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MicroRNAs and Exercise

MicroRNAs unter Einfluss körperlicher Belastung

REVIEW

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Summary

› **MicroRNAs (miRNAs)** have become a major object of investigation in the recent years. These small non-coding RNAs regulate gene expression at the post-transcriptional level and there is growing evidence that they are involved in a plethora of biological processes. With exercise as a potent trigger for adaptational responses that affect virtually all systems of the body, understanding miRNAs is a precondition for deeper insight into the adaptation of skeletal muscle (i.e. growth/regeneration) following exercise. These adaptations involve an increased need of protein synthesis regarding both resistance exercise and chronic endurance exercise. Apart from protein synthesis, miRNAs have a meaningful impact on regulating metabolic changes (e.g. muscle fiber phenotype/mitochondrial bio-genesis) as well. Altogether, these responses might be necessary to facilitate adaptation and regeneration following exercise.

› **The role of miRNAs** in circulation (c-miRNAs) has gathered considerable attention in recent years. It is of great interest whether and how c-miRNAs modulated by exercise play a role in cell-to-cell communication and might be further considered responsible for beneficial effects in peripheral organs.

› **This review** summarizes what is currently known about the impact of miRNAs in skeletal muscle and their potential role as circulating biomarkers in response to either acute and/or chronic exercise with various modalities.

Zusammenfassung

› **MicroRNAs (miRNAs)** sind in den letzten Jahren zunehmend ins Blickfeld der Forschung gerückt. Diese kleinen, nicht-kodierenden RNAs regulieren die Genexpression auf der post-transkriptionellen Ebene und es gibt immer mehr Hinweise, dass diese in eine Vielzahl von biologischen Prozessen involviert sind. Es ist bekannt, dass körperliche Aktivität einen starken Reiz für physische Anpassungsprozesse darstellt und es konnte gezeigt werden, dass miRNAs hier eine gewichtige Rolle zukommt. Das Verständnis ihrer Funktion ist die Voraussetzung für einen genaueren Blick auf die Anpassungsprozesse, z. B. in der Skelettmuskulatur, welche mit einem erhöhten Bedarf an Proteinbiosynthese nach Kraft- und längerfristigem Ausdauertraining verbunden sind. Daneben beeinflussen sie vermutlich die Regulation metabolischer Veränderungen, wie den Muskelfaserphänotyp oder die mitochondriale Biosynthese. Zusammengenommen scheinen diese Reaktionen auf körperliche Belastungen notwendig für Wachstums- und Regenerationsprozesse.

› **Aktuell erlangen miRNAs** im Blutkreislauf (c-miRNAs) immer größere Aufmerksamkeit. Ob und wie c-miRNAs hier durch körperliche Belastung moduliert werden und eine mögliche Rolle in der Zellkommunikation spielen und welche Wirkung sie auf periphere Organe ausüben, wird in der Zukunft von gesteigertem Interesse sein. Ihr Einsatz als Biomarker für physiologische Anpassungprozesse als auch in der Pathologie scheint großes Potential zu besitzen.

› **Dieser Übersichtsartikel** fasst den aktuellen Forschungsstand zum Thema miRNAs und körperlicher Aktivität zusammen und beschreibt die Auswirkungen von akuter und/oder chronischer Belastung verschiedener Ausprägungen auf miRNAs in der Skelettmuskulatur und als Biomarker im Blutkreislauf.

KEY WORDS:
MicroRNA, Exercise, Circulating MicroRNAs, Skeletal Muscle, Cardiovascular System

SCHLÜSSELWÖRTER:
MicroRNA, körperliche Aktivität, zirkulierende MicroRNAs, Skelettmuskulatur, kardiovaskuläres System

Introduction

Physical activity is a well-known trigger for many adaptational responses by modulating and supporting physiological processes that virtually affect all systems of the body. Furthermore, physical activity also plays a critical role when it comes to the treatment and prevention of various diseases and pathological conditions (23, 50, 54). Furthermore, exercise reduces physical disability with ageing and supports maintaining an independent life of the elderly (9). However, many of the exact biological mechanisms in physiological adaptations following exercise are still not fully understood. To shed more light on the underlying mechanisms in response to physical activity, microRNAs (miRNAs) have become a major object of investigation. These small non-coding RNAs regulate gene expression ›

