles in cardiac pathophysiology by linking post-transcriptional regulation, protein interaction networks, and stress-response signaling pathways. Current evidence indicates that circRNAs are involved in multiple pathological processes closely associated with HF, including cardiomyocyte injury, abnormal calcium handling, apoptosis, myocardial hypertrophy, fibrosis, inflammation, and ventricular remodeling.

Mechanistically, circRNAs not only act as miRNA sponges but also bind proteins, potentially serve as protein scaffolds, and regulate RNA modifications and translation-related processes. These diverse biological functions suggest that circRNAs may participate in both adaptive and maladaptive cardiac responses in AHF and CHF.

Despite substantial progress in recent years, clinical translation remains at an early stage. Most findings on circRNA function derive from cell-based experiments and animal models, and their relevance to human

heart failure requires further validation. Unresolved issues include stage-specific effects, cell-type heterogeneity, difficulties in detecting low-abundance transcripts, inconsistent bioinformatics workflows, small clinical sample sizes, and insufficient standardization of circRNA quantification. Future research should therefore prioritize rigorous validation of post-splicing sites, multicenter human studies, integration of single-cell sequencing and spatial transcriptomics, and standardized data analysis workflows to improve reliability and reproducibility. Given their high stability and ease of detection in body fluids, circRNAs are most likely to find initial clinical applications as biomarkers for heart failure diagnosis, risk stratification, and disease monitoring, particularly as circulating circRNAs or exosome-derived circRNAs. Therapeutic strategies based on circRNAs, including circRNA silencing, functional replacement, engineered exosome delivery, nanoparticle-mediated delivery, and CRISPR/Cas-mediated precise regulation, also show promise. However, these approaches require further optimization and validation of targeting specificity, safety, delivery efficiency, and long-term efficacy.

Overall, circRNAs provide an important framework for understanding the molecular mechanisms of heart failure. However, most available evidence derives from preclinical models of myocardial infarction, pressure overload, and cardiac remodeling rather than large-scale clinical studies. Evidence for HFpEF and heart failure with HFmrEF also remains limited. Current findings should therefore be interpreted cautiously and should not be generalized to all cases of acute and chronic heart failure without further clinical validation.

DECLARATIONS

Acknowledgments

The Figures and Graphical Abstract were created and edited using WPS Office, Adobe Photoshop and Adobe Illustrator.

Authors' contributions

Designed and supervised the study, provided funding support, wrote the final version of the manuscript, and served as the principal investigator: Zhang C
Drafted, reviewed, and revised the manuscript: Zhao X
Prepared the visualizations and critically revised the manuscript: Liu S, Su Y
All authors read and approved the final version of the manuscript.

Availability of data and materials

Not applicable.

AI and AI-assisted tools statement

Not applicable.

Financial support and sponsorship

This work was supported by the National Natural Science Foundation of China (Grant No. U23A20398); the Noncommunicable Chronic Diseases-National Science and Technology Major Project (Grant No. 2024ZD0537707); the Sichuan Science and Technology Program (Grant No. 2025YFRG0005); the People's Government of Luzhou Municipality-Southwest Medical University Science and Technology Strategic Cooperation "Science and Technology Climbing Program" (Grant No. 2025LZXNYDPD01); and the Research Start-up Foundation of Southwest Medical University (Grant No. 00040155).

