Chapter 15
MicroRNAs Mediate Beneficial Effects of Exercise in Heart

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Abstract MicroRNAs (miRNAs, miRs), a group of small non-coding RNAs, repress gene expressions at posttranscriptional level in most cases and are involved in cardiovascular physiology and disease pathogenesis. Increasing evidence has proved that miRNAs are potential regulators of exercise induced cardiac growth and mediate the benefits of exercise in a variety of cardiovascular diseases. In this chapter, we will review the regulatory effects of miRNAs in cardiac adaptations to exercise, and summarize their cardioprotective effects against myocardial infarction, ischemia/reperfusion injury, heart failure, diabetic cardiomyopathy, atherosclerosis, hypertension, and pulmonary hypertension. Also, we will introduce circulating miRNAs in response to acute and chronic exercise. Therefore, miRNAs may serve as novel therapeutic targets and potential biomarkers for cardiovascular diseases.

Keywords MicroRNA • Exercise • Cardiovascular diseases

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1 Introduction

Cardiovascular diseases (CVDs) are major causes of morbidity and mortality worldwide [1]. Currently, despite continuous advances achieved in clinical treatments including medical and surgical therapies, CVDs are still considered to be major diseases and exert a considerable emotional and economic burden [2]. In light of these, development of innovative therapeutic strategies for CVDs are urgently needed.

Physical exercise, as well as pregnancy and postnatal cardiac growth, are major stimuli for physiological cardiac hypertrophy [3]. For many years, cardiologists advocated prolonged rest for patients with CVDs especially ischemic heart diseases [4]. However, increasing number of studies have validated the multiple benefits of physical exercise in comparison to the detrimental effects of a sedentary lifestyle, making physical exercise a therapeutic modality for patients with a variety of chronic diseases, such as CVDs, type II diabetes, fatty liver, stroke, disseminated sclerosis, and malignant tumor [5–11]. Among them, further studies have demonstrated that individuals with proper level of physical exercise have lower prevalence and death rate for CVDs [12]. Thus, physical exercise has been established not only as a mean to maintain a healthy lifestyle but also as a safe and important nonpharmacological way for prevention and treatment of CVDs.

Non-coding RNAs (ncRNAs) are a diverse group of functional RNA molecules without protein-coding functions, which may range from short microRNAs (~22 nucleotides) to long non-coding RNAs (>200 nucleotides) [13, 14]. MicroRNAs (miRNAs, miRs) repress gene expressions at posttranscriptional level in most cases and are involved in various cellular processes, including differentiation, proliferation, apoptosis, migration, angiogenesis, and so on [15]. Importantly, mounting data have suggested that ncRNAs, especially miRNAs, could lead to a profound regulation of target genes and related signaling pathways, thus engaging in a variety of beneficial effects of exercise in the heart [16, 17]. This may raise a hope that miRNAs may serve as potential therapeutic targets mediating the benefits of physical exercise to combat CVDs.

In this chapter, we will provide an overview of the protective effects of physical exercise on diverse CVDs and the involvement of miRNAs in this process.

2 Cardiac Adaptations to Physical Exercise

2.1 Cardiac Growth: Cardiac Hypertrophy and Cardiomyocyte Renewal

Cardiac hypertrophy is an adaptation to increased cardiac workload including a variety of mechanical, hemodynamic, and hormonal factors [18]. There are two different forms of ventricular hypertrophy, namely physiological hypertrophy and pathological hypertrophy [19]. Both hypertrophic processes involve increased

cardiomyocyte size, enhanced protein synthesis, and recombination of sarcomere structure. However, cardiac physiological hypertrophy differs from pathological hypertrophy in its stimuli and its structural and functional adaptations [4, 20–22]. As for stimuli, physiological hypertrophy occurs in healthy individuals following exercise training, pregnancy, or postnatal growth [23, 24], while pathological hypertrophy is associated with hypertension, or loss of myocytes due to ischemic or hypoxic myocardium damages [21]. As for structural and functional adaptations, physiological hypertrophy caused by endurance exercise training mainly exhibits ventricular hypertrophy with addition of sarcomeres and increase of cell length and cardiac mass, leading to preserved even enhanced left ventricular function, reduced collagen content, and improved myocardial antioxidant capacity and mitochondrial function [22, 25]. However, besides addition of sarcomeres, pathological hypertrophy is also characterized by increased cell thickness, enhanced apoptosis, and impaired cardiomyocyte metabolism switching from fatty acid to glucose metabolism, which could ultimately lead to increased cardiac fibrosis and stiffness and progressive reduction in cardiac output [26–28].