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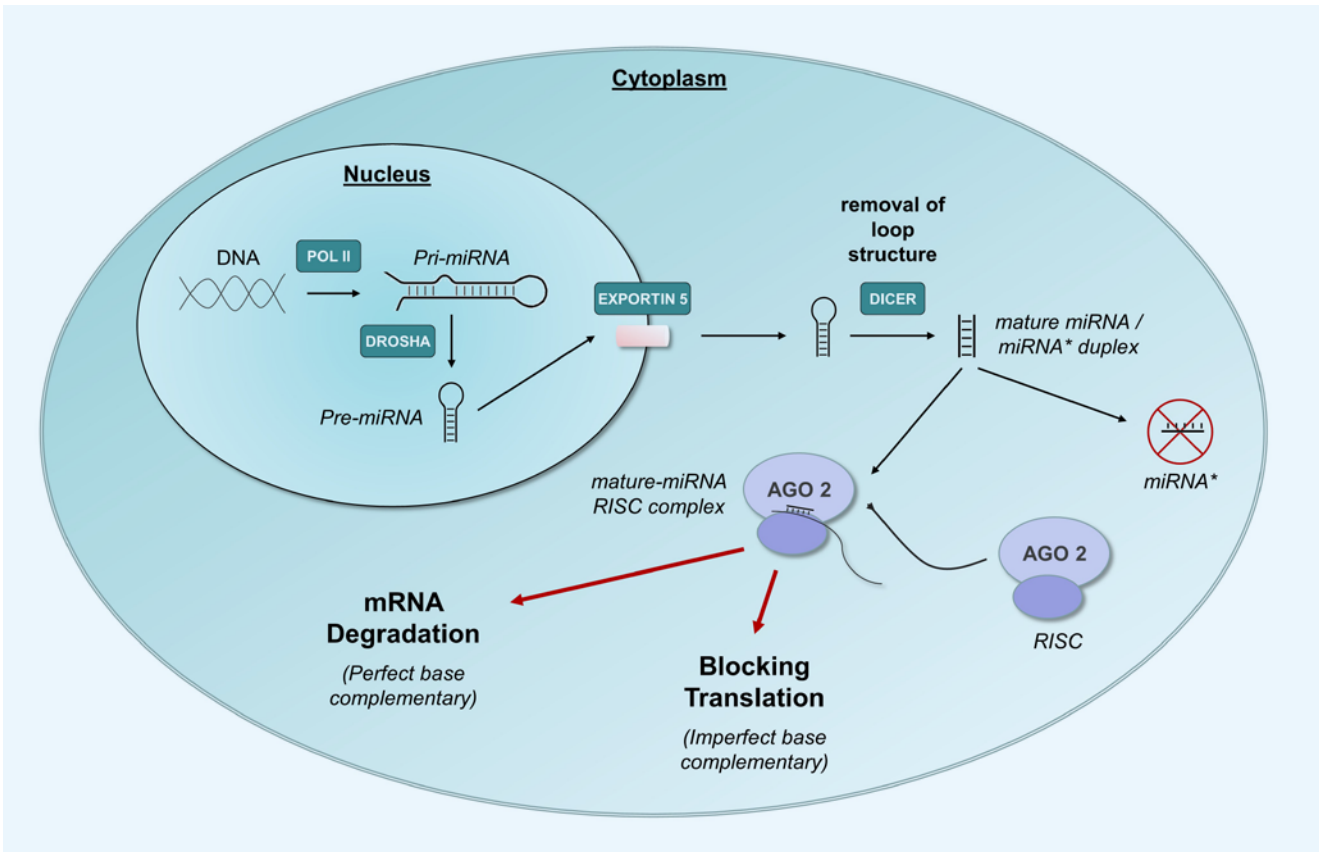

Figure 1

Schematic depiction of microRNA biogenesis and processing. After transcription, Pri-miRNA is cleaved into precursor miRNA (pre-miRNA) by the Drosha/DGCR8 microprocessor complex and exported from cell nucleus via Exportin 5. In cytoplasm, pri-miRNA is further cleaved by the Dicer/TRBP enzyme complex, which removes the terminal loop resulting in miRNA/miRNA* duplexes. One duplex strand (guide strand) is then loaded onto a binding protein of the Argonaute protein family to form the RNA induced silencing complex (RISC) which in turn binds to its respective target mRNA. The other strand, frequently referred to as star strand (miRNA*) is targeted for degradation. High or near-perfect complementarity results in cleavage and subsequently degradation of mRNA, whereas non-perfect binding results in translational inhibition.

