Review

The role of CircRNA in acute and chronic heart failure

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Abstract

Circular RNAs (circRNAs) are a class of non-coding RNAs with a unique structure that have shown significant roles in various biological processes in recent years. The generation of circRNAs is regulated by a back-splicing mechanism, which is influenced by the interactions between RNA-binding proteins and specific sequences within introns. They are characterized by high stability and conservation, enabling them to resist degradation by exonucleases. Therefore, circRNAs are predicted as potential biomarkers for diseases such as the initiation and development of heart failure(HF). circRNAs can perform various biological functions, including miRNA sponge function and protein interaction,and even act as coding molecules to translate to form proteins or

peptides. In the field of heart failure research, numerous circRNAs like circSLC8A1, circHIPK3, circ-SIRT1, and circRNA-000203 have been confirmed to modulate expression.

The potential interactions between miRNAs and their target genes,together with RNA-binding proteins and the roles of miRNAs in the development of hypertrophy,remodeling,and heart failure. In addition to these issues,circRNAs have a significant tissue specificity that modulates the Cai^{2+} signaling pathway leading to proper cardiac function. Finally, circRNAs play an important role as pacemakers in heart function under heart pressure overload conditions, providing perspectives into the functional alterations under which disease can be repressed. This review discusses the role of circRNAs in both acute and chronic heart failure under mechanical stress, providing valuable clues on possible future targets for treating heart failure.

Keywords: Circular RNAs, back splice junctoin, miRNA sponges, heart failure, myocardial hypertrophy, cardiac remodeling and therapeutic targets

INTRODUCTION

Circular RNAs refer to a type of non-coding RNA molecule with a ring-like structure, which distinguishes them from traditional linear mRNA. Unlike mRNA, which has 5' and 3' ends,circRNA is formed through a back splicing process where base pairing is accomplished when the downstream donor splice site pairs with the upstream acceptor splice site in an inverted repeat element such as an Alu sequence, which then forms a fully enclosed circular molecule[1]. Furthermore, since its biogenesis is quite complex and may be influenced by some specific RNA binding proteins (RBPs), including FUS, NF90, and NF110, that can bind to particular regions on the intron and promote the formation of circRNAs[2]. For many years, circRNAs were thought to be “useless” transcripts arising from splicing errors; however, circRNA-specific identification algorithms and high-throughput RNA-seq enabled the discovery that circRNAs play an important role in an organism, including many aspects such as regulating genes and performing various functions in cells. circRNAs do not contain 5′ caps or 3′ poly(A) tails, which are recognized by RNA exonucleases, and are more stable than linear RNAs, more conserved, and have longer half-lives[3,4]. circRNAs can therefore function as

potential biomarkers and therapeutic targets in disease,especially for heart failure initiation and progression.

HF is a complex and fatal disease, often representing the end stage of various cardiovascular diseases. Globally, heart failure has become one of the leading causes of death and disability. In China, the prevalence of heart failure continues to rise, and with an aging population, the onset age of heart failure is occurring earlier each year. The typical clinical manifestations of heart failure include dyspnea and lower limb edema, primarily from ventricular dysfunction. Heart failure can be divided into acute heart failure and chronic heart failure. Acute heart failure indicates severe cellular damage, remodeling, and structural changes in the heart muscle cells, while chronic heart failure represents mild cellular damage, remodeling, and structural changes in the heart muscle cells. In acute heart failure, severe stress on the myocardium or ischemic injury results in necrosis or apoptosis of myocardium cells, rapid onset of ventricular dysfunction, and sudden exacerbation of a condition that requires immediate interventions and treatments[5]. In chronic heart failure, the myocardium enlarges, becomes rigid or hard (due to fibrosis and calcification), thickens (hypertrophy), and ultimately causes worsening of heart failure symptoms due to overwork or unusual stress on the heart[6].

In heart failure, from both acute and chronic processes, circRNA plays a critical role. In the occurrence of acute heart failure, circRNAs can influence interactions among miRNA-proteins and regulate myocardial cell injury repair and inflammatory response[7]. and function like “sponges” for the regulation of miRNA targets’ expression by absorbing corresponding miRNAs, reducing the apoptosis and even the necrosis of cardiomyocytes, such as hsa -circRNAs modulate cardioprotective genes by competing with miR-133a binding, and they may contribute to protection against AMI injuries[8]. In chronic heart failure (CHF), the role of circRNAs is much more complex: Under chronic overloading, circRNAs may participate in regulating multiple signaling pathways in cardiomyocyte remodeling[9]; in particular, these modifications impact cardiomyocyte hypertrophy, fibrosis, and apoptosis[10]. Studies have demonstrated that circRNAs affect the metabolism and the structure of cardiomyocytes interacting with RBPs so that circRNAs impact cardiac remodeling pathway development[11]. circRNAs

overexpressed upregulate the adaptation of cardiomyocytes to mechanical loads through interacting with RBPs such as NF90/FUS, thus delaying the course of heart failure[12].