Over the past decades, the adult mammalian heart has been considered as a post-mitotic organ without any regenerative capacity [29]. However, more recent evidence has contradicted the long established belief, indicating that the adult mammalian heart sustains certain endogenous growth and regenerative capacity under some physiological or pathological conditions [30]. Actually, nearly half of cardiomyocytes are replaced during a whole human lifespan [30]. In a normal mouse heart, the turnover rate of cardiomyocytes is nearly 1.3–4.0% per year, while after myocardial injury, the rate of cardiomyocyte renewal is significantly increased, especially in the infarct border zone [31]. Importantly, physical exercise is shown as a novel strategy to endogenously enhance the limited capacity of cardiomyocytes for proliferation [32]. The potential sources of newly formed cardiomyocytes could be originated from division of pre-existing cardiomyocytes or differentiation of cardiac stem/progenitor cells [33, 34].

2.2 Angiogenesis

In cardiac physiological hypertrophy, the coordinated growth of myocardium and vasculature is an important adaptation of heart to deliver enough oxygen to the myocardium [35]. It was reported that endogenous cardiac stem cells (eCSCs) can be activated upon exercise [34]. Interestingly, these c-kit positive eCSCs were also committed to Nkx2.5 positive or Ets-1 positive cell lineages, indicating their potential to differentiate into both cardiomyocytes and vascular cells [34]. In addition, endothelial progenitor cells (EPCs), a type of circulating monocytes derived from bone marrow, can also be activated in response to exercise [36]. Acute exercise leads to a rapid increase in circulating EPCs that can maintain for up to 2–3 days after exercise termination. Furthermore, systematic and chronic exercise is able to trigger the mobilization of EPCs into the circulation from the bone marrow in both

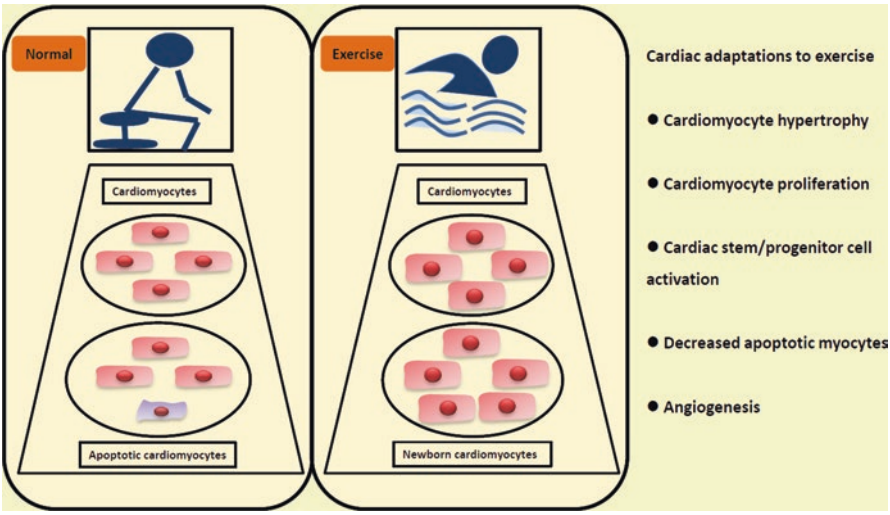

Fig. 15.1 Cardiac adaptations in response to physical exercise

healthy or diseased individuals [37]. Given the capacity of EPCs to proliferate, migrate, and differentiate into mature endothelial cells which contributes to neovascularization, exercise via promoting angiogenesis, may act as an important physical strategy or compensatory mechanism for cardiac regeneration and repair.

Taken together, the physiological adaptation of adult heart to exercise has three main components: (1) physiological hypertrophy of cardiomyocytes; (2) renewal of cardiomyocytes originated from pre-existing cardiomyocytes or cardiac stem/progenitor cells; (3) the accumulation of new microvasculature (Fig. 15.1). These cardiac physiological adaptations to physical exercise can lead to increased cardiac mass and even enhanced cardiac function.