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

REFERENCES

1. Zhang X, Wang H, Zhang Y, Lu X, Chen L, Yang L. Complementary sequence-mediated exon circularization. *Cell.* 2014;159:134-47. DOI
2. Conn SJ, Pillman KA, Toubia J, et al. The RNA binding protein quaking regulates formation of circRNAs. *Cell.* 2015;160:1125-34. DOI
3. Jeck WR, Sorrentino JA, Wang K, et al. Circular RNAs are abundant, conserved, and associated with ALU repeats. *RNA.* 2013;19:141-57. DOI PubMed PMC
4. Tan WL, Lim BT, Anene-nzelu CG, et al. A landscape of circular RNA expression in the human heart. *Cardiovasc Res.* 2017:cvw250. DOI
5. Mcdonagh TA, Metra M, Adamo M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J.* 2021;42:3599-726. DOI
6. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on clinical practice guidelines. *Circulation.* 2022:145. DOI
7. Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GMC, Coats AJS. Global burden of heart failure: a comprehensive and updated review of epidemiology. *Cardiovasc Res.* 2022;118:3272-87. DOI
8. Hao G, Wang X, Chen Z, et al. Prevalence of heart failure and left ventricular dysfunction in China: the China hypertension survey, 2012-2015. *Eur J Heart Fail.* 2019;21:1329-37. DOI
9. An D, Zeng Q, Zhang P, et al. Alpha-ketoglutarate ameliorates pressure overload-induced chronic cardiac dysfunction in mice. *Redox Biol.* 2021;46:102088. DOI PubMed PMC
10. Tran DH, May HI, Li Q, et al. Chronic activation of hexosamine biosynthesis in the heart triggers pathological cardiac remodeling. *Nat Commun.* 2020;11:1771. DOI PubMed PMC
11. 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;24:12401-10. DOI PubMed PMC
12. Gao X, Liu C, Zhang Y, et al. The circRNA CNEACR regulates necroptosis of cardiomyocytes through Foxa2 suppression. *Cell Death Differ.* 2021;29:527-39. DOI PubMed PMC
13. Madè A, Bibi A, Garcia-manteiga JM, et al. circRNA-miRNA-mRNA deregulated network in ischemic heart failure patients. *Cells.* 2023;12:2578. DOI PubMed PMC
14. Neufeldt D, Schmidt A, Mohr E, et al. Circular RNA circZFPM2 regulates cardiomyocyte hypertrophy and survival. *Basic Res Cardiol.* 2024;119:613-32. DOI PubMed PMC
15. Acharya P, Parkins S, Tranter M. RNA binding proteins as mediators of pathological cardiac remodeling. *Front Cell Dev Biol.* 2024;12:1368097. DOI PubMed PMC
16. 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;10:4317. DOI PubMed PMC
17. 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;158:128-39. DOI
18. Wang J, Gareri C, Rockman HA. G-protein-coupled receptors in heart disease. *Circ Res.* 2018;123:716-35. DOI PubMed PMC
19. Shen Z, Shao YL, Liu W, Zhang Q, Yuan L. Prediction of back-splicing sites for circRNA formation based on convolutional neural networks. *BMC Genom.* 2022;23:581. DOI PubMed PMC
20. Greene J, Baird A, Brady L, et al. cirRNA: biogenesis, function and role in human diseases. *Front Mol Biosci.* 2017;4:38. DOI PubMed PMC
21. Kirio K, Patop IL, Anduaga AM, et al. cirRNA exhibit exceptional stability in the aging brain and serve as reliable age and experience indicators. *Cell Rep.* 2025;44:115485. DOI PubMed PMC
22. Hwang HJ, Kim YK. Molecular mechanisms of circular RNA translation. *Exp Mol Med.* 2024;56:1272-80. DOI PubMed PMC
23. Ren L, Jiang Q, Mo L, et al. Mechanisms of circular RNA degradation. *Commun Biol.* 2022;5:1355. DOI PubMed PMC
24. Kristensen LS, Andersen MS, Stagsted LVW, Ebbesen KK, Hansen TB, Kjems J. The biogenesis, biology and characterization of cirRNA. *Nat Rev Genet.* 2019;20:675-91. DOI PubMed
25. Zhang L, Zhang Y, Yu F, Li X, Gao H, Li P. The circRNA-miRNA/RBP regulatory network in myocardial infarction. *Front Pharmacol.* 2022;13:941123. DOI PubMed PMC

