Review Article

Non-coding RNAs in exercise

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Abstract: Regular exercise is a well-established intervention for chronic diseases. A variety of adaptive responses in multiple organ systems are involved in the biology of exercise. The beneficial effects of physical activity are well-documented, yet the molecular and cellular mechanisms for the adaptive response to physical activities remain incompletely described. Recent findings suggest a putative role of non-coding RNAs (ncRNAs), especially microRNAs (miRNAs, miRs), in the progression and management of the physical training related changes. A number of miRNAs has been identified as modulators of exercise induced adaption in skeletal muscle or heart. miR-1, miR-126, the miR-99/100 family, miR-181, miR-1 and miR-107 were increased while miR-23, miR-696 and miR-494 were decreased in skeletal muscle after exercise. miR-222, miR-27a, miR-27b, miR-29a, miR-21, miR-144, miR-145, miR-208a, miR-30e and miR-19b were upregulated while miR-143, miR-1, miR-133a, miR-133b, miR-124, miR-99b, miR-100, miR-191a, miR-22 and miR-181a were downregulated in heart after exercise. miR-126 was increased while miR-16 and miR-21 were decreased in vessels after exercise. In addition to tissue-specific miRNAs, an altered array of miRNAs in circulation has been described during exercise. Contrast to miRNAs, little is known about long non-coding RNAs (lncRNAs) in exercise. Identification the role of ncRNAs in exercise will improve our understanding of exercise physiology and has the potential to enhance the application of current therapeutic approaches.

Keywords: Exercise; non-coding RNAs (ncRNAs); microRNAs; long non-coding RNAs (lncRNAs)

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Introduction

The benefits of exercise on human health have been recognized for centuries (1-3). Exercise is an important component in the prevention and treatment of multiple chronic diseases including cardiovascular disease (CVD) (e.g., heart failure), metabolic disorders (e.g., diabetes, obesity) (4), neurological diseases (e.g., Alzheimer's disease) (5), musculoskeletal disorders (e.g., muscular atrophy) (6) and cancer (7). Exercise challenges whole-body homeostasis and provokes widespread perturbations in numerous tissues and organs following physical training (8). Movement begins via contracting myofibers and triggers a burst of metabolic and morphological adaptations in skeletal muscle. To meet the increased metabolic activity of contracting skeletal muscle, systematically coordinated organs (cardiovascular, respiratory, neural, and endocrine) supply the contracting muscles with more fuel and O_2 to sustain a given level of activity (9). Non-coding RNAs (ncRNAs) may act as mediators of physiological processes linked to exercise adaptation. This review aims to summarize these novel molecules and may eventually help develop ncRNAs as therapeutic targets for improving exercise capacity in patients with heart failure and other diseases (*Figure 1*).

