Review

Cancer Epidemiology, Biomarkers & Prevention

A Review of Physical Activity and Circulating miRNA Expression: Implications in Cancer Risk and Progression

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Abstract

The role of circulating miRNAs (c-miRNAs) in carcinogenesis has garnered considerable scientific interest. miRNAs may contribute actively to cancer development and progression, making them potential targets for cancer prevention and therapy. Lifestyle factors such as physical activity (PA) have been shown to alter c-miRNA expression, but the subsequent impact on cancer risk and prognosis is unknown. To provide a better understanding of how PA reduces the risk of cancer incidence and improves patient outcomes, we conducted a review of the impact of PA on c-miRNA expression, which includes a comprehensive synthesis of studies examining the impacts of acute and chronic exercise on expression of c-miRNAs. While the variability in methods used to assess miRNA expression creates challenges in comparing and/or synthesizing the literature, results to date suggest that the circulating form of several miRNAs known for playing a role in cancer (c-miR-133, c-miR-221/222, c-miR-126, and c-let-7) are altered by both acute and chronic PA. Additional research should develop standardized procedures for assessing both c-miRNA and PA measurement to improve the comparability of research results regarding the direction and amplitude of changes in c-miRNAs in response to PA. *Cancer Epidemiol Biomarkers Prev; 27(1); 11–24. ©2017 AACR.*

Introduction

miRNAs are implicated in the etiology of various diseases, including cancer (1), and understanding their biologic characteristics has led to novel insights for cancer diagnosis, treatment, and prognosis (2). miRNAs are considered to be stable in healthy individuals, but external factors including lifestyle can impact their expression. Several studies have reported that physical activity (PA) can modulate miRNA expression (3–5). The impact of PA on reducing cancer risk and improving cancer progression has been well documented, but the exact mechanisms underlying these relations are not yet completely understood (6, 7). A better understanding of altered expression and function of miRNAs in response to various forms of PA could assist in clarifying the role of PA in cancer prevention and prognosis.

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miRNAs and cancer

miRNAs are a class of small noncoding RNAs that regulate gene expression posttranscriptionally, either by mRNA cleavage, mRNA destabilization, or inhibition of translation (8). Since the first miRNA was discovered by Lee and colleagues in 1993, more than 2,500 human miRNA sequences have been identified (miRBase; ref. 9). This rapid expansion of discovery can be partially explained by the broad importance of miRNAs in regular bodily functions. miRNAs are predicted to modulate more than 60% of protein-coding genes (10) and are involved in numerous integral cellular processes, including development, proliferation, metabolism, and signal transduction (11, 12). Given their regulatory importance, it is not surprising that miRNAs are widely implicated in carcinogenesis and progression. The mechanistic role of miRNAs in cancer was first discussed by Johnson and colleagues in 2005 (13) and the number of studies has been rapidly expanding ever since. In both solid and hematologic tumors, numerous miRNAs have been found to be altered, and their expression is associated with the severity and stage at diagnosis (14). In breast cancer, for example, several miRNAs have been observed as very early biomarkers of this disease (15).

The role of miRNAs in carcinogenesis and cancer progression is twofold. Both *in vivo* and *in vitro* studies have demonstrated they target either tumor suppressors or oncogenes (16). Expression of particular miRNAs can downregulate various oncogenes or reexpress tumor suppressor genes, leading to tumor suppression, whereas upregulation of other miRNAs, also referred to as oncomiRs, inhibits tumor suppressor genes or overexpress oncogenes, thereby promoting tumor cell proliferation and metastasis (16).

miRNAs are found in tissues and organs and are also released into the circulation in a remarkably stable form (17). The

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expression of those c-miRNAs has been found to be modified in numerous cancers including, but not limited to, colorectal, prostate, breast, hepatocellular, gastric, and head and neck cancers (1, 18–24). Altered c-miRNA expression was first observed in B-cell lymphoma patients by Lawrie and colleagues in 2008 (25) and it is now established that, on average, the expression of 100 c-miRNAs are altered in each cancer type. More importantly, the discovery of c-miRNAs in body fluids resulted in the implication of new possible pathways through which miRNAs may impact tumor development and progression, and led to novel insights for their use as therapeutic tools for cancer (26, 27).