At the molecular level, circRNAs regulate the progression of HF through several pathways. First, they inactivate the miRNA activity by means of the “miRNA sponge” mechanism and so spare targeted genes from suppression, which is very important in cardiac remodeling[13]. In addition, circRNAs also regulate the G protein-coupled receptor (GPCR) signaling pathway and the PI3K/Akt pathway, as well as the MAPK/ERK pathway, to regulate myocyte hypertrophy and cell apoptosis[14]. Hence, in addition to being possible therapeutic targets for treating the onset and progression of HF, circRNAs might be considered key regulators affecting the onset and development of HF.With more in-depth circRNA research, people begin to realize their role in regulating key target mRNA transcription and translating different levels, which thus provides novel ideas to diagnose and treat heart failure earlier. In the future, finding out specific circRNAs in heart failure patients and further combining them with gene editing technology might present some avenues for personalized treatment. Therefore, the research and application values of circRNA in heart failure remain abundant. As shown in Figure 1, stagespecific regulatory function of circular RNA (circRNA) on the onset and progress of heart failure.

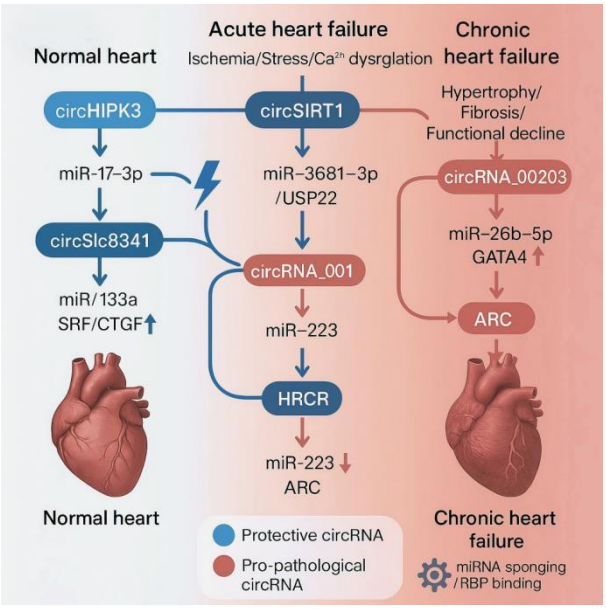

Figure 1. This figure illustrates the dynamic changes and regulatory mechanisms of circular RNAs (circRNAs) during the onset and progression of heart failure. In the

normal heart stage (left blue section), protective circRNAs (such as circHIPK3 and circSlc8341) act as miRNA sponges to inhibit miR-17-3p and miR-133a, maintaining the normal expression of myocardial genes (SRF, CTGF) and preserving cardiac structural and functional homeostasis. In the acute heart failure stage (middle blue-to-red transition zone), ischemia, stress, or calcium imbalance lead to the downregulation of protective circRNAs and upregulation of pathological circRNAs(*suchascircRNA*$_0$01), which modulate miR-223 and its downstream target ARC, participating in myocardial injury and repair. In the chronic heart failure stage (right red section), pathological circRNAs (*suchascircRNA*$_0$0203)*arefurt*her upregulated, binding to miR-26b-5p and activating GATA4 and ARC expression, thereby promoting cardiac hypertrophy, fibrosis, and functional decline. Blue arrows indicate protective pathways, red arrows indicate pathological pathways, and the gear symbol represents circRNA-mediated regulation via miRNA binding or RNA-binding proteins (RBPs).

MECHANISM, REGULATION AND MOLECULAR CHARACTERISTICS OF CIRCRNA

Back-splicing and classical splicing mechanisms

The formation of circRNA mainly relies on back-splicing, where the downstream exon's donor site is paired with the upstream exon’s acceptor site by way of anti-complementary sequences (such as Alu elements) in the flanking introns, thus forming a closed covalent-looped RNA structure[15]. circRNAs have no 5′ cap structure or 3′ poly(A) tails as seen in traditional linear mRNAs.

Back-splicing is not considered a classical splicing event because it still relies in part on the classical splicing mechanism, as shown in h cells, where a classical splicing inhibitor or spliceosome mutation results in continued circRNA production (for example, using Isoginkgetin in HeLa cells)[16]. But the absence of splicing factors such as U2snRNP in Drosophila cells leads to increased levels of circRNA synthesis[17]. It implies that,after blocking the pre-mRNA splicing process,back-splicing can generate another RNA, thereby maintaining a balance between the gene expression level and gene splicing products.

RNA-binding proteins and regulation of circRNA formation

RBPs play a critical role in circRNA formation, with FUS, for instance, able to promote a back splicing event when they recognize and associate with intronic sequences surrounding exon[18]. aiding in RNA cyclization. And for instance, NF90 and NF110 (IEF3), proteins generated from the interleukin enhancer-binding factor 3 gene, promote circRNA production from hsa-circ-0002443 by the stationarity switching (spatiotemporally determined by Arabidopsis Transcriptomes) mechanism. bilizing RNA pairing between introns[19]. Additionally, the dimerization of RBPs facilitates bridging spatial configurations that bring apart splice sites closer, completing the cyclization process[20]. Furthermore, it is noteworthy that RBPs may be engaged not only in circRNA synthesis but also carry out two-way modulations regarding circRNA degradation and function: circRNAs act as sponges of RBPs, regulating their activities; simultaneously, RBP binding influences circRNA expression and stability[21].

