Chapter

Noncoding RNAs in the Cardiovascular System: Exercise Training Effects

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Abstract

Exercise training (ET) represents a non-pharmacological treatment that can attenuate or even reverse the process of cardiovascular diseases (CVD), by stimulating protein synthesis, angiogenesis, mitochondrial biogenesis, anti-inflammatory, and anti-oxidative effects that are involved to enhance the performance and improved quality of life. Despite the benefits of exercise, the intricacies of their underlying molecular mechanisms remain largely unknown. Noncoding RNAs (ncRNAs) have been recognized as a major regulatory network governing gene expression in several physiological processes and appeared as pivotal modulators in a myriad of cardiovascular processes under physiological and pathological conditions. However, little is known about ncRNA expression and role in response to exercise. Here we review the current understanding of the ncRNA role in exercise-induced adaptations focused on the cardiovascular system and address their potential role in clinical applications for cardiovascular diseases.

Keywords: microRNA, lncRNAs, heart, vessels, exercise and cardiovascular diseases

1. Introduction

Exercise training (ET) has been shown to undergo beneficial changes in both cardiac structure and function, protecting the heart and vessels against the development of cardiovascular diseases (CVD) [1–4]. CVD are a growing cause of morbidity and mortality throughout the world and often develop after a period of abnormal heart growth termed pathological cardiac hypertrophy (CH). The occurrence of risk factors, such as diabetes, hypertension, obesity, and advanced age leads to substantial complications of CVD. Loss of cardiomyocytes and capillaries accompanied by fibrosis contributes to decreased cardiac function ultimately leading to heart failure (HF). Although current management has improved survival in patients with CVD, such therapies do not fully address the underlying cause and, as a result, HF progresses. Thus, understanding the pathways that rescue cardiovascular remodeling (CR) and function could have important clinical implications [3–6].

Genome-wide analyses and ribonucleic acids (RNA) sequencing revealed that a large part of the human genome (~99%) do not encode proteins but are transcriptionally active and give rise to a broad spectrum of noncoding RNAs (ncRNAs).

The ENCODE Project in 2000 (see https://www.encodeproject.org/), that aimed to characterize all the functional elements in the human genome, helped researchers to understand the eukaryotic genome complexity. Although ncRNAs have been considered as junk in the human genome, currently it represent as one of the newest study targets of CVD by potential role in controlling gene expression [7, 8].

Bartolomei et al. [9] discovered the first ncRNA (H19) in mice and it was one of the first maternally imprinted long ncRNAs (lncRNAs) to be identified [9]. Since then, thousands of ncRNAs have been described and are classified into two large groups: small ncRNAs, which are up to 200 nucleotides (nt), and lncRNAs, which are longer than 200 nucleotides. Small ncRNAs comprise microRNAs (miRNAs), PIWI interacting RNAs (piRNAs), transfer RNAs (tRNAs), and small nucleolar RNAs (snoRNAs). Long ncRNAs mainly refers to natural antisense transcripts and other lncRNAs. The discovery of the new class of RNAs increased our knowledge about epigenetic, transcriptional, and translational regulation of gene expression under physiological and pathological conditions. Thus, the possibility of ncRNAs as a potential tool for the treatment of CVD is of great interest [6, 8, 10–12].

ncRNAs such as miRNAs and lncRNAs are regulators of cell development, differentiation, and growth, exert their functions in both nuclear and cytoplasmic compartments. In the cardiovascular system, ncRNAs regulate cardiac development, inflammation, hypertrophy, fibrosis, and regeneration [6, 10–12]. Beyond this, altered miRNA expression can be found in the blood of patients with various CVD [10, 13]. ET is well known to promote cardiovascular profit in which it can vary according to type, intensity, and duration of exercise. However, little is known about the regulatory interaction networks among the multiple classes of RNAs or the mechanisms regulated by exercise-induced ncRNAs on heart and vessel [1, 3, 5, 14]. The contribution of ncRNAs to these adaptations has the potential not only to reveal novel aspects of cardiovascular system but also to identify new targets for prevention and treatment of the CVD.

In this review, we provide an overview of the current knowledge of the cardiovascular effects of ET on ncRNAs, with a specific focus on miRNAs, their role in regulating cardiovascular remodeling (CR) and their potential application for the treatment of CVD. These findings will provide insights that can aid in the development of new therapeutic interventions for these pathologies.

2. miRNAs, a family of small ncRNAs

miRNAs, the most popular class of small ncRNAs, are a class of single-stranded, endogenous, conserved, RNAs (~21–23 nucleotides) that regulate gene expression at the posttranscriptional level. They bind to messenger RNA (mRNA) by base pairing to complementary sequences within the 3′ untranslated region (3′UTR), and cause gene silencing through the inhibition of translation and/or degradation of mRNA [15–17]. However, recent studies have suggested that miRNA-binding sites are also located in 5′ UTRs or open reading frames (ORFs), and the mechanism of miRNA-mediated regulation from these sites has not been identified [18]. miRNA sequences are in diverse regions of the genome. Most canonical miRNAs in humans are encoded within introns of coding or noncoding genes. However, some miRNAs may be encoded by exons or may be associated in the same loci, organized as a polycistronic transcription unit. Small sequences and imperfect complementary, a single miRNA can target several to hundreds of distinct mRNAs. Conversely, an mRNA can be targeted by diverse miRNAs simultaneously, thus miRNAs are estimated to regulate the expression of more than a third of human protein-coding genes [15–17].

The first miRNA, lin-4, was discovered in *C. elegans* in 1993. Lin-4 regulates *C. elegans* development by binding to the lin-14 mRNA to inhibit lin-14 protein expression [19]. Since then, it has been recognized that miRNAs are a highly conserved class of small RNAs present in most organisms and a variety of miRNAs have been discovered suggesting that there are in excess of 2650 mature sequences in human (see http://www.mirbase.org). Studies have demonstrated that miRNAs influence several biological events, including embryogenesis, cell death, differentiation, proliferation, and cell growth. Furthermore, developments in miRNA-related technologies, such as miRNA expression profiling and synthetic oligoRNA, have contributed to the identification of miRNAs involved in a number of physiological and pathological conditions [15, 16, 20].