miRNAs as potential mediators of the association between physical activity and cancer

PA has been shown to reduce cancer risk and progression (6, 28–31). Multiple hypothesized biologic mechanisms have been proposed to explain these benefits (6, 29, 32) including reductions in chronic inflammation, regulation of metabolic factors, changes in insulin resistance, enhanced immune system function, and levels of circulating sex hormones, myokines, or adipokines (6, 29, 32, 33). The exact mechanisms, however, whereby PA alters cancer risk and progression at various cancer sites are not fully understood and additional pathways are likely. As miRNAs are now well recognized for playing important roles in carcinogenesis and cancer outcomes, they could be involved in the PA-related benefits toward cancer.

The impact of PA on miRNAs has been investigated by several research groups, but mainly in the context of physical performance, muscle pathogenesis, and muscular dysfunction related to aging, as well as in muscle disorders associated with diabetes, cancer, and inflammation (3). The majority of the miRNAs shown to be altered by either acute or chronic exercise in these studies are muscle-specific miRNAs, also called myomiRs. miRNAs are differentially expressed within various organs, and if a miRNA is expressed more than 20-fold in a specific tissue compared with the mean of its expression in other tissues, it is thus considered as a tissue-specific miRNA (34). The expression of a variety of miRNAs, and particularly myomiRs, is modulated by PA within muscle tissues (4, 35) as well as in plasma (5). Zacharewicz and colleagues (4) have published a detailed review on miRNA expression within muscles in response to PA. Here we restrict our review to miRNA expression in blood following acute or chronic PA.

c-miRNAs are currently being extensively studied due to several advantages from a clinical and etiologic perspective including a remarkable stability in the circulation, resistance to RNase activity (36), and preservation through multiple freeze–thaw cycles (37). Consequently, c-miRNAs can be easily evaluated by standard and relatively inexpensive qRT-PCR techniques, even in low concentrations (38), and their measurement is a noninvasive procedure (39). This is in stark contrast to the analysis of miRNA expression within specific tissues, which require biopsies. On the basis of these differences, c-miRNAs measured from stored blood samples will prove advantageous in the conduct of large epidemiologic studies of PA-related cancer etiology. For these reasons, in this review, we focused on the role of c-miRNAs as an underlying mechanism mediating PA's benefits against cancer through the exploration of potential links between PA-induced c-miRNA modulation and cancer-related c-miRNA expression.

The majority of c-miRNAs are derived from leukocytes and endothelial cells (40) but they can also originate from organs exposed to high blood flow (3). When exercising, the blood flow is significantly elevated, with up to 80-fold blood flow increase in times of high physical output (41, 42), leading to expression changes in miRNAs originating from various organs (43–45), and in particular from skeletal muscles. The release of miRNAs in the blood circulation can originate from destroyed tissues (46, 47), especially if the exercise load is great (48). However, increases in the expression of c-miRNAs have also been reported in the absence of cell damage markers in plasma (49). miRNAs can, in fact, be exported by active transport systems, either encapsulated in extracellular vesicles (such as exosomes; refs. 46, 50, 51), or associated with protein or lipid-based complexes [e.g., Argonaute2 (AGO2), high-density lipoproteins (HDL), and low-density lipoproteins (LDL); refs. 36, 52–54]. Importantly, increasing evidence shows that miRNAs, through their circulating form, can be transported from donor cells to recipient cells, where they exert their functions (18, 54). c-miRNAs are thus being recognized as important components in intercellular communication (53, 55, 56), and have notably been demonstrated to play key roles in crucial cellular processes, such as apoptosis, proliferation, metastasis, and immunity (56, 57). For example, exosomal-miR-105 secreted by breast cancer cells and transferred to endothelial cells have been shown to promote metastasis (58).

