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Journal of Sport and Health Science 13 (2024) 311–338

Review

Non-coding RNAs in exercise immunology: A systematic review

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Received 5 July 2023; revised 1 September 2023; accepted 19 September 2023
Available online 3 November 2023

Abstract

Regular physical exercise has been recognized as a potent modulator of immune function, with its effects including enhanced immune surveillance, reduced inflammation, and improved overall health. While strong evidence exists that physical exercise affects the specific expression and activity of non-coding RNAs (ncRNAs) also involved in immune system regulation, heterogeneity in individual study designs and analyzed exercise protocols exists, and a condensed list of functional, exercise-dependent ncRNAs with known targets in the immune system is missing from the literature. A systematic review and qualitative analysis was used to identify and categorize ncRNAs participating in immune modulation by physical exercise. Two combined approaches were used: (a) a systematic literature search for "ncRNA and exercise immunology", (b) and a database search for microRNAs (miRNAs) (miRTarBase and DIANA-Tarbase v8) aligned with known target genes in the immune system based on the Reactome database, combined with a systematic literature search for "ncRNA and exercise". Literature searches were based on PubMed, Web of Science, and SPORTDiscus; and miRNA databases were filtered for targets validated by *in vitro* experimental data. Studies were eligible if they reported on exercise-based interventions in healthy humans. After duplicate removal, 95 studies were included reporting on 164 miRNAs, which were used for the qualitative synthesis. Six studies reporting on long-noncoding RNAs (lncRNAs) or circular RNAs were also identified. Results were analyzed using ordering tables that included exercise modality (endurance/resistance exercise), acute or chronic interventions, as well as the consistency in reported change between studies. Evaluation criteria were defined as "validated" with 100% of ≥3 independent studies showing identical direction of regulation, "plausible" (≥80%), or "suggestive" (≥70%). For resistance exercise, upregulation of miR-206 was validated while downregulation of miR-133a appeared plausible. For endurance exercise, 15 miRNAs were categorized as validated, with 12 miRNAs being consistently elevated and 3 miRNAs being downregulated, most of them after acute exercise training. In conclusion, our approach provides evidence that miRNAs play a major role in exercise-induced effects on the innate and adaptive immune system by targeting different pathways affecting immune cell distribution, function, and trafficking as well as production of (anti-)inflammatory cytokines. miRNAs miR-15, miR-29c, miR-30a, miR-142/3, miR-181a, and miR-338 emerged as key players in mediating the immunomodulatory effects of exercise predominantly after acute bouts of endurance exercise.

Keywords: Immune system; Inflammation; MicroRNA; ncRNA; Physical exercise

1. Introduction

Physical exercise has been widely recognized as a potent modulator of immune responses, involving intricate molecular and cellular interactions. Effects on the immune system have been shown to depend on the type, intensity, and duration of physical exercise,[1–6] which have been analyzed in recent comprehensive reviews and meta-analyses.[7–9] Acute physical exercise triggers immediate and transient alterations in immune cell distribution, function, and trafficking.[10–12] This commonly includes an initial rise in circulating immune cells, enhanced immune surveillance, and temporary suppression of immune cell function following exercise.[13–15] In addition, an increase in neutrophils during and after physical exercise,[16] as well as stimulatory effects on macrophage effector functions, including phagocytosis and antitumor activity, have been described.[17] Regular physical exercise has been associated with specific long-term adaptations leading to overall improved function of the immune system, characterized by enhanced immune cell activity, an increase in the proportion of T cells, elevated production of anti-inflammatory cytokines, and an enhanced defense against pathogens.[14,18–20] Of note,

Peer review under responsibility of Shanghai University of Sport.
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https://doi.org/10.1016/j.jshs.2023.11.001
Cite this article: Kotewitsch M, Heimer M, Schmitz B, Mooren FC. Non-coding RNAs in exercise immunology: A systematic review. *J Sport Health Sci* 2024;13:311–38.

short- and long-term adaptations of the immune system may differ by exercise type, and it has been suggested that endurance exercise, such as running or cycling, may lead to a more pronounced modification compared to resistance exercise.[21,22] Moreover, physical exercise has been suggested to affect innate as well as adaptive immunity over the entire age range.[23,24] As a consequence, a recent meta-analysis of large prospective observational studies and randomized controlled trials showed that higher levels of habitual physical activity led to a 30%−37% risk reduction of community-acquired infectious disease and infectious disease mortality as well as an increased potency of vaccination.[15]

The effects of physical exercise on the immune system are complex and involve a range of different signaling pathways with the need for concerted regulatory actions. In recent years, the involvement of non-coding RNAs (ncRNAs) has gained considerable attention, as ncRNAs are responsive to physical exercise. In general, ncRNAs are epigenetic modulators linking biologic adaptation to environmental exposures, and an ncRNA−epigenetic feedback loop has been described in which epigenetic pro- and anti-inflammatory signatures, including histone modification and DNA methylation, may specifically regulate ncRNA expression profiles.[8,25−27] ncRNAs are also involved in the transmission of hormonal and metabolic exercise responses to the immune system, adding a significant layer of complexity to this regulatory network.[28,29] ncRNAs include a diverse range of RNA molecules that do not encode proteins but exert regulatory functions on gene expression. ncRNAs can be broadly classified into subclasses, including microRNAs (miRNAs), long ncRNAs (lncRNAs), and circular RNAs (circRNAs), each exhibiting distinct characteristics and functionalities.[30] miRNAs are small ncRNAs approximately 22 nucleotides in length with the potential to bind messenger RNAs, resulting in post-transcriptional regulation through messenger RNA degradation or translational repression.[31] miRNAs have been implicated in various biological processes and pathways, including immune cell development, inflammation, and immune responses as well as associated health and disease states.[32−34] Due to their ability to regulate multiple targets, miRNAs can effectively silence entire signaling pathways, thereby exerting specific regulatory control over various biological processes.[35,36] lncRNAs, which exceed 200 nucleotides in length, also represent key regulators of gene expression at the transcriptional and post-transcriptional level by exhibiting different functions, such as acting as scaffolds for protein complexes and miRNAs; therefore, they are known as “molecular sponges”.[37] Similar functions have been identified for circRNAs, which are generated during the pre-messenger RNA splicing process; after ligation of their 3′ and 5′ ends, they form a continuous loop structure with increased resistance to conventional RNA degrading processes, resulting in a longer half-life.

Specific exercise-induced alterations in ncRNA expression profiles have been reported in various tissues and cell types, including immune cells such as lymphocytes,[38,39] monocytes,[40] natural killer cells,[41] peripheral blood mononuclear cells,[42−44] and neutrophils.[45] These exercise-induced effects on ncRNA levels may contribute to the regulation of immune cell function, cytokine production, and overall inflammatory processes. For example, miR-155 has been identified as an important regulator of homeostasis and function of the immune system.[46] miR-155-deficient mice exhibited immunodeficiency and showed increased lung airway remodeling; analysis of $CD4^+$ T cells in these mice provided evidence that miR-155 regulates production of cytokines and chemokines.[46] In humans, miR-155 is well-known to be regulated by physical exercise, linking physical activity to components of the immune system. However, a full picture on functional ncRNAs regulated by physical exercise with known targets in the immune system is missing from the literature.

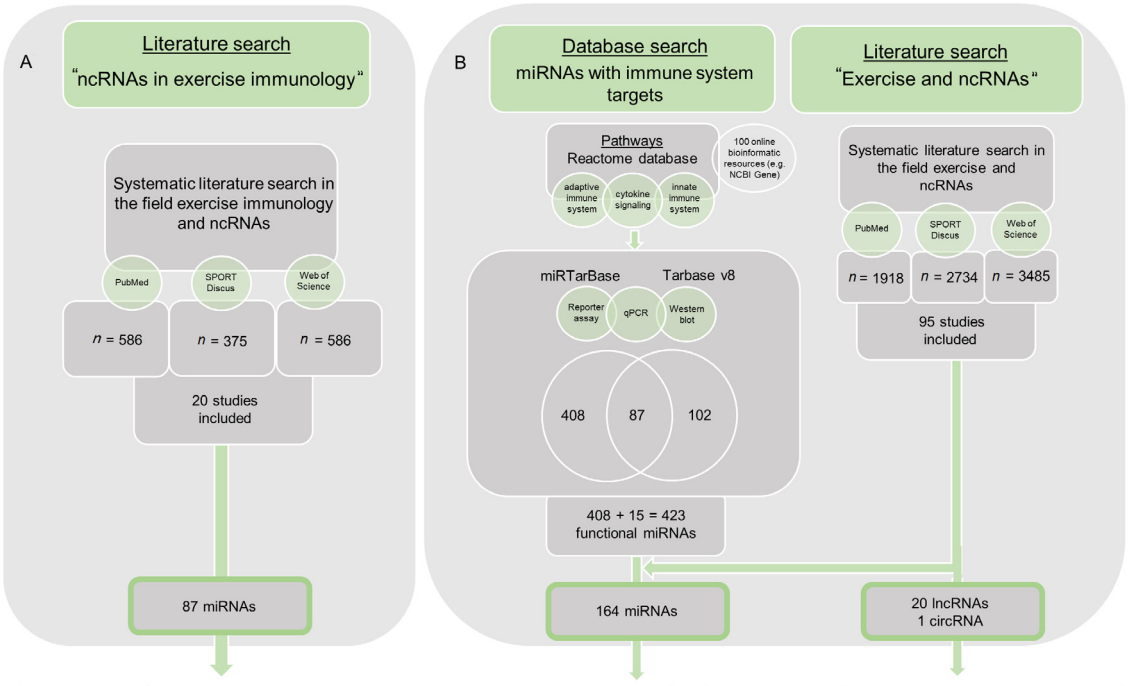
Thus, the objective of this systematic review is to identify and analyze the current body of literature pertaining to ncRNAs involved in exercise-induced immune modulation. By elucidating the specific ncRNAs that participate in immune regulation during physical exercise, we aim to gain a deeper understanding of the molecular mechanisms underlying the effects of exercise on the immune system. Such insights may have significant implications for the development and individual optimization of exercise-based interventions to strengthen immune function and improve health outcomes.

2. Methods

A systematic review was used to identify ncRNAs involved in exercise-induced immune modulation, which was followed by a qualitative analysis. The approach involved 2 separate literature searches (Fig. 1). Search A focused on reports that analyzed the effects of physical exercise on ncRNA changes in studies specifically designed to investigate the relation between physical exercise and the immune system. Search B aimed to identify all ncRNAs potentially regulated by physical exercise. ncRNAs identified in Search B were then aligned with databases on known immune system target genes (see below). To ascertain the specificity of approach B, identified ncRNAs were filtered by their functional validation (i.e., only ncRNAs with available *in vitro* experimental data were included).

2.1. Search strategy

A systematic review (PROSPERO, CRD42023408388) was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[47] and following the suggestions for reporting on qualitative summaries.[48,49] Literature searches were conducted using PubMed, Web of Science, and SPORTdiscus for “ncRNA and exercise immunology” (Search A) and “ncRNA and exercise” (Search B). The detailed search syntax by data base is provided in Supplementary Table 1. Manual searches were performed using reference lists from identified articles and reviews. Two authors (MK and BS) screened full texts for relevant reports. The individual steps of report identification, screening, and inclusion (with respective numbers) are documented in the PRISMA flow-charts (Supplementary Fig. 1 and Supplementary Fig. 2). If unclear, search results and fulfilment of



	endurance exercise[a]	
	upregulated	downregulated
validated (100%)	12 miRNAs	3 miRNAs
plausible (≥ 80%)	6 miRNAs	none
suggestive (≥ 70%)	7 miRNAs	3 miRNAs

	physical exercise	
	upregulated	downregulated
lncRNAs	6 lncRNAs	14 lncRNAs
circRNAs	1 circRNA	none

Fig. 1. Flow chart of ncRNA identification. Two different approaches were applied to identify relevant ncRNAs in exercise immunology. (A) A systematic literature search was conducted (utilizing PubMed, SPORTDiscus, and Web of Science databases) for "ncRNAs in exercise immunology". (B) Out of 1547 identified records, 20 studies were included with 87 miRNAs identified as being regulated by physical activity. To broaden the approach, a combined investigation (i.e., literature and database search) was conducted. Targets within the immune system were identified using the Reactome database.[50] Target lists were cross-referenced with experimentally validated miRNA-target databases miRTarBase[51] and Tarbase v8[52] to identify associated miRNAs. Only miRNAs validated by 3 methods (reporter gene assay, Western blot, and qPCR) were selected, and duplicates were removed subsequently. Findings were aligned with results from a second independent literature search on "physical exercise and ncRNAs" using PubMed, SPORTDiscus, and Web of Science. The search identified 95 eligible studies and reported miRNAs were filtered by miRNAs with immune targets obtained from the database search, revealing 164 specific miRNAs. Subsequently, findings from searches A and B were combined and duplicates were removed. Of note, all studies ($n = 20$) included after search A were also detected by Search B. Identified non-redundant miRNAs were categorized using evaluation criteria defined as: validated (100% of ≥3 independent studies showed identical direction of regulation), plausible (≥80%), or suggestive (≥70%). The literature search also identified 20 lncRNAs and 1 circRNA as potential regulators in exercise immunology. [a] Only miRNAs regulated by endurance exercise reached at least the category "suggestive", no miRNA described in resistance exercise fulfilled the criterion. circRNA = circular RNA; lncRNAs = long non-coding RNAs; miRNAs = microRNAs; ncRNA = non-coding RNA; NCBI = National Center for Biotechnology Information; qPCR = quantitative polymerase chain reaction.

eligibility criteria were discussed until consensus was achieved and, if necessary, a third person (FCM) was consulted to determine inclusion.

2.2. Database search

Immune system targets were identified using the open-source, open access, manually curated and peer-reviewed Reactome pathway database[50] (https://reactome.org). Targets within the innate immune system, adaptive immune system, and cytokine signaling are provided by the database. Targets were aligned with 2 different data bases on miRNA targets, the experimentally validated miRNA-target interactions database miRTarBase[51] (https://mirtarbase.cuhk.edu.cn) and DIANA-Tarbase v8[52] (https://dianalab.e-ce.uth.gr). Both databases allow the selection of different *in vitro* validation methods including reporter assays, Western blotting, and quantitative polymerase chain reaction (qPCR), all of which were selected to retrieve a validated list of functional miRNAs. Results of the 2 miRNA databases were merged, duplicates were removed, and the final list of validated functional miRNAs with known immune system targets was merged with miRNAs identified in Search B.

2.3. Eligibility criteria and data extraction

Only reports on healthy women and men ($n \geq 5$) aged ≥18 years were eligible. All study types were considered for

the analysis. Articles had to be original research (not a conference abstract, review, or book (chapter)) and be written in English (full text). Gray literatures, including reference lists, theses, or websites, were not included. Articles were excluded if (a) the article was not available as full text (after an attempt to contact the corresponding author), and (b) the description of participants and/or the intervention was not clearly described. Data were extracted by 2 reviewers (MK and BS) and tables were created including information on first author and year of publication, participants (activity/training level), type of intervention (physical exercise condition/test type applied), acute or chronic changes, sample type used for analysis, differentially expressed ncRNAs (as reported by authors), and analysis method (sequencing, microarray, qPCR). Strand information (−3p/−5p) was extracted if available.

2.4. Grouping of studies and synthesis

To provide a structured qualitative summary, studies were grouped into 2 main categories: (a) exercise type (resistance or endurance exercise) and (b) acute or chronic regulation. Studies investigating chronic regulations involved comparison of subjects/athletes with a defined (long-term) training routine to a control group, or longitudinal studies with a pre−post comparison after a defined exercise intervention. The validity of the reported findings was assessed using evaluation criteria defined as "validated" with 100% of ≥3 independent studies showing identical direction of regulation, "plausible" (≥80%), or "suggestive" (≥70%). These criteria were separately applied for the overall direction of regulation in endurance or resistance exercise, as well as for acute and chronic regulation. Thus, the certainty of the evidence was addressed using an evaluation of how directly the included studies addressed the planned question/applied methodology (measurement validity), the number of studies, and the consistency of effects across studies.

2.5. Quality assessment

Methodological quality of studies was assessed using the 11-item PEDro scale for risk of bias assessment independent of study type.[53] Studies and key outcomes were rated by 2 reviewers (MH and MK) and disagreements were discussed until consensus was reached. The researchers were not blinded to study authors, results, or publication journals.

2.6. Pathway analysis

Pathway analysis was performed against Reactome Version 85 (August 2023;[50] human targets), submitting the identified targets (Supplementary Data 1) of validated, plausible, or suggestive miRNAs to the online analysis tool (https://reactome.org). Reactome provides an overrepresentation analysis using a hypergeometric distribution test that determines whether certain pathways are enriched in the submitted data compared to what is expected by chance. A probability score, corrected for false discovery using the Benjamani−Hochberg method, is provided.

3. Results

3.1. Literature search

The literature was screened using 2 parallel approaches (Fig. 1, Supplementary Fig. 1, and Supplementary Fig. 2). Search A identified publications reporting on ncRNAs in exercise immunology (i.e., research that analyzed the effects of physical exercise on changes of the immune system and associated alterations in ncRNAs). This search identified 1547 records: $n = 586$ records on PubMed, $n = 375$ on SPORTDiscus, and $n = 586$ on Web of Science. After duplicate removal and screening of full texts, 20 studies met the eligibility criteria. Search B included a literature search for publications reporting on ncRNAs regulated by physical exercise without a specific focus on the immune system. In this approach, identified ncRNAs were filtered by a subsequent replication with 2 different target databases selecting known immunologic targets and pathways. Search B resulted in 8137 records: $n = 1918$ records on PubMed, $n = 2734$ on SPORTDiscus, and $n = 3485$ on Web of Science. After duplicate removal and screening of full texts, 95 articles[38−45,54−140] met the eligibility criteria and were included in the qualitative synthesis. Of note, Search B also identified the 20 studies[38−42,44,45,55,56,60,64,67,72,91,96,99,106,127,132,134] revealed by Search A. As a result of both searches, a total of 185 non-redundant regulated ncRNAs were identified (Fig. 1) (miRNAs, $n = 164$; lncRNAs, $n = 20$; circRNAs, $n = 1$). Eight studies reported no effect of exercise on selected ncRNAs (Supplementary Table 2). Of note, only 5 studies[71,135−138] were identified to report on lncRNAs, and 1 study[139] reported on circRNAs.

3.2. Sample type and analysis methods

Seventy-one studies[38−45,54−65,67−70,72,77−81,83,84,86,87,90,91,93−100,105−107,109−111,113−122,125−129,131−134,139,140] extracted RNA from blood or blood components, with 10 studies[38−45,60,132] specifically focusing on isolated immune cells. Nineteen studies extracted RNA from muscle tissue, 3 studies[75,103,123] from both blood and muscle. Two studies[88,89] isolated RNA from saliva and 1 study[94] from urine. Different analysis methods were used, including standard PCR-based methods for detection of candidate ncRNAs ($n = 71$). Hypothesis-free approaches included RNA sequencing ($n = 24$), next-generation sequencing ($n = 11$), microarray analysis ($n = 11$), and Nanostring technology ($n = 2$). Different definitions and statistical approaches to identify significantly altered levels of ncRNAs were applied, and 10 studies[40,41,44,45,60,84,85,92,104,116] validated their findings using PCR-based methods.