3 miRNAs Responsible for Cardiac Adaptations to Exercise

Currently, miRNAs are emerging as pivotal modulators of cardiovascular development and disease [38, 39]. miRNAs have also been reported to participate in the beneficial adaptations promoted by exercise including physiological cardiac hypertrophy (Table 15.1).

3.1 Cardiac Growth

miR-1 and miR-133 were firstly reported to be decreased in both physiological hypertrophy induced by treadmill exercise and pathological hypertrophy induced by pressure overload [40]. After that, the other study also demonstrated that miR-1 and

Table 15.1 miRNAs responsible for cardiac adaptations of exercise

Type of exercise	Cardiac adaptation	miRNA	Target genes	References
Running (interval exercise)	Hypertrophy	↓miR-1, ↓miR-133	RhoA, Cdc42, Nelfa	[40]
Swimming (continuous exercise)	Hypertrophy	↓miR-208a	Purβ	[43]
Swimming (continuous exercise)	Hypertrophy	↑miR-27a/b	ACE	[44]
		↓miR-143	ACE2	
Swimming (continuous exercise)	Hypertrophy	↑miR-21, miR-144	PTEN	[46]
		↑miR-145	TSC2	
		↓miR-124	PI3Kα	
Running/swimming (continuous exercise)	Hypertrophy/Proliferation	↑miR-222	p27, HIPK1, HMBOX1	[47]
Running/swimming (continuous exercise)	Hypertrophy/Proliferation	↑miR-17-3p	TIMP3	[48]
Swimming (continuous exercise)	Anti-fibrosis	↑miR-29c	Collagen I, Collagen III	[41]
Swimming (continuous exercise)	Angiogenesis	↑miR-126	Spread1, PI3KR2	[38]

miR-133a/b were down-regulated in physiological cardiac hypertrophy induced by two different swimming protocols, indicating that these miRNAs could be regulated by exercise regardless of exercise mode or volume (moderate and high) [41].

Unlike in pathological hypertrophy [42], the expressions of miR-208a and miR-208b were reduced in exercise group compared with sedentary group, parallel to an increase of target gene transcriptional activator protein Pur-beta (Purβ) [17, 43]. Interestingly, overexpression of Purβ inhibited β-MHC expression accompanied by increased α-MHC expression and improved ventricular compliance, suggesting that down-regulation of miR-208 may mediate the beneficial effect of exercise against CVDs [43].

It is well known that angiotensin (Ang) II is an inducer for cardiac pathological hypertrophy, while exercise-induced physiological hypertrophy is associated with increased Ang-converting enzyme 2 (ACE2) activity, which might protect against pathological hypertrophy via reducing Ang II [44]. miR-27a and miR-27b have been reported to be increased in exercise-induced physiological hypertrophy in rats and they could target ACE, while decrease of miR-143 could lead to increased ACE2 activity and reduced Ang II level [44, 45].

The phosphoinositide-3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) signaling is critically involved in the regulation of cellular proliferation and survival, and plays a positive role in exercise-induced cardiac physiological hypertrophy [46]. Exercise could elevate cardiac miR-21 and miR-144 expressions, which were both predicted by bioinformatic analysis to target phosphatase and tensin homolog (PTEN), a negative regulator of the PI3K/Akt/mTOR pathway. Besides that, miR-145 was also found to be increased after exercise training, accompanied by a decrease in its target gene tuberous sclerosis

complex 2 (TSC2, another negative regulator of the PI3K/Akt/mTOR pathway). Moreover, exercise training decreased cardiac miR-124 expression with an increase in its target gene PI3K (p110α) [46].