Stability andstructural characteristics of circRNAs

The circular structure confers high stability and conservation of circRNA, while the absence of a 5' cap and a 3' poly(A) tail enables circRNAs to withstand exonuclease degradation much more resistantly, rendering circRNAs' half-life substantially higher than that of linear RNAs[22]. The structural attributes enable the high abundance of circRNAs in the cells as well as their stability in stressed situations. circRNAs were predominantly generated by back-splicing.

They mainly reside within the nucleus but are principally located in the cytoplasm, where they are involved in different metabolic and regulatory mechanisms[23]. Their expression levels vary with the different tissues and developmental stages. circRNA profiles show significantly differential expression between different tissues or developmental stages[24]. For example, the human brain and heart show the most abundant circRNA expressions. In addition, circRNA expression is highly correlated to the functions of their host gene[25]. In summary, the production of circRNAs is the product of back-splicing and the canonical splicing mechanism, all regulated by RNA-binding protein. This special type of non-coding RNA has a circular structure, which makes it stable and conserved in both humans and other species. Because it is so similar to regular RNA but produces an alternative structure, there is the potential that circRNAs are influential players in biological processes, including gene regulation and

pathologies such as cardiovascular disease. The formation process and molecule characteristics for circRNAs are given in Figure 2.

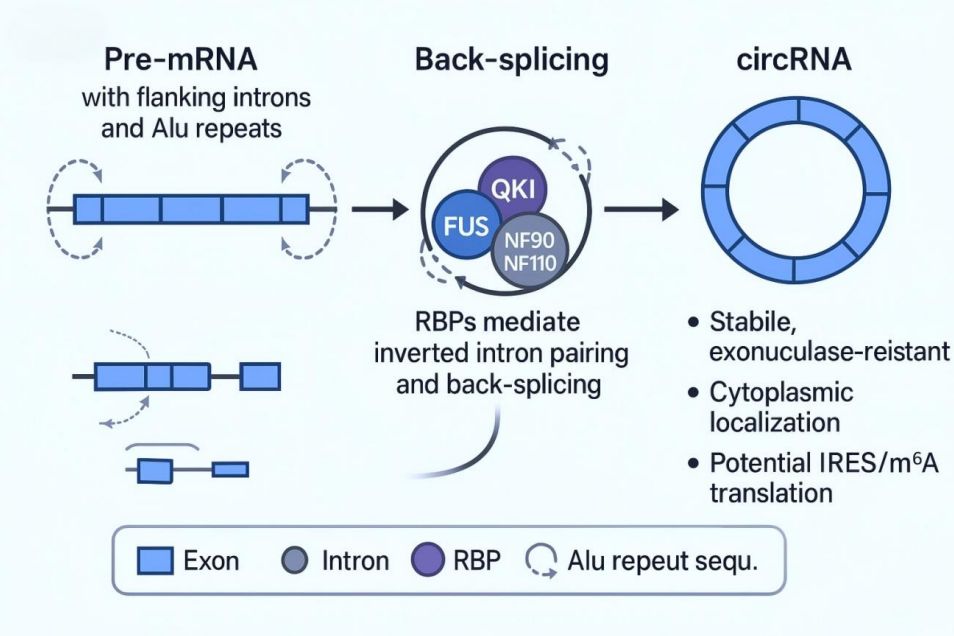

Figure 2. The figure shows the biological generation method and features of circular RNA (circRNA). On the left, the structure of pre-mRNA is shown, including pre-mRNA containing exons (blue boxes), introns (light-blue regions), and Alu-repeat sequences (gray ovals) on both sides providing the structural basis for the reverse complementary pairing. After splicing, the following steps are responsible for the generation of circRNAs. First, RBPs mediate reverse base-pairings between the intron boundaries, thus facilitating the binding of the downstream exon's donor splice site with the upstream exon's acceptor splice site, forming a closed RNA loop structure. Then the fifth process, depicted on the rightmost panel in Figure 2, is the final conversion of the transcript into a circRNA containing CCG at its own 3' end. Under certain conditions, CCG becomes recognized as the polyadenylation signal of circRNAs. size-closed, with no 5' caps or 3' poly(A) tails; extremely stable against exonuclease degradation; mainly localized in cytoplasm, participating in post-transcriptional regulation; some circRNAs can be translated using IRES or m^6A. At the bottom of the figure, legends are provided to clarify the molecular components and the mechanism of circRNA biogenesis: exons (Exon), introns (Intron), RNA-binding protein (RBP), and Alu repeat sequence.