Materials and Methods

We conducted a literature search up to March of 2016 in PubMed using the following search strategy: "miRNAs AND exercise" or "miRNAs AND physical activity" or "microRNAs AND exercise" or "microRNAs AND physical activity." Only studies conducted in humans containing data measuring c-miRNAs were included. We did not employ a minimum sample size threshold and studies with small numbers of participants were also included, as the total number of studies meeting our inclusion criteria was relatively small. Studies examining populations with disease were excluded, and all studies included in the review presented measurements among healthy subjects as underlying diseases may impact c-miRNAs. To our knowledge, there are no data on the effect of PA on c-miRNA expression in patients with cancer. One study has investigated the impact of PA on miRNA expression within tumor tissue based on an animal model, and is included in the Discussion section. We also analyzed reference lists of the identified studies for additional relevant articles. The title and abstract were examined, and full text was obtained if the article seemed eligible. No period or language restrictions were applied. We compiled the results from studies investigating c-miRNA expression in response to a single bout of PA (acute PA) in either normally active individuals (Table 1) or trained subjects (Table 2) as well as the impact of a training period and/or regular PA (chronic PA) on basal c-miRNA expression (Table 3).

Tables 1 and 2 include details on study (design, sample size, timing of blood draws), participant (age, gender, PA level), and protocol characteristics [training program if any, type of exercise (resistance or endurance exercise)]. Included in these tables are descriptions of the number of miRNAs screened, number of miRNAs altered by PA, miRNAs measured but not altered, and undetectable or unreliable miRNAs.

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Table 1. Effect of acute PA on the expression of c-miRNAs in healthy and normal activity subjects

Reference	Subjects	Type of acute PA	Plasma/serum base	No of miRNAs screened	miRNAs altered by PA (compared to basal values)			Unaltered miRNAs among the measured ones		miRNAs not detectable or unreliable	
					Immediately post-ex	During recovery					
Acute endurance exercise											
Aoi et al., 2013 (66)	10 males 21.5 ± 4.5 yrs	60-minute cycling exercise (70% $\dot{V}O_2$max)	Serum	—	miR-486↓	Post 3h: miR-486↓		NONE		miR-1 miR-133a miR-133b	miR-206 miR-208b miR-499
Banzet et al., 2013 (68)	9 males 27 to 36 yrs	30-minute uphill walking exercise (concentric)	Plasma	—	miR-181b↑ miR-214↑ miR-499-5p↑	Post 2h and 6h: miR-133a↑ miR-133b↑ Post 2h, 6h, and 1 day: miR-499-5p↑	miR-1↑ miR-208b↑	miR-181a			miR-206 miR-208a
Banzet et al., 2013 (68)	9 males 27 to 36 yrs	30-minute downhill walking exercise (eccentric)	Plasma	—	NONE	Post 2h and 6h: miR-133a↑ miR-133b↑ Post 2h, 6h, and 1 day: miR-499-5p↑ Post 6h: miR-208b↑	miR-1↑ miR-214	miR-499-5p miR-181b	miR-181a miR-208a	miR-206	
Uhlemann et al., 2014 (48)	7 males and 6 females 30.4 ± 2.0 yrs	Maximal cycle ergometry test	Plasma	—	miRNA-126↑	No recovery blood draw time points		miR-133			
Van Craenenbroeck et al., 2015 (69)	7 males and 5 females 43.4 ± 4.7 yrs	Maximal cycle ergometry test	Plasma	—	miR-150↑	No recovery blood draw time points		miR-146a miR-21	miR-126 miR-210		
Acute resistance exercise											
Sawada et al., 2013 (67)	3 males 29.9 ± 1.2 yrs	Bench press and leg press (5 sets of 10 reps with 1 min rest between sets)	Serum	1,458	NONE	Post 1 day: miR-149*↑ Post 3 days: miR-146a↓ miR-221↓		miR-20a miR-21 miR-133a miR-210	miR-222 miR-328 miR-1908	miR-299-5p	

Abbreviations: ex, exercise; wk, week; yrs, years.