Cardiomyocyte hypertrophy, as well as proliferation, are two important cellular changes during physiological cardiac growth. Recently, miR-222 and miR-17-3p have been reported to be increased in exercised heart and are necessary for exercise-induced cardiac growth [47, 48]. miR-222 can directly target P27 and HIPK1 in the regulation of cardiomyocyte proliferation, while target HMBOX1 in the regulation of cardiomyocyte hypertrophy [47]. Moreover, miR-17-3p enhances cardiomyocyte proliferation via targeting TIMP3, and induces cardiomyocyte hypertrophy by inhibition of PTEN and subsequent activation Akt [48]. However, overexpression of miR-222 or miR-17-3p alone was not sufficient to recapitulate the phenotypes of physiological growth as seen in exercised heart, suggesting that these miRNAs might work together to promote exercise-induced physiological cardiac growth in vivo [47, 48].

3.2 Anti-fibrosis

miR-29c was significantly increased in cardiac physiological hypertrophy induced by swimming exercise, and its target genes including collagen IAI and collagen IIIAI were both decreased [41]. Exercise-associated increase in miR-29c was correlated with reduced collagen concentration in the heart and improved left ventricular compliance, implying an anti-fibrosis effect of miR-29c, which might also exert protective effects against pathological cardiac remodeling [49].

3.3 Angiogenesis

Vascular endothelial growth factor (VEGF) has been reviewed as an important mediator of angiogenic responses upon different stimuli, including exercise [50]. Exercise training could promote vessel growth by increasing the expression level of miR-126 and repressing its target genes including sprouty-related protein 1 (Spread-1) and phosphoinositol-3 kinase regulatory subunit 2 (PI3KR2), which are two negative regulators of VEGF by inhibiting the PI3K/Akt/endothelial nitric oxide synthase (eNOS) pathway [38, 39].

Taken together, these data indicate that exercise can promote physiological cardiac hypertrophy through regulation of miRNAs and their specific target genes (Table 15.1). These miRNA-mRNA interactions may contribute to cardiac growth, anti-fibrosis, and angiogenesis processes in the heart upon exercise, and also probably mediate the protective effect of exercise against CVDs.

4 miRNAs Mediate Protective Effects of Exercise in CVDs

Exercise-induced cardiac protection has been appreciated for many decades, and several canonical molecular mechanisms have been proposed to contribute to the benefits of exercise. As novel mechanism, incorporating miRNAs within cardiac gene regulatory networks may provide a new opportunity for developing therapeutic interventions for CVDs.

4.1 Exercise Protects Against Myocardial Infarction

Myocardial infarction (MI) occurs when blood flow stops to a part of the myocardium causing damage to the heart muscle [51]. MI is accompanied by cardiomyocyte apoptosis, and necrosis, and hypertrophy, increased collagen deposition, and new vascularization, which results in pathological cardiac remodeling and reduced ventricular compliance [52]. As we described previously, exercise training could induce miR-29a and miR-29c in the heart, leading to reduced collagen concentration and improved ventricular compliance in healthy rats [41]. Interestingly, exercise training could also restore cardiac miR-29a and miR-29c expression levels and reduce collagen type I and III expression levels in the border and remote areas of MI [53]. This suggests an anti-fibrosis effect of exercise in rats with MI through upregulating miR-29a and miR-29c, which might serve as potential therapeutic strategy to reduce infarct size and improve cardiac function in MI patients [53].

On the other hand, impairment of cardiomyocyte contractility and calcium handling are hallmarks of left ventricular contractile dysfunction in MI [54]. Aerobic intensity-controlled interval training attenuated myocardial hypertrophy and increased myocyte contractile function in post-MI rats, accompanied with upregulated sarcoplasmic reticulum Ca2 + -ATPase 2a (Serca-2a) and sacolemmal sodium/calcium exchanger (NCX) protein levels, and enhanced intracellular Ca2+ handling and Ca2+ sensitivity in cardiomyocytes from rats with MI [55]. MI could also decrease miR-1 and increase miR-214, while exercise after MI partially restored miR-1 and miR-214 by targeting NCX and Serca-2a, respectively [56]. These molecular adaptations were associated with improved left ventricular compliance in MI hearts, and thus exercise was supposed to have a positive impact on Ca2+ handling, via regulating miR-1 and miR-214, in hearts post-MI [56].

Additionally, miR-26a was shown to be increased in mouse acute MI and human acute coronary syndromes [57]. Overexpression of miR-26a, via inhibiting its target gene SMAD1, could lead to impaired tube formation of endothelial cells in vitro and reduced angiogenesis upon exercise in vivo [57]. Interestingly, inhibition of miR-26a was associated with robust angiogenesis, reduced infarct size, and improved cardiac function even within 2 days after MI [57]. This suggests miR-26a as an important miRNA regulating angiogenetic response in ischemic cardiac diseases.