26. Li Y, Zheng Q, Bao C, et al. Circular RNA is enriched and stable in exosomes: a promising biomarker for cancer diagnosis. *Cell Res.* 2015;25:981-4. DOI PubMed PMC
27. Huang C, Liang D, Tatomer DC, Wilusz JE. A length-dependent evolutionarily conserved pathway controls nuclear export of cirRNA. *Genes Dev.* 2018;32:639-44. DOI PubMed PMC
28. Mahmoudi E, Cairns MJ. cirRNA are temporospatially regulated throughout development and ageing in the rat. *Sci Rep.* 2019;9:2564. DOI PubMed PMC
29. Bibi A, Bartekova M, Gandhi S, et al. Circular RNA regulatory role in pathological cardiac remodelling. *Br J Pharmacol.* 2024;182:316-39. DOI
30. Cheng Y, Su Y, Wang S, et al. Identification of circRNA-lncRNA-miRNA-mRNA competitive endogenous RNA network as novel prognostic markers for acute myeloid leukemia. *Genes.* 2020;11:868. DOI PubMed PMC
31. Ma C, Gu R, Wang X, et al. circRNA CDR1as promotes pulmonary artery smooth muscle cell calcification by upregulating CAMK2D and CNN3 via sponging miR-7-5p. *Mol Ther Nucl Acids.* 2020;22:530-41. DOI PubMed PMC
32. Zhang N, Wang X, Li Y, et al. Mechanisms and therapeutic implications of gene expression regulation by circRNA-protein interactions in cancer. *Commun Biol.* 2025;8:77. DOI PubMed PMC
33. Zang Y, Li J, Wan B, Tai Y. circRNA circ-CCND1 promotes the proliferation of laryngeal squamous cell carcinoma through elevating CCND1 expression via interacting with HuR and miR-646. *J Cell Mol Med.* 2020;24:2423-33. DOI PubMed PMC
34. 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;66:22-37.e9. DOI PubMed PMC
35. Zhou C, Molinie B, Daneshvar K, et al. Genome-wide maps of m^{6}A circRNAs identify widespread and cell-type-specific methylation patterns that are distinct from mRNAs. *Cell Rep.* 2017;20:2262-76. DOI PubMed PMC
36. Payea MJ, Dar SA, Malla S, Maragkakis M. Ribonucleic acid-mediated control of protein translation under stress. *Antioxid Redox Signal.* 2023;39:374-89. DOI PubMed PMC
37. Zhang J, Zhou R, Zhang H, et al. Decoding circRNA translation: challenges and advances in computational method development. *Front Genet.* 2025;16:1654305. DOI PubMed PMC
38. Shan T, Yang T, 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 PubMed PMC
39. Arrigo M, Jessup M, Mullens W, et al. Acute heart failure. *Nat Rev Dis Primers.* 2020;6:16. DOI PubMed PMC
40. Deng Y, Wang J, Xie G, Zeng X, Li H. Circ-HIPK3 strengthens the effects of adrenaline in heart failure by MiR-17-3p - ADCY6 axis. *Int J Biol Sci.* 2019;15:2484-96. DOI PubMed PMC
41. Zhang L, Wang Y, Yu F, Li X, Gao H, Li P. CircHIPK3 plays vital roles in cardiovascular disease. *Front Cardiovasc Med.* 2021;8:733248. DOI PubMed PMC
42. Xu X, Wang J, Wang X. Silencing of circHIPK3 inhibits pressure overload-induced cardiac hypertrophy and dysfunction by sponging miR-185-3p. *Drug Des Devel Ther.* 2020;14:5699-710. DOI PubMed PMC
43. Wang W, Wang L, Yang M, et al. Circ-SIRT1 inhibits cardiac hypertrophy via activating SIRT1 to promote autophagy. *Cell Death Dis.* 2021;12:1069. DOI PubMed PMC
44. Metra M, Teerlink JR. Heart failure. *Lancet.* 2017;390:1981-95. DOI
45. Lim TB, Aliwarga E, Luu TDA, et al. Targeting the highly abundant circular RNA circSLC8A1 in cardiomyocytes attenuates pressure overload induced hypertrophy. *Cardiovasc Res.* 2019;115:1998-2007. DOI
46. Yang T, Long T, Du T, Chen Y, Dong Y, Huang Z. Circle the cardiac remodeling with circRNAs. *Front Cardiovasc Med.* 2021;8:702586. DOI PubMed PMC
47. Li M, Ding W, Tariq MA, et al. A circular transcript of *ncx1* gene mediates ischemic myocardial injury by targeting miR-133a-3p. *Theranostics.* 2018;8:5855-69. DOI PubMed PMC
48. Li H, Xu J, Fang X, et al. Circular RNA circRNA_000203 aggravates cardiac hypertrophy via suppressing miR-26b-5p and miR-140-3p binding to Gata4. *Cardiovasc Res.* 2020;116:1323-34. DOI PubMed PMC
49. Wang K, Long B, Liu F, et al. A circular RNA protects the heart from pathological hypertrophy and heart failure by targeting miR-223. *Eur Heart J.* 2016;37:2602-11. DOI
50. Yuan Z, Huang S, Jin X, Li S. cirRNA in cardiovascular diseases: molecular mechanisms, therapeutic advances, and innovations. *Genes.* 2024;15:1423. DOI PubMed PMC
51. Capirossi G, Brasini S, Tremoli E, Binatti A, Roncarati R. cirRNA in cardiovascular physiopathology: from molecular mechanisms to therapeutic opportunities. *Int J Mol Sci.* 2025;26:9725. DOI PubMed PMC
52. Zhang J, Zhao F. Circular RNA discovery with emerging sequencing and deep learning technologies. *Nat Genet.* 2025;57:1089-102. DOI PubMed

