

SYSTEMATIC REVIEW

Noncoding RNA molecules mediating skeletal muscle mitochondrial function and their potential applications in exercise molecular physiology: a systematic review

Isaac A. Chavez-Guevara,¹ Héctor Vázquez-Lorente,^{2,3,4,5,10} Lourdes Herrera-Quintana,² Mariazel Rubio-Valles,⁶ Luis C. López,^{2,7,8,9} Julio Plaza-Díaz,^{3,4,5,10} and Francisco J. Amaro-Gahete^{2,8,10}

¹Faculty of Sports Campus Ensenada, Autonomous University of Baja California, Tijuana, Mexico; ²Department of Physiology, Schools of Pharmacy and Medicine, University of Granada, Granada, Spain; ³School of Health Sciences, Universidad Internacional de La Rioja, Logroño, Spain; ⁴Departament de Bioquímica i Biotecnologia, ANUT-DSM (Alimentació, Nutrició Desenvolupament i Salut Mental), Universitat Rovira i Virgili, Reus, Spain; ⁵Institut d'Investigació Sanitària Pere Virgili (IISPV), Reus, Spain; ⁶Biomedical Sciences Institute, Department of Chemical Sciences, Autonomous University of Chihuahua, Chihuahua, Mexico; ⁷Institute of Biotechnology, Biomedical Research Centre, University of Granada, Granada, Spain; ⁸Instituto de Investigación Biosanitaria Ibs, Granada, Spain; ⁹Centro de Investigación Biomédica en Red Fragilidad y Envejecimiento Saludable (CIBERFES), Granada, Spain; and ¹⁰Biomedical Research Networking Center for Physiopathology of Obesity and Nutrition (CIBEROBN), Institute of Health Carlos III, Madrid, Spain

Abstract

This systematic review investigates the role of noncoding RNAs (ncRNAs), including miRNAs, long noncoding RNAs (lncRNAs), circular RNAs (circRNAs), and transfer RNAs, in regulating mitochondrial biogenesis, dynamics, oxidative phosphorylation, and mitophagy in skeletal muscle and the potential applications of these ncRNAs in exercise molecular physiology. We conducted a comprehensive search in PubMed, Scopus, and Web of Science databases, identifying 45 relevant studies out of 2,378 records. The main findings indicate that miRNAs such as miR-128, miR-133a, miR-696, and miR-499 are critical regulators of mitochondrial function. Moreover, lncRNAs (lncEDCH1 and lncRNA-H19) and circRNA (circ-PTPN4) significantly influence mitochondrial biogenesis and function. Exercise interventions were shown to modulate the expression of these ncRNAs, particularly miR-133a and miR-696, leading to enhanced mitochondrial biogenesis and function. The review highlights the potential of these ncRNAs as biomarkers and therapeutic targets for improving mitochondrial function and treating metabolic and mitochondrial disorders. Further research is needed to explore the muscle-specific and exercise-modality-specific effects of ncRNAs to develop personalized interventions. Understanding the complex regulatory mechanisms of ncRNAs in mitochondrial adaptations can pave the way for innovative therapeutic strategies in exercise molecular physiology and metabolic health.

cell biology; energy metabolism; epigenetics; physical activity

INTRODUCTION

The mitochondrion is a key cellular organelle with important functions in energy metabolism, homeostasis, macromolecule biosynthesis, and distinct signaling pathways in skeletal muscle (1). Indeed, it represents between 2% and 8% of the myocyte volume density depending on age, sex, muscle fiber type, and physical fitness level (2–4). This highly dynamic organelle undergoes repeated cycles of fission, fusion, and translocation, thus creating complex mitochondrial networks across different cell compartments that depend on the cell's biological clock and its energy requirements (5, 6). In fact, damaged or strained mitochondria are

repaired or replaced in a circadian manner to adjust their morphology and function (6).

This mitochondrial turnover occurs through the combination of mitochondrial biogenesis and mitophagy, and their impaired regulation can lead to cardiovascular diseases and metabolic disorders (7, 8). For instance, the accumulation of dysfunctional mitochondria in the cardiac and skeletal muscle is related to insulin resistance and myocardial ischemia-reperfusion injury (7, 8), showcasing the relevance of mitochondrial structure and function to sustained health.

Distinct environmental stimuli (e.g., exercise, high-fat diet, or hypoxia) significantly alter the mitochondrial dynamics and function in skeletal muscle (9). Actually, it



Correspondence: F. J. Amaro Gahete (amarof@ugr.es).

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is well documented that both endurance and resistance exercise upregulate mitochondrial biogenesis, thus enhancing mitochondrial volume density and oxidative phosphorylation capacity (10–12). These adaptations have been mainly attributed to short-term transitions in the activity and expression of key mitochondrial (e.g., mitochondrial transcription factor A) and nuclear (e.g., nuclear respiratory factor 1) transcription factors that optimize the synthesis of several proteins involved in mitochondrial biogenesis, mitophagy, and respiration. Moreover, these processes can also be regulated by decrease or increase of specific microRNA (miRNA) molecules (13).

miRNAs are a group of small noncoding RNA molecules that regulate gene expression at the posttranscriptional level. Specifically, the binding of miRNAs to their complementary sequence on the messenger RNA molecule induces its subsequent degradation or prevents its translation in the ribosome (14). Some of these nuclear-encoded miRNAs can be imported into the mitochondrial matrix to regulate the expression of different mitochondrial DNA-encoded genes (15, 16).

