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Review

Noncoding RNAs in exercise-induced cardio-protection for chronic heart failure

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ABSTRACT

Chronic heart failure (CHF) has long been a major medical care burden on society due to its high morbidity and mortality. Although lots of evidence has demonstrated the beneficial impacts of exercise on CHF, termed exercise-induced cardioprotection (EIC), the underlying mechanisms and applicability of EIC are elusive and controversial, and thus, clinical applications are difficult. Noncoding RNAs (ncRNAs) are potential therapeutic targets for CHF. Increasing number of ncRNAs were found to play a role in EIC and CHF. The purpose of this review is to illustrate the current knowledge of ncRNAs in EIC for CHF as well as their prospective and limitations in clinical application.

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1. Introduction

Despite the development of drugs and interventional treatments, chronic heart failure (CHF), including HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF), is still the leading cause of death and will increase medical care burden in the coming decades [1,2]. Therefore, identification of more effective therapeutic approaches is urgently needed.

In contrast to the consensus in the 1970s that CHF patients should rest and reduce their exercise, exercise has now been validated to benefit the symptoms and outcomes of CHF patients and highly recommended as a non-pharmacological intervention for CHF by the European Society of Cardiology (ESC), American College of Cardiology (ACC) and American Heart Association (AHA) [1,3]. The cardioprotective effect induced by exercise, termed exercise-induced cardioprotection (EIC), has therefore become a hot research topic. However, although exercise has been demonstrated to improve the exercise capacity and quality of life of HFpEF patients, due to the limited knowledge of HFpEF, how exercise affects cardiac structure and function in HFpEF patients remains much more controversial than in HFrEF patients

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[4]. Pearson et al. reported that exercise improved cardiac diastolic function of HFpEF patients [5], but Fukuta et al. found exercise had no significant impact on both cardiac function and structure [4]. To avoid conceptual confusion, we focus only on HFrEF in this review, all the 'CHF' below represent HFrEF if not specified.

Over the years, the underlying mechanisms of EIC have been gradually revealed to be relevant with cardiac hypertrophy, cardiac fibrosis, vascular alteration and cardiac contractility [6,7], paradoxically, the development of clinical therapeutic translation is not consistent with basic science, the applicability of exercise to treat CHF is still in question due to poor compliance and low exercise tolerance of CHF patients, especially elder patients with comorbidities. In this context, finding key regulators in EIC for CHF and mimicking its function are prerequisite for benefiting more CHF patients.

Noncoding RNAs (ncRNAs) have been verified to participate in EIC and CHF, and they should have potential therapeutic value due to their high quantities and diversified functions [6]. Until now, the best-known related ncRNAs are microRNAs (miRNAs), a group of small ncRNAs that have been shown to regulate cardiac physiology and pathology by targeting genes related to cardiac hypertrophy, cardiac fibrosis, angiogenesis and many other signaling as reviewed by Bernardo BC et al. and Liu X et al. [6,7]. Besides, miRNAs have also been found in the circulation system and are incorporated into extracellular vesicles, RNA-binding proteins or high-density lipoproteins, a form called circulating miRNAs (c-miRNAs) which are easier to detect than intracellular miRNAs and are considered to be potential biomarkers [8]. Long noncoding RNAs (lncRNAs) have also received much attention because of their greater cardiac specificity and higher correlation with cardiac physiological traits than miRNAs [9]. However, due to the weak sequence conservation across species and express at a relatively low level compared to miRNAs, few of lncRNAs are well defined in EIC and CHF. Additionally, circular RNAs (circRNAs) are shown to regulate cardiac alteration with higher stability than linear RNAs [10], but the number of functional circRNAs sharply declines with regard to EIC because they are relatively newer than the other types of ncRNAs.

2. Cardiac alterations in the context of exercise and CHF

Understanding the biological basis of cardiac alterations in the context of exercise and CHF is the initial step to find therapeutic breakthrough, we therefore give a brief overview of relevant content in this section (Fig. 1). To cope with physiological stimuli including exercise training, the sympathetic nervous system (SNS) is initially activated and results in the vasoconstriction in the periphery and increase of cardiac output, while the local vasodilators subsequently come into play to allow more blood flow into the heart and skeletal muscle to meet the increased metabolic requirement in these tissues [6,11]. Consistent with the redistribution of blood and energy requirement, the heart undergoes morphological and functional alterations, of which physiological cardiac hypertrophy, adaptive vascular alteration, enhanced cardiac contractility and normal or enhanced cardiac function are best known [6,7]. Conversely, CHF inducers, such as pressure overload and myocardial infarction (MI), always damage the adaptability of the heart and eventually lead to an irreversible impairment of cardiac structure and function [11]. This process of decompensation starts with a short compensatory period which is similar to physiological stimuli-induced cardiac alteration, and then turns into maladaptive period as the pathological stress sustains [12]. The mechanisms behind it mainly include the abnormal response of cardiomyocytes, noncardiomyocytes and electrophysiological activity, which collectively cause pathological hypertrophy, unmatched vascular change, cardiac fibrosis, organelles dysfunction and reduction of cardiac contractility [13]. Meaningfully, although the cardiac phenotypes are different in the context of exercise and CHF, the underlying mechanisms of physiological and pathological alteration are not mutually independent and show some degree of interplay [6], implying the possibility of finding signaling molecules and pathways which have an impact on both two conditions and utilizing them to treat CHF by the method of mimicking the effects of EIC. To confirm this claim, we aim to initially delineate and discuss the major mechanisms of exercise- and CHF-induced cardiac alteration as follows, and then focus on ncRNAs specifically in these processes to understand their therapeutic value.

3. Physiological and pathological cardiac hypertrophy and relevant ncRNAs

Cardiac hypertrophy, induced mostly by the enlargement of cardiomyocyte, is the most obvious alteration in response to stimuli. While exercise causes physiological hypertrophy with preserved or enhanced cardiac function, CHF is generally accompanied by pathological hypertrophy with an impaired function [6,12] (Fig. 2).

