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Non-coding RNA molecules mediating skeletal muscle mitochondrial function and their potential applications in exercise molecular physiology: A systematic review

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Key points

- Non-coding RNAs, including miRNAs, lncRNAs, and circRNAs, regulate mitochondrial biogenesis, dynamics, and oxidative phosphorylation in skeletal muscle.
- miRNAs such as miR-128, miR-133a, miR-696, and miR-499 play critical roles in enhancing mitochondrial function and may serve as biomarkers for exercise adaptations.
- Exercise modulates ncRNAs (notably miR-133a and miR-696), highlighting potential therapeutic applications in metabolic health and mitochondrial disorders.
- lncRNAs (lncEDCH1, lncRNA-H19) and circRNA (circ-PTPN4) influence mitochondrial biogenesis and oxidative phosphorylation, suggesting their potential as novel therapeutic targets.
- Further research is necessary to investigate muscle-specific and exercise-modality-specific effects of ncRNAs to develop personalized exercise-based interventions.

Abstract

This systematic review investigates the role of non-coding RNAs (ncRNAs), including miRNAs, lncRNAs, circRNAs, and tRNAs, 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.

Keywords: cell biology, epigenetics, energy metabolism, physical activity

1. 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 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 non-coding RNA molecules that regulate gene expression at the post-transcriptional 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 (circRNA), transfer RNAs (tRNA), ribosomal RNAs (rRNA), and long non-coding RNA molecules (lncRNA) in skeletal muscle mitochondrial dynamics and function remains unclear at present. All these molecules also regulate gene expression at the post-transcriptional 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 non-coding RNAs that function as competing endogenous RNAs targeting the miR-15 family, thereby enhancing insulin-like growth factor 1 (IGF1)–phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) signaling and modulating the dynamics of skeletal muscle atrophy (19).

This work aimed to review the current knowledge regarding non-coding 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.

2. Methods

2.1 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 "non-coding 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-1α" OR PGC1a OR PPARGC1B OR PPRC1 OR NRF1 OR GABPA OR "GA-binding protein" OR ESRRA OR ESRRG OR PPARA OR PPARD 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 IACG and HVL, consulting a third expert author (FJAG) if uncertainty about article eligibility was present. The full review protocol was registered in PROSPERO prior to its initiation (CRD42023471420), following the Preferred Reporting

Items for Systematic Reviews and Meta-Analyses (PRISMA) statement to report the findings of the present work (20) (see **Figure 1**).

2.2 Eligibility criteria and selection process

All the original articles assessing the role of non-coding RNAs on skeletal muscle mitochondrial biogenesis, mitophagy, and function were selected for review. Those studies investigating the role of non-coding 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.

2.3 Data collection and synthesis

During the first stage of the review protocol, we identified those non-coding RNA molecules participating in mitochondrial biogenesis and function in skeletal muscle. For that purpose, we summarized the following primary outcomes: (I) non-coding RNAs (e.g., microRNAs, trRNAs, or snoRNAs), (II) mitochondrial functional parameters (e.g., volume density, oxidative phosphorylation, or fragmentation index), (III) mitochondrial proteins (e.g., complex 1-4, citrate synthase, or mitofusin 1, among others), and (IV) 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: (I) experimental models (e.g., *in vitro, in vivo,* or *ex vivo*), (II) study design (e.g., cross-sectional, longitudinal, or case-control), and (III) participants characteristics (for studies in humans), cell lines (e.g., C2C12, or L6) or species (e.g., mice, rats, or pigs).

158 During the second stage of the review protocol, we examined whether the expression levels
159 of all RNA molecules identified in phase 1 may be modified by an acute bout of exercise or
160 a long-term exercise intervention. For that purpose, we used a cross-checking approach,
161 summarizing the following primary outcomes retrieved from both original studies and
162 previous systematic reviews: (I) RNA levels modification induced by exercise (e.g.,
163 increase or decrease), (II) characteristics of the exercise interventions (e.g., intensity, type
164 of exercise, or intervention period), and (III) analyzed species (e.g., humans, mice, or rats).
165 All data were recorded by HVL, LHQ, MRV, using two Microsoft Word templates
166 previously elaborated by IACG, BE, and FJAG (Supplementary Files 1 and 2).

3. Results

3.1 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, full text unavailable) (Figure 1). Finally, the full texts of the remaining 49 manuscripts were thoroughly examined, resulting in the exclusion of 4 papers that did not meet the predefined criteria (Figure 1). A detailed description of the 45 articles summarized in this review is provided in supplementary files 1 and 2 (22-66).

3.2 Non-coding RNAs mediating mitochondrial biogenesis and function in skeletal muscle

Non-coding RNA molecules involved in skeletal muscle's mitochondrial biogenesis, dynamics, and function are graphically summarized in **Figure 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), whilst three investigations assessed the role of lncRNAs (55, 58, 62), and one work examined circRNA molecules (56). More than twenty 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.

3.2.1. 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 non-coding RNAs (ncRNAs) via transfection or in vivo delivery, followed by 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-1α 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, miR-130b, in specific contexts) was associated with downregulation of PGC-1α, 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, miR-183/96) or overexpressing others (e.g., miR-1, miR-149, miR-181a, miR-208b) tended to enhance biogenesis and oxidative phosphorylation.