According to Long et al. (13), exercise training has the capacity to modulate the expression of several miRNAs involved in the resynthesis of adenosine triphosphate in the mitochondria, most likely due to a stimulation of mitochondrial biogenesis and mitophagy in skeletal muscle. To date, however, no prior studies have mapped all those miRNAs involved in mitochondrial biogenesis and function in skeletal muscle. On the other hand, the participation of circular RNAs (circRNAs), transfer RNAs (tRNA), ribosomal RNAs (rRNA), and long noncoding RNA (lncRNA) molecules in skeletal muscle mitochondrial dynamics and function remains unclear at present. All these molecules also regulate gene expression at the posttranscriptional level (17), with circRNAs acting as miRNA sponges that repress their activity in the cytoplasm and the mitochondrion (18). Comparative transcriptomic studies have identified long noncoding RNAs that function as competing endogenous RNAs targeting the miR-15 family, thereby enhancing insulin-like growth factor 1-phosphatidylinositol 3-kinase/protein kinase B signaling and modulating the dynamics of skeletal muscle atrophy (19).

This work aimed to review the current knowledge regarding noncoding RNA molecules involved in the regulation of mitochondrial biogenesis, dynamics (i.e., fusion and fission), oxidative phosphorylation, and mitophagy in skeletal muscle. Furthermore, we also investigated which of these RNAs can be influenced by an acute bout of exercise or a long-term exercise intervention, improving mitochondrial density and function.

METHODS

Information Sources and Search Strategy

A systematic search was carried out between September and October 2025 in PubMed, Scopus, and Web of Science databases, introducing the following Boolean logic: (MicroRNA OR microRNA OR miR OR “noncoding RNA” OR tRNA OR rRNA OR snoRNAs) AND (muscle OR c2c12 OR “skeletal muscle”

AND (mitochondria OR mitochondrion OR mitochondrial) AND (“organelle biogenesis” OR PPARGC1A OR “PGC-1 α ” OR PGC1a OR PPARGC1B OR PPRC1 OR NRF1 OR GABPA OR “GA-binding protein” OR ESRRa OR ESRRG OR PPARG OR PPARG OR TFAM OR TFB1M OR TFB2M OR POLRMT OR POLG OR POLG2 OR TWNK OR SSBP1 OR TOMM20 OR TIMM23 OR HSPD1 OR HSPA9 OR MFN1 OR MFN2 OR citrate synthase OR OXPHOS OR “complex I” OR NDUFA9 OR NDUFB8 OR “NADH dehydrogenase” OR “complex II” OR SDHB OR “succinate dehydrogenase” OR “complex III” OR UQCRC2 OR “ubiquinol-cytochrome c reductase” OR “complex IV” OR COX4I1 OR “cytochrome c oxidase”). The retrieved documents were filtered by language (i.e., English and Spanish), type of documents (i.e., original and review articles), and publication stage (i.e., published or in press), without any publication date restriction. The reference list of previous review papers related to our research topic (13, 19) was also screened to identify additional studies. Then, the titles and abstracts of the retrieved documents were independently screened by I.A.C.-G. and H.V.-L., consulting a third expert author (F.J.A.-G.) if uncertainty about article eligibility was present. The full review protocol was registered in PROSPERO before its initiation (CRD42023471420), following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement to report the findings of the present work (20) (see Fig. 1).

Eligibility Criteria and Selection Process

All the original articles assessing the role of noncoding RNAs on skeletal muscle mitochondrial biogenesis, mitophagy, and function were selected for review. Those studies investigating the role of noncoding RNAs on the expression levels of transcriptional factors related to mitochondrial dynamics and function were also considered (e.g., peroxisome proliferator-activated receptors, nuclear respiratory factor 1, or estrogen receptor alpha), with no restriction related to study design or experimental models.

Data Collection and Synthesis

During the first stage of the review protocol, we identified those noncoding RNA molecules participating in mitochondrial biogenesis and function in skeletal muscle. For that purpose, we summarized the following primary outcomes: 1) noncoding RNAs (e.g., microRNAs, tRNAs, or snoRNAs), 2) mitochondrial functional parameters (e.g., volume density, oxidative phosphorylation, or fragmentation index), 3) mitochondrial proteins (e.g., complexes 1–4, citrate synthase, or mitofusin 1, among others), and 4) target genes encoding nuclear transcription factors involved in mitochondrial dynamics (e.g., PPARGC1A, NRF1, NRF2, or TFAM, among others). Secondary outcomes considered for this analysis included: 1) experimental models (e.g., in vitro, in vivo, or ex vivo), 2) study design (e.g., cross-sectional, longitudinal, or case-control), and 3) participants characteristics (for studies in humans), cell lines (e.g., C2C12 or L6), or species (e.g., mice, rats, or pigs).