The most canonical pathway of physiological hypertrophy is the insulin-like growth factor 1 (IGF1) - IGF1 receptor (IGF1R) - phosphoinositide 3-kinase (PI3K)-protein kinase B (Akt1)-mammalian target of rapamysin (mTOR) signaling axis, and activating this pathway promotes physiological hypertrophy induced by swimming and protects the heart against MI and ischemia-reperfusion injury (IRI) [12]. Other regulators, such as the mitogen-activated protein kinase (MAPK) cascade, CCAAT/enhancer binding protein-β (C/EPBβ), CBP/p300-interacting transactivator 4 (CITED4) also play a role [12]. In contrast, the calcineuirn-calcineurin-nuclear factor of the activated T cells (NFAT) axis and the Ca^{2+}/calmodulin-dependent kinase II (CaMKII)-myocyte-specific enhancer factor 2 A (MEF2A) axis are two signaling pathways responsible for promoting pathological hypertrophy. Pathological stresses, including angiotensin II (Ang II), endothelin 1 (ET-1), β-adrenergic receptor (β-AR) and transient receptor potential channels (TRPCs), are reported to activate either one or both of them in the context of transverse aortic constriction (TAC) and MI [12].

Treadmill running is known to enhance autophagy by increasing microtubule-associated protein 1 light chain 3 (LC3B) II/I ratio, reducing the p62 level and disrupting the B-cell CLL/lymphoma 2 (Bcl-2)-beclin 1 complex, thereby exerting a protective effect on the heart [14]. In regards to how exercise enhances autophagy, please refer to a recent review by Sanchez et al. [15]. Recent studies have highlighted the central role of AMPK (AMP activated protein kinase)/Fox O (forkhead box class O subfamily protein) transcription factors axis and AMPK/mTORC axis in autophagy during exercise [15]. The former axis, which is commonly activated by exhaustive and moderate intensive exercise, has been verified to promote the autophagy genes involved in autophagosome biogenesis and maturation thereby promoting the autophagy flux, while the latter axis, which exert effect differently in response to different exercise protocol, mediates autophagy mainly by modulating protein synthesis [15]. In contrast , CHF inducers inhibit autophagy and promote apoptosis by mediating the Bcl-2/beclin 1 complex and PI3K/Akt signaling pathway [6]. This phenomenon implies reciprocal inhibition between autophagy and apoptosis as well as exercise and CHF.

In addition, exercise such as treadmill running and swimming has also been demonstrated to induce cardiomyocyte proliferation with a relatively small proportion compared to cardiomyocyte enlargement (3,28). However, although enhanced cardiomyocyte proliferation is regarded as an adaptive alteration, the relationship between cardiomyocyte proliferation and CHF development remains debatable because some studies reported decreased cardiomyocyte proliferation in the TAC model, while others observed an increased alteration [12].

3.1. MicroRNAs are involved in cardiac hypertrophy

The muscle-specific miR-1 regulates cardiac hypertrophy by mediating IGF1 and Bcl-2, but whether it exerts a protective or detrimental effect on heart remains controversial considering that its expression level presents a similar decreasing trend in both treadmill exercise training and TAC condition [16,17]. Karakikes I et al. demonstrated that miR-1