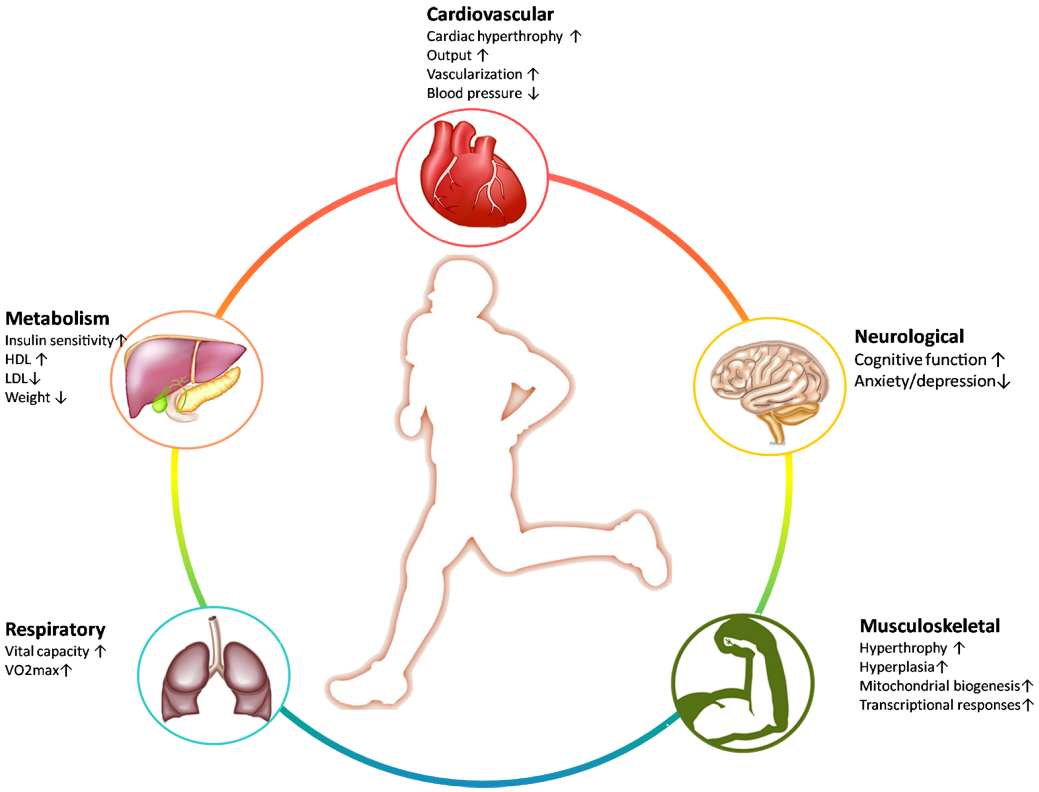

Figure 1 The benefits of exercise. HDL, high-density lipoprotein; LDL, low-density lipoprotein; VO_{2max}, peak oxygen consumption.

ncRNAs

ncRNAs, a group of small non-protein coding RNAs, account for the majority of all RNA transcripts in the cell. ncRNAs are a diverse group of endogenous RNA-based molecules, which include short (~22 nucleotides) microRNAs (miRNAs, miRs) and long non-coding RNAs (lncRNAs) (of >200 nucleotides) (10).

miRNAs, function as post-transcriptional repressors of gene expression by direct repression or mRNA decay in a sequence-dependent manner. As a class of regulatory molecules, miRNAs are intracellular mediators of adaptive processes, including muscle atrophy (11), CVD (12), aging (13) and cancer (14). The maturation process of miRNAs is an enormous and complex network requiring co-ordination of pri-miRNA transcription (15,16). This process includes cleavage by endonucleases, exportation from nucleus to cytoplasm (17), additional cleavage and then incorporation into the RNA-induced silencing complex (RISC) to inhibit target genes mRNA translation or promote mRNA degradation via canonical base-pairing to the 3'-untranslated (3'UTR) region (18). Most miRNAs are present in the genome as the form of single copy, or multiple copies or cluster (19). miR-1, miR-133a and miR-206 were highly enriched in both heart and skeletal muscle in human and mouse (20,21). Subsequent studies confirmed that a cluster of miRNAs including miR-1, miR-133a, miR-133b, miR-206, miR-208, miR-208b, miR-486, and miR-499 (22) were highly enriched in skeletal muscle, and have therefore been termed "myomiRs" (23). Growing evidences have showed that these muscle-specific miRNAs, along with other miRNAs affect exercise adjustment, suggesting the significance role of miRNAs in response to physical work (24).

Besides long protein-coding mRNAs and short noncoding transcripts, lncRNAs also play important roles in the regulation of cellular processes (25). The majority of lncRNAs are transcribed by RNA polymerase II and function as an additional regulator of the genome *via* multiple mechanisms (26). As transcriptional regulators, lncRNAs can modulate transcription initiation, elongation and termination (27). In addition, lncRNAs can also mediate gene expression in post-transcriptional processes such as splicing, transport, translation, stability of mRNA,

and subcellular localization of proteins (28-30). Indeed, a recent study has demonstrated that lncRNAs could act as cofactors, competitors, and/or decoys of RNA-binding proteins and miRNAs (31). A better understanding of how lncRNAs function can be utilized for locus-specific manipulation of gene expression is an important goal for current research efforts.

miRNAs in exercise

Recently, miRNAs adjustments in skeletal muscle (32), the heart (33) or the vasculature (34) have been widely reported, offering further support for the involvement of miRNAs in exercise adaptations. These studies have provided important pre-clinical evidence of potential therapeutic targets. Here, we will review miRNAs for their regulatory roles in physical fitness in these fields.