4.2 Exercise Protects Against Cardiac Ischemia/Reperfusion Injury

Cardiac ischemia/reperfusion (I/R) injury refers to heart damage caused when blood supply returns to the heart after a period of ischemia or lack of oxygen, which then induces a series of pathological changes including oxidative stress, inflammatory responses, Ca2+ overload, mitochondrial dysfunction, and myocardial apoptosis [58]. Burgeoning evidence indicates that physical exercise can protect against I/R injury in both clinical patients and experimental animal models by upregulating anti-oxidative capacity, promoting angiogenesis, and decreasing cardiomyocyte apoptosis [59–61]. Recently, miRNAs have been reported to underline these mechanisms mediating the protective effects of exercise against I/R injury.

miR-222 is a highly conserved member of a miRNA cluster with miR-221, which is encoded on the X chromosome [62, 63]. miR-222 has been found to be increased in the plasma of athletes after both acute and chronic exercise, suggesting a potential relevance of miR-222 with exercise [64]. Interestingly, circulating miR-222 could also be elevated after acute cardiopulmonary exercise in heart failure patients, indicating a potential role of miR-222 in mediating the beneficial effect of exercise in heart failure patients [47]. More importantly, miR-222 was proved to be necessary for exercise-induced physiological growth by promoting both hypertrophy and proliferation of cardiomyocytes through targeting P27, HIPK1, and HMBOX1 [47]. Although overexpression of miR-222 was not sufficient to recapitulate the exercise phenotype at baseline, it did protect against adverse ventricular remodeling and cardiac dysfunction after I/R injury [47]. These effects were also associated with inhibition of cardiomyocyte apoptosis and a dramatic reduction of cardiac fibrosis [47].

As overexpression of miR-222 alone was not sufficient to recapitulate the phenotypes of physiological growth observed in exercised heart, we also speculated that other molecular mechanisms (including miRNAs) must be involved in this process. Recently, miR-17-3p, a passenger miRNA that belongs to the miR-17-92 cluster, was also proved to be necessary for exercise-induced cardiac growth and have protective effects against cardiac remodeling after I/R injury, which was at least in part due to enhanced proliferation and reduced apoptosis of cardiomyocytes [48].

4.3 Exercise Protects Against Heart Failure

Heart failure (HF) often refers to congestive heart failure and occurs when the heart is unable to pump enough blood to meet the body's needs [65]. Accumulating studies indicate that exercise training has protective effect on the myocardium in patients with HF and in animal models of pathological cardiac hypertrophy and HF, which could be associated with increased exercise tolerance, improved cardiac structure and function, and reduced HF-related biomarkers during cardiac remodeling [66–70].

Currently, exercise training has been formally recommended by major guidelines as a safe and important strategy for patients with HF [71, 72]. However, the molecular mechanisms by which it exerts the therapeutic value for HF are far from understood.

Recently, Souza RW et al. conducted a miRNA expression profile in ascending aortic stenosis-induced HF rats randomized to either 10 weeks of exercise training or sedentary group [66]. Therapeutic effects of exercise in reducing cardiac remodeling and maintaining systolic and diastolic function were associated with differentially regulated miRNAs between exercise and sedentary group, including miR-208b-3p, miR-21-5p, miR-132-3p, and miR-212-3p [66]. Interestingly, some of these miRNAs were reported to regulate I/R injury or cardioprotection by ischemic pre- and post-conditioning [73–77]. Further gene-term enrichment analysis showed that these differentially regulated miRNAs between exercised or sedentary HF rats could target genes involved in programmed cell death, TGF-β signaling, cellular metabolic process, cytokine signaling, and cell morphogenesis. Among these five biological modules, programmed cell death module compromise the most enriched miRNA targets, indicating that exercise may attenuate cardiac abnormalities during HF by regulating miRNAs through apoptosis-related pathways [66].