by RNA silencing and post-transcriptional regulation of gene expression. In this regard, miRNAs can cleave mRNA strands into two pieces, destabilize the mRNA through shortening of its poly (A) tail, or translate the mRNA into proteins by ribosomes. Thus, miRNAs are involved in a plethora of biological processes like proliferation, differentiation and apoptosis (46). They consist of approximately 19-22 nucleotides (nt) in length and each single miRNA can regulate the expression of hundreds of mRNAs and proteins (7, 18). Moreover, 60% of the human protein-coding genes contain at least one conserved miRNA-binding site but there are also large amounts of non-conserved sites, suggesting that even more protein-coding genes are controlled by miRNAs (18). Thus, miRNAs can have a huge impact on the protein regulation of their target genes and it is not surprising that their dysregulation is often associated with various pathologies (46).

Biogenesis and Processing

MiRNAs are originally generated in the cell nucleus as long primary miRNAs (pri-miRNAs) transcripts of RNA polymerase II (25) (Fig. 1). These pri-miRNAs predominantly derive from introns and exons of protein coding genes or less frequently from nonprotein-coding transcripts and contain a 5' cap and a 3' poly (A) tail. They can be transcribed as individual miRNAs (monocistronic) or in clusters (polycistronic) (25, 42). Pri-miRNA is further cleaved into approximately 70nt long hairpin precursor miRNAs (pre-miRNAs) by a microprocessor complex called Drosha/DGCR8 (24, 57). This is followed by their active transportation into cytoplasm through Exportin-5 with presence of the cofactor Ran-GTP (58). In cytoplasm, pri-miRNA is cleaved by the Dicer/TRBP enzyme complex, which removes the terminal loop and results in approximately 22nt long single-stranded miR-NA/miRNA* duplexes (11, 59). Finally, one duplex strand (guide strand) is then loaded onto a binding protein of the Argonaute protein family to form the RNA induced silencing complex (RISC) which in turn binds to its respective target mRNA. The other strand, frequently referred to as star strand (miRNA*) is targeted for degradation (17).

MiRNAs act through several mechanisms, such as cotranslational protein degradation, translational inhibition and deadenylation (7, 15) (Fig. 1). Primary, they target specific complementary sequences in the 3'-UTR (untranslated region) of their target mRNAs which results either in inhibition of translation and/or degradation of the target transcript, depending on the degree of complementarity between miRNA and the target mRNA as well as the Argonaute family protein (17). High or near-perfect complementarity results in cleavage and subsequently degradation of mRNA whereas non-perfect binding results in translational inhibition (17).

The purpose of this review is to provide a summary of what is currently known about the interaction of miRNAs and exercise in skeletal muscle, cardiovascular system and their potential role as biomarkers in circulation.