3.3. Study design and exercise and training protocols

Out of the 95 included studies,[38−45,54−140] 86 studies[39−45,54−70,72,73,75,76,78−91,93−96,98−100,102−109,111−131,133−140] used a longitudinal study design with pre-post analysis to evaluate the effects of a single exercise bout or exercise training period

Table 1
Differentially expressed microRNAs in exercise.

Study	ncRNA analysis, cells/tissue (timepoint); method	Exercise protocol/subjects	Upregulated miRNAs		Downregulated miRNAs	
			Acute	Chronic	Acute	Chronic
miRNAs						
Alack et al. (2019)[38]	Lymphocytes (trained, untrained); qRT-PCR	1) Trained: marathon runners and triathletes 2) Untrained: untrained subjects	n.a.	None	n.a.	miR-27a, miR-23a
Aoi et al. (2013)[54]	Serum (baseline, post, 4 weeks post); qRT-PCR	Healthy subjects: Acute: ergometer, 60 min, 70% VO_{2max}; Chronic: ergometer, 30 min, 3×/week, 4 weeks, 70% VO_{2max}	None	None	miR-486	miR-486
Baggish et al. (2011)[55]	Plasma (baseline, post, 1 h post); qRT-PCR	Athletes: Acute: ergometer, until VO_{2max}, 5 min recovery Chronic: rowing, 5 km, 90 days	miR-146a, miR-222, miR-21, miR-221	miR-146a, miR-222, miR-21, miR-221	None	None
Baggish et al. (2014)[56]	Plasma (baseline, post, 24 h post); qRT-PCR	Marathon	miR-146a, miR-1, miR-133a, miR-499-5p, miR-208a, miR-126, miR-134	n.a.	None	n.a.
Banzet et al. (2013)[57]	Plasma (baseline, post, 2 h post, 6 h post, 24 h post, 48 h post, 72 h post); qPCR	Recreationally active subjects: 1) Uphill walking treadmill, 30 min, 1 m/s, grade of 25% 2) Backward downhill walking treadmill, 30 min, 1m/s, grade of 25%	1) miR-181b, miR-214	None	None	None
Biss et al. (2023)[58]	Plasma (baseline, post); qRT-PCR	Recreationally active subjects: 1) EMS, 20 min, individual intensity 2) Circuit training, 20 min, 4 × 6 exercises with 5 repetitions	1) miR-206, miR-133a	n.a.	None	n.a.
Chalchat et al. (2021)[59]	Plasma (baseline, 1 h post, 24 h post, 48 h post); qRT-PCR	Athletes: Running, 24 h, greatest distance	miR-1-3p, miR-133a-3p, miR-133b, miR-208a-3p, miR-208b-3p, miR-378-3p, miR-499a-5p	None	None	None
Cheema et al. (2020)[42]	PBMCs (baseline, peak exercise, 4 h post); nanostring	Healthy subjects: Ergometer, 2 min at 60 W, increase by 30 W every 2 min until VO_{2max}	none	n.a.	miR-363-3p, miR-181a-5p (♀)	n.a.
Chilton et al. (2014)[60]	White blood cells (baseline, post, 1 h post); microarray, qPCR, pooled T-cell	Healthy subjects: Running, 30 min rest, 30 min treadmill at 80% VO_{2peak}, 60 min recovery	miR-186, miR-15a, miR-96	n.a.	None	n.a.
Clauss et al. (2016)[61]	Plasma (baseline, post, 10 weeks post, 24 h post); qPCR	1) Elite runners 2) Non-elite runners Acute: marathon Chronic: 10-week training	1) miR-1, miR-133a, miR-30a 2) miR-1, miR-133a	None	None	None
Cui et al. (2015)[62]	Plasma (baseline, post); qRT-PCR	Healthy subjects: Sprint interval ergometer, 30 s all-out, 4 min active recovery	None	n.a.	miR-1, miR-133a, miR-133b, miR-122, miR-16	n.a.
Cui et al. (2016)[63]	Plasma (baseline, post); qRT-PCR	Recreationally active subjects: 1) HIIE: running, 7 × 4 min, ~85%−95% of HR_{max} 2) Vigorous-intensity continuous running exercise, distance of HIIE	miR-1, miR-133a, miR-133b, miR-206, miR-485-5p, miR-509-5p, miR-517a, miR-518f-3p, miR-520f, miR-522, miR-553, miR-888	n.a.	None	n.a.
Cui et al. (2017)[64]	Plasma (baseline, post, 1 h post, 24 h post); qRT-PCR	Recreationally active subjects: 1) Strength endurance: 3 × 16−20 repetitions, 40% 1RM, 1 min rest 2) Muscular hypertrophy: 3 × 12 repetitions, 70% 1RM, 2 min rest 3) Maximal strength: 4 × 6 repetitions, 90% 1RM, 3 min rest	1) miR-532 2) miR-181a, miR-133b 3) miR-133b	n.a.	1) miR-208b 2) miR-133a, miR-21 3) miR-133a	n.a.
Dalle Carbonare et al. (2022)[43]	PBMCs (baseline, post); qRT-PCR	Half marathon	miR-152-3p, miR-143-3p, miR-27a-3p miR-22-3p (♀), miR-100-5p (♀), miR-216-5p (♀)	n.a.	miR-30b-3p	n.a.
Danese et al. (2018)[65]	Plasma (baseline, post); qRT-PCR	Amateur runners: 21.1 km endurance running	miR-133a, miR-206	n.a.	None	n.a.

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Table 1 (Continued)

Study	ncRNA analysis, cells/tissue (timepoint); method	Exercise protocol/subjects	Upregulated miRNAs		Downregulated miRNAs	
			Acute	Chronic	Acute	Chronic
Davidsen et al. (2011)[66]	Vastus lateralis (baseline, 12 weeks post); TaqMan miRNA assay	Healthy subjects: RE, 5×/week, 12 weeks	n.a.	miR-451	n.a.	miR-378
de Gonzalo-Calvo et al. (2015)[67]	Serum (baseline, post, 24 h post, 72 h post); qRT-PCR	Amateur runners: 1) 10 km race 2) Half marathon 3) Marathon	1) miR-150-5p 3) let-7f-2-3p, let-7d-3p, miR-125b-5p, miR-143-3p, miR-148a-3p, miR-223-3p, miR-223-5p, miR-29a-3p, miR-34a-5p, miR-424-3p, miR-424-5p	None	None	None
de Gonzalo-Calvo et al. (2018)[68]	Serum (baseline, post); qRT-PCR	Highly trained subjects: 1) 10 km race 2) Half marathon 3) Marathon	1) miR-132-3p, miR-150-5p 3) miR-21-5p, miR-27-3p, miR-29a-3p, miR-30a-5p, miR-24a-5p, miR-126-3p, miR-142-5p, miR-143-3p, miR-195-5p, miR-199a-3p	n.a.	1) miR-103a-3p, miR-139-5p, miR-590-5p 3) miR-16-5p, miR-25-3p, miR-29b-3p, miR-30b-5p, miR-103-3p, miR-106b-5p, miR-107, miR-375, miR-497-5p	n.a.
Denham et al. (2016)[69]	Whole blood (baseline, post); qPCR	Healthy subjects: Cardiorespiratory testing, treadmill: increase by 1 km/h every 2 min; or ergometer, increase by 30 W/min every 2 min	None	n.a.	miR-1, miR-133a, miR-486	n.a.
Denham et al. (2018)[70]	Whole blood (baseline, 30 min post); qPCR	Healthy subjects: 1) Acute: one-off acute sprint, 4 × 30 s maximal all out 2) Chronic: sprint interval cycling, 6 × 30 s all-out, 3×/week, 6 weeks	None	None	None	3) miR-1-3p, miR-133a-3p, miR-133b-3p, miR-486-5p
De Sanctis et al. (2021)[71]	Vastus lateralis (control, highly trained); NGS	High-intensity, life-long exercise	n.a.	miR-7847-3p, miR-4298, miR-6812-5p, miR-3911, miR-4521, miR-181a-2-3p, miR-4669, miR-4486-3p, miR-486-3p, miR-20a-5p, miR-486-5p, miR-6778-5p, miR-106a-5p	n.a.	let-7c-5p, miR-3175, miR-3197, miR-6510-5p, miR-574-5p, miR-664b-3p, miR-199a-5p, miR-193a-3p, miR-4269, miR-497-5p, miR-7110-5p, miR-5100, miR-7150, miR-4429, miR-4484, miR-320d, miR-100-5p, miR-4443, miR-3651
Dimassi et al. (2018)[72]	Circulating microparticles (baseline, post); qRT-PCR	Healthy subjects: HIIE, treadmill or ergometer, 45 min, 3×/week, 8 weeks, 70%−80% HR	n.a.	miR-150, miR-124a, miR-146a, miR-320a, mIR-21	n.a.	None
D'Souza et al. (2017)[73]	Vastus lateralis (baseline, 2 h post, 4 h post); qRT-PCR	Healthy subjects: RE, 45 min, 2 × 10 repetitions warm-up, 6 × 8−10 repetitions leg press, 8 × 8−10 repetitions knee extension, 80% 1RM	miR-133a, miR-206, miR-486, miR-378b, miR-146a, miR-23a	n.a.	none	n.a.
D'Souza et al. (2017)[74]	Vastus lateralis (active, powerlifters); qRT-PCR	Recreationally active subjects, Powerlifters	n.a.	miR-206	n.a.	miR-486, miR-499, miR-133a, miR-1
D'Souza et al. (2018)[75]	1) Plasma, 2) Vastus lateralis, 3) Exosome (baseline, post, 4 h post); qRT-PCR	Healthy subjects: Ergometer, 10 × 60 s, PPO	1) miR-222-3p, miR-21-5p, miR-126-3p 2) miR-16-5p, miR-222, miR-21-5p, miR-107 3) miR-1-3p, miR-16-5p,	n.a.	1) miR-1-3p, miR-16-5p, miR-134-3p, miR-107, miR-486-5p, miR-378a-5p 2) miR-1-3p, miR-134-3p, miR-23a-3p,	n.a.

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Table 1 (Continued)

Study	ncRNA analysis, cells/tissue (timepoint); method	Exercise protocol/subjects	Upregulated miRNAs		Downregulated miRNAs	
			Acute	Chronic	Acute	Chronic
			miR-222-3p, miR-23a-3p, miR-208a-3p, miR-150-5p, miR-486-5p, miR-378a-5p, miR-126-3p, miR-23b-3p, miR-451a, miR-186-5p		miR-208a-3p, miR-150-5p	
D'Souza et al. (2019)[76]	Vastus lateralis (baseline, 2 h post, 4 h post); qRT-PCR	Recreationally active subjects, placebo group: RE: 3 exercises, 3 × 8−10 repetitions	miR-15a, miR-451, miR-499a	n.a.	None	n.a.
Eyileten et al. (2021)[77]	Plasma (marathon runners (12−24 h post), control group); qPCR	Ultra-marathon	miR-125a-5p	miR-125a-5p	None	None
Eyileten et al. (2022)[78]	Plasma (baseline, 30 min post); qPCR	Ultra-marathon	miR-125a-5p, miR-126, miR-223	n.a.	miR-15b	n.a.
Faraldi et al. (2022)[79]	1) Plasma, 2) EVs (baseline, 30 min post); qPCR	Athletes: HIE, vertical run, 3.6 km	1) miR-10b-5p, miR-195-5p, miR-29a-3p, miR-532-3p, miR-885-5p 2) miR-143-3p, miR-17-5p, miR-532-3p, miR-874-3p, miR-885-5p	n.a.	1) miR-326, miR-33a-5p 2) miR-1-3p, miR-29a-3p, miR-424-5p	n.a.
Fernández-Sanjurjo et al. (2020)[80]	Serum (baseline, post); qRT-PCR	Professional and amateur runners: 1) 10-km run 2) Half marathon 3) Marathon (separated by 1 month)	1) miR-199b-5p, miR-424-3p, miR-33a-5p, miR-551a, miR-1537, miR-223-5p, miR-1260, let-7b-3p, miR-150-5p, miR-423-5p, miR-223-3p, miR-345-5p, miR-505-3p 2) miR-425-3p, miR-33a-5p, miR-338-3p, miR-339-5p, miR-106b-3p, miR-502-3p, miR-27a-3p, miR-660-5p, miR-505-3p, miR-100-5p, miR-22-3p, miR-30e-5p, miR-497-5p, 3) miR-1972, miR-940, miR-424-3p, miR-130b-5p, miR-223-5p, miR-145-3p, miR-181c-3p, miR-501-3p, miR-1260a, miR-675-3p, miR-345-5p, miR-424-5p, miR-1-3p, miR-34a-5p, miR-629-5p, miR-30a-5p, miR-148a-3p, miR-596, miR-10b-5p, miR-30d-5p, miR-320d	n.a.	None	n.a.
Fernández-Sanjurjo et al. (2021)[81]	Serum (baseline, post); qRT-PCR	Amateur runners: Treadmill, 6 km/h increasing by 0.25 km/h every 15 s until exhaustion	miR-26b-5p, miR-183-5p, miR-379-5p,	n.a.	None	n.a.

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Table 1 (Continued)

Study	ncRNA analysis, cells/tissue (timepoint); method	Exercise protocol/subjects	Upregulated miRNAs		Downregulated miRNAs	
			Acute	Chronic	Acute	Chronic
			miR-144-5p, let-7c-5p, miR-340-5p, miR-425-3p, miR-629-5p, let-7d-5p, miR-29b-3p, miR-21-5p, miR-106b-5p, miR-150-5p			
Fyfe et al. (2016)[82]	Vastus lateralis (baseline, post, 1 h post, 3 h post); qRT-PCR	Well-trained subjects: 1) RE: leg press, 8 × 5 repetitions, 80% 1RM 2) HIT: ergometer, 10 × 2 min, 120% lactate threshold 3) MICT: ergometer, 30 min, 80% lactate threshold	none	n.a.	1) miR-133a	n.a.
Garai et al. (2021)[83]	Exosome (baseline, 0.5 years post); Nanostring	Sedentary subjects: Resistance training, 85% HR_{max} Aerobic exercise, walking or jogging, 65% HR_{max}; 3×/week for 0.5 year	n.a.	None	n.a.	let-7a-5p, let-7g-5p, miR-130a-3p, miR-142-3p, miR-150-5p, miR-15a-5p, miR-15b-5p, miR-199a-3p, miR-199b-3p, miR-223-3p, miR-23a-3p, miR-451a-3p
Gomes et al. (2014)[84]	Plasma (baseline, post); TaqMan miRNA assay, qPCR	Half marathon	miR-1, miR-133a, miR-206	n.a.	None	n.a.
Grieb et al. (2023)[85]	Vastus lateralis (baseline, post); microarray, qPCR	Sedentary subjects: Ergometer, MICT, 60 min, 90% PPO	miR-23a-5p	n.a.	miR-1, miR-133a-3p, miR-133a-5p, miR-133b, miR-499a-5p, miR-23a-3p, miR-378a-5p, miR-128-3p, miR-27a-3p, miR-126-3p, miR-152-3p	n.a.
Guescini et al. (2015)[86]	EVs (baseline, 1 h post); qRT-PCR	Recreationally active subjects: Treadmill, 40 min, 80% VO_{2max}	miR-181a-5p	n.a.	None	n.a.
Hashida et al. (2021)[87]	Serum (baseline, post); microarray	Healthy subjects: Low-intensity RE	miR-630, miR-5703	n.a.	None	n.a.
Hicks et al. (2018)[88]	Saliva (baseline, post); NGS	Recreationally active subjects: Long-run	miR-7154-3p, miR-200b-5p, miR-5582-3p, miR-6859-3p, miR-6751-5p, miR-4419a	n.a.	miR-3671, miR-5095	n.a.
Hicks et al. (2023)[89]	Saliva (baseline, 20 min post); NGS	Athletes: 1) Group 1: acute exercise, non-contact sport (long-run, treadmill, rowing), contact sport (soccer, football) 2) Group 2: chronic exercise (season-long contact sport participation)	1) miR-4510	2) miR-29a-3p, miR-29c-3p, miR-26b-3p, miR-25-3p, miR-221-3p, miR-34a-5p, miR-708-5p, miR-30b-5p, miR-532-5p	1) miR-532-5p, miR-182-5p	2) miR-3614-5p, miR-10b-5p, miR-181a-5p, miR-1290, miR-744-5p, miR-320c, miR-26b-3p, miR-1180-3p, miR-27b-5p, miR-12136, miR-320b, miR-1307-3p, miR-151a-5p, let-7e-5p
Horak et al. (2018)[90]	Plasma (baseline, 5 weeks post, 8 weeks post); qRT-PCR	Athletes: 1) Explosive strength 2) Hypertrophic strength 3) HIIT 3×/week, 8 weeks	n.a.	1) miR-222 2) miR-93, miR-16, miR-222 3) miR-93	n.a.	1) miR-16
Kangas et al. (2017)[91]	Serum (baseline, 10 years post); qPCR	Athletes: Sprint-training	n.a.	miR-21, miR-146a	n.a.	None
Koltai et al. (2018)[92]	Muscle (athletes, sedentary subjects); microarray, qRT-PCR	Athletes or sedentary subjects	n.a.	None	n.a.	miR-7
Krammer et al. (2022)[93]	Dried blood spots (baseline, 12 weeks post); qPCR	Sedentary subjects: Resistance, 3×/week; endurance 30−60 min, 2×/week; 12 weeks	n.a.	None	n.a.	miR-23a, miR-30e

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Table 1 (Continued)