The biogenesis of the miRNA starts in the nucleus; RNA polymerase II initially transcribes miRNAs into long segments of coding or noncoding RNA, known as pri-miRNAs, which are usually capped and polyadenylated. The pri-miRNAs harbor a local hairpin structure that is then cropped by a nuclear enzyme Drosha and their cofactor Pasha (also known as DGCR8) into pre-miRNAs (~70 nucleotides). After nuclear processing, the pre-miRNA is exported into the cytoplasm by Exportin-5 in a RanGTP-dependent manner. Subsequently, the enzyme Dicer removes the terminal loop of the pre-miRNAs to generate the miRNA:miRNA∗ duplex (dsRNA) of ~20–25 nucleotides. The dsRNA is loaded into the miRNA-associated multiprotein RNA-induced silencing complex (RISC), which includes the Argonaute proteins. One strand of the miRNA is preferentially retained in this complex and becomes

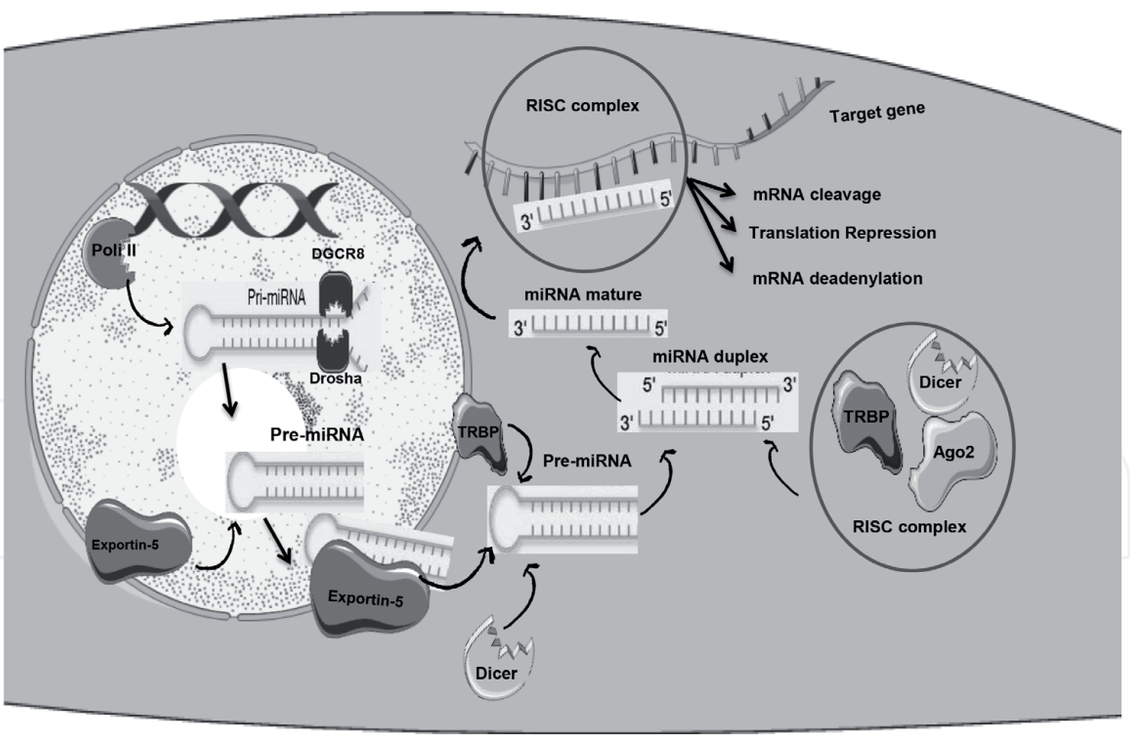

Figure 1.
miRNA biogenesis. miRNA genes are transcribed by RNA polymerase II (Pol II) to generate the primary transcripts (pri-miRNAs). The initial processing of the primary transcript is mediated by the Drosha-DiGeorge syndrome critical region gene 8 (DGCR8) complex (also known as the microprocessor complex) that generates ~70 nucleotide (nt) pre-miRNAs. Pre-miRNA has a short stem plus, which is recognized by the nuclear export factor exportin 5. Once exported from the nucleus, the cytoplasmic RNase III Dicer catalyzes the production of miRNA duplexes. Dicer, TRBP (TAR RNA-binding protein; also known as TARBP2), and Argonaute (AGO) 1–4 mediate the processing of pre-miRNA and the assembly of the RISC (RNA-induced silencing complex). Within this complex, one strand of the miRNA duplex is removed resulting in a single-stranded miRNA, partially complementary to target mRNA, which remains in the complex. miRNA complex interaction with mRNA induces posttranscriptional silencing through as both mRNA destabilization and translational repression (https://smart.servier.com/image-set-download/).

the mature miRNA depending on its thermodynamic stability; the opposite strand, known as the passenger strand, is eliminated from the complex. The RISC acts as a guide by base pairing of miRNA with its target mRNAs, resulting in mRNA cleavage, mRNA deadenylation, and translation repression (**Figure 1**). It is well recognized that pairing in the 'seed' region of the miRNA (nucleotides 2–7 or 8) appears critical for target recognition. Thus, miRNAs that bind to target mRNAs with imperfect complementarity repress target gene expression via translational silencing. In contrast, miRNAs that bind to their target mRNAs with perfect complementarily induce mRNA degradation [15–17, 20].

3. miRNAs regulation by long noncoding RNAs

Emerging evidences suggest that miRNAs may be affected by long noncoding RNAs (lncRNAs) [14, 21]. While there is plenty evidence of miRNAs involvement in exercise adaptations, investigations on lncRNAs are still lacking [14]. LncRNAs are a heterogeneous group of transcripts modulating gene expression at multiple and more complex levels than miRNAs. One way to classify lncRNAs is according to their mechanism of action: signal, decoy, guide, scaffold, enhancer, or sponge lncRNAs (see the review by [22, 23]).