miRNAs in skeletal muscle adaption to exercise

The molecular basis of skeletal muscle adaptation to exercise is reflected by changes in contractile protein morphology and function (35), mitochondrial function (36), metabolic regulation, intracellular signaling and transcriptional responses including modification of MEF2, HDACs and NRFs. As the cellular composition of muscle, myofibers are the elementary units that make various adjustments after physical work to maintain optimal function including nerve stimulation, calcium signaling, and metabolic changes (37,38). Besides these well studied molecular mechanisms, experimental studies have identified fitness-related changes of miRNAs (39). In skeletal muscle, several miRNAs have been suggested to influence muscle myogenesis, muscle mass, and metabolism through their regulation of specific myogenic regulatory factors (MRFs) gene (40-42). Many are found to be dysregulated in skeletal muscle following physical training, which further supports the association of miRNAs with exercise-induced physiological changes and muscle function alteration (43). A more complete understanding of the miRNA biogenesis machinery following exercise in skeletal muscle may better guide the application of current therapies. Collectively, we summarize miRNAs function in muscle during physical training in the following sections.

miRNAs in skeletal muscle regeneration

Aging is associated with progressive changes in skeletal muscle mass and composition, which eventually results in the decline in muscle function, a process which universally affects patient mobility and quality of life. Exercise capacity is a well-known predictor of longevity. An upregulation of pri-miR-1 and pri-miR-133a has been identified in older men (44). Skeletal muscle expression of miR-1, which is responsible for muscle growth and satellite cell function, is elevated in young men but not older men after acute resistance exercise, demonstrating a divergent age-related muscle response after exercise. In addition, a novel role of the miR-126-IGF-1 axis has been identified in the control of exercise-induced adaptation of skeletal muscle, describing the dysregulation of this pathway in aging (45). Therefore, it appears that specific miRNAs may have an important role in the development of sarcopenia and, as such, may offer a source of novel therapeutics for the aging process.

Akt-mTOR signaling is attenuated during the onset and progression of age-related muscle wasting, however, it can be activated by resistance exercise (46). The miRNA species targeting the Akt-mTOR signaling have been investigated and it was found that 26 miRNAs were dysregulated with age and/or exercise (47). Among them, the miR-99/100 family of miRNAs notably emerged as potentially important regulators of Akt-mTOR signaling and muscle protein synthesis in response to resistance exercise in young and old subjects (47).

Taken together, these observations reveal how miRNAs, aging and exercise are interrelated and display the alteration of miRNAs by exercise may thus interfere with age-related muscle decline.

miRNAs in mitochondrial biogenesis

Physical exercise induces a range of signaling pathways, contributing to the metabolic and functional adaptations of skeletal muscle. PGC-1α is a key mediator of the transcriptional response in skeletal muscle to exercise, regulating mitochondrial metabolism, angiogenesis, β-oxidation and inflammation (48). Endurance exercise significantly increased the expression of miR-181, miR-1, and miR-107 and reduced miR-23 expression in C57Bl/6J wild-type male mice (49). miR-23-mediated post-transcriptional regulation of PGC-1α is potentially involved in the complex regulatory networks that govern skeletal muscle adaptation to endurance exercise (49). These findings of that study highlight the role of miRNAs in the control of PGC-1α-induced mitochondrial biogenesis in skeletal muscle post physical activity. Similarly, miR-696 was

markedly downregulated by exercise targeting PGC-1α and regulated skeletal muscle biogenesis of mitochondria and fatty acid oxidation (50). In murine myoblast C2C12 cells during myogenic differentiation, the expression of miR-494 was markedly decreased, accompanied by an increase in mtDNA and the expression of predicted target genes for miR-494, including mitochondrial transcription factor A (mtTFA) and Forkhead box j3 (Foxj3), key transcription factors of mitochondrial biogenesis (51). Interestingly, miR-494 expression was significantly reduced in C57BL/6J mice skeletal muscle in endurance exercise, suggesting the vital role of miR-494 in exercise induced mitochondrial biogenesis via mtTFA and Foxj3 *in vivo* (51). The mRNA regulation of components of the miRNA biogenesis pathway (Drosha, Dicer and Exportin-5), muscle enriched miRNAs, (miR-1, miR-133a, miR-133b and miR-206), and several miRNAs dysregulated in muscle myopathies (miR-9, miR-23, miR-29, miR-31 and miR-181) was determined, and it was found that following an acute short-term exercise, the miRNA biogenesis pathway, as well as miR-1, miR-133a, miR-133b and miR-181a were all increased, while miR-9, miR-23a, miR-23b and miR-31 were decreased (52).