Study	ncRNA analysis, cells/tissue (timepoint); method	Exercise protocol/subjects	Upregulated miRNAs		Downregulated miRNAs	
			Acute	Chronic	Acute	Chronic
Kuji et al. (2021)[94]	1) Plasma, 2) urine (baseline, post, 2 h post, 1 day post); Illumina	Marathon	1) miR-424-5p, miR-361-5p, miR-223-3p, miR-223-5p 2) miR-218-5p, miR-3158-3p, miR-3158-5p, miR-517a-3p 1), 2) miR-582-3p, miR-23a-3p, miR-199a-3p	n.a.	None	n.a.
Lai et al. (2023)[95]	EVs (baseline, post); NGS	Recreationally active: 1500 m freestyle swimming	miR-144-3p, miR-145-3p, miR-509-5p	n.a.	miR-891b, miR-890	n.a.
Li et al. (2018)[96]	Serum (baseline, post, 3-month post); qRT-PCR	Basketball athletes: Acute: CPET, increase 2 J/s every 6 s, 60−70 rpm, VO_{2max} Chronic: 3-month basketball season	None	None	miR-146a, miR-21, miR-221, miR-210	miR-208a, miR-221
Li et al. (2020)[97]	Plasma (swimming group, control group); Illumina	Professional swimming group, Healthy subjects	n.a.	miR-451a, miR-486-5p, miR-423-5p, let-7b-5p	n.a.	miR-21-5p, let-7f-5p, miR-148a-3p, miR-146a-5p
Li et al. (2021)[98]	Serum (baseline, 30 min post); qPCR	Healthy subjects: Run, 5 km, 51%−52% VO_{2max}	miR-1, miR-146a, miR-155, miR-210	n.a.	none	n.a.
Liu et al. (2020)[99]	Serum (baseline, 12 weeks post); NGS	Healthy subjects: RE, 3×/week, 12 weeks	n.a.	miR-363-3p	n.a.	miR-146b-3p, miR-146b-5p, miR-155-3p, miR-181a-2-3p, miR-181b-5p, miR-103a-3p, miR-103b, miR-143-5p, miR-146b-3p, miR-146b-5p, miR-17-5p, miR-199a-5p, miR-204-3p, miR-378c, miR-448, miR-125b-1-3p, miR-128-3p, miR-133a-3p, miR-223-3p, miR-499a-5p
Maggio et al. (2023)[100]	EVs 1) baseline, post, 1 h post, 2 h post, 6 h post, 24 h post; 2) baseline, post, 1 h post, 2 h post; 3) baseline, post); qRT-PCR	Healthy subjects: 1) Acute aerobic exercise, treadmill, moderate intensity, 3×/week, 2 month, 40 min at 55% VO_{2max} 2) Acute maximal aerobic exercise: treadmill to exhaustion 3) Altitude aerobic exercise: treadmill, 23 sessions, 15 days, increase by 1 km/h every 3 min until exhaustion	1) miR-146a, miR-206, miR-133b 2) miR-206, miR-133b, miR-486-5p, miR-181a-5p, miR-16	n.a.	None	n.a.
Mancini et al. (2021)[101]	Vastus lateralis (football players, untrained elderly subjects); qRT-PCR	Football players Untrained subjects	n.a.	None	n.a.	miR-1303
Margolis et al. (2017)[102]	Vastus lateralis (baseline, post, 3 h post); qRT-PCR	Active subjects: Ergometer, 90 min, 2.2 liter/m	miR-206	n.a.	None	n.a.
Margolis et al. (2022)[103]	1) Serum, 2) vastus lateralis (baseline, post); qRT-PCR	Recreationally active subjects: High aerobic exercise, 2 × 72 h, 3×/day weighted run, 1×/day unweighted, 30%−65% VO_{2peak}	n.a.	2) miR-122-5p, miR-124-3p, miR-134-5p, miR-141-3p, miR-200b-3p, miR-200c-3p, miR-221-3p, miR-222-3p, miR-224-5p, miR-24-3p	n.a.	1) let-7a-5p, mIR-122-5p, miR-125-5p, miR-126-3p, miR-143-3p, miR-146a-5p, miR-150-5p, miR-19a-3p, miR-21-5p, miR-221-3p, miR-222-3p, miR-223-3p, miR-23a-3p, miR-25-3p, miR-27a-3p,

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Table 1 (Continued)

Study	ncRNA analysis, cells/tissue (timepoint); method	Exercise protocol/subjects	Upregulated miRNAs		Downregulated miRNAs	
			Acute	Chronic	Acute	Chronic
						miR-29a-3p, miR-30d-5p, miR-423-5p, miR-574-3p, miR-885-5p, miR-92a-3p, miR-107, miR-130b-3p, miR-148a-3p, miR-15a-5p, miR-26b-5p, miR-30e-5p, miR-374-5p, miR-103a-3p, miR-15b-5p, miR-16-5p, miR-191-5p, miR-22-3p, miR-24-3p, miR-26a-5p 2) miR-204-5p, miR-10a-5p, miR-196a-5p
Massart et al. (2021)[104]	Skeletal muscle (baseline, 10 days post, 14 days post); NGS, qRT-PCR	Sedentary subjects: Ergometer, 1 h at 80% VO_{2peak}, 14 days	n.a.	miR-451a, miR-107, miR-19b-3p	n.a.	miR-133a-5p, miR-1-5p
Min et al. (2016)[105]	Plasma (baseline, post, 24 h post); qRT-PCR	Marathon	miR-1, miR-133a, miR-134, miR-206	n.a.	None	n.a.
Mooren et al. (2014)[106]	Plasma (baseline, post, 24 h post); qRT-PCR	Marathon	miR-1, miR-133a, miR-206, miR-208b, miR-499	n.a.	None	n.a.
Nair et al. (2020)[107]	Exosome (baseline, post, 3 h post); Illumina	1) Sedentary subjects 2) Trained subjects Ergometer, 40 min, 70% HR	1) miR-223-3p, miR-495-3p, miR-29b-3p, miR-218-5p, miR-451a, miR-384, miR-505-3p, miR-203a-3p 2) miR-383-5p, miR-339-5p, miR-874-3p, miR-34b-3p, miR-129-2-3p, miR-138-1-3p, miR-671-3p, miR-885-5p	n.a.	1) miR-4433b-3p, miR-378c, miR-151b, miR-151a-5p 2) miR-206, miR-486-5p, miR-148a-3p, let-7b-5p, miR-629-5p, miR-16-2-3p	n.a.
Nielsen et al. (2010)[108]	Vastus lateralis (baseline, post, 3 h post); TaqMan miRNA assay	Trained subjects: Acute: ergometer, 60 min, 65% PPO Chronic: ergometer, 60−150 min, 5×/week, 12 weeks; 1 × 85%−91% PPO for 70−80 min, 1 × 75%−81% PPO for 75−81 min, 1 × 60%−66% PPO for 60−80 min, 1 × 55%−61% PPO for 120−150 min	miR-1, miR-133a	None	None	None
Nielsen et al. (2014)[109]	Plasma (baseline, post, 1 h post, 3 h post); qRT-PCR	Trained subjects: Acute: ergometer, 60 min, 65% PPO Chronic: ergometer, 60−150 min, 5×/week, 12 weeks; 1 × 85%−91% PPO for 70−80 min, 1 × 75%−81% PPO for 75−81 min, 1 × 60%−66% PPO for 60−80 min, 1 × 55%−61% PPO for 120−150 min	miR-338-3p, miR-330-3p, miR-223, miR-143, miR-139-5p, miR-1	miR-103, miR-107	miR-106a, miR-221, miR-30b, miR-151-5p, let-7i, miR-146a, miR-652, miR-151-3p	miR-342-3p, let-7d, miR-766, miR-25, miR-148a, miR-185
Pastuszak-Lewandoska et al. (2020)[39]	Lymphocytes (baseline, 12 h post); qRT-PCR	Ultra-marathon	miR-155, miR-223	n.a.	None	n.a.
Pietrangelo et al. (2023)[110]	EVs (active, inactive); qRT-PCR	Active subjects, sedentary subjects	n.a.	miR-378-5p, miR-27a-3p, miR-92a-3p	n.a.	miR-126-3p, miR-23a-3p, miR-133a, miR-206, miR-34a-5p
Podgórski et al. (2022)[140]	Whole blood (baseline, 1 week, 4 weeks, 7 weeks, 10 weeks); qRT-PCR	Active subjects: Volleyball, 10 microcycles/week, 131 training units, 10 weeks, week 1−3, 80% aerobic effort, week 4−6, 60% aerobic effort, week 7−10, 80% power-oriented training	n.a.	miR-320a, miR-486	n.a.	miR-223

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Table 1 (Continued)

Study	ncRNA analysis, cells/tissue (timepoint); method	Exercise protocol/subjects	Upregulated miRNAs		Downregulated miRNAs	
			Acute	Chronic	Acute	Chronic
Radom-Aizik et al. (2010)[45]	Neutrophils (baseline, post); microarray, qRT-PCR	Non-athletes: Acute ergometer exercise test, 20 min (10 × 2 min bouts of constant work rate); 76%−77% VO_{2peak}	miR-485-3p, miR-520d-3p, miR-181b, miR-1238, miR-193a-3p, miR-1225-5p, miR-145, miR-197, miR-212, miR-223, miR-340, miR-365, miR-505, miR-629, miR-638, miR-939, miR-940	n.a.	miR-130a, miR-151-5p, miR-126, miR-20a, miR-106a, miR-20b, miR-17, miR-93, miR-130b, miR-16, let-7i, miR-107, miR-185, miR-18a, miR-18b, miR-194, miR-22, miR-363, miR-660, miR-96, miR-125a-5p	n.a.
Radom-Aizik et al. (2012)[44]	PBMCs (baseline, post); microarray, qRT-PCR	Non-athletes: Acute ergometer exercise test, 20 min (10 × 2 min bouts of constant work rate); 76%−77% VO_{2peak}	miR-181a-2, miR-181b, miR-363, miR-1225-5p, miR-21, miR-181a, miR-181c, miR-338-3p, miR-26b, miR-132, miR-15a, miR-939, miR-7, miR-140-5p, miR-940	n.a.	miR-451, miR-486-5p, miR-125b, let-7e, miR-320, miR-151-5p, miR-31, miR-125a-5p, miR-99b, miR-652, miR-151-3p, miR-130a, miR-126, miR-199b-3p, miR-23b, miR-221, miR-199a-5p, miR-584, miR-145	n.a.
Radom-Aizik et al. (2013)[41]	Natural killer cells (baseline, post); microarray, qRT-PCR	Non-athletes: Acute ergometer exercise test, 20 min (10 × 2 min bouts of constant work rate); 76%−77% VO_{2peak}	miR-142-3p, miR-142-5p, miR-192, miR-29a, miR-29b, miR-29c, miR-30e, miR-338-3p, miR-363, miR-590-5p, miR-7	n.a.	let-7e, miR-126, miR-126, miR-130a, miR-151-5p, miR-199a-3p, miR-199a-5p, miR-221, miR-223, miR-326, miR-328, miR-652	n.a.
Radom-Aizik et al. (2014)[40]	Monocytes (baseline, post); microarray, qRT-PCR	Non-athletes: Acute ergometer exercise test, 20 min (10 × 2 min bouts of constant work rate); 82% VO_{2peak}	miR-29b, miR-29c, miR-1305, miR-362-3p, miR-660, miR-324-3p, miR-1202, miR-140-5p, miR-532-5p, miR-362-5p, miR-30e, miR-532-3p, miR-15a, miR-338-3p	n.a.	miR-199a-3p, miR-130a, miR-151-5p, miR-221, miR-23b	n.a.
Ramos et al. (2018)[111]	Plasma (baseline, post); qRT-PCR	Healthy subjects: Treadmill: 1) Variable intensity: 30 × 1 min at 6, 7 or 8 mile/h 2) Variable duration: 7 × 1 mile/h for 30, 60 or 90 min	1) 6 miles/h: miR-24, miR-146a, miR-133a, miR-222 7 miles/h: miR-1 2) 30 min: miR-133a, miR-222 60 min: miR-24, miR-146a, miR-133a, miR-222 90 min: miR-133a	n.a.	None	n.a.
Russell et al. (2013)[112]	Vastus lateralis (baseline, 3 h post, 2 days post); qRT-PCR	Healthy subjects: Acute: ergometer, 60 min, 70% VO_{2peak} Chronic: ergometer, 4 × 45 min, 1 × 60 min, 1 × 90 min, 1×/day, 10 days, 75% VO_{2peak}	None	miR-1, miR-29b	None	miR-31
Sandmo et al. (2022)[113]	Serum (baseline, 1 h post, 12 h post); qRT-PCR	Active subjects: HIE	miR-1-3p, miR-143, miR-206	n.a.	let-7c-5p, miR-7-5p, miR-17-5p, miR-106b-5p	n.a.
Sansoni et al. (2018)[114]	Whole blood (baseline, 4 weeks post, 8 weeks post); qRT-PCR	Active subjects: Sprint, 18 × 15 m, 3×/week, 8 weeks	n.a.	miR-93-5p, miR-148-3p	n.a.	miR-23a-3p, miR-100-5p, miR-24-3p, miR-122-5p, miR-125-5p
Sapp et al. (2020)[115]	Serum (baseline, post); qRT-PCR	Moderate active subjects: 1) Moderate-intensity continuous bout, ergometer, 30 min, 70−80 rpm, 60% PPO	1) miR-150-5p 2) miR-21-5p, miR-126-3p, miR-126-5p,	n.a.	None	n.a.

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Table 1 (Continued)

Study	ncRNA analysis, cells/tissue (timepoint); method	Exercise protocol/subjects	Upregulated miRNAs		Downregulated miRNAs	
			Acute	Chronic	Acute	Chronic
		2) HIIT, ergometer, 6 min 40% PPO, 3-min intervals 85% PPO, 4-min intervals 40% PPO	miR-150-5p, miR-155-5p, miR-181b-5p			
Sawada et al. (2013)[116]	Serum (baseline, post, 1 h post, 1 day post, 3 days post); microarray, qRT-PCR	Active subjects: RE: 2 consecutive exercises, 10 × 5 sets, 70% RM	miR-149	None	None	miR-146a, miR-221
Schmitz et al. (2017)[117]	Capillary blood (earlobe) (baseline, post); qRT-PCR	Moderate-trained subjects: Run, 3×/week, 4 weeks, 1) HIIT: 4 × 30 s, all-out 2) LIT: 25 min, <75% HR_{max} 3) proHIIT: 4−7 × 30 s, all-out	None	2) miR-126-3p 3) miR-126-3p, miR-126-5p	None	1), 2) miR-126-3p, miR-126-5p
Schmitz et al. (2018)[118]	Capillary blood (earlobe) (baseline, post); qRT-PCR	Moderate-trained subjects: Run, 2×/week, 4 weeks, 1) 4 × 30 HIIT group: 4 × 30 s run (all-out, 30 s recovery) 2) 8 × 15 HIIT group: 8 × 15 s run (all-out, 15 s recovery)	1) miR-222, miR-29c	None	None	None
Schmitz et al. (2019)[119]	Capillary blood (earlobe) (baseline, post); qRT-PCR	Moderate-trained subjects: Run, 4 × 30 s all-out running, 4 weeks, 1) Group 1: 4 × 30:30 (30 s sprint, 30 s recovery) 2) Group 2: 4 × 30:180 (30 s sprint, 180 s recovery)	1) miR-96-5p, miR-24 2) miR-24, miR-96-5p, miR-143	1) miR-126 2) miR-24, miR-126, miR-143	None	1) miR-96-5p 2) miR-96-5p
Schmitz et al. (2019)[120]	Capillary blood (earlobe) (baseline, post); qRT-PCR	Moderate-trained subjects: Run, 2×/week, 4 weeks, 1) 4 × 30 HIIT group: 4 × 30 s run (all-out, 30 s recovery) 2) 8 × 15 HIIT group: 8 × 15 s run (all-out, 15 s recovery)	miR-98-3p, miR-125a-5p	n.a.	None	n.a.
Shah et al. (2017)[121]	Plasma (baseline, peak exercise); Illumina	Healthy subjects: CPET, 5−15 W/min, VO_{2max}	miR-181b-5p, miR-185-5p	n.a.	None	n.a.
Sieland et al. (2021)[122]	Plasma (baseline, post); qRT-PCR	Healthy subjects: Treadmill, 20 min, 1) High-intensity, 100% individual anaerobic threshold 2) Low-intensity, 80% individual anaerobic threshold 3) Low-intensity BFR, 80% individual anaerobic threshold	1) miR-142-5p, miR-197-3p 2) miR-142-5p, miR-197-3p, miR-342-3p 3) miR-342-3p, miR-424-5p	n.a.	none	n.a.
Silver et al. (2020)[123]	1) EVs; 2) muscle (baseline, post, 3 h post); qRT-PCR	Healthy subjects: Ergometer, 5 min warm-up at 50 W, 60 min at self-selected cadence, 70% VO_{2peak}	2) miR-16	n.a.	2) miR-133a	n.a.
Telles et al. (2021)[124]	Vastus lateralis (baseline, post, 4 h post, 8 h post); qRT-PCR	Untrained subjects: 1) RE: leg extension, 2 × 10 repetitions 2) HIIE: sprint, 12 × 1 min, VO_{2peak} 3) Concurrent exercise: RE followed by HIIE	1) miR-23a-3p, miR-133a-3p, miR-133b, miR-181a-3p, miR-486 2) miR-1-3p, miR-23a-3p, miR-133a-3p, miR-133b, miR-181a-3p, miR-206, miR-486 3) miR-1-3p, miR-23a-3p, miR-133a-3p, miR-133b, miR-181a-3p, miR-206, miR-486	n.a.	None	n.a.
Tonevitsky et al. (2013)[125]	Whole blood (baseline, post, 30 min post, 1 h post); microarray	Professional athletes: Treadmill, 30 min, 80% VO_{2max}	miR-21-5p, miR-24-2-5p, miR-27a-5p, miR-181a-5p	n.a.	None	n.a.
Uhlemann et al. (2014)[126]	Plasma 1) baseline, post, 5 min post; 2) baseline, 10 min, 15 min, 30 min, 60 min, 120 min, 180 min, 240 min, 1 h post, 24 h post; 3) baseline, post; 4) baseline, post, 1 h post; qRT-PCR	Healthy subjects: 1) Study 1: maximal spiroergometry, increase by 25 W every 2 min 2) Study 2: ergometer, 4 h, 70% anaerobic threshold 3) Study 3: marathon 4) Study 4: RE, 3 × 15 repetitions	1) miR-126 2) miR-126 3) miR-126, miR-133 4) miR-133	n.a.	None	n.a.
Van Craenenbroeck et al. (2015)[127]	Plasma (baseline, 10 min after peak exercise); qRT-PCR	Healthy subjects: CPET, individualized ramp protocol, 8−10 min, 10−20 W/min, VO_{2peak}	miR-150	n.a.	None	n.a.
				n.a.	None	n.a.

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Table 1 (Continued)

Study	ncRNA analysis, cells/tissue (timepoint); method	Exercise protocol/subjects	Upregulated miRNAs		Downregulated miRNAs	
			Acute	Chronic	Acute	Chronic
Vogel et al. (2019)[128]	Plasma (baseline, post); qRT-PCR	Healthy subjects: RE 1) 4 × 75 repetitions, BFR, 30% 1RM 2) 4 × 75 repetitions, 30% 1RM 3) 3 × 30 repetitions, 70% 1RM	miR-139-5p, miR-143-3p, miR-195-5p, miR-197-3p, miR-30a-5p, miR-10b-5p			
Wahl et al. (2016)[129]	Serum (baseline, post, 30 min post, 1 h post, 3 h post); qPCR	Triathletes: Ergometer, 1) High-volume training: 2 h, 55% PPO 2) HIT: 4 × 4 min, 90%−95% PPO, 3 min active recovery 3) Sprint-interval training: 4 × 30s, all-out, 7.5 min active recovery	3) miR-126	n.a.	None	n.a.
Widmann et al. (2022)[130]	Skeletal muscle (baseline, 6 weeks post); qPCR	Sedentary subjects: Ergometer: 3×/week: 1) MICT: 60 min, 90% lactate threshold 2) HIIT: 10 min warm-up, 4 × 4 min interval at 90% HR_{max}	n.a.	1), 2) miR-379-5p, miR-10a-5p, miR-497-5p, miR-3613-5p, miR-139-3p, miR-3180-3p, miR-708-5p, miR-503-5p, miR-26-5p, miR-21-5p, miR-3613-3p 1) miR-199a-3p, miR-199b-3p, miR-432-5p, miR-487b-3p, miR-4284, miR-499a-5p, miR-433-3p, miR-34a-5p, miR-424-3p, miR-615-3p, miR-4720-5p, miR-382-5p 2) miR-7110-5p, miR-664b-3p, miR-505-5p, miR-134-5p, miR-146b-5p	n.a.	1), 2) miR-8063, miR-619-5p, miR-1180-3p 1) miR-3188, miR-6790-5p, miR-6806-3p, miR-339-3p
Xhuti et al. (2023)[131]	Plasma (baseline, post); qRT-PCR	Sedentary subjects: RE, 3×/week, 12 weeks, 10−15 repetitions	n.a.	miR-23a, miR-27a, miR-146a, miR-92a	n.a.	None
Xiao et al. (2022)[132]	Leukocytes (active, inactive); microarray, qRT-PCR	Canoeing athletes, inactive subjects	n.a.	None	n.a.	150
Yin et al. (2020)[133]	Plasma (baseline, post, 24 h post); qRT-PCR	Active subjects: 8-km run	miR-1-3p, miR-133a-3p, miR-133b	n.a.	None	n.a.
Zhou et al. (2020)[134]	Whole blood (baseline, post); qRT-PCR	Healthy subjects: 1) Acute exercise testing: ergometer, 60 min at 70% VO_{2peak} 2) CPET: 3-min rest, 3-min unloaded, workload increase until VO_{2peak}	1) miR-21	n.a.	2) miR-20a	n.a.
lncRNAs						
Bonilauri et al. (2020)[135]	Skeletal muscle (baseline, post); qRT-PCR	Untrained subjects: 1) HIIT, ergometer, 3×/week, 4 × 4min >90% VO_{2peak}; treadmill, 45 min, 70% VO_{2peak} 2) RE, 4 × 8−12 repetitions, 2×/week 3) Combined training, RE, 4×/week; ergometer, 5×/week, 30 min, 70% VO_{2peak} 4) Endurance training, ergometer, 60 min, 5×/week, 8 weeks, 70% lactate threshold	2) CYTOR[a]	n.a.	None	n.a.
De Sanctis et al. (2021)[71]	Vastus lateralis (control, highly trained); NGS	High-intensity, life-long exercise	n.a.	RP11-48O20.4, SNHG12, TP73-AS1	n.a.	SNHG7, ZFSA1, GAS5, SNHG14, SNHG16, HOXD-AS1, EMX2OS, HOTAIRM1, SNHG15, LINC00152, SNHG1, HOXC-AS1
Pandorf et al. (2020)[136]	Vastus lateralis (baseline, post); qRT-PCR	Sedentary subjects: HIIT: RE, 4 × 7 repetitions; rowing, 4 × 4 min, 90% VO_{2max}	IIa MHC	n.a.	II× MHC	n.a.