4.4 Exercise Protects Against Diabetic Cardiomyopathy

Diabetes mellitus (DM) is a group of metabolic diseases in which there are high blood sugar levels over a long period [78]. Several recent epidemiological studies have confirmed that DM was an independent predictor for heart disease and would influence 400 million people worldwide by 2030 with prevalent cardiovascular deaths [79–81]. Exercise has been described as a polypill that prevents myocardial apoptosis and fibrosis, ameliorates mitochondrial biogenesis, and preserves cardiac function in diabetic cardiomyopathy in mice [82]. Furthermore, exercise can also mitigate cardiac dysfunction in diabetic patients though the molecular mechanisms still remain uncertain [83].

Exosomes are small membrane vesicles (30–100 nm) that contain various biological contents like DNA, RNA, protein, as well as miRNA, thus participating in cell-to-cell communications [84]. Extracellular vesicles derived from stem cells or even from plasma of healthy individuals have been documented to diminish cardiomyocyte apoptosis and improve cardiac function after ischemic cardiac injury, suggesting exosomes as critical agents for cardiac repair [85, 86]. Exercise training could trigger the release of exosomes that contain miRNAs (miR-455, miR-29b, miR-323-5p, and miR-466) from diabetic hearts compared to sedentary diabetes group. Interestingly, these miRNAs were proved to bind to the 3′ region of matrix metallopeptidase 9 (MMP9) and thus silence MMP9, a gene regulating extracellular matrix remodeling [87]. Thus, a close relationship has been suggested between exercise-derived exosomes, exosomal miRNAs, and the benefit of exercise for the heart, which could delineate novel strategy to cope up with diabetic cardiomyopathy.

4.5 Exercise Protects Against Atherosclerosis

Atherosclerosis (AS), a disease associated with chronic inflammation, is characterized by thickened artery wall linked to invasion and accumulation of foam cells, proliferation of intimal smooth muscle cells, and finally formation of atheromatous (fibrofatty) plaque in the arteries [88, 89]. Actually, physical exercise is also recommended as an effective way to diminish vascular injuries in patients with AS, probably by reducing triglyceride and apolipoprotein B, enhancing tissue plasminogen activator activity, and decreasing coronary artery calcium [90, 91]. Exercise was able to reduce foam cell accumulation and plaque formation, accompanied with an increase in vascular miR-146a and miR-126 expression levels, and a decrease in vascular miR-155 expression level in apolipoprotein E-null mice fed with high-fat diet [92]. Importantly, miR-146a was further demonstrated to directly target tumor necrosis factor receptor 6 (TRAF6), a gene involved in the Toll-like receptor 4 (TLR4) signaling pathway, suggesting that exercise-induced miR-146a may protect against AS by repressing vascular inflammatory injury [92].

4.6 Exercise Protects Against Hypertension

Hypertension is a long term medical condition in which the blood pressure in the arteries is persistently elevated [93]. Long term high blood pressure represents a major risk factor for CVDs [93]. Exercise training is established as a nonpharmacological tool for treatment of hypertension by improving endothelial function, attenuating microvascular rarefaction, and reducing blood pressure [94, 95]. Exercise is also effective in reducing other CVD risk factors in patients with hypertension as evidenced by improved plasma lipoprotein-lipid profiles and insulin sensitivity [96].

For further detecting the underlying mechanisms, some studies focused on the change of miRNAs in response to exercise in hypertension. Exercise training has been found to be able to significantly reduce blood pressure and heart rate in spontaneously hypertensive rats (SHR) compared to sedentary SHR group, by regulating several angiogenesis-related miRNAs [97]. Previous studies indicated that miR-16 via targeting VEGF and Bcl-2, miR-21 via targeting Bcl-2, and miR-126 via targeting sprouty-related protein 1 (Spread-1) and phosphoinositol-3 kinase regulatory subunit 2 (PI3KR2), lead to the dysregulation of angiogenesis and apoptosis processes [98–101]. Interestingly, exercise could restore the increased miR-16 and miR-21, and the decreased miR-126 expression levels in the soleus of hypertensive rats [97]. Exercise could also activate the VEGF and anti-apoptotic signaling pathways and improve endothelial nitric oxide synthase (eNOS) level as well [97]. These data provide evidence that exercise can balance angiogenic and apoptotic pathways by regulating miRNAs, and thus prevent microvascular abnormalities in hypertension [97].