FUNCTIONAL MECHANISMS OF CIRCRNA

Circular RNAs play an important role in modulating gene expression and signal transduction inside the cells with several mechanisms;mainly they act as a miRNA sponge through ceRNA,interact with the protein molecule, and take part in the translation process under the action of IRES and m^6A modification.

Firstly, circRNAs could function as miRNA sponges that compete with miRNAs for binding to miRNA response elements (MREs), resulting in the inhibition of miRNAs from binding to target mRNAs and releasing the inhibition of target mRNA-encoded downstream genes. This is defined as the ceRNA mechanism[26]. In a typical example, CDR1as (ciRS-7) in Figure 1 contains more than 70 miR-7 binding sites in its sequence, fully regulating the expression of miR-7 target genes[27]. As such, we concluded that circRNAs also have an important post-transcriptional regulation effect.

Secondly, circRNAs can interact with RBPs to be involved in various cellular processes[28]. Some circRNAs function as “decoys” or “reservoirs” to regulate the activity of RBPs, whereas RBPs can participate in the formation and stability of circRNAs. Such as the proteins FUS and NF90/NF110 facilitate the circRNA cyclization by binding to the intronic region; cir-CCND1 binds to HuR to upregulate CCND1 expression[29]. Thus, circRNAs can perform their functions as effectors or receptors, as well as act as intermediates for signaling pathways and regulate the posttranscriptional level, and so on.

Besides their traditional function of participating in post-transcriptional regulation and participating in RNA molecular interactions, some circRNAs have unique translation functions. For example, circ-ZNF609 is the first circRNA that is confirmed to be able to translate proteins in eukaryotic cells. Legnini *et al.* (Mol Cell, 2017) reported that circ-ZNF609 is translated without a 5' cap and 3'-poly(A) tail because it contains an internal ribosome entry site (IRES), which can be used for cap-independent initiation of translation, producing a 30 kDa protein product. This translational activity was much higher upon exposure to heat shock stress, serving as regulators that controlled myocyte proliferation and differentiation[30]. In spite of lacking a cap on their 5' end and a tail at their 3' end, the internal IRES or m6A sites could trigger translation in circRNAs[31,32]. IRES-dependent translation allowed circRNAs to initiate translation during stress or

hypoxia, while m6A-modified circRNAs activated translation initiation with The circRNA translational efficiency was regulated by METTL3/4 methyltransferase and FTO demethylase[33]. This expansion increased the role of circRNA regulation over cellular functions and disease.

In summary, circRNAs act as regulators of gene expression and cellular functions via diverse mechanisms, including the miRNA-sponge role, protein interaction, and the IRES/m6A-dependent translation process. Our review offers new perspectives to guide further exploration of novel molecular mechanisms and targets to molecular mechanism-based therapeutic approaches of circRNAs, with a focus on cardiovascular disorders as clinical examples. The main functional mechanisms of circular RNA (circRNA) are shown in Figure 3.

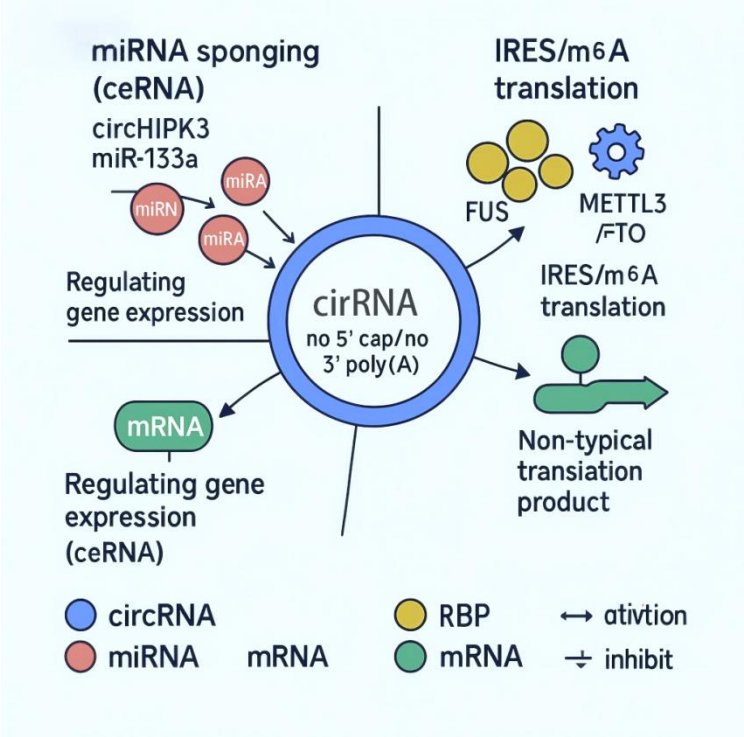

Figure 3. Schematic diagram of the principal molecular mechanisms and roles of circRNAs. The left side schematically represents the biogenesis mechanism of circRNAs as well as their functions in the development of heart failure, whereby circRNAs originate from precursor mRNA (gray striped structure), and downstream donor splice sites and upstream acceptor splice sites pair through an inverted repeat sequence (orange arrow) for the process of back splicing. RNA binding proteins such as FUS, NF90, and NF110 bind to intronic regions to promote exon cyclization so as to