Results of a systematic review of studies investigating the impact of acute PA on c-miRNA expression in healthy and "normal" activity levels in human subjects either immediately after acute exercise completion and/or several hours up to a couple days after.

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Table 2. Effect of acute PA on the expression of c-miRNAs at various time points in healthy, trained subjects

Reference	Subjects	Training program	Type of acute PA	Plasma/ Serum base	No of miRNAs screened	miRNAs altered by PA (compared to basal values)				Unaltered miRNAs among the measured ones		miRNAs not detectable or unreliable
						Immediately post-ex		During recovery				
Acute endurance exercise												
Baggish et al., 2011 (49)	10 males 19.1 ± 0.6 yrs	13 weeks rowing training	Maximal cycle ergometry test	Plasma	—	miR-146a↑ miR-222↑	miR-21↑ miR-221↑	No recovery blood draw time points		miR-20a miR-328	miR-210 miR-133a	
Tonevitsky et al., 2013 (65)	8 males 21.7 ± 2.6 yrs	Regular ski training	30-minute run on a treadmill (80% $\dot{V}O_2$max)	Serum	200	miR-24-2-5p↑ miR-27a-5p↑ miR-181a-5p↑		Post 1/2h and post 1h: miR-24-2p↓ miR-27a-5p↓ miR-181-5p↓ Post 1h: miR-21-5p↑				
Mooren et al., 2014 (70)	14 males 42.8 ± 6.0 yrs	Regular endurance training	Marathon run	Plasma	—	miR-1↑ miR-133a↑ miR-206↑	miR-208b↑ miR-499↑	Post 1 day: miR-1↑ miR-133a↑	miR-206↑	miR-21 miR-155		
Nielsen et al., 2014 (71)	13 males 28 ± 8 yrs	12 weeks endurance training (cycle ergometry)	60-minute cycle ergometry exercise (65% Pmax)	Plasma	188	miR-221↓ miR-30b↓ let7i↓ miR-652↓	miR-106a↓ miR-146a↓ miR-151-3p↓ miR-151-5p↓	Post 1h: miR-338-3p↑ miR-330-3p↑ miR-223↑ miR-139-5p↑ Post 3h: miR-1↑ miR-133a↑‡	miR-143↑ miR-145↑‡ miR-424↑‡ miR-133b↑‡			
Baggish et al., 2014 (72)	21 males 51.8 ± 1.4 yrs	Regular endurance training	Marathon run	Plasma	—	miR-126↑ miR-1↑ miR-133a↑ miR-208a↑	miR-499-5p↑ miR-208a↑ miR-134↑ miR-146a↑	Post 1 day: miR-499-5p↑				
Uhlemann et al., 2014 (48)	13 males 32.4 ± 2.3 yrs	Regular endurance training	4 h cycle ergometry exercise (70% anaerobic threshold)	Plasma	—	miR-126↑		Post 1h: NONE Post 1 day: NONE		miR-133		
Uhlemann et al., 2014 (48)	22 males 56.8 ± 5.2 yrs	Regular endurance training	Marathon run	Plasma	—	miR-126↑ miR-133↑		No recovery blood draw time points				
Gomes et al., 2014 (73)	5 males 31.6 ± 4.39 yrs	Regular endurance training	Half-marathon run	Plasma	—	miR-1↑ miR-133a↑ miR-206↑		No recovery blood draw time points				
Cui et al., 2015 (74)	18 males 20.23 ± 0.97 yrs	Regular exercise training (activity type not specified)	Cycle ergometry sprint intervals (2 sets of 30s all out sprints with 4 min rest between sets)	Plasma	—	miR-1↓ miR-133b↓ miR-133a↓	miR-122↓ miR-16↓	No recovery blood draw time points		miR-206 miR-499		
Clauss et al., 2016 (75)	15 males 40.1 ± 1.4 yrs	Marathon training ≤40 km/wk for 10 wk	Marathon run	Plasma	—	miR-1↑ miR-133a↑		Post 1 day: miR-133a↑		miR-30a miR-26a miR-29b		
Clauss et al., 2016 (75)	15 males 40.0 ± 1.7 yrs	Marathon training ≥55 km/wk for 10 wk	Marathon run	Plasma	—	miR-1↑ miR-133a↑ miR-30a↑		Post 1 day: NONE		miR-26a miR-29b		
Min et al., 2016 (76)	20 males and 8 females 53.0 ± 6.5 yrs	Regular endurance training	Marathon run	Plasma	—	miR-1↑ miR-133a↑ miR-206↑		Post 1 day: miR-499-5p↑				
Acute resistance exercise												
Uhlemann et al., 2014 (48)	4 males and 7 females 37 ± 2 yrs	Nonsupervised regular training (activity type not specified)	Lat pulldown, leg press and butterfly (3 sets of 15 reps with 1 min rest between sets)	Plasma	—	miR-133↑		Post 1h: NONE		miR-126		