During the second stage of the review protocol, we examined whether the expression levels of all RNA molecules identified in *phase 1* may be modified by an acute bout of exercise or a long-term exercise intervention. For that

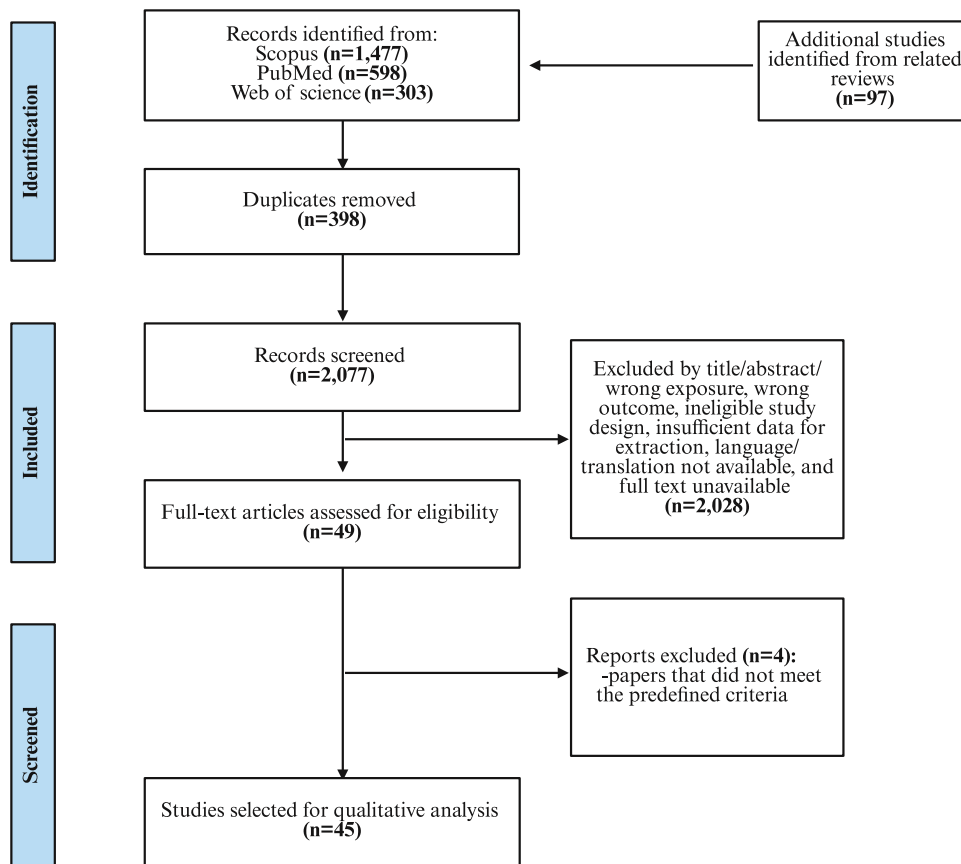


Figure 1. Flowchart of the literature search and study selection process. RNA, ribonucleic acid.

purpose, we used a cross-checking approach, summarizing the following primary outcomes retrieved from both original studies and previous systematic reviews: 1) RNA levels modification induced by exercise (e.g., increase or decrease), 2) characteristics of the exercise interventions (e.g., intensity, type of exercise, or intervention period), and 3) analyzed species (e.g., humans, mice, or rats). All data were recorded by HVL, LHQ, and MRV using two Microsoft Word templates previously elaborated by I.A.C.-G., and F.J.A.-G. (Supplemental Tables S1 and S2).

RESULTS

Literature Search and Document Selection

The search yielded 2,378 records from databases and 97 documents from two related systematic reviews (13, 21). After removing 398 duplicates, 2,077 records remained for screening. Upon reviewing their titles and abstracts, 2,028 documents were excluded as irrelevant (e.g., incorrect exposure/outcome, ineligible design, insufficient data, conference abstract only, language not available, and full text unavailable) (Fig. 1). Finally, the full texts of the remaining 49 manuscripts were thoroughly examined, resulting in the exclusion of four papers that did not meet the predefined criteria (Fig. 1). A detailed description of the 45 articles summarized in this review is provided in Supplemental Tables S1 and S2 (22–66).

Noncoding RNAs Mediating Mitochondrial Biogenesis and Function in Skeletal Muscle

Noncoding RNA molecules involved in skeletal muscle's mitochondrial biogenesis, dynamics, and function are graphically summarized in Fig. 2. More than 90% of the analyzed studies focused on miRNAs' relationship to mitochondrial biogenesis and/or function (respiration, fusion, fission, oxidation, among others) (22–54, 57, 59–61, 63–66), whereas three investigations assessed the role of lncRNAs (55, 58, 62), and one work examined circRNA molecules (56). More than 20 miRNAs were related to biomarkers of mitochondrial mass (reflecting an increase in mitochondrial biogenesis) such as mitochondrial DNA copy numbers, citrate synthase activity, other enzyme activities and methodologies related to localization and quantification such as cell fluorescence. Conversely, three miRNAs influenced mitochondrial fusion and fission, represented by mitochondrial fragmentation or cristae density.

microRNAs.