form a closed loop lacking a 5' cap and a 3' poly(A) tail (blue circle). For the function of circRNA in the middle, it works as an miRNA sponge by sequestering specific miRNAs and interfering with miRNAs' activities. Binding to target mRNAs (green striped structure), thereby regulating gene expression. The right section shows the role of circRNA in heart failure: in acute heart failure, circRNA participates in regulating myocardial cell damage repair and inflammation; in chronic heart failure, circRNA influences myocardial hypertrophy, fibrosis, and structural remodeling by modulating signaling pathways such as PI3K/Akt and MAPK/ERK. Arrows represent activation, and the inhibition symbol indicates suppressive effects. Overall, the diagram illustrates that circRNA has both regulatory and protective functions in cardiac pathological processes, with potential as a biomarker and therapeutic target for heart failure.

ROLE OF CIRCRNA IN HEART FAILURE

In recent centuries, circRNA was considered little more than a waste product from pre-mRNA splicing. In the last few years, however, it has been found that circRNAs serve as regulators in the pathogenesis and progression of heart failure (HF). They play important roles in both AHF and CHF by regulating miRNAs, participating in signal transduction, and maintaining cellular homeostasis, which may provide new molecular targets for HF diagnosis and therapy.

Research progress of circRNA in acute heart failure

Acute heart failure occurs when some external factors, including myocardial infarction, acute ischemia, and pressure overload, activate the heart failure syndrome by inducing acute myocardial cell injury, calcium homeostasis disorder, and myocardial cell apoptosis. The functions of circRNAs involved in acute heart failure have gradually been discovered by numerous studies. circRNAs act on calcium signaling pathways, myocardial cell apoptosis, and myocardial remodeling and thus influence the development of heart failure.

As an example, the circ-HIPK3 has an increased level during acute myocardial infarction (MI), and circRNA regulates intracellular Ca^{2+} levels through the miR-17-3p/ADCY6 axis to affect cardiac myocyte contraction function[34]. When circ-HIPK3 is overexpressed, it increases the expression of ADCY6 that exacerbates cardiac

remodeling and functional failure, while inhibiting circ-HIPK3 can mitigate the myocardial dysfunction caused by cimpAIRM1 and cimpAIRM2 under the condition of damage, as well as restore myocardial contractility[35,36]. Moreover, circ-HIPK3 can sponge miR-185-3p to regulate CaSR expression, thereby mediating pressure overload-induced myocardial hypertrophy and functioning as a potential protective factor[37]. circ-HIPK3 can regulate cardiac damage caused by acute heart failure. Additionally, it has been proven that circ-SIRT1 plays an important role in acute heart failure, as indicated by previous research showing that after exposure to harmful stimuli, the levels of expression for circ-SIRT1 increase. Upon Ang II stimulation or under ischemic conditions, circ-SIRT1 expression was notably downregulated. This circRNA regulates the expression of SIRT1 through the miR-3681-3p/miR-5195-3p/SIRT1 pathway, which recruits the deubiquitinase USP22 to stabilize the SIRT1 protein [38]. Circ-SIRT1 acts as an endogenous miRNA sponge to inhibit the downstream effects of miR-3681-3p and miR-5195-3p, attenuating cardiomyocyte hypertrophy and cell apoptosis, thereby contributing to protection against cardiovascular diseases such as AHF, and presenting a potential novel target for early intervention in AHF management.

Some previous research shows that the circRNAs can regulate essential physiological processes like Ca^{2+} signals and myocardial remodeling post-cardiac injury (PCI), and it has become one of the possible biomarkers of AFH and a promising therapeutic target for AFH, too. The continued investigation on circRNAs on the roles of AFH will further contribute to the development of more effective treatment strategies for AFH and improved outcomes for patients.

The role and mechanisms of circRNA in chronic heart failure

Chronic heart failure is primarily triggered by long-term pressure overload, myocardial remodeling, and compensatory myocardial hypertrophy. Long term these structural and functional alterations of the heart will result in CHF. circRNAs play a vital role in the progression of CHF; they are able to regulate cardiac remodeling via modulating myocardial cell growth, apoptosis, and fibrosis by controlling miRNA activity.