(*continued on next page*)

Table 1 (Continued)

Study	ncRNA analysis, cells/tissue (timepoint); method	Exercise protocol/subjects	Upregulated miRNAs		Downregulated miRNAs	
			Acute	Chronic	Acute	Chronic
Trewin et al. (2022)[137]	Vastus lateralis (baseline, post, 3 h post); qRT-qPCR	Healthy subjects: Ergometer, 1 h, 70% VO_{2peak}	TUG1	n.a.	None	n.a.
Wohlwend et al. (2021)[138]	vastus lateralis (baseline, 3 h post); qRT-PCR	Healthy subjects: RE, n.a.	CYTOR	n.a.	None	n.a.
circRNAs						
Meinecke et al. (2020)[139]	Plasma (baseline, post, 24 h post); qPCR	Marathon	None	n.a.	MBOT2	n.a.

Notes: Information on significantly regulated ncRNAs was extracted from eligible studies according to authors' information. For studies involving a control group, significant between-group differences were extracted. Strand information (−3p/−5p) was extracted if available.

[a] There were 205 lncRNAs differentially expressed after HIIT, 43 lncRNAS after RE, 15 lncRNAs after combined training, and 52 lncRNAs after endurance training.

Abbreviations: BFR = blood flow-restriction; circRNA = circular RNA; CPET = cardiopulmonary exercise testing; CYTOR = cytoskeleton regulator RNA; EMS = electromyostimulation; EVs = extracellular vesicles; HI(I)E = high-intensity (interval) exercise; HI(I)T = high-intensity (interval) training; HR = heart rate; HR_{max} = maximum heart rate; IIa MHC = major histocompatibility complex class 2a; lncRNA = long non-coding RNA; LIT = low-intensity training; MBOAT2 = membrane bound O-acyltransferase domain containing 2; MICT = moderate-intensity continuous training; miRNA = microRNA; n.a. = not applicable; ncRNAs = non-coding RNAs; NGS = next-generation sequencing; PBMCs = peripheral blood mononuclear cells; PPO = peak power output; qPCR = quantitative polymerase chain reaction; qRT-PCR = quantitative real-time polymerase chain reaction; RE = resistance exercise; RM = repetition maximum; RNA = ribonucleic acid; rpm = revolutions per minute; TUG1 = taurine up-regulated 1; VO_{2max} = maximal oxygen consumption; VO_{2peak} = peak oxygen uptake.

(Table 1). Nine studies[38,71,74,77,92,97,101,110,132] investigated intergroup effects between an exercise intervention group and a control group. Fifty-seven studies[39–45,56,58,60,62–65,68,69,73,75,76,78–82,84–88,94,95,98,100,102,105–107,111,113,115,120–129,133–139] examined the acute effects of exercise on changes in miRNA levels, 21 studies[38,66,71,72,74,83,90–93,97,99,101,103,104,110,114,130–132,140] examined chronic exercise effects (resistance exercise, $n = 6$; endurance exercise, $n = 15$), and 17 studies[54,55,57,59,61,67,70,77,89,96,108,109,112,116–119] investigated changes for both conditions. The largest body of studies investigated the effect of endurance exercise. In detail, 10 studies[40–42,44,45,69,81,121,127,134] analyzed changes during cardiopulmonary exercise testing (ergometer, treadmill), 18 studies[39,43,56,61,65,67,68,77,78,80,84,94,105,133,139] focused on long distance running (marathon, 5-km race, *etc.*), 23 studies[38,54,57,60,75,85,86,95,98,100,102–104,107–109,111,112,122,123,125,132,137] investigated various aerobic exercises (e.g., cycling, swimming, and moderate-intensity continuous training), 16 studies[62,63,70,72,79,91,113–115,117–120,129,130,136] used high-intensity (interval) training, 3 studies[89,101,140] analyzed team sports (e.g., soccer and volleyball), 6 studies[71,82,90,124,126,135] investigated resistance exercise and high-intensity (interval) training or aerobic exercise in separate subgroups, 2 studies[83,93] analyzed combined resistance and aerobic exercise, and 2 studies[55,96] investigated cardiopulmonary exercise testing and aerobic exercise in combination. Only 12 studies[58,64,66,73,74,76,87,99,116,128,131,138] investigated the specific effect of resistance training on ncRNA levels (Table 1).

3.4. Identified ncRNAs by exercise modality

A total of 164 miRNAs with targets in the immune system were identified as being regulated by physical exercise and were categorized by the aforementioned definition as validated (100% of studies reporting identical effects, with ≥3 studies available), plausible (≥80% of studies), or suggestive (≥70% of studies) (Table 2). For resistance exercise, miR-206 was validated as it showed significant upregulation in 4 independent studies.[58,73,74,124] miR-133a was identified as plausible as it showed significant downregulation in 4 independent studies[64,74,82,99] and upregulation in 1 study.[73] No miRNAs were categorized as suggestive for resistance exercise. For endurance exercise, 85 miRNAs were detected in fewer than 3 independent studies, and 48 miRNAs showed <70% concordance of regulation over independent studies. The remaining miRNAs were categorized as follows: 15 miRNAs showed 100% concordance in their regulation and were categorized as validated (Table 2), with 12 miRNAs being consistently elevated after endurance exercise, and 3 miRNAs being consistently downregulated; 6 miRNAs were upregulated in ≥80% of studies and were thus classified as plausible; 10 miRNAs were categorized as suggestive as more than 70% of studies suggested concordance in regulation, with 7 miRNAs being upregulated and 3 suggesting downregulation by endurance exercise. A separate analysis of acute and chronic effects using the categories explained above revealed 22 miRNA acutely up-regulated and 1 miRNA (miR-130a) acutely downregulated during endurance exercise (Supplementary Table 3). Only miR-206 was validated as upregulated by acute resistance exercise. No miRNA was identified as being chronically regulated with the required evidence. The systematic literature search identified only 6 studies[71,135–139] reporting effects of physical exercise on other ncRNAs in healthy individuals, including a total of 6 and 14 lncRNAs with higher or lower expression after physical exercise, respectively (Table 1). Out of these, only 1 lncRNA, cytoskeleton regulator RNA (CYTOR), was reported in 2 independent studies.[135,138] Only 1 study[139] reporting on changes in circRNAs (MBOAT2) was identified.

Table 2
Summary of validated microRNAs in exercise immunology.

miRNA	Studies (*n*)/ direction	Immune system target genes	Exercise mode/studies (*n*)	Acute/chronic regulation/ studies (*n*)	Sample/studies (*n*)
Endurance validated	**Upregulated**				
15a	3 ↑	*IRAK2, CDKN1A, CHUK, BCL2, CCND1, VEGFA, FOXO1, CRKL*	• Aerobic exercise • Cardio(pulmonary) exercise testing (2)	ACUTE	Blood
29c	4 ↑	*COL3A1, ITGB1, CDC42, AKT2, BCL2, MCL1, MMP2, PTEN*	• HI(I)T • cardio(pulmonary) exercise testing (2) • team sports	Acute (3)/chronic (1)	Blood (3)/saliva (1)
30a	3 ↑	*PIK3CD, CD99, BECN1, HSPA5, TP53, ATF1, ATG5, NCAM1, VIM*	• Long-distance running (3)	Acute	Blood
30e	3 ↑	*NFKBIA, TP53*	• Long-distance running • Cardio(pulmonary) exercise testing (2)	Acute	Blood
132	3 ↑	*RAF1, KLHL11, MAPK1, CDKN1A, FOXO1*	• Long-distance running (2) • Cardio(pulmonary) exercise testing	Acute	Blood
142	3 ↑	*RAC1, HMGB1, Rab3a, CTNNB1, PTPN23, PTEN, SOCS1, ITGAV, SMAD3, IL6ST*	• Long-distance running • Cardio(pulmonary) exercise testing • Aerobic exercise	Acute	Blood
143	7 ↑	*KRAS, HRAS, NFATC1, AKT1, MAPK7, CD44, BCL2, PTGS2, ABL2, FSCN1, SDC1*	• Long-distance running (3) • HI(I)T (2) • Cardio(pulmonary) exercise testing • Aerobic exercise	Acute	Blood
155	3 ↑	*MYD88, IRAK3, PDCD4, TAB2, NFKB1, PIK3R1, BCL10, INPP5D, SOCS1, RNF123, IKBKE, JUN, FADD, RHOA, SDCBP, ANXA2, NOS3, NOS2, DOCK1, FOXO3, MYC, CSF1R*	• Long-distance running (2) • HI(I)T	Acute	Blood
181a	6 ↑	*CARD11, RAP1B, HRAS, KRAS, CBLB, MAP2K1, MAPK1, DDX3X, BCL2, PRKCD, ATG5, IFNG, CDKN1B, BCL2L11, TIMP1, RALA*	• Cardio(pulmonary) exercise testing • HI(I)T (2) • Aerobic exercise (3)	Acute	Blood (5)/muscle (1)
181b	5 ↑	*PTEN, RAP1B, CREB1, FOS, BCL2, CYLD*	• Cardio(pulmonary) exercise testing (4) • Aerobic exercise	Acute (4)/chronic (1)	Blood
338	5 ↑	*ADAM17, IRS2, MMP2*	• Long-distance running • Cardio(pulmonary) exercise testing (3) • Aerobic exercise	Acute	Blood
451a	4 ↑	*ATF2, MIF, CPNE3, ADAM10, RAB14, IL6R*	• Aerobic exercise (4)	Acute (2)/chronic (2)	Blood (3)/muscle (1)
	Downregulated				
let-7e	3 ↓	*MMP9, CCND1, FASLG*	• Cardio(pulmonary) exercise testing (2) • Team sports	Acute (2)/chronic (1)	Blood (2)/saliva (1)
103a	3 ↓	*STAT1, CREB1*	• Long-distance running (2) • HI(I)T	Acute (2)/chronic (1)	Blood
130a	4 ↓	*TNF*	• Cardio(pulmonary) exercise testing (4)	Acute	Blood
Plausible	**Upregulated**				
21	12 ↑ 3 ↓	*PTEN, RASGRP1, MYD88, VHL, IRAK1, MMP9, BCL2, APAF1, LRRFIP1, EIF4A2, SMAD7, IL12A, SMARCA4, FASLG, MTAP, PDCD4, STAT3*	*Upregulated* • Long-distance running (2) • HI(I)T (4) • Cardio(pulmonary) exercise testing (2) • Aerobic exercise (4) *Downregulated* • Cardio(pulmonary) exercise testing • HI(I)T • Aerobic exercise	Acute (9)/chronic (6)	Blood (13)/muscle (2)

(*continued on next page*)

Table 2 (Continued)

miRNA	Studies (*n*)/ direction	Immune system target genes	Exercise mode/studies (*n*)	Acute/chronic regulation/ studies (*n*)	Sample/studies (*n*)
29b	5 ↑ 1 ↓	*COL1A1, COL3A1, CDC42, AKT2, AKT3, HMGB1, HUWE1, BCL2, GRN, STAT3, MCL1, VEGFA, MMP2*	*Upregulated* • Long-distance running • Cardio(pulmonary) exercise testing (2) • aerobic exercise (2) *Downregulated* • Long-distance running	Acute (5)/chronic (1)	Blood (5)/muscle (1)
34a	4 ↑ 1 ↓	*HSPA9, SRC, RICTOR, MAP2K1, CD44, BCL2, TNF, MYC, CCND1, BIRC5, IL6R*	*Upregulated* • Long-distance running (2) • Aerobic exercise • Team sports *Downregulated* • Aerobic exercise	Acute (2)/chronic (3)	Blood (3)/muscle (1)/saliva (1)
206	9 ↑ 2 ↓	*KRAS, ANXA2*	*Upregulated* • Long-distance running (6) • HI(I)T (2) • Aerobic exercise *Downregulated* • Aerobic exercise (2)	Acute (10)/chronic (1)	Blood (10)/muscle (1)
222	7 ↑ 1 ↓	*PTEN, SOCS1, FOS, CD47, STAT5A, CDKN1B, FOXO3, MMP1, SOD2*	*Upregulated* • Cardio(pulmonary) exercise testing • HI(I)T (2) • Aerobic exercise (4) *Downregulated* • HIT	Acute (6)/chronic (2)	Blood (6)/muscle (2)
424	5 ↑ 1 ↓	*AKT3, CUL2, SIAH1, MAP2K1, SMAD7, CCND1, HIF1A*	*Upregulated* • Long-distance running (3) • HI(I)T • Aerobic exercise *Downregulated* • HI(I)T	Acute (5)/chronic (1)	Blood (5)/muscle (1)
Suggestive	**Upregulated**				
7	3 ↑ 1 ↓	*RELA, RAF1, PSME3, RAPGEF3, REL, PIK3R3, CUL5, FOS, CKAP4, BCL2, PTK2*	*Upregulated* • HI(I)T • Cardio(pulmonary) exercise testing (2) *Downregulated* • Aerobic exercise	Acute (2)/chronic (2)	Blood (3)/muscle (1)
24	5 ↑ 2 ↓	*PIK3R3, PSAP, NOS3, IFNG, CDKN1B, BCL2L11, MYC, TGFB1, CCND1*	*Upregulated* • HI(I)T (3) • Aerobic exercise (2) *Downregulated* • HI(I)T (2)	Acute (4)/chronic (3)	Blood (6)/muscle (1)
29a	5 ↑ 2 ↓	*PIK3R1, PTEN, COL3A1, ITGB1, ICAM1, CDC42, AKT2, AKT3, BCL2, MUC1, RNASEL, TRIM68, FOXO3, MCL1, MMP2, VEGFA, CRKL*	*Upregulated* • Long-distance running (2) • Cardio(pulmonary) exercise testing • Team sports • HI(I)T *Downregulated* • HI(I)T (2)	Acute (5)/chronic (2)	Blood (6)/saliva (1)
145	3 ↑ 1 ↓	*TLR4, CCND1, NRAS, YES1, CD44, IFNB1, MUC1, STAT1, EIF4E, IRS1, ADAM17, TNFSF13, SOX2, CDKN1A, FSCN1, MYC, VEGFA, SMAD3*	*Upregulated* • Long-distance running • Cardio(pulmonary) exercise testing • Aerobic exercise *Downregulated* • Cardio(pulmonary) Exercise testing	Acute	Blood
150	8 ↑ 3 ↓	*TP53, CREB1, P2RX7, EP300, CCR6, MUC4, STAT5B, CISH, CDKN1B, ZEB1*	*Upregulated* • Long-distance running (5) • HI(I)T (2)	Acute (8)/chronic (3)	Blood (10)/muscle (1)

(*continued on next page*)

Table 2 (Continued)

miRNA	Studies (*n*)/ direction	Immune system target genes	Exercise mode/studies (*n*)	Acute/chronic regulation/ studies (*n*)	Sample/studies (*n*)
			• Aerobic exercise *Downregulated* • Aerobic exercise (2) • HI(I)T		
223	8 ↑ 3 ↓	*CHUK, PTEN, ICAM1, FBXW7, MEF2C, TXNIP, NLRP3, LIF, FOXO3, FOXO1, S1PR1*	*Upregulated* • Long-distance running (5) • Cardio(pulmonary) exercise testing (2) • Aerobic exercise *Downregulated* • Cardio(pulmonary) exercise testing • Team sports • HI(I)T	Acute (9)/chronic (2)	Blood
532	3 ↑ 1 ↓	*STAT3*	*Upregulated* • HI(I)T • Cardio(pulmonary) exercise testing • Team sports *Downregulated* • Team sports	Acute (3)/chronic (1)	Blood (3)/saliva (1)
	Downregulated				
25	1 ↑ 3 ↓	*PTEN, CDH1, FBXW7, TP53, SMAD7, BCL2L11, TWIST1*	*Upregulated* • Team sports *Downregulated* • long-distance running • HI(I)T • aerobic exercise	Acute (1)/chronic (3)	Blood (3)/saliva (1)
30b	1 ↑ 3 ↓	*BECN1, SOCS1, TP53, CAT, ATG12, BCL6, PIK3CD*	*Upregulated* • team sports *Downregulated* • Long-distance running (2) • aerobic exercise	Acute (3)/chronic (1)	Blood (3)/saliva (1)
122	1 ↑ 3 ↓	*RAC1, NOD2, PLD1, ADAM10, PKM*	*Upregulated* • HI(I)T *Downregulated* • HI(IT) (3)	Acute (1)/chronic (3)	Blood (3)/muscle (1)
Resistance validated	**Upregulated**				
206	4 ↑	*KRAS, ANXA2*	• Resistance training	Acute (3)/chronic (1)	Blood (1)/muscle (3)
Plausible	**Downregulated**				
133a	1 ↑ 4 ↓	*COL1A1, CDC42, PPP2CA, PNP, ARPC5, BCL2L1, ANXA2, FSCN1, MCL1, TGFB1, FBXO6*	• Resistance training	Acute (3)/chronic (2)	blood (3)/muscle (2)

Notes: Evaluation criteria were defined as: validated (100% of ≥3 independent studies showed identical direction of regulation), plausible (≥80%), or suggestive (≥70%). Endurance exercise includes long-distance running (marathon, 5-km race, *etc.*), HI(I)T, cardio (pulmonary) exercise testing (treadmill, ergometer), aerobic exercise (e.g., cycling, swimming, moderate-intensity continuous training), team sports (e.g., soccer and volleyball). Number in brackets indicates the number of studies. Strand information (-3p/-5p) was not used as a large number of studies did not provide this information. ↑, significant upregulation reported; ↓, significant downregulation reported.
Abbreviations: HI(I)T = high-intensity interval training; HIT = high-intensity training; miRNA = microRNA; RNA = ribonucleic acid.