Similar to miRNAs, lncRNAs have been shown to be involved in CVD with several reports about their specific expression in different cardiac diseases [21, 24–30]. In this context, it was recently showed that H19, which is a maternally imprinted lncRNA, is implicated in CVD [24, 31]. H19 is highly expressed during embryogenesis but is strongly repressed after birth, with a significant re-expression of lncRNA H19 in CVD. Liu et al. [24] showed that miRNA-675 mediates the anti-hypertrophic effect of H19 on cardiomyocytes acting as a negative regulator of cardiac hypertrophy. In addition, it was demonstrated that H19 exon1 encodes miR-675-3p and miR-675-5p, which are up-regulated in pathological CH. Prediction algorithms identified a pro-hypertrophic factor, Ca/calmodulin-dependent protein kinase IIδ (CaMKIIδ), as potential targets for miR-675-3p and miR-675-5p, which was confirmed by luciferase reporter gene assays [24]. Moreover, high H19 expression has been linked to hyperhomocysteinemia, a known risk factor for coronary artery disease [32]. Furthermore, H19 was reported to sponge let-7 family miRNAs, which are believed

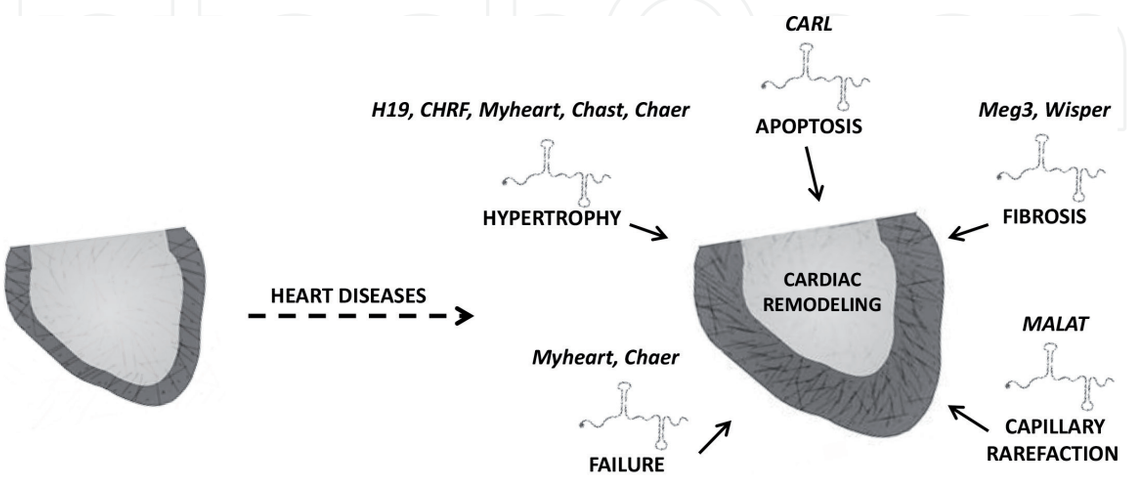

Figure 2.
Cardiac disease-induced cardiac remodeling (CR) is characterized by an aberrant profile of myocardium growth, accompanied by fibrosis, apoptosis, and cardiac dysfunction. lncRNAs H19, CHRF, Myheart, Chast, and Chaer have been described to regulate pathological cardiac hypertrophy; cardiac fibroblast-enriched lncRNAs Meg3 and Wisper controlling cardiac fibrosis; and lncRNAs CHRF, Myheart, and Chaer associated with heart failure in response to cardiac injury.

to have atheroprotective role [21, 33]. Thus, lncRNA-miRNA-mRNA axis reveals a promising therapeutic strategy for CVD.

Cardiac hypertrophy-related factor (CHRF) [26], myosin heavy-chain-associated RNA transcripts (Myheart) [25], cardiac hypertrophy-associated epigenetic regulator (Chaer) [27], cardiac hypertrophy-associated transcript (Chast) [28], cardiac fibroblast-enriched lncRNA maternally expressed 3 (Meg3) [29] and Wisp2 super-enhancer-associated RNA (Wisper) [30] are lncRNAs linked to CR (**Figure 2**). Additionally, recent gain- and loss-of-function studies, both *in vitro* in cell lines and *in vivo* in mouse models, have demonstrated that lncRNAs play critical roles in cardiovascular biology and diseases.

4. Heart, exercise, and miRNAs

4.1 Cardiac remodeling and dysfunction: exercise training effects

The mammalian heart is a muscle and is the first organ to form in the embryo. The development of heart is highly complex and involves the integration of multiple cell types as well as a connection between vascular system and blood vessels. However, its uninterrupted development and function are determinant to organism survival [34, 35]. The primary function of heart is to contract and pump blood throughout the circulatory system to deliver oxygen and nutrients to tissues and to transport carbon dioxide back to the lungs [36, 37]. This organ can be remodeled according to environmental stimuli or external stimuli.

Cardiac remodeling (CR) is an adaptation to increased cardiac overload including a variety of mechanical, hemodynamic, and hormonal factors that promotes changes in structure, dimensions, mass, shape, and functions of the heart as well as cardiac cells [34, 38], and has been generally defined as either physiological (i.e., normal) or pathological (i.e., detrimental) [34]. Physiological growth occurs in response to exercise, pregnancy, or postnatal growth [34] causing heart hypertrophy, which is reversible and characterized by normal cardiac morphology and function [39]. On the other hand, in pathological hypertrophy, contractile performance, for example, can be perturbed or reduced in response to diverse pathophysiological stimuli, which also causes the typically heart remodeling, in association with increases in myocyte cell volume [36, 39]. However, it can slowly progressives to become maladaptive, leading to a decompensation in cardiac function [40].

Cardiac dysfunction is the main consequence of pathological CR, a process that involves a complex series of transcriptional, signaling, structural, electrophysiological, and functional events, occurring within the cardiac myocyte and in the other cellular elements within the ventricle (fibroblasts, endothelial cells, T-cells, etc.). Thus, it starts with genetic changes in response to cardiac insults, with re-expression of fetal genes (atrial and β-type natriuretic peptide, β-myosin heavy chain, and α-skeletal muscle actin), fibrosis, endothelial dysfunction, and inflammation. Consequently, cellular and molecular changes occur, resulting in progressive loss of ventricular function, asymptomatic at first, that evolves to signs and symptoms of HF [41–43].

ET is the most effective non-pharmacological intervention to prevent or reduce cardiovascular disturbances [2, 44]. ET can be classified as static or dynamic and leads to two different types of intermittent chronic cardiac overload, which induces morphological changes in the heart [45]. This changes will depend on factors such as the type of exercise used (aerobic or resistance), volume (training time), intensity (degree of training load), and frequency of ET (number of training session

at any given time) [2, 45], and is directly related to maximal aerobic capacity or VO_2 max [42]. It is known that ET is one of major stimuli for physiological cardiac hypertrophy (CH) [46]. The main physiological responses attributed to CR are the increase in contractility, the improvement of the transient Ca^{2+} intracellular, increase in expansion with significant improvements in myocardial oxygenation, and additional endothelium-dependent functions that prevent ischemic events [42].