Studies have found that circSlc8a1 is significantly upregulated in a pressure overload-induced myocardial hypertrophy model. For example, in the transverse aortic

constriction (TAC)-induced pressure overload hypertrophy model, myocardial-specific circSlc8a1 (also known as circSLC8A1 or CircNCX1) is significantly upregulated[39]. It sponges miR-133a to release inhibition on downstream target genes (such as Ctgf, Srf, and Adcy6); for example, Adcy6 can amplify hypertrophic signaling to promote myocardial cell hypertrophy and cause ventricular remodeling[40]. Further experiments found that knocking down circSlc8a1 can relieve myocardial hypertrophy and can slow the progress of heart failure, whereas overexpression of circSlc8a1 leads to worsened heart dysfunction. Mechanically, circSlc8a1 regulates the expression of downstream target genes—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 dysfunction of cardiac function[41]. This study elucidates the disease process of circSlc8a1 in the progression of chronic heart failure and provides a possible new treatment target for early-stage heart failure. circRNA-000203 was upregulated in an Ang II-induced myocardial hypertrophy model. circRNA-000203 sponges miR-26b-5p and miR-140-3p to relieve inhibition on the transcription factor GATA4, thereby promoting myocardial hypertrophy and fibrosis development[42]. Experiments show that interfering with circRNA-000203 or overexpressing related miRNAs can significantly reverse its pathogenic effects, suggesting that circRNA-000203 may be an important molecular target for chronic heart failure treatment. In addition, circRNA HRCR has been shown to have a defensive role in chronic heart failure. By targeting miR-223 to sponge its interaction with the downstream anti-apoptotic gene ARC (Apoptosis Repressor with Caspase Recruitment Domain), HRCR reduces myocardial cell apoptosis and improves heart function[43]. Through exploring HRCR, we found that different circRNAs exert opposing roles during the progression of heart failure; some of them promote pathological change, and some provide protection.

In summary, circRNAs take part in the pathogenesis of CHF by exhibiting dual regulators, among which circSlc8a1 and circRNA-000203 enhance myocardial hypertrophy and fibrosis, while HRCR exerts protection by inhibiting apoptosis, which provides new avenues for exploring whether they could be potential therapeutic targets. The roles of circRNAs involved in regulation between circRNAs in AFH and CHF are depicted in Figure 4.

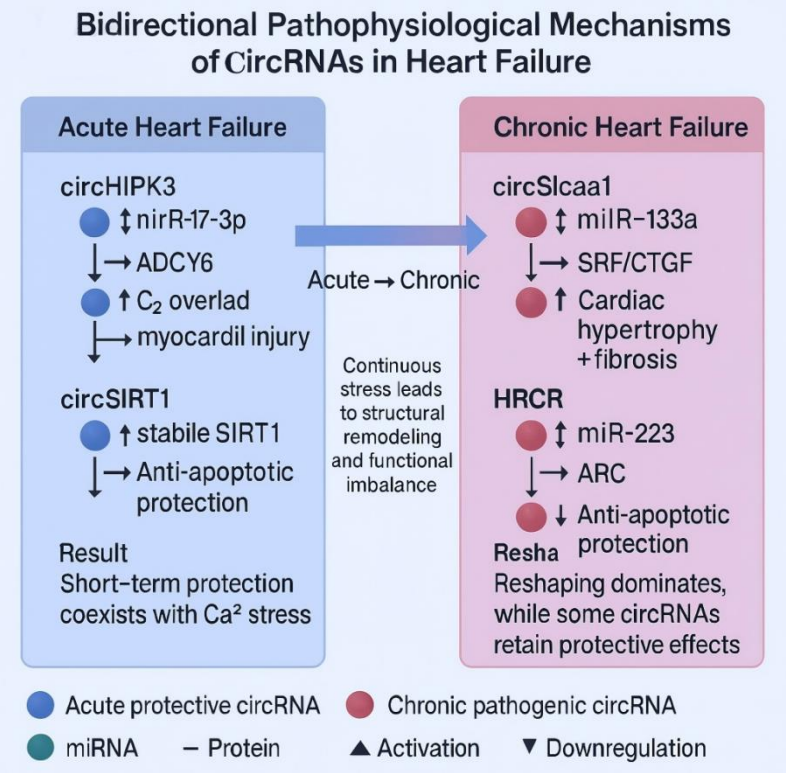

Figure 4. Schematic diagram of the bidirectional pathophysiological mechanisms of circRNA in heart failure. This figure illustrates the directional pathophysiological mechanisms of circRNAs in HF. The schematic describes the two-way regulation performed by circRNAs on AHF as well as CHF. On the left-hand side is AHF, first shown on the left-hand side: circRNA, such as circHIPK3 in the AHF stage, helps sequester miR-17-3p to upregulate ADCY6. It causes Ca^{2+} overload, cardiac myocyte damage, circSIRT1 stabilizing SIRT1 protein, and activating deubiquitase USP22, exerting an anti-apoptotic protective effect that provides short-term protection of the myocardium under acute stress. CircSlc8 is increased in CHF (coral light red), with persistent up-regulation of pathogenic circRNAs, and retains some protective circRNAs. CircSlc8a1 sponges miR-133a to activate the SRF/CTGF pathway, promoting myocardial hypertrophy and fibrosis; HRCR sponges miR-223 to upregulate the anti-apoptotic gene ARC, offering protection. The central arrow shows how the switch between the acute and the chronic phase occurs via persisting stress-induced myocardial structural remodeling and functional imbalance as seen by its status at any point during development. The blue circles in the graph above signify acute protective circRNAs. The red circles denote chronic pathogenic circRNAs; blue and red arrows symbolize signal activation and suppression, respectively. It can be seen that circRNAs have a

bidirectional regulatory function at the onset and development of heart failure: they produce short-term protective effects during the acute period and facilitate myocardial remodeling and functional impairment during the chronic stage; hence, they are indispensable in forming cardiomyopathy pathogenesis from the staging diagnosis to targeted therapy aspects.