Mitochondrial dynamics were consistently modulated across studies. miR-106b exerted bidirectional effects—its overexpression reduced MFN2 and PGC-1α and increased fragmentation, whereas silencing restored fusion and mitochondrial content—while miR-128 overexpression suppressed PGC-1α, NRFs, and OPA1, leading to fragmentation and lower OCR. Other miRNAs affected respiratory and energetic performance: for instance, miR-208b increased PGC-1α, 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 PPARγ pathways, miR-29a influencing ACADL and PPARδ, 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.

3.2.2. Long non-coding and circular RNAs

Beyond microRNAs, long non-coding RNAs (lncRNAs) generally displayed pro-mitochondrial activity in skeletal muscle. LncEDCH1 and H19 promoted PGC-1α, 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-1α 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 Supplementary Table 1.

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-1α, NRF1, NRF2), genome maintenance and biogenesis factors (TFAM, OPA1), mitochondrial dynamics proteins (DRP1, 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 Figure 2.

3.3 Acute and chronic effects of exercise on non-coding RNAs mediating mitochondrial biogenesis and function in skeletal muscle.

The effects of distinct exercise interventions on non-coding RNA expression are illustrated in Figure 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% VO_{2peak}) (58). Of those studies assessing the acute effects of aerobic exercise on non-coding 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 whilst treadmill running was the only exercise modality used in mice. Mitochondrial and nuclear genes targeted by each non-coding RNA are summarized in detail in the supplementary file 3. Over 12 miRNAs were found to regulate the expression levels of PPARGC1A, the master co-transcriptional regulator that targets downstream genes involved in mitochondrial biogenesis, mitophagy, and oxidative phosphorylation. Additionally, 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 multi-week 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-1α/PPARGC1A, TFAM, NRF1), assessment of mitochondrial dynamics (MFN1, MFN2), and quantification of OXPHOS gene expression. Functional and structural endpoints encompassed mtDNA content, CS activity, cytochrome c abundance, and respiratory flux (O_2 consumption).

3.3.1. 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.

3.3.2. Endurance training

Multi-week endurance training protocols generally shifted ncRNA expression toward a pro-mitochondrial regulatory profile. Six weeks of treadmill running increased PGC-1α, NRF1, TFAM, and COX1 expression, accompanied by higher mtDNA content, while 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-1α, although NRF1, TFAM, and mtDNA levels were unaltered. Four-week treadmill protocols produced similar effects: one study reported lower miR-696 with higher PGC-1α, 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-1α 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.

3.3.3. Population/muscle-specific nuances

In rats, twelve weeks 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, eight weeks of cycling training—mirrored by a comparable mouse treadmill model—reduced let-7b-5p expression while upregulating PPARGC1A. A twelve-week 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 O_2 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 twelve-week 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. 3.3.4. 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, 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 PPARGC1A, TFAM, and NRF1, together with upregulation of OXPHOS genes and improved indices of mitochondrial biogenesis and fusion (e.g., mtDNA content, 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 Supplementary Table 2. 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.

4. Discussion

This review comprehensively analyzes the role of non-coding 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 non-coding RNA networks that regulate mitochondrial biogenesis and function.

To date, most of the studies analyzed have validated the role of non-coding 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. Additionally, investigating the up- or down-regulation 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 3D 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-week endurance training (swimming for 200 min; 5 days/week) in the

388 *extensor digitorum longus* muscle of rats, whereas miR-451b and miR-15b were
389 downregulated in the *soleus* muscle. Wada et al. (50) also noted that miR-23a increased in
390 *fast plantaris* after 4-week voluntary running in mice, while the same RNA remained
391 unchanged in the *soleus* muscle. However, the opposite effect was found when
392 overexpressing miR-23a in that same study since biomarkers of mitochondrial biogenesis
393 decreased in the soleus muscle of mir-23a transgenic mice while no changes were observed
394 in the fast *plantaris* muscles.

395 This leads us to ask whether miRNAs governing mitochondrial biogenesis and function are
396 muscle specific, considering that mitochondrial volume density is higher in oxidative
397 muscles where oxidative phosphorylation are commonly observed (71). In support of this
398 hypothesis, Howald et al. (72) reported that miRNA expression differed between type I and
399 type II muscle fibers in response to muscle damage. However, we may also argue that
400 miRNAs related to mitochondrial biogenesis may change predominantly in type II muscle
401 fibers given that the increase in mitochondrial volume density after endurance training is
402 more pronounced in these muscle fibers than in highly oxidative type I muscle fibers (55%
403 vs. 35%) (72). A comprehensive approach that includes samples from both oxidative and
404 glycolytic muscles may provide a more comprehensive understanding of exercise-induced
405 mitochondrial biogenesis and function.

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

Finally, while the current review has focused extensively on miRNAs, it is equally important to study the role of other non-coding 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 non-coding 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 (73-75). 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.

5. Conclusion

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 ten 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 non-coding RNA modulate of mitochondrial function and gene expression.

CRediT authorship contribution statement

Investigation, IACG, HVL, LHQ, MRV; Conceptualization and Methodology: IACG, BE, HVL, FJAG; Resources and data curation: IACG, HVL, LHQ, MRV, JPD; Formal analysis: IACG, BE, FJAG; Supervision and project administration, IACG, FJAG. All the

authors have read, edited and approved the final version of the manuscript and agreed with the order of presentation of the authors.

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Supplementary Table 1. Doi: 10.6084/m9.figshare.30438728

Supplementary Table 2. Doi: 10.6084/m9.figshare.30438740

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Figure legends

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

Figure 2. Non-coding RNA molecules involved in skeletal muscle's mitochondrial biogenesis, dynamics, and function. microRNA (miR), circular RNA (circ), long non-coding RNA (lncRNA/lncEDCH).

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