The majority of experiments were conducted in C2C12 myotubes, complemented by ex vivo skeletal muscle samples from mice (C57BL/6, transgenic lines), rats (Sprague-Dawley; infant rats; high- vs. low-capacity runners), pigs, chickens, pacu fish, porcine satellite cells, and primary human skeletal muscle cells. Most designs involved gain- or loss-of-function manipulations of noncoding RNAs (ncRNAs) via transfection or in vivo delivery, followed by

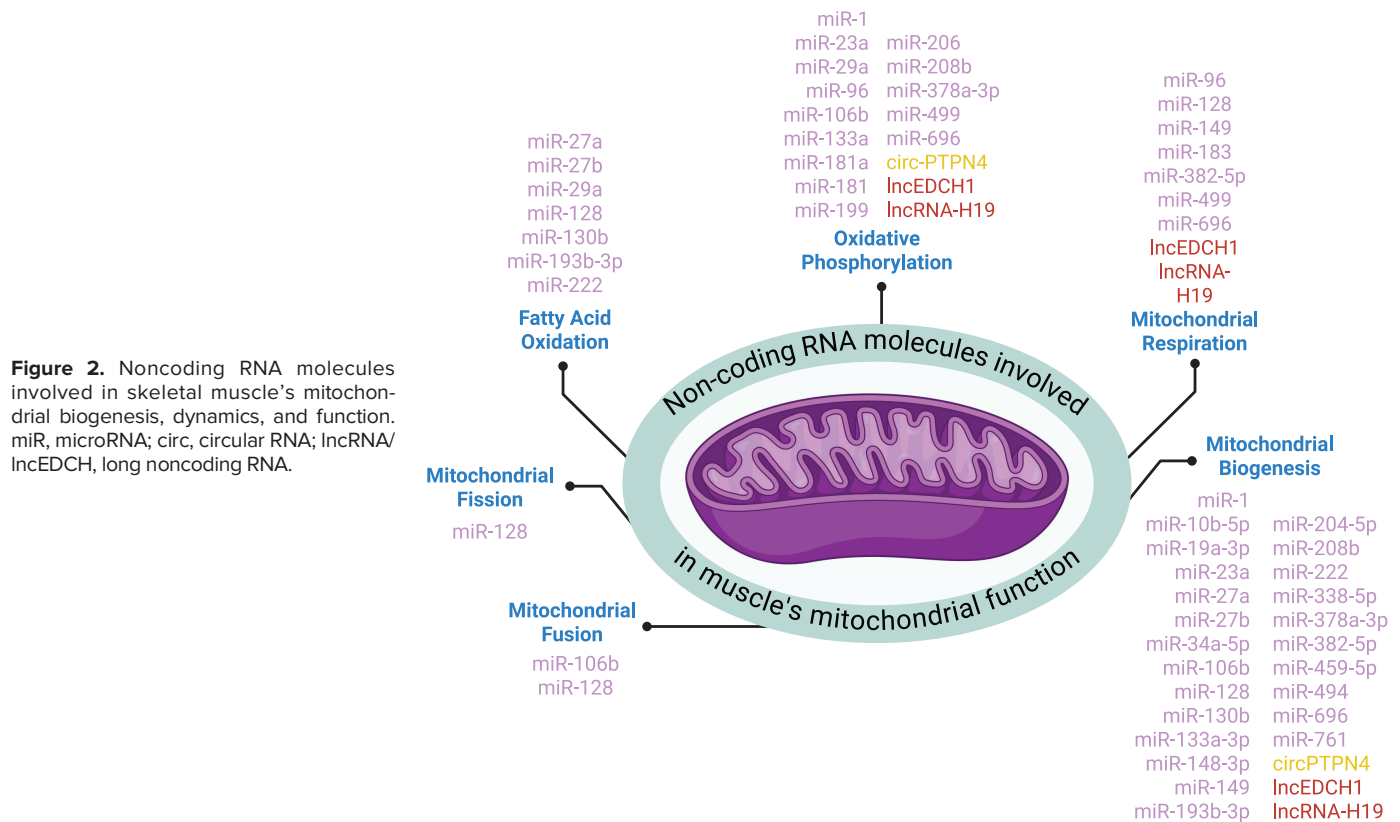


Figure 2. Noncoding RNA molecules involved in skeletal muscle's mitochondrial biogenesis, dynamics, and function. miR, microRNA; circ, circular RNA; lncRNA/ lncEDCH, long noncoding RNA.

downstream analyses of gene and protein expression and mitochondrial phenotypes. Common assays included mitochondrial DNA (mtDNA) copy number, citrate synthase (CS) activity, oxygen consumption rate (OCR), ATP content, succinate dehydrogenase (SDH) staining or activity, and morphological assessments by fluorescence or electron microscopy.

Frequently investigated molecular targets comprised PGC-1 α and TFAM (biogenesis); MFN1, MFN2, OPA1, and DRP1 (dynamics); NRF1, NRF2, and SIRT1 (transcriptional and metabolic control); and lipid-oxidation markers such as CPT1b and ACADL. Overall, overexpression of several miRNAs (e.g., miR-27b, miR-494, miR-696, miR-761, and miR-130b, in specific contexts) was associated with the downregulation of PGC-1 α , TFAM, or related axes, resulting in reduced mitochondrial biogenesis and function (lower mtDNA, OCR, or ATP). In contrast, silencing inhibitory miRNAs (e.g., miR-106b, miR-204-5p, and miR-183/96) or overexpressing others (e.g., miR-1, miR-149, miR-181a, and miR-208b) tended to enhance biogenesis and oxidative phosphorylation.