Expression of myomiRs, including miR-1, miR-133a, miR-133b and miR-206, were decreased after 12 weeks of endurance training in human muscle biopsies (53). Following 14 days after regular training, the levels myomiRs returned to baseline (53). Currently, the specific details of myomiRs directly alter human physiology in response to endurance exercise remains unknown. The details by which myomiRs alter human physiology in response to endurance exercise remain unknown.

However, it appears that exercise-induced miRNA alterations may be involved in the regulation of fundamental processes such as skeletal muscle regeneration, gene transcription and mitochondrial biogenesis, thereby contributing to skeletal muscle adaptation to exercise.

miRNAs in cardiovascular adaption to exercise

Exercise stimulates the hearts of athletes, resulting in physiological cardiac hypertrophy (54). In addition, exercise has been reported to provide sustainable protection against myocardial infarction (55) and ischemia-reperfusion injury (56). In contrast to pathological cardiac hypertrophy, which is featured with poor prognosis and heart failure (57), exercise-induced cardiac hypertrophy is generally accepted as protective, in some instances improves cardiac function, and does not progress to heart failure. This physiologic cardiac adaptation is characterized by an increase in heart size and cardiac output, resistance to and recovery from injury, and improved vascularization (3,33,57,58). Recently, miRNAs have received increasing attention in physical activity and cardiovascular health (59). The identification of miRNAs differentially regulated during physiological growth may open new therapeutic approaches for heart failure.

miRNAs in cardiac growth

Recently, miRNAs screening identified differentially expressed miRNAs that occur in response to physical training, and miR-222 was found to be upregulated in two distinct models of exercise (60). Circulating miR-222 increased in heart failure patients undergoing cardiopulmonary exercise testing. Inhibition of miR-222 by anti-miRs *in vivo* prevented exercise-induced cardiac growth. miR-222 cardiac overexpression mice were protected against ischemia-induced cardiac dysfunction and remodeling, implying a therapeutic cardioprotective role of miR-222 (61). Pathological left ventricular hypertrophy (LVH) is associated with increased local cardiac the renin angiotensin system (RAS) levels, represented by augmented angiotensinogen, angiotensin-converting enzyme (ACE) and angiotensin II (Ang II). Angiotensin-converting enzyme 2 (ACE2), a novel cardiac RAS, can maintains the important balance between the Ang II and Ang [1–7], favoring cardiovascular homeostasis. Swimming exercise training could decrease cardiac ACE and Ang II levels and increase ACE2 and Ang [1–7] levels (62). In addition, aerobic exercise training increased miR-27a and miR-27b, targeting ACE and decreased miR-143 targeting ACE2 in the heart, contributing to physiological LVH (62). miR-29 has also been reported to be decreased in cardiac hypertrophy induced by exercise in rat (63). Microarray analysis demonstrated downregulation of miR-1, miR-133a, and miR-133b and upregulation of miR-29a, however, only expression of miR-29a was associated with a significant decrease in LV collagen and an inverse correlation with hydroxyproline concentration indicating improved LV compliance and beneficial cardiac effects (63). The activation of PI3K/AKT/mTOR plays a critical role in the induction of physiological, but not pathological, cardiac hypertrophy (64-67). Recent work has suggested that the expression of miR-21, miR-144, and miR-145 were up-regulated in swimming exercise training-induced left ventricular remodeling while miR-124 was decreased (68).

Moreover, they found that those miRNAs targeting the PI3K/AKT/mTOR signaling pathway and its negative regulators. A link between miRNAs and the PI3K/AKT/mTOR pathway has also been discovered in a rat model of cardiac hypertrophy induced by chronic swimming, in which miR-208a, miR-133b, miR-30e and miR-19b were upregulated, while miR-99b, miR-100, miR-191a, miR-22 and miR-181a were downregulated (69). Most of these miRNAs (e.g., miR-99, miR-100, miR-208, miR-181 and miR-19) were also associated with cardiac hypertrophy and apoptosis, principally acting *via* PI3K/Akt/mTOR and MAPK signaling pathways (69). A better understanding of miRNAs and the cellular pathways regulating exercise induced physiological cardiac hypertrophy may also assist in the development of treatments for CVD. Recently, a global analysis of miRNA expression in exercise-induced LVH identified an increase in miR-150 levels after 35 days and a decrease in miR-26b, miR-27a and miR-143 after 7 days of voluntary exercise (70). Further studies are needed to validate the targets of these miRNAs and to determine their functions in cardiac adaptation to physical training.