In contrast to pathological CH that occurs in response to continuous stimulus on heart (arterial hypertension, valve disease, or aortic stenosis, for example), CH induced by ET consists of a frequent, but intermittent stimulus cardiac hemodynamic overload [2]. Thus, a pressure overload in response to resistance training, for example, causes an increase in the width of the cardiac myocytes without dilation of the chamber and causes a concentric left ventricle (LV) hypertrophy [39]. On the other hand, the increase in size of cardiomyocytes by aerobic ET is mainly associated with an eccentric LV hypertrophy phenotype, induced by volume overload, with predominant myocyte growth in series, promoting dilation of the cardiac chamber. Either concentric or eccentric CH by ET is not followed by fibrosis and re-expression of fetal genes, which is linked to preserved or improved cardiac function [39, 44].

Medeiros et al. [47] showed that CH induced by moderate aerobic ET causes resting bradycardia in rats by an increase in cardiac vagal activity, which is associated to increased VO_2 peak [44, 47, 48] and an increase in nitric oxide (NO) and angiogenesis levels in heart of experimental animals. The increased cross-sectional area in the heart contributes to the increase in ventricular systolic volume and cardiac output, which improves aerobic capacity [49]. Thus, ET has been widely used as a preventive therapeutic strategy for prevention or treatment of diseases in cardiovascular system. However, the underlying molecular mechanisms that regulate ET responses have not been fully elucidated, especially with regard to CH [50]. In this sense, emerging evidences have shown that miRNAs may play an important role in both heart development and CR [44, 51] as in the pathogenesis of HF through their ability to regulate the expression levels of genes that govern the process of adaptive and maladaptive CR [52]. Besides, miRNAs can mediate the beneficial effects of ET in heart in both physiological and pathological CR well as in cardiac disorders [2, 53, 54].

Therefore, in the below section we will highlight the role of miRNAs in both physiological CR well as diseased heart. In another section, we will highlight what is known until now about the effects of ET in the regulation of miRNA expression in heart in these different scenarios.

4.2 miRNAs in cardiac remodeling and heart diseases

The miRNAs may be essential regulators in the development and normal physiology. Dysregulation of miRNA expression has been found to correlate with CR and disease in both human and mouse [55, 56]. Therefore, identification of a signature of miRNAs is an essential and promising prerequisite for the study of the biological functions of this class of molecules in the cardiovascular system [57, 58].

A single miRNA can be highly expressed in one tissue and may not have, or have a low expression in another [58]. In this sense, miRNA-1, -133, -206, and -208 are muscle specific and are primarily expressed in the cardiac and skeletal muscle [57, 59], with miRNA-208 being solely expressed in heart [57]. During cardiac development, the expression of miRNA-1 increases, which promotes a decrease in levels of the heart and neural crest derivatives expressed 2 levels (Hand2), a gene-target, reaching it at the levels found in mature cardiac myocytes [57]. miRNA-1 also promotes myogenesis, targeting the histone deacetylase 4 (HDAC4). The

miRNA-1 family represents more than 40% of all the miRNAs expressed in the heart [60], which consists of a subfamily composed of miRNA-1-1, miRNA-1-2 and miRNA-206.

The miRNA-133 family consists of the subfamily miRNA-133a-1, 133a-2, and 133b. miRNA-133, like miRNA-1, also plays an important role in cardiac development. In fact, the deletion of miRNA-133 results in severe cardiac malformations, together with embryonic and post-natal lethality, as a consequence of an insufficient number of cardioblasts [57].

The miRNA-208a, -208b, and -499 are specifically encoded by introns of Myh6 (α-MHC), Myh7 (β-MHC), and Myh7b, respectively. In mice, Myh7/miRNA-208b is expressed in the embryonic heart and Myh6/miR-208a is expressed predominantly in the postnatal stages. Myh7 is re-expressed in the adult's heart only after cardiac stress. Myh7b/miRNA-499 is expressed in the embryonic heart and in the adult heart [61]. However, the targeted deletion of miRNA-208a in mice results in only a mild cardiac phenotype, such as the ectopic expression of rapid muscle markers of the skeleton and the impaired ability to respond to postnatal stress. Therefore, this scenario suggests a not so essential role of these three miRNAs during cardiac development [51, 62].

Considering the importance of miRNAs even in heart development, it is understandable that dysregulation in its expression is implicated in a variety of pathological disorders, including diabetes, various cancers, and CVD [51]. Pathological CH, unlike the physiological CH promoted by ET, is a common response to various cardiac disorders, which includes not only hypertension, but also cardiac ischemic disease, valvular diseases, and endocrine disorders, and is therefore, considered the major determinant of mortality and morbidity in CVD [58, 63]. Currently, existent literature suggest that mainly miRNA-1, -18b, -21, -133, -195, and -208 play important roles in modulating CH [52].

In this sense, Carè et al. [64] found a decrease in expression of both miRNA-133 and miRNA-1 in three different animal models of CH, including hypertrophy induced by pressure overload, hypertrophy induced by Akt overexpression, and adaptive CH in mice and humans [64]. However, *in vitro* overexpression of these miRNAs inhibited hypertrophy, while *in vivo* inhibition of miRNA-133 promoted a pronounced and sustained CH. In this same study, three new specific targets for miRNA-133 have been identified, which include RhoA and CH regulatory GDP-GTP exchange protein; the Cdc42, a signal transduction kinase implicated in hypertrophy; and Nelf-A/WHSC2, a nuclear factor involved in cardiogenesis [64]. miRNA-1, in turn, controls cardiac myocyte growth by negatively regulating the expression of calcium-calmodulin signaling components, Mef2a and Gata4, which are key transcription factors that mediate calcium-dependent changes in gene expression [65].

Cheng et al. [55] showed that miRNAs are aberrantly expressed in culture of neonatal cardiomyocytes stimulated with angiotensin II or phenylephrine, and that miRNA-21 knockdown exerts a negative effect on cardiomyocyte hypertrophy *in vitro*. The mitogen-activated protein kinase (MAPK), FasLigand (FasL), and homolog of deleted phosphatase on chromosome 10 (PTEN) are targets that have already been validated for miRNA-21, which stimulate the Akt pathway [66, 67]. In addition, there is evidence that depletion of miRNA-21 exerts anti-apoptotic and pro-proliferative effects on rat proliferative vascular smooth muscle cells (VSMCs) [68]. On the other hand, overexpression of miRNA-1 (which was aberrantly downregulated in induced-hypertrophy model in mouse), prevented the hypertrophic growth of cardiac myocytes that were stimulated by endothelin-1 [67].