Mitochondrial dynamics were consistently modulated across studies. miR-106b overexpression reduced MFN2 and PGC-1 α and increased fragmentation, while its silencing restored fusion and mitochondrial content. Additionally, miR-128 overexpression suppressed PGC-1 α , NRFs, and OPA1, leading to fragmentation and lower OCR. Other miRNAs affected respiratory and energetic performance. For instance, miR-208b increased PGC-1 α , mtDNA content, and ATP levels, whereas miR-1 enhanced OCR without altering CS activity. Fatty acid oxidation was also prominently

represented, with miR-27a/b acting on PPAR γ pathways, miR-29a influencing ACADL and PPAR δ , and several studies monitoring CPT1b expression.

Collectively, the most recurrent miRNAs—including the miR-27 family (miR-27a/b), miR-494, miR-696, miR-23a, miR-29a, and miR-106b—emerged as central regulators of mitochondrial biogenesis, oxidative phosphorylation, and network dynamics (fission and fusion) in skeletal muscle.

Long noncoding and circular RNAs.

Beyond microRNAs, long noncoding RNAs (lncRNAs) generally displayed pro-mitochondrial activity in skeletal muscle. lncEDCH1 and H19 promoted PGC-1 α , CPT1, SIRT1, and TFAM expression, accompanied by increased respiratory performance, including enhanced oxygen consumption rate (OCR), succinate dehydrogenase (SDH) activity, and fatty acid oxidation. In contrast, the single circular RNA entry (circPTPN4) exhibited reduced PGC-1 α but increased mitochondrial DNA (mtDNA) content and SDH activity following overexpression. Species- and model-dependent nuances were observed—for instance, sodium butyrate-fed pigs showed higher miR-208b expression together with upregulated biogenesis markers, whereas exercise-mimicking stimulation in mice and human myotubes elicited comparable mitochondrial outcomes. Nevertheless, the principal biogenesis and oxidative phosphorylation (OXPHOS) endpoints remained largely consistent across experimental systems. Detailed per-study protocols, targets, and regulatory directions are provided in Supplemental Table S1.

Integrative mapping revealed that six ncRNAs—miR-128, miR-133a, miR-149, miR-208b, miR-499, and lncRNA

H19—exhibited the widest regulatory spectrum across mitochondrial pathways. These molecules collectively targeted major transcriptional and coactivator hubs (PPARGC1A/PGC-1 α , NRF1, and NRF2), genome maintenance and biogenesis factors (TFAM and OPA1), mitochondrial dynamics proteins (DRP1 and MFN1), and multiple OXPHOS components (e.g., ATP synthase subunits, cytochrome c, cytochrome c oxidase, and selected *complex I* subunits).

In contrast, miR-27b, lncEDCH1, and circPTPN4 were associated with a more limited set of mitochondrial targets, typically fewer than five. Collectively, these findings identify miR-128, miR-133a, miR-149, miR-208b, miR-499, and H19 as central ncRNA regulators orchestrating mitochondrial biogenesis, dynamics, and respiration in skeletal muscle. Comprehensive interactions are illustrated in Fig. 2.

Acute and Chronic Effects of Exercise on Noncoding RNAs Mediating Mitochondrial Biogenesis and Function in Skeletal Muscle

The effects of distinct exercise interventions on noncoding RNA expression are illustrated in Fig. 3. Most of the studies examined the acute and chronic effect of aerobic exercise on miRNA molecules and biomarkers of mitochondrial biogenesis and/or function (53, 54, 57, 59–62, 64, 66), with only one study focused on the acute modification of lncRNA Tug1 after a single session of aerobic exercise (i.e., cycling for 60 min at 70% peak oxygen consumption) (58). Of those studies assessing the acute

effects of aerobic exercise on noncoding RNA molecules, two were carried out in mice, and four were conducted in humans (mostly young men). Regarding the type of exercise, stationary cycling was mainly used in human studies, whereas treadmill running was the only exercise modality used in mice. Over 12 miRNAs were found to regulate the expression levels of PPARGC1A, the master cotranscriptional regulator that targets downstream genes involved in mitochondrial biogenesis, mitophagy, and oxidative phosphorylation. In addition, seven miRNAs were found to regulate the expression of NRF1 and TFAM, key transcriptional regulators that mediate mitochondrial DNA transcription and replication.

Across human and rodent studies, experimental protocols ranged from acute aerobic exercise bouts (e.g., 60–90 min of cycling or treadmill running) to multiweek endurance training interventions (treadmill, swimming, or voluntary wheel running). Muscle biopsies were most frequently obtained from the *vastus lateralis* or *gastrocnemius*, complemented by mechanistic studies in C2C12 and electrical pulse stimulation (EPS) models.

Outcome measures typically included ncRNA expression profiling (RT-qPCR or RNA-seq), evaluation of transcriptional regulators of mitochondrial biogenesis (PGC-1 α /PPARGC1A, TFAM, and NRF1), assessment of mitochondrial dynamics (MFN1 and MFN2), and quantification of OXPHOS gene expression. Functional and structural endpoints encompassed mtDNA content, CS activity, cytochrome c abundance, and respiratory flux (O₂ consumption).