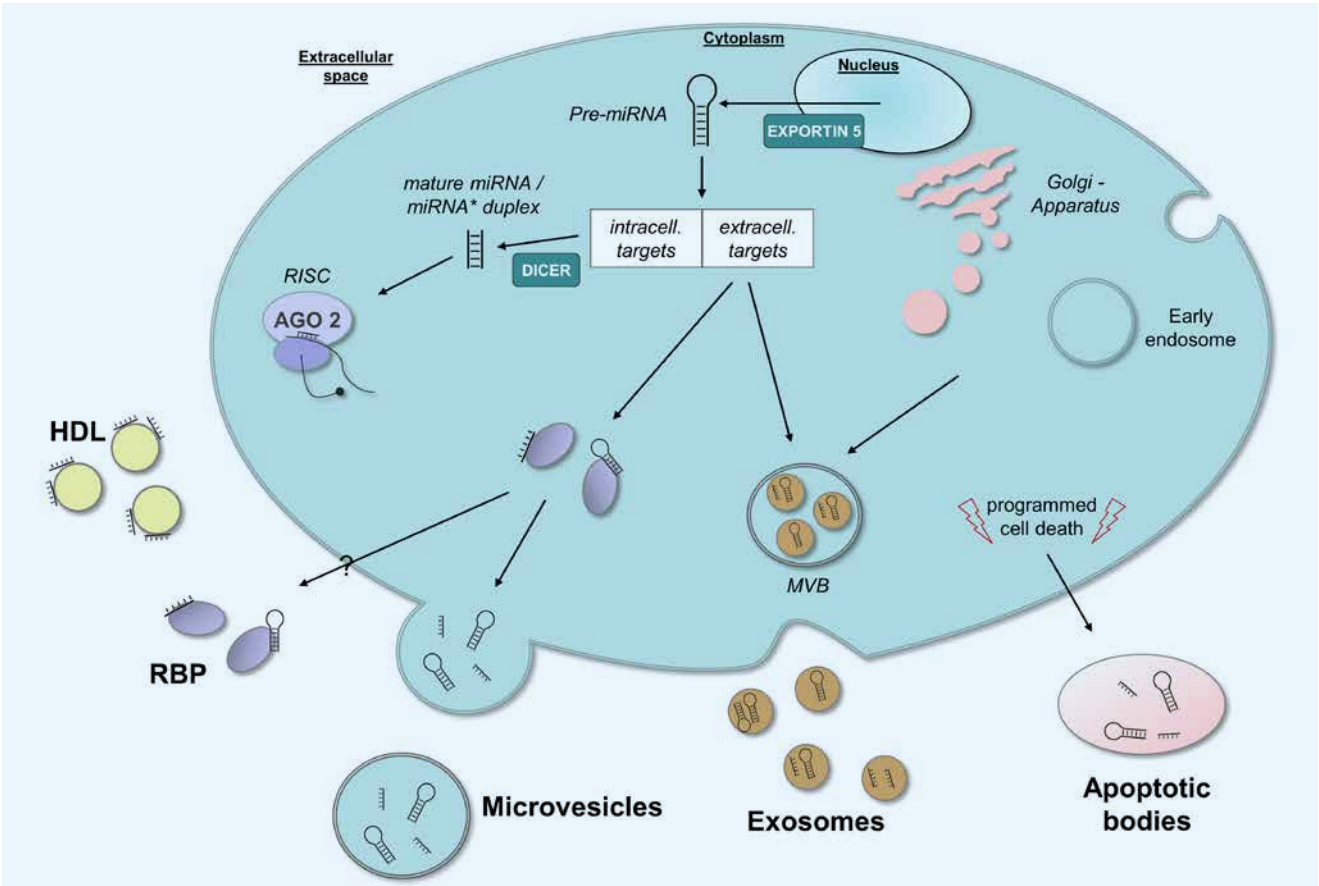

Figure 2

MicroRNAs are secreted into circulation via multiple carriers, including exosomes, microvesicles and apoptotic bodies or bound to proteins like HDL (high density lipoprotein) and RNA-binding proteins (RBP). This provides protection from RNases and thus degradation when delivered into circulation. C-miRNAs are thought to be released or leaked into circulation in response to stress, injury or tissue damage. Though, the exact release mechanisms (active/passive) as well as uptake of microRNAs into multivesicular bodies (MVB) are still in need for clarification.

Skeletal Muscle

There are more than 150 miRNAs expressed in the muscle but only a small population is frequent object of investigation and considered muscle-specific. These miRNAs are called myomiRs and include miR-1, -133a, -133b, -206, -208a, -208b, -486 and -499. Furthermore, the myomiRs miR-1, -133, -206, and -499 account for almost 25% of miRNA expression (28, 30). Most of these myomiRs are expressed in both, heart and skeletal muscle with the exception of miR-208a, which is cardiac-specific and miR-206 which is expressed in skeletal muscle only (28).