3.5. Agreement between blood and muscle samples

A limited number of studies has analyzed miRNAs from both blood and muscle to investigate whether liquid biopsies provide a means of mirroring physiological processes in the working muscle.[75,103,123] Margolis et al.[103] demonstrated that miR-24, miR-122, and miR-222 displayed different expression profiles in blood and muscle in terms of chronic exercise. A similar finding was reported by D'Souza et al.[75] for miR-150. However, D'Souza et al.[75] also showed that miR-21 and miR-222 exhibited elevated expression in both blood and muscle after an acute exercise bout. In general, only a small number of studies investigating miRNAs in muscle tissues has been identified in the current review. In addition to miR-222, miR-21 has been reported to be upregulated in endurance exercise in 12 independent studies,[44,55,68,72,75,81,91,103,115,125,130,134] of which 2 studies[75,130] also reported upregulation in muscle.

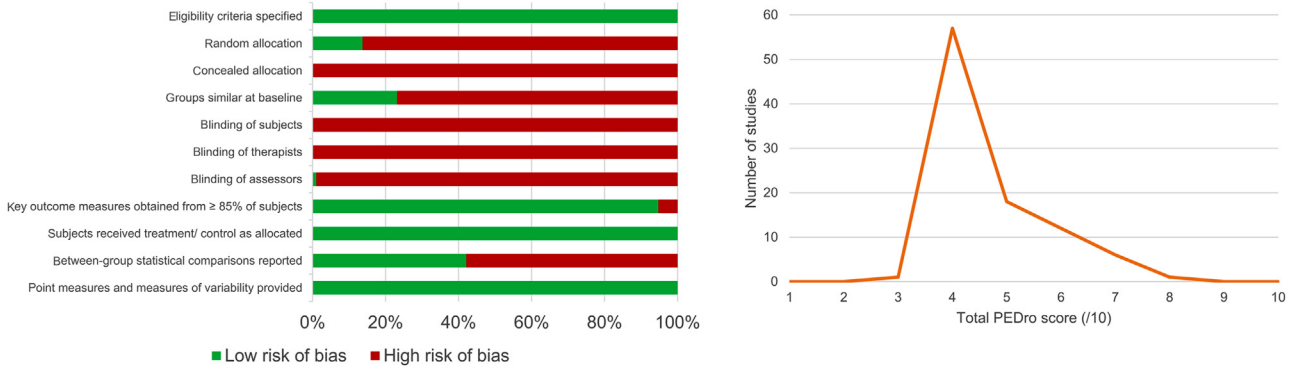

Fig. 2. Risk of bias analysis of included studies. The PEDro scale was used to assess risk of bias, and all items were scored irrespective of the individual study design. Overall risk of bias was rated as "high".

Table 3
Identified pathways by miRNA validation status.

	Entities				Reactions	
	Found	Ratio	*p*	FDR	Found	Ratio
Validated miRNAs						
Pathway name						
MyD88 cascade initiated on plasma membrane	21 / 109	0.007	1.11e-16	3.89e-15	63 / 70	0.005
TLR6:TLR2 cascade	27 / 133	0.009	1.11e-16	3.89e-15	70 / 78	0.005
MyD88:MAL(TIRAP) cascade initiated on plasma membrane	27 / 133	0.009	1.11e-16	3.89e-15	68 / 76	0.005
TLR5 cascade	21 / 109	0.007	1.11e-16	3.89e-15	63 / 71	0.005
TLR10 cascade	21 / 109	0.007	1.11e-16	3.89e-15	63 / 71	0.005
TRAF6-mediated induction of NF-κB and MAP kinases upon TLR7/8 or 9 activation	21 / 116	0.008	1.11e-16	3.89e-15	53 / 60	0.004
MyD88-dependent cascade initiated on endosome	21 / 117	0.008	1.11e-16	3.89e-15	66 / 75	0.005
TLR2 cascade	27 / 136	0.009	1.11e-16	3.89e-15	70 / 80	0.006
TLR1:TLR2 cascade	27 / 136	0.009	1.11e-16	3.89e-15	68 / 78	0.005
TLR7/8 cascade	21 / 118	0.008	1.11e-16	3.89e-15	66 / 79	0.006
TLR9 cascade	21 / 121	0.008	1.11e-16	3.89e-15	66 / 80	0.006
TRIF(TICAM1)-mediated TLR4 signaling	21 / 121	0.008	1.11e-16	3.89e-15	53 / 70	0.005
MyD88-independent TLR4 cascade	21 / 121	0.008	1.11e-16	3.89e-15	53 / 72	0.005
TLR4 cascade	29 / 165	0.011	1.11e-16	3.89e-15	78 / 107	0.007
TLR3 cascade	21 / 116	0.008	1.11e-16	3.89e-15	52 / 73	0.005
TLR cascades	29 / 202	0.013	1.11e-16	3.89e-15	128 / 198	0.014
IL-4 and IL-13 signaling	58 / 211	0.014	1.11e-16	3.89e-15	20 / 47	0.003
Cytokine signaling in immune system	138 / 1039	0.068	1.11e-16	3.89e-15	312 / 745	0.052
Signaling by interleukins	117 / 658	0.043	1.11e-16	3.89e-15	199 / 505	0.035
Innate immune system	74 / 1341	0.088	1.11e-16	3.89e-15	259 / 725	0.051
Immune system	188 / 2627	0.172	1.11e-16	3.89e-15	589 / 1664	0.116
Diseases of signal transduction by growth factor receptors and second messengers	39 / 498	0.033	1.11e-16	3.89e-15	166 / 478	0.033
Signaling by receptor tyrosine kinases	46 / 623	0.041	1.11e-16	3.89e-15	257 / 746	0.052
Signal transduction	101 / 3028	0.199	1.11e-16	3.89e-15	851 / 2536	0.177
IL-12 family signaling	22 / 96	0.006	1.11e-16	3.89e-15	36 / 114	0.008
Plausible miRNAs						
Pathway name						
IL-4 and IL-13 signaling	35 / 211	0.014	1.11e-16	2.08e-14	23 / 47	0.003
Signaling by interleukins	54 / 658	0.043	1.11e-16	2.08e-14	188 / 505	0.035
Cytokine signaling in immune system	68 / 1039	0.068	1.11e-16	2.08e-14	248 / 745	0.052
Immune system	83 / 2627	0.172	1.11e-16	2.08e-14	356 / 1664	0.116
IL-12 family signaling	15 / 96	0.006	2.22e-16	3.33e-14	53 / 114	0.008
Extra-nuclear estrogen signaling	15 / 111	0.007	1.89e-15	2.36e-13	18 / 39	0.003
Estrogen-dependent nuclear events downstream of ESR-membrane signaling	10 / 29	0.002	1.25e-14	1.34e-12	10 / 12	8.39e-04
IL-12 signaling	13 / 84	0.006	2.94e-14	2.74e-12	18 / 56	0.004
Gene and protein expression by JAKSTAT signaling after IL-12 stimulation	12 / 73	0.005	1.50e-13	1.25e-11	6 / 36	0.003
ESR-mediated signaling	17 / 256	0.017	1.98e-12	1.49e-10	30 / 114	0.008
Signal transduction	50 / 3028	0.199	6.73e-11	4.57e-09	516 / 2536	0.177

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Table 3 (Continued)

	Entities				Reactions	
	Found	Ratio	*p*	FDR	Found	Ratio
Generic transcription pathway	35 / 1586	0.104	1.15e-10	7.12e-09	135 / 884	0.062
Signaling by receptor tyrosine kinases	22 / 623	0.041	1.74e-10	9.92e-09	168 / 746	0.052
Insulin-like growth factor-2 mRNA binding proteins (IGF2BPs/IMPs/VICKZs) bind RNA	6 / 13	8.53e-04	5.15e-10	2.73e-08	2 / 3	2.10e-04
Signaling by nuclear receptors	17 / 386	0.025	1.06e-09	5.28e-08	30 / 196	0.014
RNA polymerase II transcription	35 / 1728	0.113	1.17e-09	5.37e-08	135 / 945	0.066
FLT3 signaling	8 / 48	0.003	1.77e-09	7.80e-08	9 / 43	0.003
Diseases of signal transduction by growth factor receptors and second messengers	18 / 498	0.033	6.97e-09	2.86e-07	108 / 478	0.033
Gene expression (transcription)	35 / 1917	0.126	1.76e-08	6.86e-07	135 / 1090	0.076
Signaling by VEGF	10 / 140	0.009	4.66e-08	1.73e-06	54 / 86	0.006
Signaling by SCF-KIT	7 / 51	0.003	7.06e-08	2.47e-06	22 / 39	0.003
FOXO-mediated transcription	9 / 110	0.007	7.28e-08	2.47e-06	54 / 85	0.006
RUNX3 regulates WNT signaling	4 / 10	6.57e-04	7.80e-07	2.50e-05	4 / 5	3.49e-04
Signaling by phosphorylated juxtamembrane, extracellular and kinase domain KIT mutants	5 / 28	0.002	1.58e-06	4.74e-05	8 / 11	7.69e-04
Signaling by KIT in disease	5 / 28	0.002	1.58e-06	4.74e-05	8 / 26	0.002
Suggestive miRNAs						
Pathway name						
FOXO-mediated transcription	18 / 110	0.007	1.11e-16	1.94e-14	79 / 85	0.006
IL-4 and IL-13 signaling	51 / 211	0.014	1.11e-16	1.94e-14	22 / 47	0.003
Cytokine signaling in immune system	95 / 1039	0.068	1.11e-16	1.94e-14	271 / 745	0.052
Diseases of signal transduction by growth factor receptors and second messengers	34 / 498	0.033	1.11e-16	1.94e-14	165 / 478	0.033
Signaling by interleukins	72 / 658	0.043	1.11e-16	1.94e-14	164 / 505	0.035
Immune system	125 / 2627	0.172	1.11e-16	1.94e-14	465 / 1664	0.116
Estrogen-dependent nuclear events downstream of ESR-membrane signaling	12 / 29	0.002	4.44e-16	6.66e-14	11 / 12	8.39e-04
Extra-nuclear estrogen signaling	17 / 111	0.007	2.78e-15	3.64e-13	20 / 39	0.003
Signal transduction	72 / 3028	0.199	3.79e-14	4.43e-12	721 / 2536	0.177
Generic transcription pathway	50 / 1586	0.104	7.89e-14	8.29e-12	393 / 884	0.062
Signaling by receptor tyrosine kinases	30 / 623	0.041	9.89e-13	9.40e-11	255 / 746	0.052
Transcriptional regulation by RUNX3	15 / 118	0.008	1.77e-12	1.54e-10	28 / 47	0.003
RNA polymerase II transcription	50 / 1728	0.113	2.02e-12	1.58e-10	393 / 945	0.066
ESR-mediated signaling	20 / 256	0.017	2.11e-12	1.58e-10	44 / 114	0.008
Innate immune system	42 / 1341	0.088	1.84e-11	1.29e-09	177 / 725	0.051
Disease	60 / 2528	0.166	2.21e-11	1.44e-09	272 / 1787	0.125
IL-7 signaling	9 / 31	0.002	4.58e-11	2.71e-09	14 / 26	0.002
PI3K/AKT signaling in cancer	14 / 124	0.008	4.67e-11	2.71e-09	8 / 21	0.001
Gene expression (transcription)	50 / 1917	0.126	8.86e-11	4.78e-09	395 / 1090	0.076
FLT3 signaling	10 / 48	0.003	9.20e-11	4.78e-09	13 / 43	0.003
Signaling by SCF-KIT	10 / 51	0.003	1.64e-10	8.22e-09	23 / 39	0.003
FOXO-mediated transcription of cell cycle genes	8 / 27	0.002	4.80e-10	2.25e-08	22 / 22	0.002
Signaling by phosphorylated juxtamembrane, extracellular and kinase domain KIT mutants	8 / 28	0.002	6.36e-10	2.74e-08	10 / 11	7.69e-04
Signaling by KIT in disease	8 / 28	0.002	6.36e-10	2.74e-08	10 / 26	0.002
PIP3 activates AKT signaling	19 / 322	0.021	8.29e-10	3.34e-08	65 / 88	0.006

Notes: Table shows the 25 most relevant pathways sorted by *p* value. Pathway analysis was performed against Reactome Version 85 (August 2023;[50] human targets), using the identified targets of validated, plausible, or suggestive miRNAs.
Abbreviations: AKT = AKT Serine/Threonine Kinase 1; BP = binding protein; ESR = estrogen receptor; FDR = false discovery rate; FLT3 = fms like tyrosine kinase 3; FOXO = forkhead box O; IGF2 = insulin like growth factor 2; IL = interleukin; IMPs = IGF2 mRNA binding proteins; JAKSTAT = janus kinase/signal transducer and activator of transcription; KIT = KIT proto-oncogene, receptor tyrosine kinase; MAL = Myelin and lymphocyte protein; MAP = mitogen-activated protein; miRNA = microRNA; MyD88 = myeloid differentiation primary response protein; NF-κB = nuclear factor kappa B; PI3K = phosphoinositide-3-kinase; PIP3 = phosphatidylinositol (3,4,5)-trisphosphate; RNA = ribonucleic acid; RUNX3 = Runt-related transcription factor 3; SCF = stem cell factor; TICAM1 = TIR domain containing adaptor molecule 1; TIR = toll/interleukin-1 receptor-like protein; TIRAP = TIR domain containing adaptor protein; TLR = toll-like receptor; TRAF6 = TNF receptor associated factor 6; TRIF = TIR-domain-containing adapter-inducing interferon-β; VEGF = vascular endothelial growth factor; VICKZs = Vg1 RBP/Vera, IMP-1,2,3, CRD-BP, KOC, ZBP-1 (family of RNA-binding proteins).

3.6. Risk of bias

All studies were rated using the full 11-item PEDro scale. Since the minority of studies were performed in a randomized control design and blinding of participants and therapists was not possible due to the nature of the intervention, the overall risk of bias was high, with 7 out of 11 items suggesting significant risk of bias (Fig. 2 and Supplementary Fig. 3).

3.7. Pathway analysis

Pathway analysis of the identified miRNAs by category (validated, plausible, suggestive) revealed several biological pathways and signaling cascades not only limited to the immune system (Table 3). Of note, 16 of the top 25 overrepresented pathways regulated by the identified validated miRNAs had Toll-like receptor (TLR) cascades as major targets (Fig. 3 and Table 3).

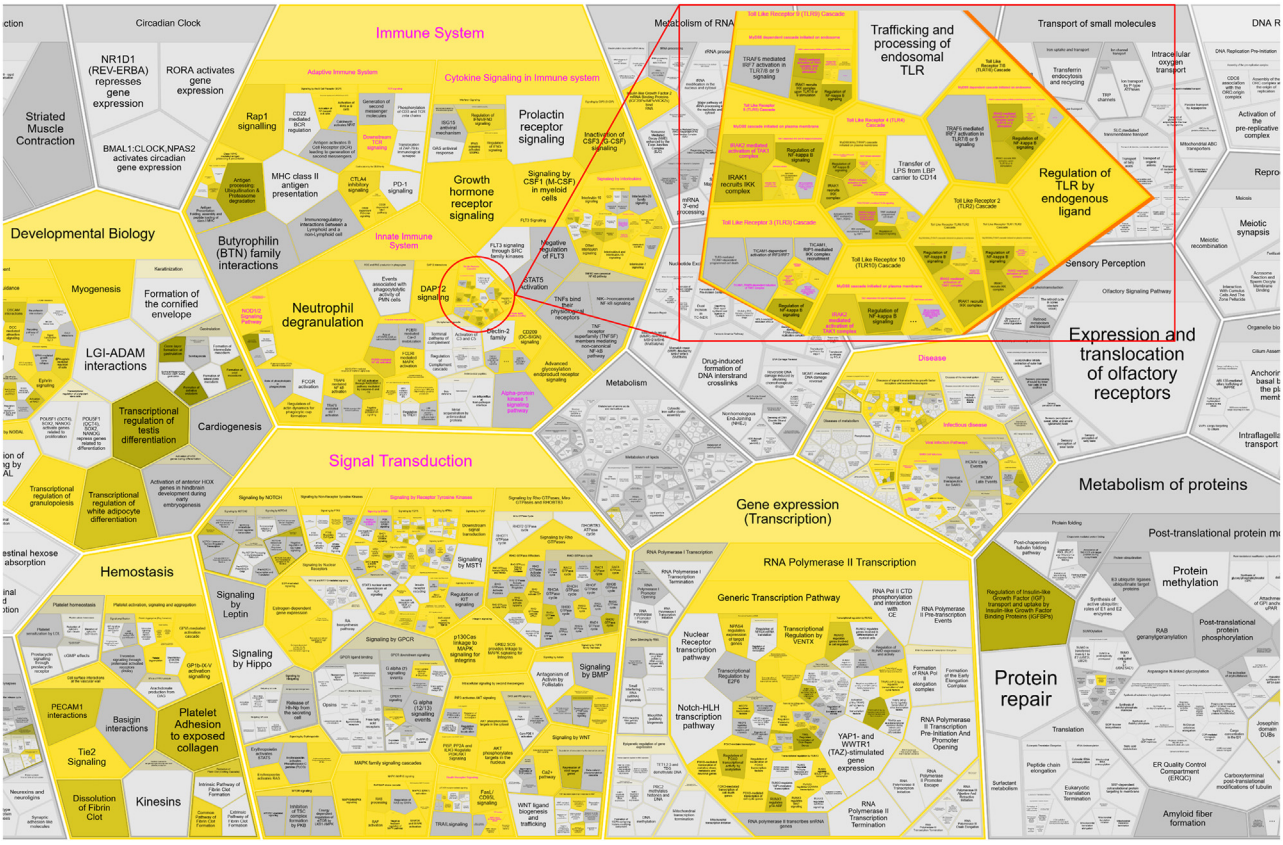

Fig. 3. TLR cascades are main targets of validated exercise-dependent miRNAs. Visualization of overrepresented pathways (yellow) was performed using the Reactome online analysis tool (Version 85, human targets). Identified targets of validated miRNAs were submitted to determine pathway enrichment. Darker shades indicate lower *p* values. Inlet shows image magnification of TLR cascades within the immune system cluster. Overall image has been cropped for visualization. Details are given in Table 3. ADAM = a disintegrin and metalloproteinase; BCR = breakpoint cluster region; BMAL = basic helix–loop–helix arnt like; BMP = bone morphogenetic protein; BTN = butyrophilin; CD22 = cluster of differentiation 22; CD95L = tumor necrosis factor ligand superfamily member 6; CSF3 = colony-stimulating factor 3; CTLA= cytotoxic T-lymphocyte associated protein; DAP = death-associated protein; ER = estrogen receptor; ERBA = avian erythroblastosis virus; FLT3 = FMS-like tyrosine kinase 3; G-CSF = granulocyte colony-stimulating factor; GPCR = G protein-coupled receptor; HLH = hemophagocytic lymphohistiocytosis; IGF = insulin like growth factor; IRAK2 = interleukin 1 receptor associated kinase 2; LGI = leucine-rich glioma inactivated; LPS = lipopolysaccharide; M-CSF = macrophage colony-stimulating facto; MAPK = mitogen-activated protein kinase; MHC = major histocompatibility complex; miRNAs = microRNAs; NR1D1 = nuclear receptor subfamily 1 group D member 1; NPAS2 = neuronal PAS domain protein 2; PD = programmed cell death protein; PECAM1 = platelet and endothelial cell adhesion molecule 1; RAP = member of RAS oncogene family; RNA = ribonucleic acid; RORA = RAR related orphan receptor A; TAZ = Tafazzin family protein; TCR = T cell receptor; TLR = Toll-like receptor; VENTX = VENT Homeobox; WNT = wingless/Int-1; WWTR1 = WW domain-containing transcription regulator 1; YAP1 = Yes1-associated transcriptional regulator 1.