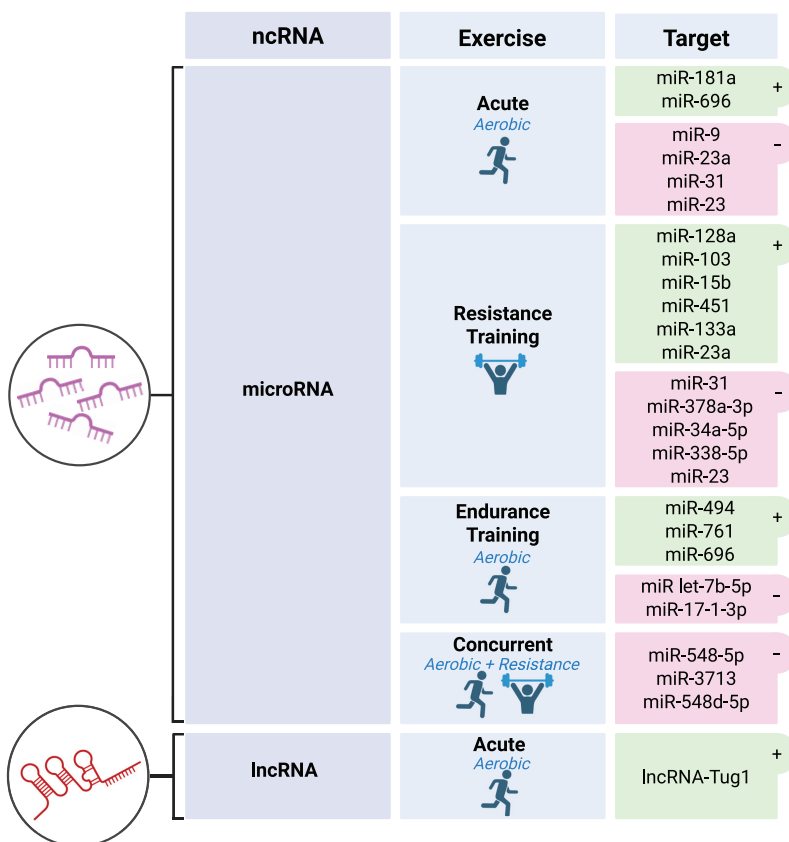


Figure 3. Effects of different exercise interventions on non-coding RNAs expression.

Acute exercise.

In humans, a single 60-min cycling session upregulated lncRNA Tug1, whereas *PPARGC1A*, TFAM, and NRF1 remained unchanged in the *vastus lateralis*. In parallel EPS experiments, *PPARGC1A* and TFAM expression increased, supporting an early mitochondrial biogenesis response. In mice, 90-min treadmill running decreased miR-23 while concomitantly elevating *PPARGC1A*, CS activity, and cytochrome c content. Other acute human exercise responses included downregulation of miR-9, miR-23a, and miR-31, together with upregulation of miR-181a, consistent with NRF1 activation. Short-term interval swimming (7 days) lowered miR-494 expression and was accompanied by increased TFAM levels and mtDNA content.

Although not all molecular targets changed uniformly at the protein level, the overall pattern indicates a transcriptional activation of mitochondrial biogenic and respiratory programs following an acute exercise stimulus.

Endurance training.

Multiweek endurance training protocols generally shifted ncRNA expression toward a pro-mitochondrial regulatory profile. Six weeks of treadmill running increased PGC-1 α , NRF1, TFAM, and COX1 expression, accompanied by higher mtDNA content, whereas miR-133a levels rose and CS activity remained unchanged. Eight weeks of voluntary wheel running reduced miR-494 and miR-696 expression and elevated PGC-1 α , although NRF1, TFAM, and mtDNA levels were unaltered. Four-week treadmill protocols produced similar effects: one study reported lower miR-696 with higher PGC-1 α , whereas another observed decreased miR-10b-5p and increased miR-148a-3p, together with OXPHOS gene upregulation and elevated mtDNA (CS and HADH unchanged). Swimming-based endurance training reduced miR-17-1-3p expression and enhanced MFN1 and MFN2 levels, indicative of increased mitochondrial fusion.

In a miR-23a transgenic model subjected to voluntary running, the *plantaris* muscle showed elevated PGC-1 α and cytochrome c oxidase subunits, whereas wild-type runners exhibited miR-23a downregulation with comparable protein increases; the *soleus* muscle remained unchanged, underscoring fiber-type-specific regulation.

Collectively, these findings demonstrate that sustained endurance training promotes a coordinated shift in ncRNA expression patterns favoring mitochondrial biogenesis, fusion, and respiratory competence, with distinct adaptations across muscle phenotypes.

Population/muscle-specific nuances.

In rats, 12 wk of swimming exercise increased miR-128a expression in the *extensor digitorum longus* without changes in *PPARGC1A*, whereas in the *soleus*, miR-451 and miR-15b decreased concomitantly with elevated *PPARGC1A* levels. In humans, 8 wk of cycling training—mirrored by a comparable mouse treadmill model—reduced let-7b-5p expression while upregulating *PPARGC1A*. A 12-wk supervised intervention in sedentary adults with pre-obesity or obesity resulted in lower miR-494 levels and increased OXPHOS gene expression, accompanied by higher mtDNA content and enhanced mitochondrial O₂ flux. Conversely, a high-intensity program in physically active men increased miR-494, suggesting a

training-status-dependent regulation of this molecule. In women completing a 12-wk concurrent training protocol, miR-3713 decreased in parallel with elevated AK3 protein, a factor associated with mitochondrial energetic homeostasis.