Cardiac fibrosis is an important contributor for the development of cardiac dysfunction in diverse pathological conditions, such as myocardial infarction (MI),

ischemic, dilated, hypertrophic cardiomyopathies, and HF and can be defined as an inappropriate accumulation of extracellular matrix proteins in the heart [69]. The exacerbated expression of extracellular matrix proteins is determinant in the differentiation between physiological and pathological CH [2]. In this sense, the negative regulation of miRNA-29 with anti-miRNAs *in vitro* and *in vivo* in a MI model induces the expression of collagens, whereas miRNA-29 overexpression in fibroblasts reduces this expression, suggesting this miRNA as a regulator of cardiac fibrosis [46]. Currently, the miRNA-29 family has been validated as a regulator of the gene expression of collagen I, III, fibrillin I, and elastin and is involved in pathological CH and the HF process [46, 51, 66]. In addition, decreased expression of the miRNA-29 family, miRNA-24, and miRNA-320 occurs after MI, and the decrease in miRNA-29 expression promotes fibrosis and scar formation in the heart [51].

Through microarray analysis, van Rooij et al. [56] related the miRNAs found both in response to hypertrophy and HF and identified more than 12 miRNAs dysregulated in the heart of mice. Many of these miRNAs were similarly regulated in failing human hearts. Interestingly, overexpression of miRNA-23a, miRNA-23b, miRNA-24, miRNA-195, or miRNA-214 induced hypertrophic growth in cardiomyocyte culture, whereas overexpression of miRNA-150 or miRNA-181b decreased cell size of the cardiomyocyte. The miRNA-23a knockdown attenuated hypertrophy [56] and the overexpression of miRNA-195 *in vivo* alone (transgenic mouse), was sufficient to lead to hypertrophy and HF [56]. The miRNA-23a is transcriptionally regulated by the nuclear factor of activated T cells, cytoplasmic 3 (NFATc3), which mediates the signaling pathway of cardiac stress. Thus, miRNA-23a overexpression can triggers a hypertrophic response by means of its target-gene muRF1 (muscle specific ring finger protein 1), an anti-hypertrophic protein, while negative regulation of miRNA-23a abolishes CH induced by isoproterenol in mice [70]. Other miRNAs exhibited pro-hypertrophic profile, including miRNA-208, -21, -18b, -27, and -9 [56].

Transgenic overexpression of miRNA-208a in the adult heart of mice is enough to induce hypertrophic growth, resulting in pronounced repression of regulatory target-genes, such as THRAP1 and myostatin (negative regulators of muscle growth and hypertrophy). In contrast, the deletion of cardiac miRNA-208a protects these animals from CH in response to hemodynamic cardiac stress by canceling the re-expression of fetal gene β-MHC [71]. In addition, therapeutic inhibition of miRNA-208 (by subcutaneous delivery of anti-miRNA-208a) reduces deleterious CR, improves cardiac function, and survival during HF in hypertensive rats [72]. Curiously, inhibition of cardiac-specific miR-208a may have therapeutic usefulness in a variety of metabolic disorders, such as obesity and type-2 diabetes in the setting of cardiac dysfunction by targeting and increasing MED13 in heart [73].

miRNA-199a is predominantly expressed in cardiomyocytes, where it maintains cell size and may play a role in the regulation of CH [56]. miRNA-199 is down-regulated under hypoxic conditions in cardiac myocytes (SIRT1) and hypoxia-1α inducible factor (HIF-α), an essential transcription factor for induction of the gene network of response to hypoxia. Thus, miRNA-24, miRNA-29, miRNA-199, and miRNA-320 represent potential therapeutic targets for ischemic injury in cardiac myocytes [51].

An overexpression of miRNA-22 was sufficient to induce pathological CH [74], showing itself as an essential miRNA for this process. On the other hand, the silencing of miRNA-22 in the heart of mice abolished CH and remodeling in response to two independent stressors: the infusion of isoproterenol and the activated calcineurin transgene. In addition, SIRT1 and HDAC4 were validated as target genes for miRNA-22 in the heart [74]. miRNA-155 is also required for the development

of CH in response to stress. In fact, the knockout of miRNA-155 in mice suppresses pathological CR, in addition to preventing the progression of HF [75].

The miRNA-34 family (miRNA-34a, -34b, and -34c) expression levels are elevated in both hearts of mice with cardiac stress and in aging process, as well as in patients with HF [76, 77]. In this way, inhibition with antimiR-34a/antimiR-34 has emerged as a promising therapeutic strategy [78]. miRNA-34a appears to be an essential regulator in cardiac repair and regeneration after MI in the heart. In fact, in a study by Yang et al., miRNA-34a mimic delivery limited cardiomyocyte proliferation and subsequent MI recovery in mice, whereas antimiR-34a treatment improved remodeling post infarction. Furthermore, in isolated cardiomyocytes, miRNA-34a directly regulated cell cycle activity and death, via modulation of its targets, which include Bcl2, Cyclin D1, and SIRT1 [79]. Thus, at first, modulation of miRNA-34a appears to be important in the process of repairing adult myocardium after injury. The study conducted by Baker et al. showed that miRNA-34a is induced by oxidative stress (OE) in patients with chronic obstructive pulmonary disease, reducing the gene expression of SIRT1 and SIRT6 in bronchial epithelial cells [80]. Thus, miRNA-34a antigens may have therapeutic potential in several pathological conditions, including CH.

In addition, Bernardo et al. [76] showed that only the inhibition of the whole miRNA-34 family, but not the inhibition of miRNA-34 alone, improves cardiac function in mice with preexisting hypertrophy induced by TAC and also attenuates the pathological remodeling of the LV after MI [76]. In this same work, four targets for miRNA-34 (vinculin, Sema4b, Pofut1, and Bcl6) were validated, which were positively regulated and associated with the cardiac protection found in both TAC and/or MI mice treated with the antimiR-34 LNA. Thus, the authors believe that, since LNA-based therapies have already entered clinical trials, inhibition of the entire miRNA-34 family has great therapeutic potential.