3.8. Summary of findings

In response to resistance exercise, there is evidence for upregulation of miR-206 and downregulation of miR-133a. In response to endurance exercise, miRNAs 15a, 29c, 30a, 30e, 103a, 130a, 132, 142, 143, 155, 181a, 181b, 338, 451a, and let-7e showed consistent elevation in 100% of all included studies, whereas miRNAs 103a, 130a, and let-7e were consistently downregulated.

4. Discussion

This review aimed to systematically summarize findings on ncRNAs involved in exercise-induced immune modulation to gain a deeper understanding of the molecular mechanisms underlying the effects of physical exercise on the immune system. Two approaches to identify relevant literature were applied and large databases for the identification of specific miRNA targets within the immune system were used. Of note, this approach included the selection of only those targets that had been confirmed by different *in vitro* techniques. Findings of this concerted approach were then qualitatively analyzed using ordering tables including exercise modalities, acute and chronic conditions as well as sample type studied and number of studies reporting comparable results. The most stringent criterium that was applied demanded that all included studies (100%, ≥3 studies) that investigated the effects of exercise on the regulation of a ncRNA reported identical effects. Following this framework, our main findings are as follows: (a) 15 miRNAs with immune system targets were validated to be regulated by endurance training, 12 of which were upregulated and 3 of which were downregulated; (b) the largest number of identified miRNA was responsive to acute exercise bouts and only miR-130a was identified to be downregulated by endurance exercise; (c) data on studies investigating ncRNAs in resistance training were limited, validating miR-206 to be upregulated and suggesting miR-133a to be

downregulated; and (d) the still-limited number of studies restricts a valid conclusion on whether changes in circulatory miRNAs reflect physiological changes in the muscle cell. Of note, the analysis of biological pathways regulated by the identified validated miRNAs revealed several TLR cascades as a major target with 16 out of the 25 most significant pathways comprising members of this family of evolutionarily conserved transmembrane glycoprotein receptors. TLRs are known to recognize various danger signals/patterns from both exogenous and endogenous origins called pathogen/damage-associated molecular patterns. Exercise-related damage-associated molecular patterns include (among others) heat shock proteins and cell-free DNA. To this point, a recent systematic review reported diverse effects on various TLR subtypes, depending on type and modality of exercise.[141] Moreover, some evidence exists that the anti-inflammatory effects of exercise may be mediated through TLR pathway modulation, which involves, among others, miR-155.[142]

We focus the discussion below mainly on 6 miRNAs that have been identified as validated by our current approach and which are supported by the largest body of literature in the field. All of them were consistently upregulated by acute endurance exercise, including different modalities such as long-distance running, high-intensity exercise as well as (moderate) intensity aerobic exercise. Of note, the currently available literature highlights effects of these miRNAs on various types of T cells in comparison to other immune cell types that play a role in exercise immunology (e.g., natural killer cells, neutrophils).

4.1. miR-143

With respect to alterations of the immune system, miR-143 has been shown to influence the differentiation and function of $CD8^+$ T (cytotoxic T) cells. Zhang et al.[143] demonstrated that inducible overexpression of miR-143 promotes the differentiation of central memory $CD8^+$ T cells in an *in vitro* model, reduces $CD8^+$ T-cell apoptosis, and increases proinflammatory cytokine secretion such as interferon gamma and interleukin 2 (IL-2). In this model, T-cell glucose transporter-1 was identified as a regulatory target of miR-143 and inhibition of T-cell glucose transporter-1 leads to reduced glucose uptake, affecting T-cell differentiation. Transfection of miR-143 in peripheral blood mononuclear cells has been shown to target AP-1 transcription complex components, leading to upregulation of tumor necrosis factor alpha and IL-2 expression while reducing IL-6 expression.[144] Thus, acute upregulation of miR-143 through physical activity may positively impact $CD8^+$ T-cell differentiation and may lead to transient proinflammatory cytokine secretion. Moreover, miR-143 may modulate glucose metabolism in T cells, potentially affecting T-cell function, as was recently shown for physical exercise under fasting conditions.[145] Additionally, miR-143 overexpression leads to the downregulation of oncogenic Kirsten rat sarcoma virus and genes involved in cancer-related signaling pathways[146] and so has potential implications for cancer prevention.

4.2. miR-181a

miR-181a has been shown to be an important regulator of T-cell aging, affecting diverse signaling pathways that impact the activation threshold of the T-cell receptor in T-cell response.[147] Of note, miR-181a expression in naïve T cells has been described as declining with increasing age, and lower miR-181a levels have been linked to disturbed vaccine and antiviral responses in older individuals.[148] A decline in T cell miR-181a expression might thus contribute to age-related defects in adaptive immunity, which are known to be ameliorated by regular aerobic endurance exercise. In addition, a role of miR-181a in the regulation of mitogen-activated protein kinase/extracellular signal-regulated kinase signaling in monocyte-derived dendritic cells (DCs) has been suggested, and sustained expression of miR-181a in DCs may induce higher levels of cluster of differentiation protein 209 (CD209), which is involved in the phagocytosis of various pathogens.[149] Thus, exercise-induced upregulation of miR-181a may have broader implications for immune health as it targets components of the adaptive and innate immune system.

4.3. miR-338

miR-383 seems to play a role in the innate immune system as its expression in macrophage is responsive to lipopolysaccharides as well as polyinosinic-polycytidylic acid (poly(I:C)), a synthetic dsRNA mimicking virus infection.[150] In addition, miR-338 may play a role in the function of regulatory T cells (Treg), which represent a pivotal regulatory component of the adaptive immune system, fine-tuning inflammatory responses. Treg cells are marked by Forkhead-Box-Protein P3 (FOXP3) expression, and increased FOXP3 expression has been reported in some exercise interventions.[151] Of note, miR-338 overexpression *in vitro* has been shown to attenuate FOXP3 expression by targeting runt-related transcription factor 1,[152] and elevated levels of miR-338 after acute exercise may be involved in a negative feedback loop regulating Treg development and function. In addition, it has been suggested that miR-338 is a suppressor of T-cell lymphoblastic lymphoma and that miR-338 upregulation inhibits migration and proliferation of cultured T-cell lymphoblastic lymphoma cells.[153]

4.4. miR-155

One of the most well-studied miRNAs is miR-155, which is expressed in major immune cells and plays a crucial role in $CD8^+$ T-cell responses and memory formation against infections.[154] It has been demonstrated that miR-155 is essential for optimal $CD8^+$ T-cell function. Its *in vivo* overexpression enhances primary $CD8^+$ T-cell responses and inhibits senescence and functional exhaustion, while its absence results in an intrinsic defect of $CD8^+$ T cells, affecting proliferation.[155] miR-155 targets multiple pathways in macrophages, DCs, T and B lymphocytes,[156] and it may be a pivotal regulator in the adaptive and innate immune systems. It may thus be inferred that engaging in regular exercise might positively impact $CD8^+$ T-cell function.

4.5. miR-30a

While data on the role of miR-30a in the immune system is still scarce, it has been reported that miR-30a may have the potential to resolve inflammation partly by targeting IL-1α in immune cells.[157] Of note, adipose tissue macrophages from mice fed a high-fat diet have been reported to be skewed towards the M1 inflammatory phenotype, which was associated with downregulation of miR-30a as well as 30c and 30e. Inhibition of miR-30a in bone marrow-derived macrophage triggered pro-inflammatory cytokine production and M1 macrophage polarization.[158] It has been suggested that miR-30 may attenuate macrophage activation through regulation of the Delta Like Canonical Notch Ligand 4−Notch pathway and, thus, may hold therapeutic potential for regulating macrophage-driven inflammatory and metabolic disorders. Therefore, miR-30a may represent a factor by which repeated aerobic endurance exercise could reduce pro-inflammatory states in metabolic diseases.

4.6. miR-142

Comparable to miR-338, miR-142 is thought to play a role in the regulation of Treg cells since deactivation of miR-142 in Treg cells has been reported to lead to severe systemic autoimmune diseases, attributed to the breakdown of peripheral T-cell tolerance.[159] Accordingly, miR-142 deficiency results in the excessive production and signaling of interferon gamma and compromised Treg cell homeostasis. In murine models, miR-142 has been identified as a regulator of DC homeostasis,[160] and deficiency of miR-142 in mice led to an impairment of $CD4^+$ DC homeostasis resulting in a severe defect in $CD4^+$ T-cell priming. The upregulation of miR-142 through physical activity could thus potentially have positive effects on immune system regulation and may aid in maintaining the balance of Treg cells. This might enhance the homeostasis and function of $CD4^+$ DCs, leading to improved priming of $CD4^+$ T cells and potentially suppressing autoimmune processes while enhancing regular immune responses.

4.7. miRNAs, the immune system, and cardiovascular health

The role of physical exercise not only in maintaining or promoting cardiovascular health but also in cardiovascular rehabilitation has been widely acknowledged.[161,162] While the general link between cardiovascular health and immunologic alterations by physical exercise can be seen in the pivotal contribution of monocytes, macrophages, and T and B cells to the development of atherosclerosis, it can also be seen in the inflammatory responses that connect lipids and other risk factors via a series of pathways to cardiovascular health and disease.[163,164] However, the complex, time-dependent immunomodulatory details of this axis are far from being well understood. It has already been suggested that miRNAs contribute to the beneficial effects of physical exercise[165] and the monitoring of cardioprotective training success.[166] On this point it is important to note that circulating miRNAs are commonly preserved by association with either RNA-binding proteins or small membranous vesicles, including microvesicles and exosomes, which are shed from the plasma membrane into the extracellular environment to regulate targets in (remote) recipient cells.[117,167,168] It has been shown that significant amounts of exosomes can be released from endothelial cells and other cell types into circulation upon exercise-dependent effectors, including shear stress, hypoxia, and other factors.[169,170] In addition, a sorting mechanism in miRNA-releasing (vascular) cells has been proposed, which guides specific miRNAs to enter exosomes resulting in a concentration of selected miRNAs.[171] Moreover, regular exercise training could result in elevated basal miRNA expression and, thus, an increased pool of concentrated miRNAs to be secreted.[7]

The miRNAs identified in this current approach target several genes that play important roles in both the immune and cardiovascular systems. These include vascular endothelial growth factor A[172] (target of miR-1, -15a, -29a/b, -145) and Forkhead box protein-1/3 (FOXO-1/3; target of miR-15a, -27a, -29a, -132, -155, -222/3), both key regulators of vessel formation and maturation,[173] as well as intercellular adhesion molecule-1 (target of miR-29a, -223), which is involved in initial leukocyte invasion into the vessel wall,[174,175] Activator protein 1 transcription factor subunit FOS (target of miR-7, -181b, -222), which regulates extracellular matrix proteins,[176] as well as different ADAM disintegrin and metalloproteinases (target of miR-122, -145, -338, -451a) involved in shedding of cytokines such as tumor necrosis factor alpha.[177] It seems thus evident, that physical exercise regulates miRNAs with shared targets in different systems of the body, which likely contributes to the observation that physical exercise has multiple overlapping systemic effects. Of note, our investigation suggests that levels of miRNAs are mostly regulated by acute exercise and that chronic alterations are less frequent, which might be related to the observation that chronic alterations are often indicative of pathophysiological conditions. For example, miR-145 and -155 are chronically reduced in patients with coronary artery disease,[178] but can also be induced by exercise in coronary artery disease and may thus contribute to the beneficial effects of exercise on vascular health and potentially counteract the detrimental changes associated with coronary artery disease. With respect to miRNAs and cardiovascular health, it is of interest that miR-126, which is well-known for its anti-atherosclerotic and vasculoprotective effects,[169] has not been identified as suggestive miRNA involved in exercise-based immunomodulation, which underlines the specificity of our approach.

4.8. Are circulating miRNAs indicative of exercise-dependent changes of muscular processes?

So far, the number of miRNAs analyzed from both blood and muscle is still limited and more data is needed to strengthen the current findings. However, comparison of the identified changes in muscular and circulating miRNA levels may suggest that a specific miRNA profile, including miR-21 and -222 in the blood, might mirror physiological processes

and respective triggers of long-term adaptation to acute endurance exercise in the muscle. Thus, these miRNAs could enable the assessment and management of physical activity as liquid biopsies might provide insights into the effectiveness of particular exercise interventions concerning desired outcomes, such as enhancing immune system function, improving vascular health, or mitigating premature skeletal muscle aging.[179,180] It is important to note that miRNAs exhibit tissue-specific functions and miRNAs encapsulated in muscle-derived exosomes participate in local skeletal muscle communication but also act in an endocrine manner,[181,182] suggesting a coordinated response to an exercise stimulus across different tissue via circulating miRNAs.

4.9. Other ncRNAs in physical exercise

Only 6 studies[71,135–139] were identified that examined other ncRNAs in relation to physical exercise without suggesting a (direct) relation to the immune system. One study analyzed changes of circRNA MBOT2, which was significantly reduced 24 h after a marathon race,[139] and 5 studies[71,135–138] reported on alterations in lncRNA levels in response to physical exercise in healthy humans. While the overall data on lncRNAs in physical exercise is still scarce, 1 lncRNA, CYTOR, was reported to be increased after resistance exercise by 2 independent studies.[135,138] While the involvement of CYTOR in virus infection of B lymphocytes has been proposed,[183] its expression was observed to be increased in the vastus lateralis 3 h after leg extension exercise, promoting myogenic differentiation.[138] Of note, CYTOR has been shown to sponge endurance exercise-dependent miR-24, -206, and -155[184–186] and may thus be involved in the differential adaptation processes in response to endurance or resistance exercise. Thus, the competing endogenous RNA (ceRNA) networks of lncRNA and miRNA and their roles in the regulation of different exercise stimuli should be investigated in future research.

4.10. Limitations

Some limitations may exist in the current analysis. Publication and reporting bias may affect the present review since data may have remained unreported or unpublished because of unexpected/contradictory, negative, or insignificant results. The overall risk of bias was high, as different study types were included and blinding of participants and therapists was not possible due to the nature of the interventions. Furthermore, the record search was limited to studies published in English, and inclusion of data reported in other languages may have altered the results preliminary in categories with smaller numbers of available studies. Missing information on miRNA strand type may also have affected the results. Additionally, it is important to note that different methods used by individual studies to determine ncRNA changes introduce some heterogeneity. In particular, hypothesis-free sequencing or array-based identification methods should be combined with validation methods such as real-time PCR or functional analyses.

5. Conclusion

The findings of this systematic review suggest that ncRNAs in general and miRNAs in particular play a major role in exercise-induced effects on the innate and adaptive immune systems by targeting different pathways affecting immune cell distribution, function, and trafficking as well as the production of (anti-)inflammatory cytokines, which are associated with an overall enhanced defense against pathogens. Major effects of functional miRNAs with known targets in the immune system were seen after acute bouts of endurance exercise, while consistent effects of either resistance training or long-term training programs on miRNA expression were limited. However, our stringent systematic approach provides evidence that specific miRNAs, including miR-30a, miR-142, miR-143, miR-181a, miR-155, and miR-338, are key players in mediating the beneficial systemic effects of physical exercise on the immune system. Moreover, these exercise-inducible miRNAs may contribute to the crosstalk between the immune and cardiovascular system with major implications for the prevention of infections, chronic inflammatory conditions, and autoimmune diseases. However, further research is needed to elucidate the underlying mechanisms and explore the potential of miRNA-based interventions in promoting immune health and disease prevention. Additionally, the role of lncRNAs in the field of exercise immunology warrants further investigation.

Acknowledgments

We greatly acknowledge the help of Dr. Marc Teschler for reviewing the literature search results. FCM and BS are supported by the European Commission within the Horizon 2020 framework program (Grant No. 101017424).

Authors' contributions

FCM, MK, MH, and BS performed the systematic literature search, screened records and extracted data, interpreted results, and drafted the manuscript. All authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

Competing interests

BS filed a patent in the field of noncoding RNAs (US Patent App. 17/622,149, 2022). All the support had no involvement in the study design and writing of the manuscript or the decision to submit it for publication. The other authors declare that they have no competing interests.

Supplementary materials

Supplementary materials associated with this article can be found in the online version at doi:10.1016/j.jshs.2023.11.001.