POTENTIAL AND CHALLENGES OF CIRCRNA IN HEART FILURE

In a word, circRNAs can act as important players from a mechanistic standpoint, and their clinical translation potential is beginning to become evident; as a novel therapeutic target for HF, circRNAs have attracted great attention, and their clinical potentials are huge. circRNAs were found to be critically involved in cardiomyocyte hypertrophy, cardiac remodeling, and stress response.

In particular, the miRNA sponge mechanisms regulate myocardial cell growth, apoptosis, and fibrosis[44]. circRNAs participate in regulating the occurrence and development of myocardial hypertrophy and heart failure by competitively binding to miRNAs[45]. As shown by circSlc8a1 and circHipk3, they may modulate the signaling pathway related to cardiac function and consequently promote the progression of myocardial hypertrophy and heart failure[46]; the miRNA miR-17-3p/ADCY6 axis alleviates myocardial fibrosis and enhances heart function, as well as offering protection against acute heart failure[47]. Meanwhile, circ-SIRT1 sponges miR-3681-3p and miR-5195-3p to enhance the expression of the host gene SIRT1 and recruit the deubiquitinase USP22 to stabilize the SIRT1 protein, which could repress myocardial hypertrophy and halt the development of heart failure[48].

Besides, the function of circRNA in heart failure cannot be generalized by just one or two functions or mRNAs. Some circRNAs are heart-tissue-specific, and they show distinct tissue- and stage-specific gene expression patterns at different stages of disease. Some of them are highly expressed in cardiomyocytes but absent or present only to a very low level in most other tissues in adult cardiomyopathy patients[49]. Therefore, in normal conditions, tissue-specific circRNAs can regulate distinct biological processes depending on their cell types and their associated physiological or pathological states[50]. circRNAs' distinctive transcription pattern provides us with a systematic way to define

circRNA-based signatures that involve multiple genes/pathways[51]; using these signatures as biomarkers/treatment targets for different stages/types of HF.

Though there is great potential for circulating RNAs in heart failure studies, there are still many challenges ahead. First, circRNA's regulatory mechanisms are very complicated; e.g., they interact with miRNA, protein, or even other kinds of ncRNAs. Second, spatiotemporally how circRNAs participate in different cardiac pathologic states is not completely clarified, which presents difficulties in developing circRNAs as therapeutic targets. Lastly, the interactions between circRNAs and other molecular pathways, especially their roles in cardiac remodeling, cell apoptosis, and stress responses, require further study. Therefore, future research should focus on exploring the mechanisms of circRNA's bidirectional regulatory roles in heart failure and, combined with precise gene-editing technologies, push for the clinical application of circRNAs, providing new solutions for early diagnosis, targeted therapy, and disease prevention in heart failure. The research and clinical translation roadmap of circular RNA (circRNA) in precision therapy for heart failure is shown in Figure 5.

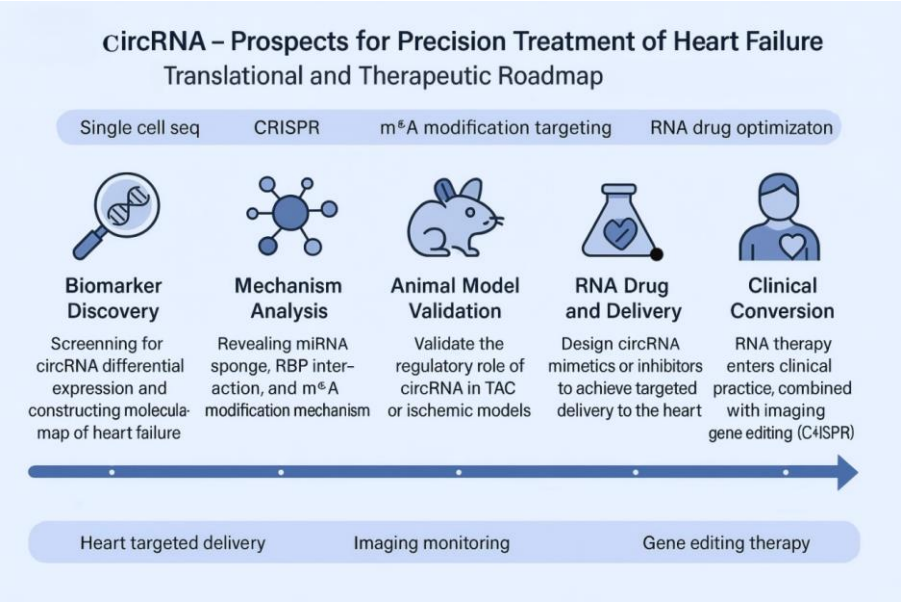

Figure 5. Translational and therapeutic roadmap of circRNA in precision therapy for heart failure. This figure is a translational and therapeutic roadmap of circRNA involved in precision therapy for heart failure. It not only illustrates how circRNAs result in heart failure (the right panel) but also portrays the biogenesis process of circRNAs (the left panel). Precursor mRNA is formed via back-splicing, which occurs with the assistance