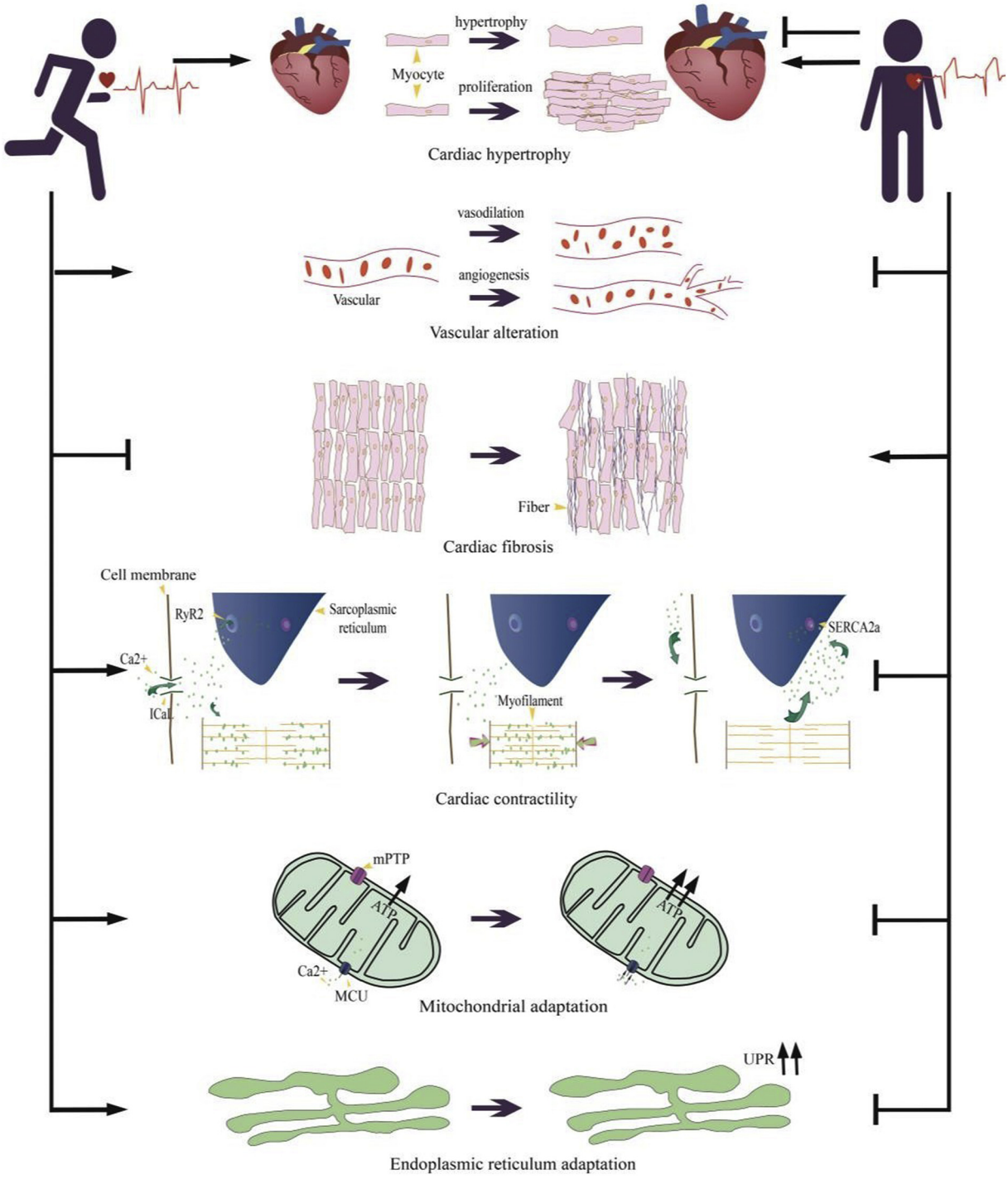

Fig. 1. Cardiac alterations in the context of exercise and CHF. Exercise induces beneficial alteration such as physiological hypertrophy, enhanced vascular alteration and cardiac contractility, adaptive organelle alteration especially mitochondria and endoplasmic reticulum. Conversely, CHF inducers cause maladaptive alteration including pathological hypertrophy, mismatched vascular alteration, increased cardiac fibrosis, impaired contractility and organelle function.

restoration reversed adverse cardiac remodeling caused by pressure overload via inhibiting cardiac hypertrophy and apoptosis [18], while Zhai et al. indicated that inhibiting miR-1 attenuated hypoxia/re-oxygenation (H/R)-induced apoptosis of cardiomyocytes by targeting Bcl-2 [19]. Interestingly, one study stated that the decline in miR-1 occurs earlier than cardiac mass alteration, suggesting that miR-1 is more likely the cause but not the consequence of pathogenesis [16]. Mooren FC et al. reported that c-miR-1 correlates with left ventricular fractional shortening and maximum oxygen (VO_2max) in a marathon protocol, suggesting its potential role as a biomarker for assessing cardiac alteration and cardiopulmonary fitness during exercise. Another muscle-specific miRNA, miR-133, is also arguable in its regulatory role [20]. While Dong et al. noted that the decrease of miR-133 is positively related to the activation of calcineurin/NFAT signaling [21], indicating its role in promoting pathological hypertrophy, the decrease of miR-133 was also found in 8 weeks of treadmill training and 10 weeks of swimming training mice as reported by and Care et al. and Soci et al. [16,22], this similar variation trend under both physiological and pathological condition raises the question that whether miR-133 exerts anti-hypertrophic effect under any circumstances with same degree or not. Interestingly,