53. Nielsen AF, Bindereif A, Bozzoni I, et al. Best practice standards for circular RNA research. *Nat Methods.* 2022;19:1208-20. DOI PubMed PMC
54. Szabo L, Salzman J. Detecting circular RNAs: bioinformatic and experimental challenges. *Nat Rev Genet.* 2016;17:679-92. DOI PubMed PMC
55. Siede D, Rapti K, Gorska A, et al. Identification of cirRNA with host gene-independent expression in human model systems for cardiac differentiation and disease. *J Mol Cell Cardiol.* 2017;109:48-56. DOI
56. Hatzimanolis O, Sykes AM, Cristino AS. cirRNA in neurological conditions - computational identification, functional validation, and potential clinical applications. *Mol Psychiatry.* 2025;30:1652-75. DOI PubMed PMC
57. Wen N, Peng D, Xiong X, et al. Cholangiocarcinoma combined with biliary obstruction: an exosomal circRNA signature for diagnosis and early recurrence monitoring. *Sig Transduct Target Ther.* 2024;9:107. DOI PubMed PMC
58. Dong J, Zeng Z, Huang Y, Chen C, Cheng Z, Zhu Q. Challenges and opportunities for circRNA identification and delivery. *Crit Rev Biochem Mol Biol.* 2023;58:19-35. DOI
59. Young T, Chang Wang K, James Varley A, Li B. Clinical delivery of circular RNA: lessons learned from RNA drug development. *Adv Drug Delivery Rev.* 2023;197:114826. DOI PubMed
60. Cao X, Cai Z, Zhang J, Zhao F. Engineering circular RNA medicines. *Nat Rev Bioeng.* 2024;3:270-87. DOI
61. You Q, Yu J, Pan R, Feng J, Guo H, Liu B. Decoding the regulatory roles of circular RNAs in cardiac fibrosis. *Non-coding RNA Res.* 2025;11:115-30. DOI PubMed PMC
62. Bo X, Li Q, Chen S, et al. Evidence and perspectives on miRNA, circRNA, and lncRNA in myocardial ischemia-reperfusion injury: a bibliometric study. *J Cardiothorac Surg.* 2025;20:66. DOI PubMed PMC
63. Pan R, Koo C, Su W, You Q, Guo H, Liu B. cirRNA modulate cell death in cardiovascular diseases. *Cell Death Discov.* 2025;11:214. DOI PubMed PMC