Collectively, these findings highlight the importance of muscle type, sex, and training status as modulators of ncRNA-mitochondrial interactions, underscoring the context-dependent plasticity of mitochondrial regulatory networks in response to endurance exercise.

Overall pattern.

Collectively, endurance-type exercise—both acute and chronic—tends to downregulate inhibitory miRNAs (e.g., miR-23/23a, miR-494, miR-696, miR-761, miR-3713, let-7b-5p, and miR-17-1-3p) and/or upregulate pro-mitochondrial regulators, including lncRNA Tug1 and context-dependent increases in miR-133a, miR-148a-3p, and miR-181a. These molecular adaptations are consistently associated with enhanced expression of PGC-1 α , TFAM, and NRF1, together with upregulation of OXPHOS genes and improved indices of mitochondrial biogenesis and fusion (e.g., mtDNA content and MFN1/2 expression).

Notably, substantial heterogeneity was observed across muscle types, species, training volumes, and health status. In several studies, mitochondrial implications were inferred from canonical roles of transcriptional targets rather than directly assessed through functional assays.

A comprehensive summary of experimental protocols, sampling times, muscle-specific findings, and regulatory directionality is provided in Supplemental Table S2. Overall, the evidence supports a conserved ncRNA-mediated mechanism by which endurance exercise promotes transcriptional activation of mitochondrial biogenesis and remodeling programs in skeletal muscle.

DISCUSSION

This review comprehensively analyzes the role of noncoding RNAs, particularly miRNAs, in regulating skeletal muscle mitochondrial biogenesis and function. Major findings indicate that miR-128, miR-133a, miR-499, and miR-696 alongside lncEDCH1 and lncRNA-H19, are critical regulators of mitochondrial biogenesis, oxidative phosphorylation, and mitochondrial dynamics. The review also highlights that several miRNAs target the same genes and modulate similar molecular processes, suggesting a robust regulatory mechanism in which different miRNAs can compensate for one another, helping to maintain optimal mitochondrial function and cellular performance. Many of these miRNAs were upregulated or downregulated after a single bout of exercise or a long-term exercise intervention, suggesting that such miRNAs may simultaneously optimize mitochondrial function and overall metabolic health. Whether such miRNAs interact with lncRNA Tug1, lncEDCH1, lncRNA-H19, and circ-PTPN4 to induce mitochondrial adaptations to exercise warrants further study. Moreover, microarrays or next-generation sequencing techniques should be applied to define noncoding RNA networks that regulate mitochondrial biogenesis and function.

To date, most of the studies analyzed have validated the role of noncoding RNA molecules in mitochondrial biogenesis or function through transfection assays in cultured C2C12 cells. However, whether the expression levels of these RNAs are altered in patients with type 2 diabetes or metabolic syndrome—conditions in which mitochondrial dysfunction is a common feature (7, 8)—requires further investigation, especially considering C2C12 is an immortalized myoblast cell line derived from adult mouse satellite cells. Demonstrating that the levels of these RNAs differ between healthy individuals and patients with metabolic disorders would help establish molecular targets that could be modified through exercise interventions. In addition, investigating the up- or downregulation of these RNAs in patients with mitochondrial myopathies may contribute to the development of novel therapeutic strategies to alleviate muscle weakness, reduce muscle atrophy, and improve exercise intolerance (67).

In principle, these miRNAs or their corresponding inhibitors could be delivered to skeletal muscle, mimicking mitochondrial biogenesis and bioenergetic adaptations stimulated by exercise. This approach would require the development of synthetic vehicles (e.g., biodegradable three-dimensional matrices or nanocarriers) that overcome the limitations associated with miRNA therapies, ensuring stable and efficient delivery to target tissues, minimizing off-target effects, and reducing immune responses (68, 69). That strategy may open new possibilities for personalized medicine approaches to the treatment of metabolic and muscular disorders.

It should be acknowledged that exercise epigenetics is still in its infancy. Indeed, the influence of various exercise modalities on the RNA molecules reported here warrants further investigation. Egan and Sharples (70) also highlighted that exercise-induced changes in miRNAs may depend on factors such as sex, age, and fitness level, adding another layer of complexity to our understanding of the potential molecular adaptations; this is especially relevant given that most studies focused on male mice or humans, with few studies including females.

Whether miRNA adaptations in response to exercise depend on the structure of the biopsied or dissected muscle also warrants investigation. Gaál et al. (57) reported that miR-128a was increased after 12-wk endurance training (swimming for 200 min; 5 days/wk) in the *extensor digitorum longus* muscle of rats, whereas miR-451b and miR-15b were downregulated in the *soleus* muscle. Wada et al. (50) also noted that miR-23a increased in fast *plantaris* after 4-wk voluntary running in mice, whereas the same RNA remained unchanged in the *soleus* muscle. However, the opposite effect was found when overexpressing miR-23a in that same study since biomarkers of mitochondrial biogenesis decreased in the *soleus* muscle of miR-23a transgenic mice, whereas no changes were observed in the fast *plantaris* muscles.