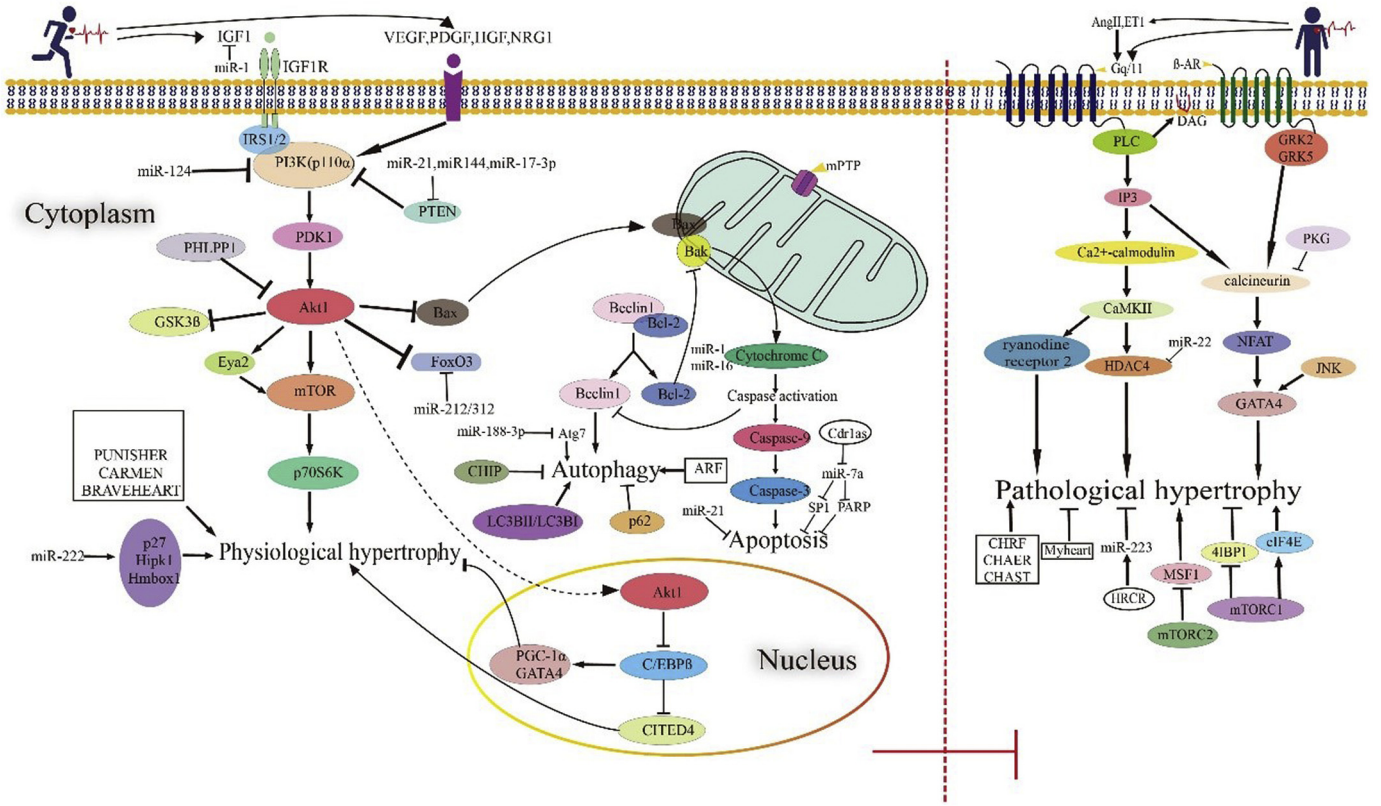

Fig. 2. Mechanisms of physiological and pathological hypertrophy. IGF1-IGF1R-PI3K-Akt1 pathway plays the major role in physiological hypertrophy, while VEGF, PDGF, HGF and NRG1 also play a part. In response to exercise, cell proliferation and autophagy are enhanced while apoptosis is inhibited. Oppositely, calcineuirn-NFAT pathway and Ca^{2+}-calmodulin contribute to pathological hypertrophy, accompanied by increased apoptosis and impaired cardiac function. Several miRNAs, lncRNAs (symbolized by square with name in it) and circRNAs (symbolized by circle with name in it) regulate hypertrophic response via targeting different molecules.

one study found an increase of miR-133 in the mice heart after 8 weeks of swimming training [23], which further make it more difficult to study the role of miR-133 in EIC for CHF because the exercise protocol may influence the impact of miR-133 on heart.

MiR-124 is a potential regulator in EIC for CHF as it has been reported to aggravate MI-induced cardiac hypertrophy by promoting apoptosis via downregulating STAT3 [24] and the downregulation of it promoted swimming-induced cardiac hypertrophy by upregulating PI3K3α [25]. Besides, upregulated levels of miR-21, miR-144 and miR-145 after 8 weeks of swimming training are also thought to promote physiological cardiac hypertrophy via mediating phosphatase and tensin homolog (PTEN) or TSC2, two main inhibitors of the PI3K-Akt-mTOR pathway [25]. However, Zhao Y et al. failed to observe the same results for miR-21 as it only slightly increased with intensive swimming protocol (30 min at the beginning and increased by 10 min per week, one time a day until the fifth week and increased to twice a day, 5 days/ week, 8 weeks), and one of its targets, programmed cell death 4 (PDCD4), which aggravates MI [26], exhibited no change in either moderate (30 min at the beginning and increased by 10 min per week, one time a day, 5 days/ week, 8 weeks) or intensive swimming protocol [27]. This paradox reminds us again that the functional hypothesis of ncRNAs in EIC may associated with types of exercise protocols. MiR-16 is also thought to participate in EIC for CHF because its increased expression along with a decreased level of Bcl-2 was found in hypertension, while swimming training conversely normalized this change [28]. Similarly, miR-222 was also demonstrated to induce exercise-induced cardiac hypertrophy and protect the heart against ischemic injury mainly by mediating cardiomyocyte proliferation regulators, including p27, Hipk1 and Hmbox1 [29]. Intriguingly, its function has been found to be closely associated with other miRNAs. For example, similar variation trends of miR-222, miR-34a and miR-210 were observed in both PI3K-induced cardiac hypertrophic and dnPI3K transgenic mice, and physiological hypertrophy could be promoted only by overexpressing both miR-222 and miR-17-3p, not by either alone [29,30]. Collectively, these findings suggest that several miRNAs may have impact on EIC for CHF with the help of other miRNAs. To elucidate the interactive mode among different miRNAs, studies involving co-forced expression of miRNAs (such as miR-222 and miR-17-3p) are needed.

Many other miRNAs have also been recognized as modulators in cardiac hypertrophy. Nevertheless, due to lack of conclusive functional evidence from both exercise and pathological protocols, their roles in EIC for CHF remain to be clarified. For instance, miR-22, which is abundantly expressed mainly in the heart, was shown to promote cardiac hypertrophy induced by isoproterenol infusion via targeting histone deacetylase 4 (HDAC4). The miR-212/132 family was also reported to aggravate cardiac hypertrophy induced by TAC via modulating FoxO3, a well-known antihypertrophic and proautophagic factor, while antagomir-mediated knockdown of miR-132 weakened this effect and alleviated the progression to CHF [31].

3.2. Effects of lncRNAs and circular RNAs on cardiac hypertrophy

Myosin heavy chain associated RNA transcript (Mhrt) is widely known as a cardiac-specific lncRNA that protects the heart against pathological hypertrophy via binding to the helicase domain of Brg1, a chromatin-remodeling factor that triggers maladaptive alteration [32], however, no exercise protocol was used to clarify the role of Mhrt in EIC for CHF. Another cardiac-associated lncRNA named Braveheart (Bvht) has also been verified to have a critical role in the epigenetic regulation of cardiac development by mediating mesoderm progenitor 1 (Mesp1), a transcription factor for cardiac differentiation [33]. However, since no human homolog has been identified, the value of Bvht may be

lower than expected. Two other lncRNAs, cardiac mesoderm enhancer-associated noncoding RNA (Carmen) and fetal-lethal non-coding developmental regulatory RNA (Fendrr), were reported to regulate cardiac differentiation by modifying the chromatin structure of related genes through interacting with polycomb repressive complex 2 (PRC2) [34,35]. Recently, Kontaraki and colleagues discovered significantly higher expression levels of Carmen, Fendrr and Mhrt in peripheral blood mononuclear cells of hypertensive patients than in healthy controls, and Carmen was revealed to have a positive correlation with left ventricular mass index, while Fendrr and Mhrt had a negative correlation with hypertrophy [35]. Moreover, cardiac hypertrophy-associated transcript (Chast) and cardiac hypertrophy-associated epigenetic regulator (Chaer) were also demonstrated to promote TAC-induced pathological hypertrophy by impeding autophagy and modifying epigenetic changes of hypertrophic genes respectively [36,37].