miRNAs in vascular remodeling

miR-126 and its validated targets, Sprouty-related protein 1 (Spred-1) and phosphoinositol-3 kinase regulatory subunit 2 (PI3KR2), were demonstrated to negatively regulate angiogenesis via the VEGF pathway inhibition in a rat model of swimming (71). In consist with it, hypertensive rats undertaking 10 weeks of swimming reduced blood pressure and heart rate, the expression of anti-angiogenic miRNAs miR-16 and miR-21 decreased in the soleus muscle, while miR-126 increased (72). Furthermore, physical activity increased angiogenic factors—VEGF, PI3KR2, and endothelial NO synthase (eNOS) in hypertension and inhibited apoptotic signaling (bcl2). Additionally, it was clearly indicated that exercise-induced angiogenic miRNAs influenced vascular disease, correcting capillary rarefaction and changes in fiber type distribution in hypertension and promoting a balance between angiogenic and apoptotic factors to prevent microvascular abnormalities in hypertension (72).

Circulating miRNAs (ci-miRNAs) adaption to exercise

Recently, several studies have demonstrated that miRNAs can be detected in the circulatory system and have been identified as a potential new class of biomarkers for health and disease (73-75). Mature miRNAs are released into body fluids by extracellular vesicles (76) or associated with RNA-binding proteins such as Argonaute2 (77) or lipoproteins such as HDL/LDL (78) secreted from various cell types including skeletal muscle (79). ci-miRNAs deliver the vesicle content to specific recipient target cells, exerting a paracrine function (80). It has been reported that exercise not only affects miRNA expression in the tissue but also in the circulation. ci-miRNAs can be easily sampled by body fluid and are stable following freezing, thawing, and temperature changes. Physical activity is associated with altered levels of ci-miRNAs, indicating that ci-miRNAs can be used as biomarkers to monitor such conditions (34).

To find exercise-associated alteration in ci-miRNAs expression in human, a profile of specific ci-miRNAs involved in angiogenesis (miR-20a, miR-210, miR-221, miR-222 and miR-328) (81), inflammation (miR-21 and miR-146a) (82), skeletal and cardiac muscle contractility (miR-21 and miR-133a) (83,84), and hypoxia/ischaemia adaptation (miR-21, miR-146a and miR-210) (85,86) have been analyzed in healthy competitive athletes before, during, and after acute exhaustive exercise testing. The levels of miR-20a, miR-21, miR-146a, miR-221 and miR-222 have been reported to be elevated in plasma after a 90-day period of aerobic exercise training. Among those miRNAs, they observed that peak levels of miR-146a and miR-20a positively correlated to peak oxygen consumption (V_{O2max}), providing a feasible method of using ci-miRNAs as a biomarker of physical fitness (87). Later, if muscle-specific (miR-1, miR-133a, miR-133b, miR-208a, miR-208b, and miR-499) or muscle-related (miR-181 and miR-214) miRNAs were involved in physical activity was investigated. It was found that plasma levels of miR-1, miR-133a, and miR-133b were significantly increased 2 to 6 h after exercise, with a larger response following downhill training, while miR-181b and miR-214 were transiently up-regulated at the end of uphill exercise training (88). Other studies have been conducted to measure changes in muscle enriched ci-miRNAs in response to exercise. Circulating miR-486 (c-miR-486) was found to decrease after acute and chronic exercise, while other muscle enriched miRNAs such as miR-1, miR-16, miR-133a, miR-133b, miR-206, miR-208b and miR-499, have been difficult to measure due to low base-line expression levels. c-miR-486 displayed an inverse correlation with V_{O2max}, suggesting that reduction of c-miR-486 mediates metabolic changes during physical exercise (89). In contrast with previous

studies, another study evaluated the ci-miRNA profile after aerobic fitness and showed that the circulating levels of miR-149* increased, whereas miR-146a and miR-221 were significantly decreased. The microarray analysis revealed no changes in circulating levels of muscle specific miRNAs following acute resistance exercise. These differences imply that the changes in ci-miRNAs may be strongly influenced by exercise type, duration, and intensity (90).