Resistance Exercise

Resistance exercise is placing a high mechanical load onto the muscle leading to a number of adaptations with hypertrophy of the muscle as the most prominent one. First indications for miRNAs and their implication in muscle adaptation were discovered by McCarthy and Esser and Drummond et al. (13, 29). They showed that decreases in miR-1 and miR-133 levels following functional overload in mice and resistance exercise in human lead to an amplified activation of the IGF/AKT signaling pathway and subsequently enhanced protein synthesis. In a study by Davidsen et al. it was investigated whether different expression levels of miRNAs were able to explain how well individuals will respond to a 12-week resistance training (12). Subjects were separated into "low-responders" and "high-responders" based on the changes in lean body mass following training. As for the high-responders, miRNA expression was unaffected in the vastus lateralis muscle, whereas significant changes in miR-378 (decrease) and miR-451 (increase) could be demonstrated in low responders. In addition, the authors showed a significant positive correlation between the changes in lean body mass and miR-378 abundance, thus leading them to speculate that a decrease in miR-378 expression levels might be responsible for low gains in muscle mass. As noticed by Kirby and McCarthy, this notion is accompanied by Gagan et al. whose data of an in vitro study displayed that miR-378 stimulates myogenic differentiation by directly repressing MyoR (Myogenic Repressor) (19, 22, 26). It was shown that the transcriptional activity of the myogenic transcription factor MyoD was increased by an overexpression of miR-378 and thus a repression of the antagonistic MyoR. Furthermore, this myogenic differentiation and the satellite cell-mediated myonuclear addition to existing muscle have been suggested to positively influence hypertrophy in humans (36).

The role of miRNAs is even more apparent when considering the different responses to exercise in context of ageing. There is a reduced capacity and a diminished adaptability of ageing skeletal muscle to exercise and other anabolic stimuli which may contribute to the age-induced loss of muscle mass and function: sarcopenia (16).

Following an acute bout of resistance exercise in young and old subjects, Rivas et al. found miR-1 and miR-126 as essential negative regulators for lean body mass in old men and thus ›

Table 1

MicroRNAs and acute exercise. Resistance Exercise (RE); Endurance Exercise (EE); Human (H); Mouse (M); Rat (R); 1 Repetition maximum (1RM); Maximal oxygen uptake (VO_{2max}); Maximal power output (P_{max}); Individual anaerobic threshold (IAT); No Change (NC).

SPECIES	n	TYPE	MODALITY	miRNA EXPRESSION	PUTATIVE EFFECT	REF.
			Skeletal Muscle			
H	16	RE	80% of 1 RM (in young/old)	miR-1, -126 (remained elevated in elderly)	Reduced protein synthesis (elderly)	(41)
H	6	RE	70% of 1RM	↓miR-1	Hypertrophy	(13)
H	18	EE	Exercise capacity test in elderly	miR-1, -133a, -133b (elevated in elderly)	Adaptation with ageing	(34)
H	9	EE	Cycle Ergometer (continuous & interval)	↑miR-1, -133a, -133b, -181a; ↓miR-9, -23a, -23b, -31	Muscle regeneration, Mitochondrial biogenesis	(43)
H	10	EE	65% of P_{max}	↑miR-1, -133	Exercise-induced adaptation	(35)
M	7	EE	Treadmill running	↑miR-1, -107, -181; ↓miR-23	Mitochondrial biogenesis	(44)
			Circulation			
H	12	RE	70% of 1RM	↑miR-149*; ↓miR-221, -146a	Exercise-induced adaptation	(45)
H	11	RE	Additional eccentric loads	↑miR-133; miR-126 (NC)	Cell damage marker	(49)
H	13	EE	Marathon run	↑miR-1, -133, -206, -499, -208b	Cardiovascular adaptation / Fitness marker	(31)
H	21	EE	Marathon run	↑miR-1, -133a, -499, -208a, -126, -146a	Cardiorespiratory fitness biomarker	(5)
H	11	EE	Cycle Ergometer (70% of VO_{2max})	↓miR-486	Regulating insulin signaling	(2)
H	9	EE	Eccentric exercise (dowhnhill running)	↑miR-1, -133a, -133b, -208b	Muscle damage marker	(6)
H	24	EE	Exercise capacity test	↑miR-21, -210, -222 (in low VO_{2max} individuals)	Biomarkers of fitness level	(8)
H	8	EE	Treadmill running (80% of VO_{2max})	↑miR-21, -24, -27a, -181a	Exercise-induced adaptation	(47)
H	22	EE	Maraton run	↑miR-126, -133	Cell damage marker	(49)
H	12	EE	Bicycling for 4h at 70% IAT	↑miR-126; miR-133 (NC)	Cell damage marker	(49)
H	13	EE	Exercise capacity test	↑miR-126; miR-133 (NC)	Cell damage marker	(49)
H	10	EE	Exercise capacity test	↑miR-21, -146a, -222, -221	Marker of cardiovascular fitness	(4)

for adaptivity in response to exercise by presumably regulating IGF-1 signaling (41). Further in vitro-analysis showed that manipulation of miR-126 levels (inhibition) had a direct positive effect on phosphorylation levels of different downstream targets of IGF-1 and its activation. They summarized that a preserved expression of miR-1 and miR-126 in elderly subjects following resistance exercise might explain to some extent the weaker protein synthesis response that was observed in this cohort.