In addition to acting as epigenetic regulators as above, lncRNAs also exert biological functions as competitive endogenous RNAs (ceRNAs). For example, cardiac hypertrophy related factor (Chrf) was found to be increased in TAC mice and CHF patients and to promote pathological hypertrophy via targeting miR-489 [38], while autophagy-promoting factor (Apf) and lncRNA-Ror were demonstrated to regulate autophagy and the hypertrophic response via targeting miR-188-3p and miR-133 [39,40]. Metastasis-associated lung adenocarcinoma (Malat1), a tumor-associated lncRNA, has been shown to act as a sponge of miR-320, miR-204 and miR-150, and inhibiting its expression was reported to alleviate cardiac injury induced by IRI and MI by mediating cell death [41,42]. These findings collectively indicated the therapeutic potential of lncRNAs in treating CHF, nevertheless, due to lack of the exercise research, whether these lncRNAs play a role in EIC for CHF via mediating cardiac hypertrophy or not need to be clarified.

With regard to circular RNAs, circ-Amotl1 was found to be highly expressed in neonatal human cardiac tissue, and its overexpression potentiates the nuclear translocation of pAKT, thereby playing a protective role in cardiovascular disease (CVD) [43]. Moreover, heart-related circRNA (Hrcr) has been shown to inhibit TAC-induced pathological hypertrophy by acting as a miR-223 sponge [44], while Cdr1as aggravates MI-induced cell apoptosis via regulating miR-7a [45]. Similar to lncRNAs, there has been little evidence concerning the role of circRNAs in exercise-induced physiological hypertrophy.

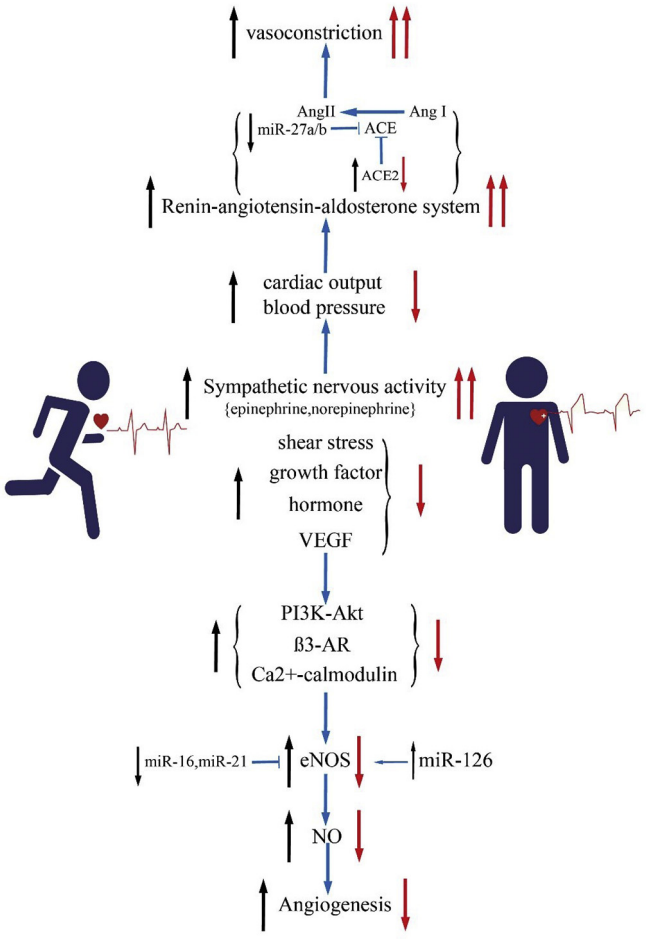

Fig. 3. Vascular alteration in the context of exercise and CHF. SNS and RAAS are activated and induce vasoconstriction in response to stimuli. While exercise stimulates beneficial regulators which further increases activities of PI3K-Akt, β3-AR, Ca^{2+}-calmodulin, eNOS and NO, CHF always induces a much longer stimulation of SNS and RAAS with lower activities of vasodilative factors, thus breaking the balance between heart mass and blood vessels and ultimately resulting in an irreversible cardiac damage.

4. Vascular alteration and relevant ncRNAs

Vascular alteration is the main response for maintaining perfusion and adequate supply in the context of cardiac hypertrophy, while exercise-induced hypertrophy accompanies by an adaptive vascular alteration with vasodilation of the coronary vasculature and an increased angiogenesis at a similar increased rate of cardiomyocyte enlargement, pathological cardiac hypertrophy always couples with an impaired vascular alteration and a subsequently impaired cardiac function [6,46]. Vascular alteration involves functional and structural changes, in which the SNS, renin-angiotensin-aldosterone system (RAAS) and growth factors such as vascular endothelial growth factor (VEGF) are involved mostly by mediating β3-AR, PI3K-Akt signaling and NO synthases (NOSs) (3,13) (Fig. 3), the details of mechanisms could be obtained in reference 6 and 46.