To test the effect of physical work on endothelial cell damage, miR-126, as a marker for endothelial injury, was assessed by PCR analysis in plasma samples from healthy individuals following different endurance exercise tests, including maximal symptom-limited exercise test, bicycling, marathon, and resistance exercise. Circulating miR-126 increased in endurance exercise protocols as we mentioned above, providing evidence of endothelial damage caused by endurance exercise (91). Moreover, eccentric resistance training was found to cause increased levels of miR-133. Marathon completion leads to significant skeletal muscle damage, cardiac muscle stress/injury, and systemic inflammation, as reflected by statistically significant increases in circulating conventional biomarkers, including miRNAs. A cohort of miRNAs is involved in the dynamic regulation of ci-miRNAs before and after completion of prolonged, submaximal aerobic training (i.e., marathon run). ci-miRNAs enriched in muscle (miR-1, miR-133a, miR-499–5p) and cardiac tissue (miR-208a) display extremely low expression levels in plasma under resting conditions before marathon running, whereas ci-miRNAs enriched in the vascular endothelium (miR-126) and inflammatory miRNAs (miR-146a) are expressed at relatively higher levels (92). All candidate ci-miRNAs were found to be disproportionately increased immediately after the marathon and declined to pre-race levels or lower after 24 h of race completion. Another recent report of heart/muscle specific miRNAs in human before, directly after, and 24 h after a marathon run demonstrated a significant increase of miR-1, miR-133a, miR-206, miR-208b, and miR-499 (93). However, miR-499 and miR-208b returned to baseline, whereas the others were still raised 24 hours later. Significant correlations between V_{O2max}, running speed at individual anaerobic lactate threshold (VIAS) and miR-1, miR-133a, miR-206, and the athlete's aerobic performance capacity were found. In contrast, the expression of fibrosis/inflammation-associated miR-21 and miR-155 were not affected by exercise. Using a global ci-miRNA screen in young healthy men following an acute endurance exercise or 12-week endurance training, levels of ci-miRNAs including miR-338-3p, miR-330-3p, miR-223, miR-139-5p, miR-143 and miR-1 were found to be increased while the level of eight ci-miRNAs (miR-106a, miR-221, miR-30b, miR-151-5p, let-7i, miR-146a, miR-652 and miR-151-3p) decreased after acute exercise. Chronic alterations of ci-miRNAs in response to a 12-week endurance training have also been measured. Seven ci-miRNAs significantly decreased (miR-342-3p, let-7d, miR-766, miR-25, miR-148a, miR-185 and miR-21), while two ci-miRNAs significantly increased after the training period (miR-103 and miR-107) (94). As mentioned above, moderate aerobic exercise has been associated with strong anti-inflammatory mechanisms. The global response of circulating inflammation-related miRNAs (c-inflammamiRs) in response to different doses of acute exercise was investigated. The profiles of c-inflammamiRs before, immediately after, and 24 hours after participants ran 10-km and marathon races showed an increase in miR-150-5p immediately after the 10-km race while levels of 12 c-inflammamiRs were increased immediately after the marathon (let-7d-3p, let-7f-2-3p, miR-125b-5p, miR-132-3p, miR-143-3p, miR-148a-3p, miR-223-3p, miR-223-5p, miR-29a-3p, miR-34a-5p, miR-424-3p and miR-424-5p) (95). Taken together, these results indicate a clear dose-dependent effect of aerobic exercise on systemic inflammation and c-inflammamiR responses.

It has long been recognized that physical exercise has important benefits for diabetes. miR-192 and miR-193b have been identified as significantly increased in the prediabetic state but not in diabetic patients (96). Furthermore, circulating levels of miR-192 and miR-193b return to baseline in both prediabetic humans and glucose-intolerant mice undergoing chronic training, suggesting it may be a novel maker of pre-diabetes and a leading indicator for therapeutic exercise intervention.

These results suggest the possibility of ci-miRNAs as an alternative, non-invasive and real-time circulating biomarker for exercise-induced tissue adaptation (*Tables 1* and 2, *Figure 2*).

lncRNAs and exercise

Although only a small number of functional lncRNAs have been well characterized to date, they can function via numerous paradigms and are key regulatory molecules in the cell. The discovery of lncRNAs highlights the rising interest in the roles of lncRNAs as a potentially new and crucial frontier for health and diseases. Recently, a

Table 1 MicroRNAs expression is influenced by differences exercise type, duration, intensity and tissue