This leads us to ask whether miRNAs governing mitochondrial biogenesis and function are muscle specific, considering that mitochondrial volume density is higher in oxidative muscles where oxidative phosphorylation are commonly observed (71). In support of this hypothesis, Howald et al. (72) reported that miRNA expression differed between

type I and type II muscle fibers in response to muscle damage. However, we may also argue that miRNAs related to mitochondrial biogenesis may change predominantly in type II muscle fibers given that the increase in mitochondrial volume density after endurance training is more pronounced in these muscle fibers than in highly oxidative type I muscle fibers (55% vs. 35%) (72). A comprehensive approach that includes samples from both oxidative and glycolytic muscles may provide a more comprehensive understanding of exercise-induced mitochondrial biogenesis and function.

Reproducibility remains an outstanding issue, since most RNAs have been examined in only one study. Only few miRNAs were assessed by two independent studies in mice, which reported similar changes of mitochondrial oxidative phosphorylation and respiration after the suppression or overexpression of these miRNAs.

Finally, although the current review has focused extensively on miRNAs, it is equally important to study the role of other noncoding RNAs (i.e., lncRNAs, circRNAs, tRNAs, and snRNAs/snoRNAs) in mitochondrial biogenesis and function. Our analysis revealed that lncEDCH1 and lncRNA-H19 were increased after acute aerobic exercise and after intramuscular injection in human and chicken muscle, respectively, thereby augmenting expression levels of *PPARGC1A*. These findings suggest that these lncRNAs may influence mitochondrial dynamics and oxidative phosphorylation. Nevertheless, circRNAs, tRNAs, and sn/snoRNAs also play crucial roles in the regulation of mitochondrial gene expression and energy metabolism. For instance, emerging evidence suggests that circRNAs bind to complementary sequences of microRNAs, preventing their coupling to mRNAs; this, in turn, may alter the expression of enzymes and proteins involved in mitochondrial function (18). Similarly, tRNAs and sn/snoRNAs have been implicated in mitochondrial protein synthesis and in maintaining mitochondrial integrity (17).

The exploration of these noncoding RNAs in the context of exercise-induced mitochondrial adaptations could uncover novel regulatory mechanisms and therapeutic targets. Indeed, understanding how these RNAs interact with mitochondrial biogenesis pathways could lead to the development of innovative interventions to enhance mitochondrial mass and function in patients with metabolic and mitochondrial disorders. This is particularly important since endurance exercise has shown benefits in both mouse models and patients with mitochondrial myopathies (73, 74). Future research should aim to elucidate the specific roles of lncRNAs, circRNAs, tRNAs, and sn/snoRNAs in mitochondrial biogenesis, particularly in response to different exercise modalities (acute and chronic effects) and physiological conditions. This comprehensive approach will not only expand our knowledge of mitochondrial biology but also pave the way for personalized medicine strategies to improve metabolic health and exercise performance.

Conclusions

miR-128, miR-133a, miR-696, and miR-494, alongside lncEDCH1 and lncRNAH19 seem to be critical modulators of muscle mitochondrial health. Collectively, these RNAs regulate the expression of more than 10 genes encoding

important proteins involved in muscle mitochondrial biogenesis, oxidative phosphorylation, and mitochondrial dynamics. The expression of miR-133a and miR-696 change in response to endurance exercise, suggesting novel epigenetic mechanisms that govern skeletal muscle remodeling. Additional RNAs such as miR-let-7b-5p, miR-17-1-3p, miR-15b, and the lncRNATug1 were also affected by an exercise intervention; however, their precise molecular mechanisms require further analysis.

The small number of studies reporting each miRNA and the limited evidence validating the action of these miRNAs in human muscle highlight the need for future investigations. Understanding muscle-specific adaptations to different training modalities in populations with cardiometabolic diseases or mitochondrial myopathies will shed light on how noncoding RNA modulate of mitochondrial function and gene expression.

DATA AVAILABILITY

The datasets supporting the findings reported have been provided as supplementary material.

SUPPLEMENTAL MATERIAL

Supplemental Table S1: <https://doi.org/10.6084/m9.figshare.30438728>.

Supplemental Table S2: <https://doi.org/10.6084/m9.figshare.30438740>.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

I.A.C.-G., H.V.-L., L.H.-Q., M.R.-V., and F.J.A.-G. conceived and designed research; I.A.C.-G., H.V.-L., L.H.-Q., M.R.-V., and F.J.A.-G. analyzed data; I.A.C.-G., H.V.-L., L.H.-Q., L.C.L., J.P.-D., and F.J.A.-G. interpreted results of experiments; I.A.C.-G., H.V.-L., L.H.-Q., and M.R.-V. prepared figures; I.A.C.-G., H.V.-L., and F.J.A.-G. drafted manuscript; I.A.C.-G., H.V.-L., L.H.-Q., M.R.-V., L.C.L., J.P.-D., and F.J.A.-G. edited and revised manuscript; I.A.C.-G., H.V.-L., L.H.-Q., M.R.-V., L.C.L., J.P.-D., and F.J.A.-G. approved final version of manuscript.

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