One of the master regulators of vascular alteration is miR-126, a miRNA that is enriched in endothelial cells (EC) and mediates angiogenesis from the embryonic to adult stage [47]. Silva et al. showed that an increase in miR-126 induced by swimming training contributed to enhanced angiogenesis via targeting sprout-related protein 1 (Spred-1) and phophoinositol-3 kinase regulatory subunit 2 (PI3KR2), two negative regulators of the VEGF pathway [48]. The author also demonstrated that a single miR-126 is sufficient to guide vascular alteration. However, this viewpoint needs further confirmation because current evidence is insufficient to affirm the existence of a “president miRNA” located at the top of a pathway without being influenced by other factors. MiR-27a/b also plays a role in vascular alterations because a similar change of increased miR-27a/b and decreased angiotensin converting enzyme (ACE) has been revealed during swimming training, implying its functional role in mediating exercise-induced vascular alteration [49]. Meaningfully, miR-27 has also been found to be highly associated with atherosclerosis and some metabolic processes such as lipid metabolism, implying its role as a biomarker or therapeutic target for atherosclerosis [50]. Moreover, miR-143/145 cluster, an another widely characterized regulator in the vasculature, has been proved to be associated with cardiovascular development and CVD especially hypertension and pulmonary arterial hypertension [51], while miR-143 was reported to regulate vasodilation by upregulating ACE2 after intensive swimming training [49] Considering they all play a regulatory role in both exercise and cardiac disease, miR-27 and miR-143 may become valuable therapeutic target for EIC for CHF, but further researches involving more typical cardiac pathological models such as TAC and MI are needed in order to confirm their role in the process of CHF. In addition to regulating cardiac hypertrophy as described in section 3.1, miR-16 and miR-21 were also shown to participate in vascular alteration via mediating VEGF signaling and nNOSs as a decrease of miR-16 and miR-21 paralleled an increase of capillary supply was observed by Fernandes and colleagues in swimming protocol [28], this finding further indicated their research value in EIC for CHF.

Compared to miRNAs, there are much less lncRNAs and circRNAs which were revealed to have an impact on exercise and CHF via

mediating vascular alteration. SENCR, a vascular-enriched lncRNA, was demonstrated to stimulate angiogenesis of EC similar to miR-126, and its expression was found to be decreased in the vessel wall of patients with coronary artery disease (CAD) [52]. To better understand this domain, more studies including either exercise or pathological condition are needed in order to clarify the exact role of SENCR in EIC for CHF as well as find more functional ncRNAs.

5. Cardiac fibrosis and relevant ncRNAs

Cardiac fibrosis, which arising from extracellular matrix (ECM) with an excessive amount of collagen content and an imbalanced collagen I/III ratio, is a common feature of damaged hearts and induces cardiac stiffness and cardiac dysfunction, thereby leading to CHF [6]. Meaningfully, Exercise training not only alters cardiac morphology without developing fibrosis but also attenuates cardiac fibrosis induced by pressure overload, aging and MI, indicating its therapeutic value in reversing cardiac fibrosis [53]. Numerous regulators, including norepinephrine, Ang II, ET-1, MAPKs, calcineurin-NFAT and transforming growth factor β (TGF-β) signaling, are reported to participate in this process [6,53].

MiR-29 is a well-known fibroblast-enriched miRNAs [26]. While the downregulation of miR-29 was found to be accompanied by upregulation of ECM-related genes in MI [54], swimming training increased miR-29 thereby improving cardiac function [22], indicating the potential role of miR-29 in EIC for CHF. MiR-208a, known as the cardiac-specific miRNA with the highest expression, was found to regulate the myosin heavy chain (MHC) with a tendency to isoform β-MHC under pathological conditions [54]. Swimming training induced a decrease in miR-208a along with a decrease in β-MHC and an increase in α-MHC, while inhibition of miR-208a suppressed β-MHC expression and cardiac fibrosis [55], implying the role of miR-208a in impairing ventricular compliance.

Moreover, the miR-15 family, involving miR-15a, miR-15b, miR-16, miR-195, miR-497 and miR-322, has also been revealed to regulate cardiac fibrosis by mediating the TGF-β pathway, and using locked nucleic acid-modified (LNA-modified) anti-miRs to inhibit miR-15 indeed resulted in serious fibrosis in TAC mice [56], which manifested the feasibility of targeting miR-15 to alleviate cardiac fibrosis in some degree. Similarly, miR-34a was also shown to aggravate MI-induced cardiac fibrosis via the TGF-β pathway by targeting Smad4 [57], while miR-199b was reported to inhibit TAC-induced fibrosis by suppressing calcineurin-NFAT pathway [58]. However, the role of miR-15 family and miR-34a in cardiac fibrosis was only explored and shown in pathological condition, in order to verify whether they also work in exercise, more studied are needed. Besides, there is much less evidence for the roles of functional lncRNAs and circRNAs in cardiac fibrosis than there is for miRNAs, with only one circRNA, circRNA_010567 shown to inhibit cardiac fibrosis induced by Ang II via mediating the TGF-β pathway [10].

6. Cardiac contractility and relevant ncRNAs

Action potential (AP) and excitation-contraction coupling (*E*-C coupling) contribute jointly to cardiac contractility by regulating ion channels and Ca^{2+} cycling, while the β-ARs pathway is highly associated with the initial change of contractility [6]. In response to stresses, stimulated β-ARs couples to the stimulatory G protein (Gs) - cyclic adenosine monophosphate (cAMP) - protein kinase A (PKA) signaling which induces the phosphorylation of several regulators including L-type calcium channels (I_{caL}), ryanodine receptors 2 (RyR2) and phospholamban (PLB). This alteration along with the subsequently enhanced activity of sarcoplasmic reticulum Ca^{2+}-ATPase 2a (SERCA2a), Na^{+}-Ca^{2+} exchanger (NCX), mitochondrial calcium uniporter (MCU) and CaMKII collectively improve Ca^{2+} cycling, thereby promoting cardiac contractility. The number and type of ion channels also change to meet the energy requirement [6]. As for our concern, exercise enhances cardiac contractility by transiently stimulating β-ARs signaling and transforming ion channels adaptively as reviewed by Bernardo and colleagues [6], while CHF inducers impair contractility on account of maladaptive alteration, including long-term activated β-ARs and intracellular Ca^{2+} overload [6]. Notably, exercise has also been shown to ameliorate impaired Ca^{2+} cycling and contractility induced by pathological stimuli, indicating its therapeutic value for treating CHF [6].