Therefore, it is clear that miRNAs play pivotal roles in cardiovascular development and disease [51, 56]. Recent evidences show that miRNAs are dynamically regulated by exercise [1, 54, 81]. Thus, the elucidation of the relationship between ET and miRNAs in heart in physiological and pathological (i.e., hypertension, HF, spinal cord injury, etc.) conditions is fundamental to understand how exercise regulates the cardiovascular system at the molecular level, which may be promising for the development of new drugs [2].

4.3 miRNAs regulation by exercise training in cardiac remodeling and heart diseases

The miRNA-1 and miRNA-133 are decreased in both aerobic treadmill-induced physiological hypertrophy and pressure overload-induced pathologic hypertrophy [64]. Additionally, swimming training is recognized for its efficiency in inducing myocardial hypertrophy and a significant increase in LV end-diastolic volume in rats [82]. In study conducted by Soci et al. [66], female rats were submitted to two swimming protocols (one moderate and other with high volume training to mimic an active individual and an elite athlete, respectively) for 10 weeks and developed physiological CH in a proportional way to the training volume. It was associated to a down regulation of miRNAs-1, -133a, and -133b in LV of trained rats also compared to sedentary group, which is inversely proportional to the physiological CH [66]. These results suggest that these myomiRs can be regulated by exercise, regardless of type (running or swimming) or volume (moderate and high) training, maintaining a similar expression profile [1]. Besides, Ma et al. [49] found that CH in rats induced by swimming exercise correlates with the modulation of other miRNAs, including miRNA-21, miRNA-124, miRNA-144, and miRNA-145 [49]. These miRNAs have as

validated targets Pik3a, PTEN, and TSC2, which are negative regulators of the PI3K/AKT/mTOR signaling pathway. Importantly, Liu et al. [5] showed that the inhibition of miRNA-222 *in vivo* completely blocked cardiac and cardiomyocyte growth in response to exercise while reducing markers of cardiomyocyte proliferation. Indeed, the authors revealed that miRNA-222 delivery was sufficient to protect the heart against dysfunction and adverse remodeling after ischemic injury [5].

In the same work cited before, Soci et al. [66] found an increase in miRNA-29c expression in LV in response to swimming training, which was inversely correlated with a decrease in both collagen I and III expression as well as in OH-proline concentration, being essential for the improvement of LV compliance observed in rats [66]. These findings exhibit an important integrative and regulatory role for miRNAs in the fibrotic response of trained heart.

Other work from our group showed that swimming training also causes an increase in miRNA-126 in the heart of rats, targeting and decreasing in expression of Spred-1, which contributes to angiogenesis in this tissue [83]. Although Pi3kr2 is also a well-validated target for miRNA-126, it was not altered by the swimming protocol. Physiological CH also involves the regulation of some miRNAs related to increased expression of angiotensin receptor-1 (AT1R), regardless of the participation of Ang-II. In parallel, increased angiotensin-converting enzyme 2 (ACE2), angiotensin (1–7), and Ang-II receptor in heart, suggest that miRNAs are involved in the regulation of the non-classical renin-angiotensin-aldosterone system (RAAS), counteracting the classic cardiac RAAS in CH [2, 54]. Fernandes et al. [54] evaluated that swimming alter the expression of cardiac miRNAs targeting the components of the RAAS, which were associated with the development of ventricular CH in rats [54]. In fact, swimming training increased the expression of miRNAs-27a and 27b by targeting the angiotensin-converting enzyme (ACE) and decreased miRNA-143 expression by targeting ACE2 in the heart of healthy rats.

Differently from which is found in pathological CH [61], high volume ET decreases the expression of cardiac miRNA-208a in healthy, induces the upregulation of targets such as THRAP-1, Purβ, and Sox6, and improves the balance between βMHC and αMHC gene expression [2, 84]. In addition, in recent study, Fernandes et al. [85] showed that aerobic ET prevents weight gain and pathological CH in obese Zucker rats, via increase of cardiac MED13 by regulation of miRNA-208. Thus, miRNA-208 represents a potential potent therapeutic target for modulation of cardiac function and remodeling during progression of heart disease.

In addition, the study conducted by Fernandes et al. [86] showed that swimming training reestablishes the peripheral levels of the -16, -21, and -126 miRNAs associated with revascularization in hypertension. This alteration was accompanied by normalization of vascular endothelial growth factor (VEGF), endothelial nitric oxide synthase (eNOS), and phosphatidylinositol-3 kinase regulatory subunit (PI3KR2) in parallel to a normalization of pro-apoptotic (Bad) and anti-apoptotic mediators (Bcl-2, Bcl-x, and p-Badser112: Bad ratio) [86].

Swimming ET restores the miRNA-29a and miRNA-29c levels of the heart and prevents the deposition of type I and III collagen in the border zone as well as in remote regions of the infarcted myocardium of rats, which can contribute to the improvement of the ventricular function induced by the aerobic training [87]. Cardiac fibrosis, which impairs cardiac contractility, is a major aspect of the remodeling process after MI. Impaired cardiomyocyte contractility and calcium transient are hallmarks of LV contractile dysfunction [88]. In this sense, Melo et al. [81] showed that moderate aerobic ET also restores cardiac Ca^{2+} transient after MI, regulating miRNA-1 and miRNA-214 levels [81]. Additionally, resistance training has been shown to induce CH, with improved cardiac function of isolated cardiomyocytes, which is partially explained by the decrease of miRNA-214 and

the increase of gene SERCA2a expression [81]. There are few studies that demonstrate the protective role of resistance training in heart through changes in miRNA expression pattern. Thus, there is a potential role of these miRNAs in promoting cardioprotective effects on CR.

5. Vascular, exercise, and miRNAs

The vascular disease in its various forms is one of the leading causes of death worldwide, and in accordance with the projection of the World Health Organization, this number only increases in the next 30 years [89]. ET prevents the progression of vascular diseases and reduces cardiovascular morbidity and mortality. ET also ameliorates vascular changes including endothelial dysfunction and arterial remodeling and stiffness, usually present in type 2 diabetes, obesity, hypertension, and metabolic syndrome [90].

Although there are major advances in the surgical area, the great challenge that anyone who presents a framework of CVD remains the prevention of this disease. Currently, there are some ways to alleviate this disease such as the use of beta-blockers, ACE inhibitors, statins; all these strategies are for mitigate the risk factors such as hypertension and dyslipidemia. Already in more severe cases, surgical procedures such as coronary artery bypass grafting, angioplasty (in severe cases of atherosclerosis), and others are performed [91–93].