After twelve weeks of eccentric ergometer training or conventional resistance training in elderly subjects, Mueller et al. reported a downregulation of miR-1 associated with an increased expression of IGF-1 in both modalities (32). The change in miR-1 might be an indication for muscle remodeling following sustained training but these results for miR-1 are in contrast to the ones from Rivas et al. (41) after an acute bout of resistance exercise. So it is mostly speculative which role miRNAs are playing in the adaptation to acute and chronic resistance exercise in elderly, even more when considering that miR-1 is down-regulated after an acute bout of resistance exercise in young but not old subjects (41). However, these studies were inconclusive. It is speculated that adaptation processes in elderly require more time with miRNAs as possible important factors in regulating this process.

Endurance Exercise

Following endurance exercise, miR-1 and miR-133 expression was reported to be increased before but not after twelve weeks of endurance training in the vastus lateralis muscle (35). Additionally, basal expression levels of miR-1, miR-133a, miR-133b and miR-206 were downregulated after twelve weeks of training compared to pre-training status but reverted to their pre-training levels within 14 days after ending the training intervention. Similarly, conducting a six week long cycling training in young sedentary healthy men, Keller et al. observed decreased expression levels for miR-1 and miR-133 at the end of the intervention (20).

With regard to a shorter timeperiod, Russell et al. subjected untrained individuals to a tenday combined moderate- or high-intensity endurance cycling training. In contrast to the results of Nielsen et al., an increase of miR-1 after 10 days of training was demonstrated, which was accompanied by an increase of miR-29b and a decrease of miR-31 (35, 43). Subsequent to a single bout performed before training, they observed an increase in miR-1, miR-133a, miR-133b, miR-181a and a decrease of miR-9, miR-23a, miR-23b and miR-31. They further found negative correlations between miR-31 levels with HDAC4 (histone deacetylase 4; a transcriptional repressor of muscle gene expression) and NFR1 (nuclear respiratory factor 1) levels which represent predicted targets of miR-31 (43).

To shed more light on the complex networks that are associated with exercise adaptation and the possible implication of miRNAs, Safdar et al. subjected mice to an acute bout of aerobic exercise (44). The exercise bout was followed by a significant upregulation of miR-1, miR-107 and miR-181 and by a downregulation of miR-23 three hours after exercise. MiR-181 is reported to target a repressor (Hox-A11) of MyoD and therefore appears to be involved in mediating myoblast differentiation and muscle regeneration (33). Given the fact, that PGC-1α regulates mitochondrial biogenesis and contains putative binding sites for miR-23 (21, 53), reduced expression of miR-23 was associated with a high abundance of both, protein and mRNA levels of its target, PGC-1α. Furthermore, this was accompanied by an increased expression of several downstream targets of PGC-1α involved in mitochondrial biogenesis (44). In a similar approach, Aoi et al. showed that four weeks of forced wheel running in mice resulted in a decrease of miR-696, another miRNA that is predicted to target PGC-1α (3). With unchanged PGC-1α mRNA levels but elevated PGC-1α protein expression, miR-696 might act by blocking translation. Moreover, Yamamoto et al. found that a novel miRNA, miR-494, may play a crucial role in mitochondrial biogenesis by modulating the mitochondrial transcription factor A (mtTFA) and the nuclear transcription

Table 2

MicroRNAs and chronic exercise. Resistance Exercise (RE); Endurance Exercise (EE); Human (H); Mouse (M); Rat (R); 1 Repetition maximum (1RM); Maximal oxygen uptake (VO_{2max}); Maximal power output (P_{max}); Not available (n/a).