4.7 Exercise Protects Against Pulmonary Hypertension

Pulmonary hypertension (PH) refers to an increase of blood pressure in the pulmonary arterial system. Pulmonary arterial hypertension (PAH) is the most common form characterized by sustained vasoconstriction, vascular remodeling of small pulmonary arteries, in situ thrombosis, and chronic inflammation, that leads to increased mean pulmonary arterial pressure and ultimately right heart failure and death [102]. Despite significant progress in treatment, the three-year survival of patients with PAH is a little bit higher than 50% and the quality of life remains severely affected [103]. More recently, a body of clinical evidence has shown the safety and efficacy of exercise training in PAH [104, 105]. Exercise training was demonstrated to be effective to enhance exercise tolerance, improve quality of life, and possibly increase survival rate in patients with PAH associated with connective tissue diseases [106]. Exercise training could also significantly lower right ventricular end diastolic pressure, reduce pulmonary artery thickness, and decrease right ventricular interstitial volume in monocrotaline-induced PAH [107]. Despite the certain beneficial effect of exercise on PAH, the mechanisms involved especially the role of miRNAs need to be further explored.

5 Circulating miRNAs in Response to Exercise

Circulating miRNAs (c-miRNAs) are the most investigated ncRNAs detected in the serum or plasma of humans and animals. c-miRNAs are usually protected from degradation as they can be packaged into membrane vesicles such as exosomes or microvesicles [108]. Additionally, c-miRNAs can be packaged into lipoproteins or Ago proteins as part of RNA-induced silencing complexes [109, 110]. As c-miRNAs can be released at rest or upon tissue injury or physiological stress such as exercise training, c-miRNAs may serve as unique biomarkers of disease states and exercise physiology [111–113].

The dose-response relationship between leisure-time physical activity and mortality was investigated by a pooled analysis, and it was indicated that moderate- or even vigorous-intensity physical exercise was associated with longevity benefit [114]. Noteworthy, no excess mortality risk was found even with ten times the recommended minimum level of leisure-time physical exercise [114]. Thus, leisure-time physical exercise should be highly recommended to inactive individuals [114]. Increasing number of studies reported the alteration of c-miRNAs implicated in muscle adaptations, angiogenesis, and inflammation during physical exercise. However, little is known about the effects of different type, intensity, and duration of exercise on c-miRNAs. In this section, we will summarize the potential changes of major c-miRNAs in response to different modes of exercise.

5.1 Circulating miRNAs in Acute Exercise

miR-1, miR-133, miR-206, miR-208b, and miR-499, also called muscle-enriched miRNAs (myomiRs), are highly abundant in cardiac and/or skeletal muscles while their expression levels in circulation are very low in healthy individuals [115]. An acute bout of endurance exercise (marathon) could induce the rapid increase of circulating miR-1, miR-133a, miR-206, miR-208b, miR-499, and miR-206, supporting the notion of distinct c-miRNA changes would in response to exercise [116]. Twenty-four hours after the marathon run, miR-208b and miR-499 returned to baseline levels, while other c-miRNAs still enhanced [116]. Moreover, miR-1, miR-133a, and miR-206 expression levels were positively correlated with the maximum oxygen uptake (VO2max), an indicator of exercise capacity, while no correlations were found between c-miRNAs and cardiac damage biomarkers such as troponin T and troponin I, indicating that the release of myomiRs into circulation might be used as unique biomarkers for exercise physiology rather than consequences of cell death [116]. However, another study reported that circulating miR-1 and miR-133a were increased immediately after marathon, but declined very close to baseline levels 24 hours after race completion [113]. Interestingly, circulating miR-133a has also been reported to be unchanged after an acute exhaustive exercise test, suggesting that the regulation of c-miRNAs might be closely related to exercise type, intensity, and duration [64].

miR-126 is enriched in vascular endothelium and miR-146a is an important regulator of inflammation [117, 118]. Circulating miR-146a and miR-126 were both increased immediately after a marathon run, and rapidly returned to baseline levels 24 hours later [113]. However, in another study, circulating miR-146 was down-regulated immediately after an acute exercise bout in young healthy men [119]. In addition, circulating miR-146a level has also been reported to be unchanged at 0 h, 1 h, and 24 h after an acute resistance exercise, while it began to decrease at 3 days post exercise in healthy young males [120]. These different regulatory patterns of c-miRNAs indicate that participants, as well as exercise type, intensity, and duration may affect changes of c-miRNAs in response to exercise.