Despite these strategies of mitigate the risk factors, this is still not enough since the rate of individuals affected and morbimortality has been increasing in relation to this class of diseases. So, the search for new therapies and approaches to prevent the onset and reduce the progression of vascular disease is desperately needed. Therefore, the processes time consuming since the mechanisms involved in this disease are not yet fully understood.

Atherosclerosis is the main cause of CVD. This is a chronic inflammatory disease that affects the blood vessels and arteries of medium or large size, usually in the areas of bifurcation, due to the non-laminar flow, leading to an endothelial dysfunction due to chronic exposure to pro-inflammatory molecules, and also to an inhibition of anti-inflammatory molecules, such as NO, this causes a narrowing of the arterial lumen due to atheroma plaque, impeding blood flow [94, 95].

In this disease, the blood flow changes from laminar to turbulent, due to the narrowing of the vascular lumen, the endothelial cells (EC) respond to this flow, that is, to the shear stress, this response is due to mechanosensors genes present on the cell surface and also the activation of the adhesion molecules and other inflammatory cytokines that are activated to alleviate the excess of cholesterol low-density lipoprotein (LDL) that is encompassed in the vascular intima [96–98].

Another important factor that has been widely studied in vascular diseases and in atherosclerosis are the miRNAs, which can regulate the cellular phenotype of both VSMCs and EC, such as the proliferation, migration, and cell growth, and can also regulate the handling of lipids and inflammatory molecules [99–101].

5.1 miRNA-126

miRNA-126, for example, can regulate both inflammation and angiogenesis (the process of new vessel formation). This miRNA is basically expressed in platelets and EC, which in turn play an important role in the blood circulation, as well, regulating vascular tone, recruitment of other cells, and even vascular homeostasis [102, 103], and the transcription of this miRNA is regulated by the transcription factor Ets1, which is known for their role in specific gene expression in EC [104]. Harris et al.

[104] demonstrated that miRNA-126 negatively regulates the vascular cell adhesion molecule (VCAM-1). This protein mediates the adhesion of lymphocytes, monocytes, eosinophils, and basophils of the vascular endothelium, thus interfering with the adhesion of leukocytes induced by tumor necrosis factor (TNF) in the endothelium, which may decrease leukocyte infiltration in the vascular wall and also in the interaction of leukocytes with EC [104].

This miRNA can influence the reduction of apoptotic cells contained in the vascular thrombus, softening the inflammatory reaction characteristic of atherosclerosis; so the miRNA-126 has an anti-atherosclerotic effect, which is also related to the G 16 protein signaling regulator, which results in recruitment of circulating progenitor cells, leading to stabilization of atherosclerotic plaque [105, 106]. Studies show that on deletion of this miRNA, vascular integrity decreases; in the case of infarcted individuals, a defect in cardiac neovascularization occurs [107].

This miRNA may be pro-angiogenic because of its binding to the PI3K pathway, which is important in regulating mitogenesis, cell differentiation, and insulin-stimulated glucose transport, and mitogen-activated protein kinases (MAPKs) that respond to extracellular stimuli and regulate various cellular activities such as gene expression, mitosis, differentiation, cell survival, and apoptosis. PI3K pathway promotes the suppression of the sprouty-related EVH1 domain containing protein-1 protein (Spred-1) that generally inhibits the signaling pathway [108–111].

Recent studies showed that the miRNA-126 levels in the circulatory system increase to varying degrees after different ET protocols [1]. It is already known that regular aerobic exercise has a positive effect on arterial endothelial function, mainly by increasing circulating NO and reducing endothelin-1. Aerobic exercise can also improve vascular endothelial and mitochondrial function to protect blood vessels, thus reducing the incidence of CVD [83, 112, 113].

Recent study demonstrated that the plasma levels of miRNA-126 were increased in obese subjects after an acute aerobic exercise session [114] Already noted that improvement of vascular endothelial function in adolescents after 6 weeks of aerobic exercise combined with dietary control may be related to changes in serum level miRNA-126, this improved peripheral vasodilator capacity, indirectly reflecting the improvement of vascular endothelial function in obese adolescents [115]. This increase of serum levels of the miRNA-126 through ET represents the beneficial aspects for obese individuals and associated diseases such as CVD. This may be related to the increase of NO provided by physical training, which is already well established in the literature, that aerobic exercise increases the expression and phosphorylation of endothelial nitric oxide synthase (eNOS) and with that the levels of oxidative stress decreased, leading to an increase in the use of NO and an increase in vascular function [90, 102, 116–118].

5.2 miRNA-21

miRNA-21 regulates cell proliferation through your gene target PTEN, which is a protein that acts as phosphatase and operates primarily on dephosphorylation in the PI3K/Akt signaling pathway. PTEN suppresses Akt signaling, which decreases the activity of eNOS and PTEN also inhibits the expression of VCAM-1 in EC stimulated by TNF-α [119]. A pathological condition that increases the expression of the miRNA-21 is shear stress in your state turbulent flow [120]. miRNA-21 also contributes to phenotypic change in EC, which is induced by transforming growth factor β (TGF-β) [121]. These data indicate that miRNA-21 modulates vascular homeostasis through PTEN and Akt.

Although miRNA-21 has been involved in promoting the proliferation of VSMCs in response to a series of models of vascular mechanical injury, its role remains to be defined in the formation of atherosclerotic lesion [68]. miRNA-21 also mediates VSMC differentiation from the contractile phenotype to the synthetic through TGF-β and BMP signaling in a single posttranscriptional processing step, implying that Smad proteins can control the maturation of miRNAs [122].

It was demonstrated by [86] that aerobic ET has a beneficial effect on the regression of arterial hypertension, restoring the normal expression of miRNA-16, -21, and -126 of skeletal muscle microcirculation, normalization of levels of VEGF, eNOS, and PI3KR2, as well as proapoptotic (bad) and antiapoptotic mediators (Bcl-2, Bcl-x, and p-Badser112: Bad ratio), indicating that the balance between angiogenesis and apoptotic factors that can prevent microvascular abnormalities in rats hypertensive, demonstrating once again the protective effect of aerobic physical training.