SPECIES	n	TYPE	DURATION	MODALITY	miRNA EXPRESSION	PUTATIVE EFFECT	REF.
Skeletal Muscle							
H	56	RE	12 wks	80% of 1RM	↑miR-451; ↓miR-378	Reduced hypertrophy in low responders	(12)
H	27	RE	12 wks	RE with eldery	↓miR-1	Muscle remodeling	(32)
M	n/a	RE	7 days	Mechanical overload	↓miR-1, -133	Hypertrophy	(29)
H	9	EE	10 days	Cycle ergometer (continuous & interval)	↑miR-1, -29b; ↓miR-31	Muscle regeneration, Mitochondrial biogenesis	(43)
M	6	EE	7 days	Swimming	↓miR-494	Mitochondrial biogenesis	(56)
H	27	EE	12 wks	Cycle ergometer with elderly	↓miR-1	Muscle remodeling	(32)
H	24	EE	6 wks	Cycle ergometer (70% VO_{2max})	↓miR-1, -133	Exercise-induced adaptation	(20)
M	8	EE	4 wks	Treadmill running	↓miR-696	Mitochondrial biogenesis	(3)
H	10	EE	12 wks	Cycle ergometer (55-91% of P_{max})	↓miR-1, -133a, -133b, -206	Exercise-induced adaptation	(35)
Circulation							
H	11	EE	4 wks	Cycling (70% of VO_{2max})	↓miR-486	Regulating insulin signaling	(2)
H	10	EE	90 days	Rowing (at low stroke rates)	↑miR-20a, -21, -146a, -222, -221	Marker of cardiovascular fitness	(4)

factor Forkhead box J3 (FOXJ3) during myocyte differentiation and skeletal muscle adaptation in response to physical exercise in mice (56).

In a recent study, Nielsen et al. investigated the regulation of myomiRs in skeletal muscle during ageing (34). The expression of miR-1, miR-133a and miR-133b was elevated in older men compared to young men following a maximal oxygen consumption test (VO_{2max}). Considering their prior findings that myomiRs are downregulated in young men as physical fitness increases (35), this might be based on the decline of physical activity with aging as the most relevant factor involved in the age-dependent upregulation of miR-1 and miR-133a/b and a therefore blunted adaptation to exercise (34).

To date, many studies predominantly focus on the analysis of the expression of myomiRs with miR-1, miR-133, and miR-206 as the most common ones. Summarizing the findings of studies comprising skeletal muscle and aside methodical differences as well as differences in subjects training status, there is a trend of increased levels for miR-1 and miR-133 after an acute exercise bout or short-term training and a return to baseline or down-regulation with sustained training. Comparing both exercise types, resistance exercise appears to be downregulating these myomiRs. Considering their putative targets, e.g. IGF1-pathway, the overall responses of these miRNAs provide deeper insight into the adaptation of skeletal muscle (i.e. growth/regeneration) following exercise. These adaptations involve an increased need of protein synthesis regarding both, resistance exercise and chronic endurance exercise (14). Moreover, apart from protein synthesis miRNAs seem to have a great impact on regulating metabolic changes (e.g. phenotype/mitochondrial biogenesis) as well. Altogether these responses might be necessary to facilitate adaptation and regeneration following exercise (Tab. 1 and Tab. 2).

Circulation

The role of miRNAs in circulation (c-miRNAs) has gathered great interest in recent years. Though, their origin and function is still not fully known and the field is yet in its infancy. Some miRNAs are highly expressed in specific tissues and those miRNAs are thought to be released or leaked into circulation in response to stress, injury or tissue damage (55). Another explanation might be a direct cell-to-cell communication and miRNAs therefore are being secreted and undergo active trafficking. They are thereby thought to target neighboring cells to exert a paracrine function (10). For transportation, mature miRNAs are either incorporated into vesicular structures like exosomes, microvesicles and apoptotic bodies or bound to proteins like HDL and RNA-binding proteins after pre-miRNA processing and released into circulation (Fig. 2). This incorporation/binding provides protection from RNases and thus degradation when delivered into circulation (55). For a closer look on the exact nature and biological relevance of circulating miRNAs the interested reader is referred to the works of Turchinovich and colleagues and Xu et al. (48, 55).

Regarding exercise, c-miRNAs might be potential new biomarkers for adaptational processes (e.g. skeletal and cardiac muscle adaptations), physical fitness as well as recovery in response to physical exercise (2, 4, 6, 8, 31, 45, 49). For example, Baggish et al., Bye et al. and Mooren et al. found several correlations between miRNAs and VO_{2max} (4, 8, 31).Though these results must be further validated, changes in the levels of certain c-miRNAs might act as potential biomarkers for cardiovascular fitness as VO_{2max} is a good indicator of cardiovascular health and can be used as a predictor of cardiovascular mortality (54).