Ref.	Tissues	Model	Duration	MicroRNAs
Baggish *et al*., 2011	Plasma	Rowing training	90 days	miR-20a, -21, -146a, -221, -222↑
Banzet *et al*., 2013	Plasma	Walking exercises	2/6/24/48/72 h	mir-1, -133a, -133b,-181b, -214,
Russell *et al*., 2013	Muscle	Cycling exercise	3 h	miR-1, -133a, -133-b, -181a,; miR-9, -23a, -23b, -31↓
		Short-term training	10 days	miR-29be; miR-31↓
Aoi *et al*., 2013	Plasma	Cycling exercise	3 h/24 h/4 weeks	miR-486↓
Sawada *et al*., 2013	Plasma	Bench/leg press	0 h/1 h/1 day/3 days	miR-149*↑; miR-146a, -221↓
Uhlemann *et al*., 2014	Plasma	Maximal symptom limited exercise test		miR-126
		Limited exercise test, bicycling		miR-126
		Marathon; resistance exercise		miR-126,-133e; miR-133,
Baggish *et al*., 2014	Plasma	Marathon	0/24 h	miR-1, miR-133a, -208a, -146a, -134, -126, 499–5p↑
Mooren *et al*., 2014	Plasma	Marathon	0/24 h	miR-1, -133a, -206, -208b, -499↑
Nielsen *et al*., 2014	Plasma	Cycle ergometer exercise	0/1/3 h	miR-338-3p, -330-3p, -223, -139-5p, -143 ,-1↑; miR-106a, -221, -30b, -151-5p, -146a, -652, -151-3p, let-7i6
			12 weeks	miR-103, -107↑; miR-342-3p, -766, -25, -148a, -185, -21, let-7d↓
de Gonzalo-Calvo *et al*., 2015	Plasma	Marathon		let-7d-3p, let-7f-2-3p, miR-125b-5p, -132-3p, -143-3p, -148a-3p, miR-223-3p, -223-5p, -29a-3p,-34a-5p, -424-3p, -424-5p↑
Parrizas *et al*., 2015	Plasma			miR-192, -193b9
Rivas *et al*., 2014	Muscle	Resistance exercise		miR-126n
Safdar *et al*., 2009	Muscle	Running	3 h	miR-181, -1, -107↑; miR-230
Aoi *et al*., 2010	Muscle	Running	4 weeks	miR-21g; miR-696l
Nielsen *et al*., 2010	Muscle	Endurance training	10 weeks	miR-1, -133a, -133b a, -206↓
Fernandes *et al*., 2012	Muscle	Swimming	10 weeks	miR-126s; miR-16, -21↓
D. A. Silva ND *et al*., 2012	Muscle	Swimming	10 weeks	miR-126s
Yamamoto *et al*., 2012	Muscle	Swimming	10 weeks	miR-494s
Russell *et al*., 2013	Muscle	Endurance training	3 h/10 days	miR-1, -133a, -133-b , -181a↑; miR-9, -23a, -23b, -31↓
Liu *et al*., 2015	Cardiac samples	Running or swimming	3 weeks	miR-222 ↑
Fernandes *et al*., 2011	Cardiac samples	Swimming	10 weeks	miR-27a,-27bl; miR-143,
Soci *et al*., 2011	Cardiac samples	Swimming	10 weeks	miR-29as; miRNAs-1, -133a, -133b↓
Ma *et al*., 2013	Cardiac samples	Swimming	8 weeks	miR-21, -144, -145↑; miR-124
Martinelli *et al*., 2014	Cardiac samples	Metal wheels	7/35 days	miR-150h; miR-26b, -27a, -143↓
Ramasamy *et al*., 2015	Cardiac samples	Swimming	8 weeks	miR-208a,-133b,-30e,-19b1; miR-99b, -100, -191a, -22, -181a↓

Table 2 Potential roles of major microRNAs in response to exercise

MicroRNAs	Regulation	Target	Outcome	Ref.
miR-126	Up	IGF-1	Skeletal muscle regeneration	(45)
miR-99/100	Up	Akt-mTOR signalling	Skeletal muscle regeneration	(47)
miR-23	Up	PGC-1α	Skeletal muscle mitochondrial biogenesis	(49)
miR-696	Up	PGC-1α	Skeletal muscle mitochondrial biogenesis	(50)
miR-494	Up	PGC-1α	Skeletal muscle mitochondrial biogenesis	(51)
miR-222	Up	P27/Hipk1/Hmbox1	Cardiac hypertrophy	(62)
miR-27a/b	Up	ACE	Cardiac hypertrophy	(63)
miR-143	Down	ACE2	Anti-cardiac Hypertrophy	(63)
miR-21/miR-144	Up	Pten	Cardiac hypertrophy	(69)
miR-145	Up	TSC2	Cardiac hypertrophy	(69)
miR-124	Down	PIK3α	Anti-cardiac Hypertrophy	(69)
miR-126	Up	Spred-1/ PI3KR2	Angiogenesis	(72,73)
miR-16	Down	VEGF /Bcl-2	Anti-angiogenesis/apoptosis	(73)
miR-21	Down	Bcl-2	Apoptosis	(73)