Some other miRNAs have also been found to be modulated by exercise. miR-106a, miR-221, miR-30b, miR-151-5p, let-7i, miR-146a, miR-652, and miR-151-3p were robustly down-regulated immediately after an acute exercise bout. miR-338-3p, miR-330-3p, miR-223, miR-139-5p, and miR-143 were up-regulated at 1 hour after exercise and miR-1 was elevated at 3 h after exercise [119]. Additionally, a rapid decrease of muscle-enriched miR-486 in circulation after an acute exercise was found [121], indicating that exercise may reduce the release of myomiRs into circulation, or perhaps accelerate the uptake of specific c-miRNAs from circulation into certain recipient tissues and cells, though the mechanisms remain largely unknown.

Table 15.2 Circulating miRNAs in response to exercise

Types of exercise	Categories	Changed c-miRNA	References
Acute exercise			
Marathon running	Athlete	↑miR-1/133a/206/208b/499	[113, 116]
Marathon running	Athlete	↑miR-146a/126	[113]
Cycle ergometer exercise	Normal	↓miR-146a	[119, 120]
Cycle ergometer exercise	Normal	↓miR-106a/221/30b/151/652/let-7i	[120]
		↑miR-338-3p/330-3p/223/139-5p/143/1	
Chronic exercise			
Rowing exercise training	Athlete	↑miR-20a	[64]
Cycle ergometer exercise	Normal	↓miR-342-3p/766/25/148a/185/21/let-7d	[119]
		↑miR-103/107	

5.2 Circulating miRNAs in Chronic Exercise

Little is known about the regulation and function of c-miRNAs in chronic exercise. After 12 weeks of chronic endurance training, miR-342-3p, miR-766, let-7d, miR-25, miR-148a, miR-185, and miR-21 were decreased while miR-103 and miR-107 were increased in plasma [119]. In addition, circulating miR-20a was increased after a 90 days period of rowing training, but not affected by acute exercise in healthy competitive athletes [64]. Noteworthy, the change in circulating miR-20a quantitatively correlated with the change in VO2max, indicating a potential role of miR-20a as a biomarker for chronic exercise fitness [64]. The altered circulating miRNAs in response to exercise were listed in Table 15.2.

6 Conclusions

In this chapter, we summarize the current knowledge about miRNAs responsible for cardiac adaptations to physical exercise and address their roles in mediating the protective effects of exercise against diverse CVDs, including MI, IRI, HF, diabetic cardiomyopathy, AS, hypertension, and PH. Also, we discuss changes of circulating miRNAs in response to acute and chronic exercise. These evidences highly suggest that miRNAs could serve as potential biomarkers for exercise physiology as well as novel therapeutic targets to combat CVDs.

Mounting evidence has confirmed the roles of miRNAs mediating the beneficial effects of exercise. However, limitations of these studies should be acknowledged. First, mechanistic regulations of miRNAs in response to exercise are still unclear. The dysregulation of miRNAs in the settings of acute as well as chronic exercise may rely upon either de novo miRNA transcription or post-transcriptional processing of premature miRNAs forms [122]. Circular RNAs may act as miRNA sponge

by inhibiting miRNA activity, thus regulate cardiac adaptations to exercise [123]. Second, individuals may response differently to variable type, intensity, and duration of exercise. Thus, subsequent studies are needed to evaluate the regulation of miRNAs upon different modes of exercise across diverse populations. Third, the exact cellular sources as well as the secretion mechanisms of exercise-induced circulating miRNAs remain largely unknown. Despite that skeletal muscle function is closely related and contributes to circulating miRNAs upon exercise stimuli, other tissue or cell types such as myocardium, cardiac fibroblasts, and vascular endothelial cells should be explored as potential sources of circulating miRNAs [124]. Finally, the biological functions of exercise-induced miRNAs in physiological cardiac hypertrophy as well as their potential in CVD therapeutics deserve further explorations.

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