References

1. Goh J, Ladiges WC. Exercise enhances wound healing and prevents cancer progression during aging by targeting macrophage polarity. *Mech Ageing Dev* 2014;**139**:41–8.
2. Brines R, Hoffman-Goetz L, Pedersen BK. Can you exercise to make your immune system fitter? *Immunol Today* 1996;**17**:252–4.
3. Keast D, Cameron K, Morton AR. Exercise and the immune response. *Sports Med* 1988;**5**:248–67.
4. Mackinnon LT. Current challenges and future expectations in exercise immunology: Back to the future. *Med Sci Sports Exerc* 1994;**26**:191–4.
5. Pedersen BK, Nieman DC. Exercise immunology: Integration and regulation. *Immunol Today* 1998;**19**:204–6.
6. Robson PJ, Blannin AK, Walsh NP, Castell LM, Gleeson M. Effects of exercise intensity, duration and recovery on *in vitro* neutrophil function in male athletes. *Int J Sports Med* 1999;**20**:128–35.
7. Makarova JA, Maltseva DV, Galatenko VV, et al. Exercise immunology meets MiRNAs. *Exerc Immunol Rev* 2014;**20**:135–64.
8. Tarnowski M, Kopytko P, Piotrowska K. Epigenetic regulation of inflammatory responses in the context of physical activity. *Genes (Basel)* 2021;**12**:1313. doi:10.3390/genes12091313.
9. Wessner B, Gryadunov-Masutti L, Tschan H, Bachl N, Roth E. Is there a role for microRNAs in exercise immunology? A synopsis of current literature and future developments. *Exerc Immunol Rev* 2010;**16**:22–39.
10. Lancaster GI, Halson SL, Khan Q, et al. Effects of acute exhaustive exercise and chronic exercise training on type 1 and type 2 T lymphocytes. *Exerc Immunol Rev* 2004;**10**:91–106.
11. Graff RM, Kunz HE, Agha NH, et al. β_2-Adrenergic receptor signaling mediates the preferential mobilization of differentiated subsets of CD8+ T-cells, NK-cells and non-classical monocytes in response to acute exercise in humans. *Brain Behav Immun* 2018;**74**:143–53.
12. Rowbottom DG, Green KJ. Acute exercise effects on the immune system. *Med Sci Sports Exerc* 2000;**32**(Suppl. 7):S396–405.
13. Pedersen BK, Ullum H. NK cell response to physical activity: Possible mechanisms of action. *Med Sci Sports Exerc* 1994;**26**:140–6.
14. Gleeson M. Immune function in sport and exercise. *J Appl Physiol (1985)* 2007;**103**:693–9.
15. Chastin SFM, Abaraogu U, Bourgois JG, et al. Effects of regular physical activity on the immune system, vaccination and risk of community-acquired infectious disease in the general population: Systematic review and meta-analysis. *Sports Med* 2021;**51**:1673–86.
16. Pyne DB. Regulation of neutrophil function during exercise. *Sports Med* 1994;**17**:245–58.
17. Woods J, Lu Q, Ceddia MA, Lowder T. Special feature for the Olympics: Effects of exercise on the immune system: Exercise-induced modulation of macrophage function. *Immunol Cell Biol* 2000;**78**:545–53.
18. McFarlin BK, Flynn MG, Phillips MD, Stewart LK, Timmerman KL. Chronic resistance exercise training improves natural killer cell activity in older women. *J Gerontol A Biol Sci Med Sci* 2005;**60**:1315–8.
19. Handzlik MK, Shaw AJ, Dungey M, Bishop NC, Gleeson M. The influence of exercise training status on antigen-stimulated IL-10 production in whole blood culture and numbers of circulating regulatory T cells. *Eur J Appl Physiol* 2013;**113**:1839–48.
20. Weinhold M, Shimabukuro-Vornhagen A, Franke A, et al. Physical exercise modulates the homeostasis of human regulatory T cells. *J Allergy Clin Immunol* 2016;**137**:1607–10. e8.
21. Sellami M, Bragazzi NL, Aboghaba B, Elrayess MA. The impact of acute and chronic exercise on immunoglobulins and cytokines in elderly: Insights from a critical review of the literature. *Front Immunol* 2021;**12**:631873. doi:10.3389/fimmu.2021.631873.
22. Schlagheck ML, Walzik D, Joisten N, et al. Cellular immune response to acute exercise: Comparison of endurance and resistance exercise. *Eur J Haematol* 2020;**105**:75–84.
23. Meyer-Lindemann U, Moggio A, Dutsch A, Kessler T, Sager HB. The impact of exercise on immunity, metabolism, and atherosclerosis. *Int J Mol Sci* 2023;**24**:3394. doi:10.3390/ijms24043394.
24. Stewart LK, Flynn MG, Campbell WW, et al. Influence of exercise training and age on CD14+ cell-surface expression of Toll-like receptor 2 and 4. *Brain Behav Immun* 2005;**19**:389–97.
25. Flowers E, Won GY, Fukuoka Y. MicroRNAs associated with exercise and diet: A systematic review. *Physiol Genomics* 2015;**47**:1–11.
26. Dos Santos JAC, Veras ASC, Batista VRG, et al. Physical exercise and the functions of microRNAs. *Life Sci* 2022;**304**:120723. doi:10.1016/j.lfs.2022.120723.
27. Yao Q, Chen Y, Zhou X. The roles of microRNAs in epigenetic regulation. *Curr Opin Chem Biol* 2019;**51**:11–7.
28. LaPerriere A, Ironson G, Antoni MH, Schneiderman N, Klimas N, Fletcher MA. Exercise and psychoneuroimmunology. *Med Sci Sports Exerc* 1994;**26**:182–90.
29. Hoffman-Goetz L, Pedersen BK. Exercise and the immune system: A model of the stress response? *Immunol Today* 1994;**15**:382–7.
30. Esteller M. Non-coding RNAs in human disease. *Nat Rev Genet* 2011;**12**:861–74.
31. Bartel DP. MicroRNAs: Genomics, biogenesis, mechanism, and function. *Cell* 2004;**116**:281–97.
32. Hirschberger S, Hinske LC, Kreth S. MiRNAs: Dynamic regulators of immune cell functions in inflammation and cancer. *Cancer Lett* 2018;**431**:11–21.
33. Chandan K, Gupta M, Sarwat M. Role of host and pathogen-derived microRNAs in immune regulation during infectious and inflammatory diseases. *Front Immunol* 2020;**10**:3081. doi:10.3389/fimmu.2019.03081.
34. Li Y, Tan J, Miao Y, Zhang Q. MicroRNA in extracellular vesicles regulates inflammation through macrophages under hypoxia. *Cell Death Discov* 2021;**7**:285. doi:10.1038/s41420-021-00670-2.
35. Makeyev EV, Maniatis T. Multilevel regulation of gene expression by microRNAs. *Science* 2008;**319**:1789–90.
36. Sumathipala M, Weiss ST. Predicting miRNA-based disease-disease relationships through network diffusion on multi-omics biological data. *Sci Rep* 2020;**10**:8705. doi:10.1038/s41598-020-65633-6.
37. Olgun G, Sahin O, Tastan O. Discovering lncRNA mediated sponge interactions in breast cancer molecular subtypes. *BMC Genomics* 2018;**19**:650. doi:10.1186/s12864-018-5006-1.
38. Alack K, Krüger K, Weiss A, et al. Aerobic endurance training status affects lymphocyte apoptosis sensitivity by induction of molecular genetic adaptations. *Brain Behav Immun* 2019;**75**:251–7.
39. Pastuszak-Lewandoska D, Domańska-Senderowska D, Kiszałkiewicz J, et al. Expression levels of selected cytokines and microRNAs in response to vitamin D supplementation in ultra-marathon runners. *Eur J Sport Sci* 2020;**20**:219–28.
40. Radom-Aizik S, Zaldivar Jr FP, Haddad F, Cooper DM. Impact of brief exercise on circulating monocyte gene and microRNA expression: Implications for atherosclerotic vascular disease. *Brain Behav Immun* 2014;**39**:121–9.
41. Radom-Aizik S, Zaldivar F, Haddad F, Cooper DM. Impact of brief exercise on peripheral blood NK cell gene and microRNA expression in young adults. *J Appl Physiol (1985)* 2013;**114**:628–36.
42. Cheema AK, Sarria L, Bekheit M, et al. Unravelling myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): Gender-specific changes in the microRNA expression profiling in ME/CFS. *J Cell Mol Med* 2020;**24**:5865–77.
43. Dalle Carbonare L, Dorelli G, Li Vigni V, et al. Physical activity modulates miRNAs levels and enhances MYOD expression in myoblasts. *Stem Cell Rev Rep* 2022;**18**:1865–74.
44. Radom-Aizik S, Zaldivar Jr F, Leu SY, Adams GR, Oliver S, Cooper DM. Effects of exercise on microRNA expression in young males peripheral blood mononuclear cells. *Clin Transl Sci* 2012;**5**:32–8.
45. Radom-Aizik S, Zaldivar F, Oliver S, Galassetti P, Cooper DM. Evidence for microRNA involvement in exercise-associated neutrophil gene expression changes. *J Appl Physiol (1985)* 2010;**109**:252–61.
46. Rodriguez A, Vigorito E, Clare S, et al. Requirement of bic/microRNA-155 for normal immune function. *Science* 2007;**316**:608–11.
47. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *Syst Rev* 2021;**10**:89. doi:10.1186/s13643-021-01626-4.

48. Campbell M, McKenzie JE, Sowden A, et al. Synthesis without meta-analysis (SWiM) in systematic reviews: Reporting guideline. *BMJ* 2020;**368**:l6890. doi:10.1136/bmj.l6890.
49. Lucas PJ, Baird J, Arai L, Law C, Roberts HM. Worked examples of alternative methods for the synthesis of qualitative and quantitative research in systematic reviews. *BMC Med Res Methodol* 2007;**7**:4. doi:10.1186/1471-2288-7-4.
50. Gillespie M, Jassal B, Stephan R, et al. The reactome pathway knowledgebase 2022. *Nucleic Acids Res* 2021;**50**:D687–92.
51. Huang HY, Lin YC, Cui S, et al. miRTarBase update 2022: An informative resource for experimentally validated miRNA-target interactions. *Nucleid Acids Res* 2022;**50**:D222–30.
52. Karagkouni D, Paraskevopoulou MD, Chatzopoulos S, et al. DIANA-TarBase v8: A decade-long collection of experimentally supported miRNA-gene interactions. *Nucleic Acids Res* 2018;**46**:D239–45.
53. Verhagen AP, de Vet HC, de Bie RA, et al. The Delphi list: A criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. *J Clin Epidemiol* 1998;**51**:1235–41.
54. Aoi W, Ichikawa H, Mune K, et al. Muscle-enriched microRNA miR-486 decreases in circulation in response to exercise in young men. *Front Physiol* 2013;**4**:80. doi:10.3389/fphys.2013.00080.
55. Baggish AL, Hale A, Weiner RB, et al. Dynamic regulation of circulating microRNA during acute exhaustive exercise and sustained aerobic exercise training. *J Physiol* 2011;**589**:3983–94.
56. Baggish AL, Park J, Min PK, et al. Rapid upregulation and clearance of distinct circulating microRNAs after prolonged aerobic exercise. *J Appl Physiol (1985)* 2014;**116**:522–31.
57. Banzet S, Chennaoui M, Girard O, et al. Changes in circulating microRNAs levels with exercise modality. *J Appl Physiol (1985)* 2013;**115**:1237–44.
58. Biss S, Teschler M, Heimer M, et al. A single session of EMS training induces long-lasting changes in circulating muscle but not cardiovascular miRNA levels: A randomized crossover study. *J Appl Physiol (1985)* 2023;**134**:799–809.
59. Chalchat E, Charlot K, Garcia-Vicencio S, et al. Circulating microRNAs after a 24-h ultramarathon run in relation to muscle damage markers in elite athletes. *Scand J Med Sci Sports* 2021;**31**:1782–95.
60. Chilton WL, Marques FZ, West J, et al. Acute exercise leads to regulation of telomere-associated genes and microRNA expression in immune cells. *PLoS One* 2014;**9**:e92088. doi:10.1371/journal.pone.0092088.
61. Clauss S, Wakili R, Hildebrand B, et al. MicroRNAs as biomarkers for acute atrial remodeling in marathon runners (The miRathon study—A sub-study of the Munich marathon study). *PLoS One* 2016;**11**:e0148599. doi:10.1371/journal.pone.0148599.
62. Cui SF, Li W, Niu J, Zhang CY, Chen X, Ma JZ. Acute responses of circulating microRNAs to low-volume sprint interval cycling. *Front Physiol* 2015;**6**:311. doi:10.3389/fphys.2015.00311.
63. Cui SF, Wang C, Yin X, et al. Similar responses of circulating microRNAs to acute high-intensity interval exercise and vigorous-intensity continuous exercise. *Front Physiol* 2016;**7**:102. doi:10.3389/fphys.2016.00102.
64. Cui S, Sun B, Yin X, et al. Time-course responses of circulating microRNAs to 3 resistance training protocols in healthy young men. *Sci Rep* 2017;**7**:2203. doi:10.1038/s41598-017-02294-y.
65. Danese E, Benati M, Sanchis-Gomar F, et al. Influence of middle-distance running on muscular micro RNAs. *Scand J Clin Lab Invest* 2018;**78**:165–70.
66. Davidsen PK, Gallagher IJ, Hartman JW, et al. High responders to resistance exercise training demonstrate differential regulation of skeletal muscle microRNA expression. *J Appl Physiol (1985)* 2011;**110**:309–17.
67. de Gonzalo-Calvo D, Dávalos A, Montero A, et al. Circulating inflammatory miRNA signature in response to different doses of aerobic exercise. *J Appl Physiol (1985)* 2015;**119**:124–34.
68. de Gonzalo-Calvo D, Dávalos A, Fernández-Sanjurjo M, et al. Circulating microRNAs as emerging cardiac biomarkers responsive to acute exercise. *Int J Cardiol* 2018;**264**:130–6.
69. Denham J, Prestes PR. Muscle-enriched microRNAs isolated from whole blood are regulated by exercise and are potential biomarkers of cardiorespiratory fitness. *Front Genet* 2016;**7**:196. doi:10.3389/fgene.2016.00196.
70. Denham J, Gray A, Scott-Hamilton J, Hagstrom AD. Sprint interval training decreases circulating microRNAs important for muscle development. *Int J Sports Med* 2018;**39**:67–72.
71. De Sanctis P, Filardo G, Abruzzo PM, et al. Non-coding RNAs in the transcriptional network that differentiates skeletal muscles of sedentary from long-term endurance- and resistance-trained elderly. *Int J Mol Sci* 2021;**22**:1539. doi:10.3390/ijms22041539.
72. Dimassi S, Karkeni E, Laurant P, Tabka Z, Landrier JF, Riva C. Microparticle miRNAs as biomarkers of vascular function and inflammation response to aerobic exercise in obesity? *Obesity (Silver Spring)* 2018;**26**:1584–93.
73. D'Souza RF, Markworth JF, Aasen KMM, Zeng N, Cameron-Smith D, Mitchell CJ. Acute resistance exercise modulates microRNA expression profiles: Combined tissue and circulatory targeted analyses. *PLoS One* 2017;**12**:e0181594. doi:10.1371/journal.pone.0181594.
74. D'Souza RF, Bjørnsen T, Zeng N, et al. MicroRNAs in muscle: Characterizing the powerlifter phenotype. *Front Physiol* 2017;**8**:383. doi:10.3389/fphys.2017.00383.
75. D'Souza RF, Woodhead JST, Zeng N, et al. Circulatory exosomal miRNA following intense exercise is unrelated to muscle and plasma miRNA abundances. *Am J Physiol Endocrinol Metab* 2018;**315**:E723–33.
76. D'Souza RF, Zeng N, Markworth JF, et al. Whey protein supplementation post resistance exercise in elderly men induces changes in muscle miRNA's compared to resistance exercise alone. *Front Nutr* 2019;**6**:91. doi:10.3389/fnut.2019.00091.
77. Eyileten C, Fitas A, Jakubik D, et al. Alterations in circulating microRNAs and the relation of microRNAs to maximal oxygen consumption and intima-media thickness in ultra-marathon runners. *Int J Environ Res Public Health* 2021;**18**:7234. doi:10.3390/ijerph18147234.
78. Eyileten C, Wicik Z, Fitas A, et al. Altered circulating microRNA profiles after endurance training: A cohort study of ultramarathon runners. *Front Physiol* 2022;**12**:792931. doi:10.3389/fphys.2021.792931.
79. Faraldi M, Sansoni V, Perego S, et al. Acute changes in free and extracellular vesicle-associated circulating miRNAs and myokine profile in professional sky-runners during the Gran Sasso d'Italia vertical run. *Front Mol Biosci* 2022;**9**:915080. doi:10.3389/fmolb.2022.915080.
80. Fernández-Sanjurjo M, Úbeda N, Fernández-García B, et al. Exercise dose affects the circulating microRNA profile in response to acute endurance exercise in male amateur runners. *Scand J Med Sci Sports* 2020;**30**:1896–907.
81. Fernández-Sanjurjo M, Díaz-Martínez ÁE, Díez-Robles S, et al. Circulating microRNA profiling reveals specific subsignatures in response to a maximal incremental exercise test. *J Strength Cond Res* 2021;**35**:287–91.
82. Fyfe JJ, Bishop DJ, Zacharewicz E, Russell AP, Stepto NK. Concurrent exercise incorporating high-intensity interval or continuous training modulates mTORC1 signaling and microRNA expression in human skeletal muscle. *Am J Physiol Regul Integr Comp Physiol* 2016;**310**:R1297–311.
83. Garai K, Adam Z, Herczeg R, et al. Physical activity as a preventive lifestyle intervention acts through specific exosomal miRNA species-evidence from human short- and long-term pilot studies. *Front Physiol* 2021;**12**:658218. doi:10.3389/fphys.2021.658218.
84. Gomes CPC, Oliveira Jr GP, Madrid B, Almeida JA, Franco OL, Pereira RW. Circulating miR-1, miR-133a, and miR-206 levels are increased after a half-marathon run. *Biomarkers* 2014;**19**:585–9.
85. Grieb A, Schmitt A, Fragasso A, et al. Skeletal muscle MicroRNA patterns in response to a single bout of exercise in females: Biomarkers for subsequent training adaptation? *Biomolecules* 2023;**13**:884. doi:10.3390/biom13060884.
86. Guescini M, Canonico B, Lucertini F, et al. Muscle releases alpha-sarcoglycan positive extracellular vesicles carrying miRNAs in the bloodstream. *PLoS One* 2015;**10**:e0125094. doi:10.1371/journal.pone.0125094.