5.3 miRNA-221/222

The miRNA-221/222 is expressed in EC, VSMCs, and hematopoietic cells. It has been shown that the endothelial progenitor cells of patients with coronary artery disease have an increased expression of these miRNAs, these cells have a factor important in endothelial integrity and vascular repair [123]. One of the target genes of these miRNAs is signal transducer and activator of transcription 5A (Stat5A), a transcription factor involved in the regulation of cell proliferation and migration, it has been identified that Stat5A is negatively regulated by miR-222 and it has been observed in EC of atherosclerotic lesions that Stat5A is low expression, so it is possible that Stat5A may be a new therapeutic target for atherosclerosis [103, 123, 124].

The study by Liu et al. [123] also demonstrated that miRNA-221/222 has opposite biological functions depending on the cell; the study observed that inhibition of miRNA-221/222 is able to increase reendothelization, whereas in VSMC neointimal formation was significantly reduced. Thus, miRNA-221/222 could be an ideal therapeutic target in patients with atherosclerosis, angioplasty, stent implantation, or myocardial revascularization surgery [123].

5.4 miRNA-146a

The increased expression of the miRNA-146a has been observed in vascular injury after balloon angioplasty. This miRNA can mediate cell-to-cell communication between VSMCs and CE and also other cell types in the vessel wall [125]. A study by Sun et al. [126] attested that transcription of miRNA-146a is regulated by the transcriptional factors KLF-4 (Krüppel-like factor 4) and KLF-5 (Krüppel-like factor 5) and they play an important role in promoting proliferation of VSMCs (*in vitro*) and when the carotid artery is injured with a balloon catheter there occurs a hyperplasia of the neointima (*in vivo*) [126]. Ji et al. [68] also found an increase in miRNA-146a in injured arteries, resulting in a remarkable formation of neointima. In this study, the expression of several miRNAs in the wall of the vessel after angioplasty was observed for the first time [68]. In the study by Chen et al. [127], several miRNAs have been shown to play roles such as proliferation, cell differentiation, and apoptosis in the inflammatory responses of monocytes and macrophages with stimulation of oxidized LDL that are primordial in the development of atherosclerosis [127].

Cao et al. [128] observed that levels of miRNA-146a and miRNA-21 were increased in atherosclerotic plaques and that these miRNAs suppress the expression of Notch2 (neurogenic locus notch homolog protein) which is a membrane protein, and Jag1 (Jagged1) is a cell surface protein [128]. These provide important negative feedback on the proliferation of VSMCs in response to vascular injury, so inhibitions of these miRNAs may present a new strategy for the prevention of fibroproliferative vascular diseases.

5.5 miRNAs-143/145

The miRNAs-143/145 have an important role in the differentiation of VSMC as well as miRNA-146a, with a critical role in cell phenotype change [129, 130]. Boettger et al. [130] demonstrated that the detection of miRNA-143 and miRNA-145 altered the VSMC phenotype from contractile (physiological) to synthetic (pathological), in which this led to neointimal formation in elderly mice [130]. Another study highlighted the suppression of these miRNAs in human aneurysms [131]. Several targets of miRNA-143 and miRNA-145 have been reported in which they regulate the functions of VSMCs, for example, the transcription factors KLF-4 (Krüppel-like factor 4), myocardin, Elk-1 (ELK1, ETS member of the family of oncogenes), and KLF5. In addition, the ACE has been shown to contribute to vascular tonus dysregulation and to reduce blood pressure in mice with high expression of miRNA-143/145 [129, 130]. Thus, these miRNAs through their targets are antiatherosclerotic and have the function of regulating the phenotype of the VSMCs and inhibit the formation of neointima.

5.6 Others miRNAs

Other miRNAs are also involved with EC and VSMCs like miRNA-27b and let-7. Kuehbacher et al. [103] demonstrated that inhibition of miRNA-27b and let-7f in the EC significantly reduced the onset of the endothelium, therefore when these miRNAs are with increased expression, it is suggested that it has a pro-angiogenic action [103]. It has also been observed that shear stress increases the expression of miRNA-27b supporting an activity endothelial protection [132]. Other miRNA vascular protector is the miRNA-296 which regulates directly the substrate of tyrosine kinase regulated by the hepatocyte growth factor (HGS), a protein responsible for the degradation of pro-angiogenic receptors VEGFR2 and PDGFRβ, promoting angiogenesis [133, 134]. The miRNA-130a was also identified as angiogenic, targeting the homeobox anti-angiogenic GAX (homeobox-stop-growth), and HoxA5 proteins. It has been observed that miRNA-130a antagonizes the inhibitory effects of GAX on the proliferation, migration, and formation of EC [135].

That said, miRNAs are important regulators of vascular cell functions and contribute to many vascular diseases, such as coronary artery disease and, in general, atherosclerosis. It is supposed that the human genome encodes several miRNA genes, but only a few vascular-specific miRNAs have been identified so far. In addition, there is only some information about its specific functions of the cell type and target genes. Many studies have revealed an aberrant miRNA expression profile under pathological conditions. Thus, miRNAs can be used as new biomarkers and, on the other hand, may represent powerful new therapeutic targets. Several miRNA-based therapeutic strategies are used to modify miRNA expression as therapeutic approaches; one of miRNA modulators is physical training, as already mentioned in miRNAs-126 and 21.

6. Conclusions

ET, especially aerobic exercise, plays a protective role in the cardiovascular system and has been used as a non-pharmacological therapeutic tool for the prevention and treatment of CVD. Although much knowledge already exists, there is insufficient evidence to establish a direct link between epigenetic modulations and changes, caused by exercise, in the heart and blood vessels [42]. There is currently evidence that the protective effects of aerobic ET involve changes in pattern expression of specific miRNAs by positively regulating cardiovascular remodeling. In fact, miRNAs play important roles in the regulation of distinct processes in mammals, and although they exhibit limited complementarity with their target RNAs, it is still sufficient for them to regulate various physiological processes, including cell proliferation, differentiation, migration, angiogenesis, apoptosis, tissue development, and remodeling [14, 136, 137]. However, new studies to understand the pathways and mechanisms in which the ET acts on the miRNAs are required. Thus, studies with miRNAs hope to broaden the perspective of its use in the correction of pathological processes from miRNAs therapy, contributing as a therapeutic intervention in cardiovascular damages as well as for the survival and quality of life of patients.

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Conflict of interest

There are no conflicts of interest.

Notes/Thanks/Other declarations

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