of RNA-binding proteins such as FUS, NF90, *et al.*, and then exons close up in an inverted splicing fashion to finally generate circular RNAs (inverted repeats, such as the Alu sequences). The middle portion demonstrates the function of circRNA inside the cells—that circRNA serves as a sponge for miRNAs by binding to miRNAs, which regulate the expression of the corresponding genes, thereby affecting the biological functions of the myocardial cells and delaying the process of necrosis and apoptosis. The right side focuses on how circRNAs play roles in cardiac failure. With regard to being involved in acute heart failure by regulating miRNA and proteins, circRNAs play a key part in myocardial injury repair, anti-inflammation, pro-inflammatory response, and inhibition of cell proliferation in CHF. They also play a role in regulating PI3K/Akt and MAPK/ERK signaling pathways to regulate myocardial hypertrophy, cardiac remodeling, etc. In short, circRNAs have various regulatory effects on the occurrence and development of heart failure, being a potential biomarker or therapeutic target for treating HF.

FUTURE RESEARCH DIRECTIONS

Further studies of circRNA in acute and chronic heart failure should fully investigate its mechanism. Presently it has been found out that circRNAs mainly take effect on gene regulation via miRNA sponging, interaction with RBPs, as well as translation through IRES/m6A. In spite of this, detailed analysis about circRNAs-involved regulatory networks in myocardial stress response, calcium homeostasis, energy metabolism and fibrosis is needed to figure out the roles of circRNAs in these processes. Besides, current work should explore the dynamic expression characteristics of circRNAs at various pathological stages, including their tissue-specificity and their interplays with signaling pathways, using integrative technologies such as high-throughput omics and single-cell sequencing to construct circRNA regulatory network, providing an indispensable step toward the further unraveling the mysteries behind the underlying molecular mechanisms of heart failure.

Moreover, circRNAs possess excellent potential to translate to clinical diagnosis and serve as a platform for associations among multiple diseases, benefitting from their distinct features, such as high stability, strong conservation, and obvious tissue specificity. In future work, researchers could investigate the commonly used regulatory

pathway of circRNAs in heart failure and other diseases, such as coronary artery disease (CAD), diabetes (DM), and cancer (C). circRNAs' shared regulatory mechanisms need to be investigated for diagnostic biomarkers. In addition, functional characterization is necessary for future investigation of circRNA-related multi-disease molecular patterns. Developing circRNA-related gene editing or RNA drugs targeting strategies and improving the in vivo delivery efficiency or circRNA-specific expression may provide new evidence on the circRNA application in precision medicine or the innovations in the early diagnostic approaches or targeted therapy strategies for treating heart failure.

CONCLUSION

This review delves deeply into the complicated role played by circRNA in the state of acute or chronic heart failure, discussing their mechanism of regulation on the heart's function. In particular, circRNAs impact the state of cardiomyocytes, play a role in myocardial hypertrophy, contribute to cardiac remodeling, and ultimately lead to heart failure due to a variety of methods, including being miRNA sponges, forming interactions with RNA-binding proteins, and regulating protein translation.circRNAs protect the heart by mediating the myocardial cell injury-repair process and inflammatory response; yet chronic heart failure involves upregulated circRNAs that control the dysregulation of cardiomyocyte hypertrophy, fibrosis, and cell apoptosis. Besides, the high tissue specificity and great stability of circRNAs make them precious biomarkers and bring more opportunities in the aspect of the identification of the early diagnosis and treatment of HF.

The contribution of circRNAs to the process of heart failure has started to be observed, but how they are regulated and through what mechanism are currently unknown. Future studies may look into the changes of circRNA-spatiotemporal expression profile across different types of pathological conditions and identify whether circRNAs also play roles in CVD. Moreover, we need to understand more about other factors in the circRNA-mediated multi-pathway regulations that govern heart failure.

The application of circRNAs as therapeutic targets in clinical practice is currently fraught with technical issues related to how to achieve efficient delivery and regulation, but this does not affect their huge potential for precision medicine and personalized

treatments; therefore, despite having many problems at present, circRNAs provide some help in discovering novel circRNA-based mechanisms for cardiac failure diagnosis and treatment, to some extent.

DECLARATIONS

Authors' contributions

Designed and directed the study, provided funding support for the study, wrote the final Version of the manuscript, and is the PI of this study: CX.Z;

Wrote the manuscript and reviewed and revised the manuscript: XW.Z;

Performed visualization and provided critical revisions: SLY.L and YJ.S;

Data authentication is not applicable.

All authors read and approved the final version of the manuscript.

Availability of data and materials

Not applicable.

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Conflict of interest

The authors declare that they have no competing interests.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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