87. Hashida R, Matsuse H, Kawaguchi T, et al. Effects of a low-intensity resistance exercise program on serum miR-630, miR-5703, and Fractalkine/CX3CL1 expressions in subjects with no exercise habits: A preliminary study. *Hepatol Res* 2021;**51**:823–33.
88. Hicks SD, Jacob P, Middleton FA, Perez O, Gagnon Z. Distance running alters peripheral microRNAs implicated in metabolism, fluid balance, and myosin regulation in a sex-specific manner. *Physiol Genomics* 2018;**50**:658–67.
89. Hicks SD, Onks C, Kim RY, et al. Refinement of saliva microRNA biomarkers for sports-related concussion. *J Sport Health Sci* 2023;**12**:369–78.
90. Horak M, Zlamal F, Iliev R, et al. Exercise-induced circulating microRNA changes in athletes in various training scenarios. *PLoS One* 2018;**13**:e0191060. doi:10.1371/journal.pone.0191060.
91. Kangas R, Törmäkangas T, Heinonen A, et al. Declining physical performance associates with serum FasL, miR-21, and miR-146a in aging sprinters. *Biomed Res Int* 2017;**2017**: 8468469. doi:10.1155/2017/8468469.
92. Koltai E, Bori Z, Osvath P, et al. Master athletes have higher miR-7, SIRT3 and SOD2 expression in skeletal muscle than age-matched sedentary controls. *Redox Biol* 2018;**19**:46–51.
93. Krammer UDB, Sommer A, Tschida S, et al. PGC-1α methylation, miR-23a, and miR-30e expression as biomarkers for exercise- and diet-induced mitochondrial biogenesis in capillary blood from healthy individuals: A single-arm intervention. *Sports (Basel)* 2022;**10**:73. doi:10.3390/sports10050073.
94. Kuji T, Sugasawa T, Fujita SI, Ono S, Kawakami Y, Takekoshi K. A pilot study of miRNA expression profile as a liquid biopsy for full-marathon participants. *Sports (Basel)* 2021;**9**:134. doi:10.3390/sports9100134.
95. Lai Z, Lin W, Yan X, Chen X, Xu G. Fatiguing freestyle swimming modifies miRNA profiles of circulating extracellular vesicles in athletes. *Eur J Appl Physiol* 2023;**123**:2041–51.
96. Li Y, Yao M, Zhou Q, et al. Dynamic regulation of circulating microRNAs during acute exercise and long-term exercise training in basketball athletes. *Front Physiol* 2018;**9**:282. doi:10.3389/fphys.2018.00282.
97. Li F, Bai M, Xu J, Zhu L, Liu C, Duan R. Long-term exercise alters the profiles of circulating micro-RNAs in the plasma of young women. *Front Physiol* 2020;**11**:372. doi:10.3389/fphys.2020.00372.
98. Li D, Wang P, Wei W, et al. Serum microRNA expression patterns in subjects after the 5-km exercise are strongly associated with cardiovascular adaptation. *Front Physiol* 2021;**12**: 755656. doi:10.3389/fphys.2021.755656.
99. Liu HW, Cheng HC, Tsai SH, Sun WH. Effect of progressive resistance training on circulating adipogenesis-, myogenesis-, and inflammation-related microRNAs in healthy older adults: An exploratory study. *Gerontology* 2020;**66**:562–70.
100. Maggio S, Canonico B, Ceccaroli P, et al. Modulation of the circulating extracellular vesicles in response to different exercise regimens and study of their inflammatory effects. *Int J Mol Sci* 2023;**24**:3039. doi:10.3390/ijms24033039.
101. Mancini A, Vitucci D, Orlandella FM, et al. Regular football training down-regulates miR-1303 muscle expression in veterans. *Eur J Appl Physiol* 2021;**121**:2903–12.
102. Margolis LM, McClung HL, Murphy NE, Carrigan CT, Pasiakos SM. Skeletal muscle myomiR are differentially expressed by endurance exercise mode and combined essential amino acid and carbohydrate supplementation. *Front Physiol* 2017;**8**:182. doi:10.3389/fphys.2017.00182.
103. Margolis LM, Hatch-McChesney A, Allen JT, et al. Circulating and skeletal muscle microRNA profiles are more sensitive to sustained aerobic exercise than energy balance in males. *J Physiol* 2022;**600**:3951–63.
104. Massart J, Sjögren RJO, Egan B, et al. Endurance exercise training-responsive miR-19b-3p improves skeletal muscle glucose metabolism. *Nat Commun* 2021;**12**:5948. doi:10.1038/s41467-021-26095-0.
105. Min PK, Park J, Isaacs S, et al. Influence of statins on distinct circulating microRNAs during prolonged aerobic exercise. *J Appl Physiol (1985)* 2016;**120**:711–20.
106. Mooren FC, Viereck J, Krüger K, Thum T. Circulating microRNAs as potential biomarkers of aerobic exercise capacity. *Am J Physiol Heart Circ Physiol* 2014;**306**:H557–63.
107. Nair VD, Ge Y, Li S, et al. Sedentary and trained older men have distinct circulating exosomal microRNA profiles at baseline and in response to acute exercise. *Front Physiol* 2020;**11**:605. doi:10.3389/fphys.2020.00605.
108. Nielsen S, Scheele C, Yfanti C, et al. Muscle specific microRNAs are regulated by endurance exercise in human skeletal muscle. *J Physiol* 2010;**588**:4029–37.
109. Nielsen S, Åkerström T, Rinnov A, et al. The miRNA plasma signature in response to acute aerobic exercise and endurance training. *PLoS One* 2014;**9**:e87308. doi:10.1371/journal.pone.0087308.
110. Pietrangelo T, Santangelo C, Bondi D, et al. Endurance-dependent urinary extracellular vesicle signature: Shape, metabolic miRNAs, and purine content distinguish triathletes from inactive people. *Pflugers Arch* 2023;**475**:691–709.
111. Ramos AE, Lo C, Estephan LE, et al. Specific circulating microRNAs display dose-dependent responses to variable intensity and duration of endurance exercise. *Am J Physiol Heart Circ Physiol* 2018;**315**:H273–83.
112. Russell AP, Lamon S, Boon H, et al. Regulation of miRNAs in human skeletal muscle following acute endurance exercise and short-term endurance training. *J Physiol* 2013;**591**:4637–53.
113. Sandmo SB, Matyasova K, Filipcik P, et al. Changes in circulating microRNAs following head impacts in soccer. *Brain Inj* 2022;**36**: 560–71.
114. Sansoni V, Perego S, Vernillo G, et al. Effects of repeated sprints training on fracture risk-associated miRNA. *Oncotarget* 2018;**9**:18029–40.
115. Sapp RM, Chesney CA, Eagan LE, et al. Changes in circulating microRNA and arterial stiffness following high-intensity interval and moderate intensity continuous exercise. *Physiol Rep* 2020;**8**:e14431. doi:10.14814/phy2.14431.
116. Sawada S, Kon M, Wada S, Ushida T, Suzuki K, Akimoto T. Profiling of circulating microRNAs after a bout of acute resistance exercise in humans. *PLoS One* 2013;**8**:e70823. doi:10.1371/journal.pone.0070823.
117. Schmitz B, Schelleckes K, Nedele J, et al. Dose-response of high-intensity training (HIT) on atheroprotective miRNA-126 levels. *Front Physiol* 2017;**8**:349. doi:10.3389/fphys.2017.00349.
118. Schmitz B, Rolfes F, Schelleckes K, et al. Longer work/rest intervals during high-intensity interval training (HIIT) lead to elevated levels of miR-222 and miR-29c. *Front Physiol* 2018;**9**:395. doi:10.3389/fphys.2018.00395.
119. Schmitz B, Niehues H, Lenders M, et al. Effects of high-intensity interval training on microvascular glycocalyx and associated microRNAs. *Am J Physiol Heart Circ Physiol* 2019;**316**:H1538–51.
120. Schmitz B, Breulmann FL, Jubran B, et al. A three-step approach identifies novel shear stress-sensitive endothelial microRNAs involved in vasculoprotective effects of high-intensity interval training (HIIT). *Oncotarget* 2019;**10**:3625–40.
121. Shah R, Yeri A, Das A, et al. Small RNA-seq during acute maximal exercise reveal RNAs involved in vascular inflammation and cardiometabolic health: Brief report. *Am J Physiol Heart Circ Physiol* 2017;**313**: H1162–7.
122. Sieland J, Niederer D, Engeroff T, et al. Effects of single bouts of different endurance exercises with different intensities on microRNA biomarkers with and without blood flow restriction: A three-arm, randomized crossover trial. *Eur J Appl Physiol* 2021;**121**:3243–55.
123. Silver JL, Alexander SE, Dillon HT, Lamon S, Wadley GD. Extracellular vesicular miRNA expression is not a proxy for skeletal muscle miRNA expression in males and females following acute, moderate intensity exercise. *Physiol Rep* 2020;**8**:e14520. doi:10.14814/phy2.14520.
124. Telles GD, Libardi CA, Conceição MS, et al. Time course of skeletal muscle miRNA expression after resistance, high-intensity interval, and concurrent exercise. *Med Sci Sports Exerc* 2021;**53**:1708–18.
125. Tonevitsky AG, Maltseva DV, Abbasi A, et al. Dynamically regulated miRNA-mRNA networks revealed by exercise. *BMC Physiol* 2013;**13**:9. doi:10.1186/1472-6793-13-9.
126. Uhlemann M, Möbius-Winkler S, Fikenzer S, et al. Circulating microRNA-126 increases after different forms of endurance exercise in healthy adults. *Eur J Prev Cardiol* 2014;**21**:484–91.

127. Van Craenenbroeck AH, Ledeganck KJ, Van Ackeren K, et al. Plasma levels of microRNA in chronic kidney disease: Patterns in acute and chronic exercise. *Am J Physiol Heart Circ Physiol* 2015;**309**:H2008–16.
128. Vogel J, Niederer D, Engeroff T, et al. Effects on the profile of circulating miRNAs after single bouts of resistance training with and without blood flow restriction-a three-arm, randomized crossover trial. *Int J Mol Sci* 2019;**20**:3249. doi:10.3390/ijms20133249.
129. Wahl P, Wehmeier UF, Jansen FJ, et al. Acute effects of different exercise protocols on the circulating vascular microRNAs -16, -21, and -126 in trained subjects. *Front Physiol* 2016;**7**:643. doi:10.3389/fphys.2016.00643.
130. Widmann M, Mattioni Maturana F, Burgstahler C, et al. miRNAs as markers for the development of individualized training regimens: A pilot study. *Physiol Rep* 2022;**10**:e15217. doi:10.14814/phy2.15217.
131. Xhuti D, Nilsson MI, Manta K, Tarnopolsky MA, Nederveen JP. Circulating exosome-like vesicle and skeletal muscle microRNAs are altered with age and resistance training. *J Physiol* 2023;**601**:5051–73.
132. Xiao F, Yang Y, Xiao L, et al. Reduction of T cells and Hsa-miR150-5p in female canoeing athletes: Preliminary evidence between exercise training and immune. *J Strength Cond Res* 2022;**36**:e106–13.
133. Yin X, Cui S, Li X, et al. Regulation of circulatory muscle-specific microRNA during 8 km run. *Int J Sports Med* 2020;**41**:582–8.
134. Zhou Q, Shi C, Lv Y, Zhao C, Jiao Z, Wang T. Circulating microRNAs in response to exercise training in healthy adults. *Front Genet* 2020;**11**:256. doi:10.3389/fgene.2020.00256.
135. Bonilauri B, Dallagiovanna B. Long non-coding RNAs are differentially expressed after different exercise training programs. *Front Physiol* 2020;**11**:567614. doi:10.3389/fphys.2020.567614.
136. Pandorf CE, Haddad F, Owerkowicz T, Carroll LP, Baldwin KM, Adams GR. Regulation of myosin heavy chain antisense long noncoding RNA in human vastus lateralis in response to exercise training. *Am J Physiol Cell Physiol* 2020;**318**:C931–42.
137. Trewin AJ, Silver J, Dillon HT, et al. Long non-coding RNA Tug1 modulates mitochondrial and myogenic responses to exercise in skeletal muscle. *BMC Biol* 2022;**20**:164. doi:10.1186/s12915-022-01366-4.
138. Wohlwend M, Laurila PP, Williams K, et al. The exercise-induced long noncoding RNA CYTOR promotes fast-twitch myogenesis in aging. *Sci Transl Med* 2021;**13**:eabc7367. doi:10.1126/scitranslmed.abc7367.
139. Meinecke A, Mitzka S, Just A, et al. Cardiac endurance training alters plasma profiles of circular RNA MBOAT2. *Am J Physiol Heart Circ Physiol* 2020;**319**:H13–21.
140. Podgórski R, Cieśla M, Podgórska D, et al. Plasma microRNA-320a as a potential biomarker of physiological changes during training in professional volleyball players. *J Clin Med* 2022;**11**:263. doi:10.3390/jcm11010263.
141. Favere K, Bosman M, Delputte PL, et al. A systematic literature review on the effects of exercise on human Toll-like receptor expression. *Exerc Immunol Rev* 2021;**27**:84–124.
142. Bayraktar R, Bertilaccio MTS, Calin GA. The interaction between two worlds: microRNAs and Toll-like receptors. *Front Immunol* 2019;**10**:1053. doi:10.3389/fimmu.2019.01053.
143. Zhang T, Zhang Z, Li F, et al. miR-143 regulates memory T Cell differentiation by reprogramming T cell metabolism. *J Immunol* 2018;**201**:2165–75.
144. Pan S, Li M, Yu H, et al. microRNA-143-3p contributes to inflammatory reactions by targeting FOSL2 in peripheral blood mononuclear cells from patients with autoimmune diabetes mellitus. *Acta Diabetol* 2021;**58**:63–72.
145. Mooren FC, Krueger K, Ringseis R, et al. Combined effects of moderate exercise and short-term fasting on markers of immune function in healthy human subjects. *Am J Physiol Regul Integr Comp Physiol* 2020;**318**:R1103–15.
146. Kent OA, Fox-Talbot K, Halushka MK. RREB1 repressed miR-143/145 modulates KRAS signaling through downregulation of multiple targets. *Oncogene* 2013;**32**:2576–85.
147. Ye Z, Li G, Kim C, et al. Regulation of miR-181a expression in T cell aging. *Nat Commun* 2018;**9**:3060. doi:10.1038/s41467-018-05552-3.
148. Kim C, Ye Z, Weyand CM, Goronzy JJ. miR-181a-regulated pathways in T-cell differentiation and aging. *Immun Ageing* 2021;**18**:28. doi:10.1186/s12979-021-00240-1.
149. Lim CX, Lee B, Geiger O, et al. miR-181a Modulation of ERK-MAPK signaling sustains DC-SIGN expression and limits activation of monocyte-derived dendritic cells. *Cell Rep* 2020;**30:**3793−805.e5.
150. Hong Y, Vu TH, Lee S, et al. Comparative analysis of exosomal miRNAs derived from lipopolysaccharide and polyinosinic-polycytidylic acid-stimulated chicken macrophage cell line. *Poult Sci* 2022;**101**:102141. doi:10.1016/j.psj.2022.102141.
151. Proschinger S, Winker M, Joisten N, Bloch W, Palmowski J, Zimmer P. The effect of exercise on regulatory T cells: A systematic review of human and animal studies with future perspectives and methodological recommendations. *Exerc Immunol Rev* 2021;**27**:142–66.
152. Xu M, Liu Q, Li S, et al. Increased expression of miR-338-3p impairs Treg-mediated immunosuppression in pemphigus vulgaris by targeting RUNX1. *Exp Dermatol* 2020;**29**:623–9.
153. Wang L, Sui M, Wang X. miR-338-3p suppresses the malignancy of T-cell lymphoblastic lymphoma by downregulating HOXA3. *Mol Med Rep* 2019;**20**:2127–34.
154. Vigorito E, Kohlhaas S, Lu D, Leyland R. miR-155: An ancient regulator of the immune system. *Immunol Rev* 2013;**253**:146–57.
155. Ji Y, Fioravanti J, Zhu W, et al. miR-155 harnesses Phf19 to potentiate cancer immunotherapy through epigenetic reprogramming of CD8+ T cell fate. *Nat Commun* 2019;**10**:2157. doi:10.1038/s41467-019-09882-8.
156. Hsin JP, Lu Y, Loeb GB, Leslie CS, Rudensky AY. The effect of cellular context on miR-155-mediated gene regulation in four major immune cell types. *Nat Immunol* 2018;**19**:1137–45.
157. Jiang X, Xu C, Lei F, et al. MiR-30a targets IL-1α and regulates islet functions as an inflammation buffer and response factor. *Sci Rep* 2017;**7**:5270. doi:10.1038/s41598-017-05560-1.
158. Miranda K, Yang X, Bam M, Murphy EA, Nagarkatti PS, Nagarkatti M. MicroRNA-30 modulates metabolic inflammation by regulating Notch signaling in adipose tissue macrophages. *Int J Obes (Lond)* 2018;**42**:1140–50.
159. Wang WL, Ouyang C, Graham NM, et al. microRNA-142 guards against autoimmunity by controlling Treg cell homeostasis and function. *PLoS Biol* 2022;**20**:e3001552. doi:10.1371/journal.pbio.3001552.
160. Mildner A, Chapnik E, Manor O, et al. Mononuclear phagocyte miRNome analysis identifies miR-142 as critical regulator of murine dendritic cell homeostasis. *Blood* 2013;**121**:1016–27.
161. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2019;**140**:e596–646.
162. Hansen D, Abreu A, Ambrosetti M, et al. Exercise intensity assessment and prescription in cardiovascular rehabilitation and beyond: Why and how: A position statement from the Secondary Prevention and Rehabilitation Section of the European Association of Preventive Cardiology. *Eur J Prev Cardiol* 2022;**29**:230–45.
163. Wolf D, Ley K. Immunity and inflammation in atherosclerosis. *Circ Res* 2019;**124**:315–27.
164. Libby P. The changing landscape of atherosclerosis. *Nature* 2021;**592**:524–33.
165. Schuler G, Adams V, Goto Y. Role of exercise in the prevention of cardiovascular disease: Results, mechanisms, and new perspectives. *Eur Heart J* 2013;**34**:1790–9.
166. Schmitz B, Brand SM. Circulating non-coding RNAs as functional markers to monitor and control physical exercise for the prevention of cardiovascular disease. *Eur Heart J* 2018;**39**:3551. doi:10.1093/eurheartj/ehy455.
167. Arroyo JD, Chevillet JR, Kroh EM, et al. Argonaute2 complexes carry a population of circulating microRNAs independent of vesicles in human plasma. *Proc Natl Acad Sci U S A* 2011;**108**:5003–8.
168. Zernecke A, Bidzhekov K, Noels H, et al. Delivery of microRNA-126 by apoptotic bodies induces CXCL12-dependent vascular protection. *Sci Signal* 2009;**2**:ra81. doi:10.1126/scisignal.2000610.

169. Schmitz B. Regulation of antiatherogenic miR-126 by physical exercise. *Am J Physiol Heart Circ Physiol* 2021;**321**:H663–4.
170. Deregibus MC, Cantaluppi V, Calogero R, et al. Endothelial progenitor cell derived microvesicles activate an angiogenic program in endothelial cells by a horizontal transfer of mRNA. *Blood* 2007;**110**:2440–8.
171. Zhang J, Li S, Li L, et al. Exosome and exosomal microRNA: Trafficking, sorting, and function. *Genomics Proteom Bioinforma* 2015;**13**:17–24.
172. Naito H, Iba T, Takakura N. Mechanisms of new blood-vessel formation and proliferative heterogeneity of endothelial cells. *Int Immunol* 2020;**32**:295–305.
173. Paik JH. FOXOs in the maintenance of vascular homoeostasis. *Biochem Soc Trans* 2006;**34**:731–4.
174. Schmitz B, Vischer P, Brand E, et al. Increased monocyte adhesion by endothelial expression of VCAM-1 missense variation *in vitro*. *Atherosclerosis* 2013;**230**:185–90.
175. Vischer P, Telgmann R, Schmitz B, et al. Molecular investigation of the functional relevance of missense variants of ICAM-1. *Pharmacogenet Genomics* 2008;**18**:1017–9.
176. Schmitz B, Salomon A, Rötrige A, et al. Interindividual transcriptional regulation of the human biglycan gene involves three common molecular haplotypes. *Arterioscler Thromb Vasc Biol* 2013;**33**:871–80.
177. Kawai T, Elliott KJ, Scalia R, Eguchi S. Contribution of ADAM17 and related ADAMs in cardiovascular diseases. *Cell Mol Life Sci* 2021;**78**:4161–87.
178. Fichtlscherer S, De Rosa S, Fox H, et al. Circulating microRNAs in patients with coronary artery disease. *Circ Res* 2010;**107**:677–84.
179. Borja-Gonzalez M, Casas-Martinez JC, McDonagh B, Goljanek-Whysall K. Aging Science Talks: The role of miR-181a in age-related loss of muscle mass and function. *Transl Med Aging* 2020;**4**:81–5.
180. Agostini S, Mancuso R, Costa AS, et al. Sarcopenia associates with SNAP-25 SNPs and a miRNAs profile which is modulated by structured rehabilitation treatment. *J Transl Med* 2021;**19**:315. doi:10.1186/s12967-021-02989-x.
181. Mytidou C, Koutsoulidou A, Zachariou M, et al. Age-related exosomal and endogenous expression patterns of miR-1, miR-133a, miR-133b, and miR-206 in skeletal muscles. *Front Physiol* 2021;**12**:708278. doi:10.3389/fphys.2021.708278.
182. Hergenreider E, Heydt S, Tréguer K, et al. Atheroprotective communication between endothelial cells and smooth muscle cells through miRNAs. *Nat Cell Biol* 2012;**14**:249–56.
183. Wang C, Li D, Zhang L, et al. RNA sequencing analyses of gene expression during Epstein-Barr virus infection of primary B lymphocytes. *J Virol* 2019;**93**:e00226–319.
184. Du J, Yu W, Peng L, Zhang T. The long noncoding RNA cytoskeleton regulator RNA (CYTOR)/miRNA-24-3p axis facilitates nasopharyngeal carcinoma progression by modulating GAD1 expression. *J Oncol* 2023;**2023**:6027860. doi:10.1155/2023/6027860.
185. Keqi H, Handong L. The long non-coding RNA cytoskeleton regulator (CYTOR) sponges microRNA- 206 (miR-206) to promote proliferation and invasion of HP75 cells. *Curr Cancer Drug Targets* 2021;**21**:526–35.
186. Yuan Y, Wang J, Chen Q, et al. Long non-coding RNA cytoskeleton regulator RNA (CYTOR) modulates pathological cardiac hypertrophy through miR-155-mediated IKKi signaling. *Biochim Biophys Acta Mol Basis Dis* 2019;**1865**:1421–7.