MiR-214 has been found to protect heart against IRI via regulating Ca^{2+} cycling-related factors including NCX1 and CaMKII [59], while Melo et al. indicated that the down-regulation of miR-214 induced by resistance training contributed to the enhanced expression level of SERCA2a, thereby improving cardiac contractility [60], which further suggests a role of miR-214 in EIC for CHF. Through the combined utilization of high throughput and gain- and loss- of function method, Wahlquist and colleagues noted that upregulated miR-25 which appeared in HF patients and mice, contributed to impaired cardiac contractility by suppressing SERCA2a [61]. Moreover, a lncRNA termed ZNFX1 antisense RNA 1 (ZFAS1) has been demonstrated to be markedly increased in MI mice and induce intracellular Ca^{2+} overload and contractility dysfunction by inhibiting SERCA2a [62]. However, the exact role of miR-25 and ZFAS1 in EIC for CHF should be further clarified using both exercise protocols and pathological models.

7. Organelles alterations and relevant ncRNAs

Organelles are the basis for cellular activity, among which mitochondria and the endoplasmic reticulum (ER) are important due to their capacity to supply energy and process protein. Normally functioning mitochondria and ER are essential to maintain biological function. While mitochondrial function is influenced by the state of mitochondrial fusion and fission, the functional effect of ER is closely linked with unfolded protein response (UPR) [63]. The effect of exercise and CHF on these two organelles has been gradually revealed. Jiang et al. indicated that MI caused mitochondrial dysfunction by disrupting the balance between mitochondrial fusion and fission via increasing the fusion protein mitofusin (mfn2) and type 1 optic atrophy (OPA1), decreasing the fission protein dynamin-related protein1 (DRP1) and suppressing the extracellular signal-regulated kinase (ERK)1/2- c-Jun NH2-terminal protein kinase (JNK) —P53 signaling pathway, while treadmill training rescued these alterations via readjusting proteins and signaling pathways [64]. Moreover, treadmill training also blunted MI- induced maladaptive ER stress by suppressing UPR markers including GRP78, DERLIN-1 and CHOP, as reported by Bozi et al. [65].

The number of ncRNAs related to organelles alteration is limited, not to mention their role in EIC for CHF, as thus, more researches focus on this topic need to be established. At present, cardiac-apoptosis related lncRNA (Carl) and mitochondrial dynamic related lncRNA (Mdrl) are proved to inhibit mitochondrial fission and apoptosis induced by MI or IRI via suppressing miR-539 and miR-361 [66], while mitochondrial fission and apoptosis-related circRNA (MFCR) regulate mitochondrial alteration by suppressing miR-652-3p [67].

8. Limitations and prospective

At present, drugs are still the main therapeutic approaches for CHF. Although pharmacological interventions indeed benefit CHF patients, they are not able to reverse or radically solve the pathogenesis of CHF [9,68]. A growing number of studies have demonstrated the beneficial effect of exercise on the heart and regarded exercise as a non-pharmacological intervention for CHF patients; however, although exercise indeed represses and reverses the progression of CHF, how to achieve the widespread utilization of the benefit of exercise and timely evaluation of its effectiveness has not yet been established. With the development of bioinformatics and technologies, ncRNAs have gained increasing attention and are considered to be potential therapeutic targets in several areas, including cardiovascular disease.

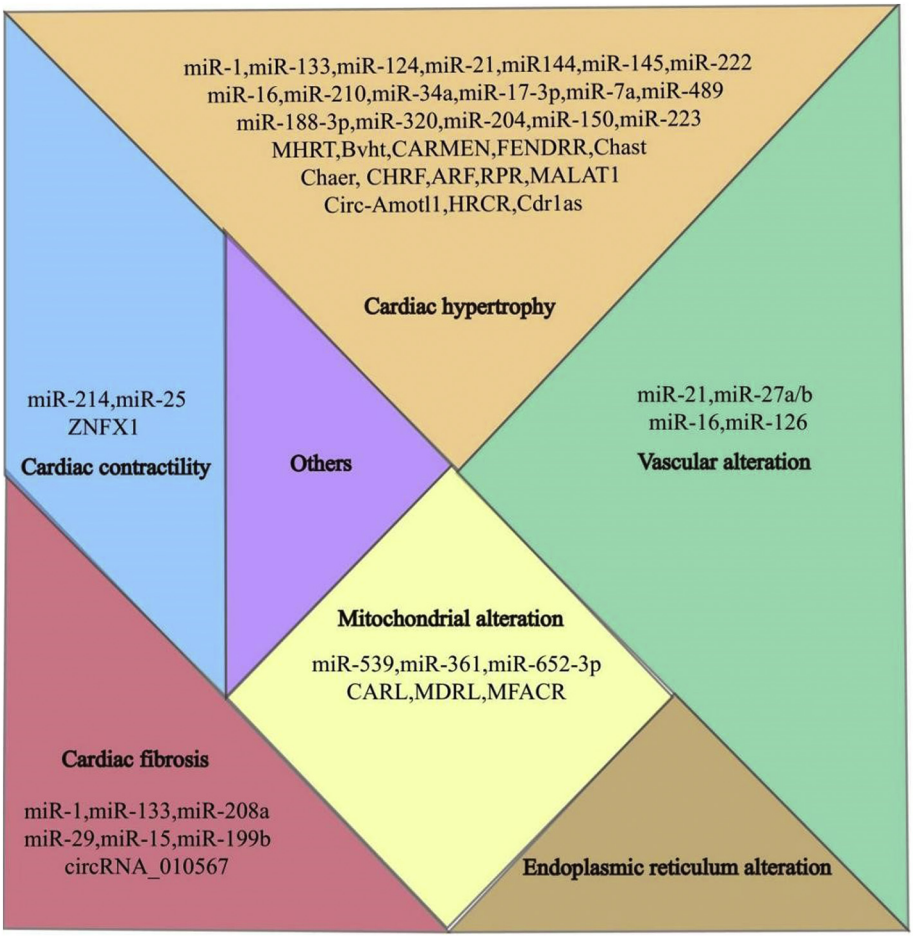

Fig. 4. Main mechanisms and functional ncRNAs in EIC for CHF. Vascular alteration in response to exercise and CHF inducers. ICardiac hypertrophy, vascular alteration, cardiac fibrosis and contractility, organelle alteration especially mitochondrial and endoplasmic reticulum alteration are six domains we mainly concern. Here we group ncRNAs along with their related function which we mentioned in this review.