PIK3α, phosphoinositide-3-kinase catalytic alpha polypeptide; PTEN, phosphatase and tensin homolog; TSC2, tuberous sclerosis complex 2; Spred-1, sprouty-related protein 1; PI3KR2, phosphoinositol-3 kinase regulatory subunit 2; Hipk1, homeodomain interacting protein kinase 1;Hmbox1, homeobox containing 1.

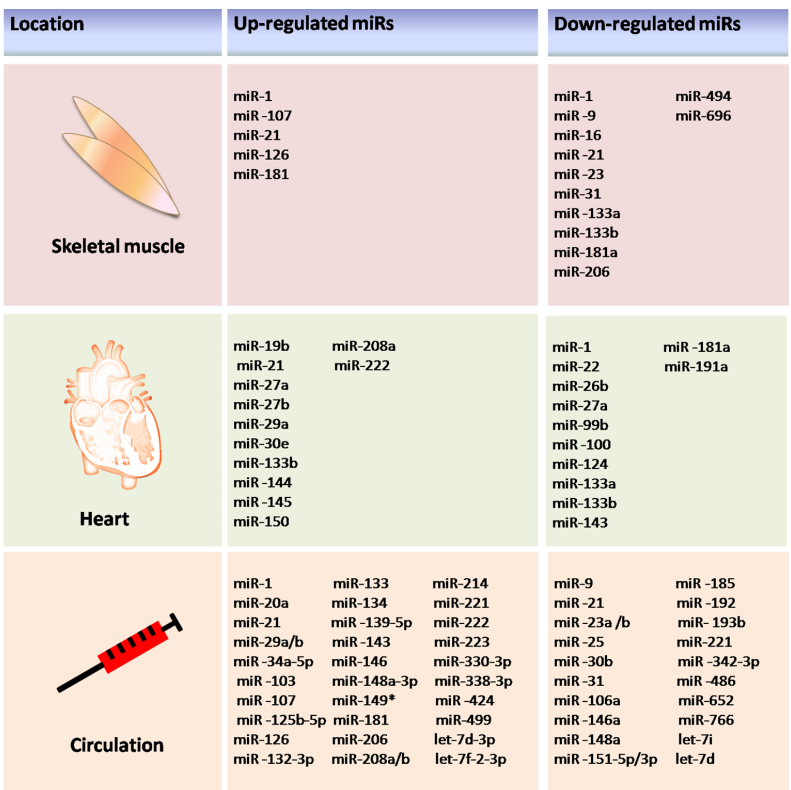

Figure 2 Regulation of microRNAs by exercise in skeletal muscle, heart and circulation.

conserved skeletal muscle-specific micropeptide, named myoregulin (MLN), encoded by a putative lncRNA, was discovered (97). MLN was embedded in the SR membrane, colocalized with SERCA1 and regulated Ca^{2+} handling by inhibiting SERCA pump activity. MLN KO mice showed improved exercise performance and Ca^{2+} handling in muscle. Those data linked the association of lncRNAs and skeletal muscle in physical training. Further studies to fully understand the role of lncRNAs for exercise will be of particularly interest.

Conclusions

Regular exercise directly alters skeletal muscle function, nutrient metabolism and muscle strength, along with reducing the risk of CVD, type 2 diabetes, and certain types of cancer. miRNAs have provided new insight into the understanding of the molecular mechanisms underlying exercise induced adaptations in skeletal muscle, the heart or the vasculature. Multiple studies in both animal models and humans suggest that miRNAs are dynamically regulated with physical activity. Unlike the well-known studies of miRNAs in fitness, little is known about lncRNAs in exercise training. The role of lncRNAs in exercise adaptation in skeletal muscle, the heart or the circulating system should be explored and developed further. Identifying the exercise-mediated signals regulating miRNAs and lncRNAs will be an important therapy and make physical work the most effective intervention to in the fight for the prevent disease development.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/ncri.2017.09.01). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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