Screening the relevant literature, a putative trend in the expression profile of some muscle-specific miRNAs in circulation is apparent. When performing acute exercise bouts, expression levels of myomiRs miR-1, miR-133a/b and 208b seem to be increased (Tab. 1). However, due to a lack of studies comprising sustained resistance training and only a few studies comprising sustained endurance training (Tab. 2) their expression levels with chronic exercise are not clear. Additionally, one has to consider methodical differences and differences in subjects training status. Future studies should examine the expression levels at different time points and with various exercise intensities to shed more light on the underlying mechanisms of increased secretion into the circulation. For a more comprehensive view, putative genderspecific differences should be considered as well.

An increased exercise load (e.g. marathon run) appears to be a major contributor to c-miRNA secretion as it is accompanied by increased cell damage (31, 49). Though, it must be considered that miRNAs not only are secreted from tissue (actively secreted or following cell damage) but also from cells within the circulation itself (i.e. leucocytes) and to date their exact origin is not clarified (48, 51). There are also open questions about the exact nature of the release of c-miRNAs following acute exercise bouts and with sustained training. Makarova et al. ›

depicted, that with existing evidence of the apparent release of miRNAs without cell damage, the source for such a rapid increase of c-miRNA levels following acute and intense bouts of exercise might be already synthesized miRNA (4, 5, 27, 45). Sustained exercise training on the other hand might induce stable changes in c-miRNA levels resulting from an altered basal expression (27). It is further difficult to discriminate, whether levels of certain miRNAs are initiated by exercise or disease as many pathological states influence miRNA expression patterns and thus providing great challenges upon future development of miRNAs in a diagnostical environment (1). It is of great interest, whether and how c-miRNAs modulated by exercise play a role in cell-to-cell communication and might be further considered responsible for beneficial effects in peripheral organs.

There is also growing evidence that indicates a crucial role for miRNAs in modulating immune functions in response to exercise. Radom-Aizik and colleagues conducted several studies that included different immunerelated cell types such as neutrophils, natural killer cells (NK cells), monocytes and peripheral blood mononuclear cells (PBMCs) in general. They subjected healthy young men to cycle ergometer exercise to investigate the response of miRNAs in these circulating cell populations. Blood sampling followed immediately after the acute exercise bouts and showed differentially expression for 38 miRNAs in neutrophils (39), 34 miRNAs in PBMCs (38), 23 miRNAs in NK cells (37) and 19 miRNAs in monocytes (40). Interestingly, miR-126, miR-130a, and miR-151-5p showed a similar response in PBMCs, NK cells and neutrophils. Gaining further knowledge about the molecular mechanisms of stress response, Tonevitsky et al. revealed miRNA-mRNA regulatory networks during exercise and recovery (47). Exercise was able to modulate the levels of miR-21, miR-24-2, miR-27a and miR-181a. A Pathway analysis showed that these miRNAs are presumably responsive to exercise, modulating apoptosis, immune function, protein membrane trafficking and in regulating transcription (47). Together, these miRNAs seem to be important in inflammatory responses to exercise but their exact implication needs to be clarified.

However, c-miRNAs may serve as potential biomarkers or mediators of physiological adaptations. With new methods being developed for an improved detection of mRNA or miRNAs from capillary blood for instance the door is further opened for a widespread use of miRNA-analysis as a tool for monitoring athletic performance and adaptation (52).

Conclusion

MiRNAs have been shown to be involved in many biological processes crucial in response to physical activity. With more knowledge about the regulating properties of miRNAs in virtually all parts of the body our understanding about exercise adaptation and regeneration is even growing stronger in the coming years. This opens the door for exciting new approaches for monitoring athletic performance, adaptation and regeneration. As miRNAs are also involved in various pathological conditions they might act as valuable biomarkers in diagnosis and in prognosis for several diseases. Furthermore, this makes them promising novel therapeutic agents for the treatment of diseased individuals. However, the analysis of miRNAs is still a young field and many results need to be validated in future studies.

Conflict of Interest
The authors have no conflict of interest.

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