As mentioned before, knowledge about ncRNAs in EIC for CHF has gradually increased (Fig. 4). However, several issues still need to be elucidated. Firstly, the time effect is an unsolved question because the biological function of exercise, the pathogenesis of CHF and the regulatory role of ncRNAs are different at different stages. Considering that the therapeutic goal varies from stage to stage, finding molecules that have specific functions in a specific situation is a practical approach. Secondly, lacking of unified exercise standards and comprehensive supervised settings is also a major obstacle. Although studies have accepted that aerobic moderate-intensity exercise is the most effective exercise for CHF patients, while resistant and strenuous exercise, such as long-term high-level endurance exercise, is not beneficial for the heart and may even put the heart at risk [69]. Current exercise protocol is still unlikely to produce uniform outcomes due to individual differences. Therefore, a supervised setting during exercise training for CHF patients is urgently needed to ensure the efficacy of exercise and the safety of patients. In this case, finding effective indicators of the intensity of exercise are a prerequisite because exercise intensity is thought to be more important than duration in reducing mortality of CHF and the currently used parameters heart rate and rated perceived exertion scale (RPE) do not provide sufficient information [70]. Additionally, we should note that current human studies are far from perfect on account of the confounding factors, including selection bias, methodological and individual difference, lifestyle and medical intervention, gender and age, are difficult to eliminate, and their impact on the heart result in uncertain outcomes [7].

MiRNAs are considered ideal therapeutic targets because their structural features and biological function are liable to imitate and validated in physiological and pathological conditions. At present, there are two methods to manipulate miRNAs. One is to deliver miRNA mimics to augment the beneficial effect of miRNAs, another is to inhibit the activities of miRNAs by injecting antagomiRs [71]. As for clinical application, an inhibitor against miR-122, miravirsen, has already been used to treat hepatitis C virus, while other manipulated miRNAs associated with CHF, such as antagomiRs against miR-34a, miR-21 and miR-208a, are still far from being tested in clinical trials [71]. Given that different administration and distribution methods could affect the efficacy and safety of miRNAs product in an uncontrollable manner, coupled with the fragile system in a state of CHF, the road to using miRNAs to treat CHF is indeed more difficult than that for other diseases [71].

C-miRNAs can be cell- or- tissue specific and reflect the physiological and pathological status to some extent and thus may serve as biomarkers. Several studies have illustrated the c-miRNAs profile in exercise and CHF, but the interrelationship between these two has not yet been elucidated [8,72]; Also, on account of heterogeneity of methodological approaches and different nomenclature of ncRNAs and diverse results, the reliability and validity of c-miRNAs as biomarkers need further elucidation [73]. In addition, c-miRNAs showed different changes in different exercise modalities. For example, c-miR-20a was altered only with sustained training, with a higher correlation with VO_2max, while c-miR-146a was increased only with acute exercise [74]. C-miR-1, c-miR-133a/b and c-miR-208b were also found unchanged during concentric exercise but increased during early recovery of eccentric exercise, while c-miR-181b and c-miR-214 increased during concentric but not eccentric exercise. Moreover, marathon runs significantly upregulated c-miR-1, c-miR-133a, c-miR-499, and c-miR-208a, while only the

last two returned to pre-exercise levels after twenty-four hours [72]. Some studies indicated that c-miR-1, c-miR-34a, c-miR-126, c-miR-133a/b, c-miR-192, c-miR-194, c-miR-208b and c-miR-423-5p could be biomarker for CHF, but these findings have not been further verified [71,72].

Although targeting lncRNAs is thought to have fewer off-target effects than targeting miRNAs based on their higher tissue and cell specificity [9], due to their relatively low expression level and unsatisfactory depth of sequencing, current knowledge of lncRNAs is still scarce. In addition, current approaches of manipulating lncRNAs, such as gain- and loss-of-function protocols, also have issues need to be concerned. For one, deleting lncRNA genes that overlap a coding gene could have inexplicable consequences. For another, overexpressing lncRNAs may overstate their real function because lncRNAs always act in a dose-dependent manner [9]. Besides, several genome-wide studies have recently demonstrated that numerous functional micropeptides are encoded in lncRNAs, suggesting the exact function of lncRNAs is confusing [75]. Furthermore, because most lncRNAs are not conserved and some cardiac-specific lncRNAs have failed to be found in the human genome, identifying lncRNAs that acts both in primates and humans should be given priority. As for circRNAs, although their function in exercise and CHF remains largely unknown, with the development of bioinformatics and RNA sequencing techniques, plus the characteristics of abundant quantity, higher stability and conservation among species, this type of ncRNAs is expected to be a hotspot in EIC for CHF.

It is obvious that many ncRNAs were studied in either exercise or diseases model with only a few of them were studied in both exercise and pathological protocol. Nevertheless, even though the number of functional ncRNAs in EIC for CHF is limited, we are still optimistic about the prospect of this topic as technology advances, knowledge enriches and an urgently need for finding effective therapeutic target to treat CHF in a method of mimicking the beneficial effect of EIC.

9. Search strategy and selection criteria

Data from this review were identified by searches of PubMed and Web of Science and references from relevant articles using the following keywords, alone or in combination: “exercise”, “chronic heart failure”, “noncoding RNAs”, “ncRNAs”, “microRNAs”, “lncRNAs”, “circRNAs”. Only articles and reviews published in English between 1990 and 2018 were included.

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