Abbreviations: ex, exercise; no, number; reps, repetitions; wk, week; yrs, years.

‡Borderline significant miRNAs.

Results of a systematic review of studies investigating the impact of acute PA on c-miRNA expression in healthy trained human subjects either immediately after acute exercise completion and/or several hours up to a couple days after.

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Table 3. Effect of chronic/regular/long-term PA on c-miRNA levels in healthy subjects

References	Type of study	Participants characteristics	Training program	Blood draw timing and plasma /serum base	No of miRNAs screened	miRNAs altered by chronic PA		miRNAs measured but not altered by chronic PA		miRNAs not detectable/unreliable	
Chronic endurance exercise											
Baggish et al., 2011 (49)	Intervention	10 males 19.1 ± 0.6 yrs Very trained	13 weeks rowing training	At least 12 h post exercise -plasma	—	miR-146a↑ miR-222↑ miR-21↑	miR-221↑ miR-20a↑	miR-328 miR-210	miR-133a		
Aoi et al., 2013 (66)	Intervention	10 males 21.5 ± 4.5 yrs Normally active	4 weeks cycling training	2 days post training period -serum	—	miR-486↓				miR-1 miR-133a miR-133b miR-206	miR-208b miR-486 miR-499
Nielsen et al., 2014 (71)	Intervention	7 males 28 ± 5 yrs Normally active	12 weeks of supervised training on cycle ergometer	3 days and 5 days post training period -plasma	188	miR-342-3p↓ let-7d↓ miR-103↑ miR-107↑ miR-766↓ miR-25↓ miR-148a↓	miR-185↓ miR-21↓ miR-148b↓‡ miR-133a↓‡ miR-92a↓‡ miR-29b↓‡				
Wardle et al., 2015 (78)	Observational	20 males 22.6 ± 3.7 yrs Trained (endurance athletes) vs. control (not active)	Trained: 13 h of training per week	At least 12 h post PA -plasma	—	miR-222↑		miR-16-2 miR-20a-1 miR-103a miR-192	miR-451 miR-21 miR-146a miR-221	miR-1 miR-133a miR-206 miR-499	
Clauss et al., 2016 (75)	Intervention	15 males 40.1 ± 1.4 yrs Normally active	Marathon training: Running of ≤40 km/ week for 10 weeks	After the training period -plasma	—	NONE		miR-1 miR-133a miR-30a	miR-26a miR-29b		
Clauss et al., 2016 (75)	Intervention	15 males 40.0 ± 1.7 yrs Trained	Marathon training: Running of ≥55 km/ week for 10 weeks	After the training period -plasma	—	NONE		miR-1 miR-133a miR-30a	miR-26a miR-29b		
Chronic resistance exercise											
Wardle et al., 2015 (78)	Observational	20 males 22.2 ± 2.1 yrs Trained (resistance athletes) vs. Control (not active)	Trained: 13 h of training per week	At least 12 h post PA -plasma	—	miR-222↓		miR-16-2 miR-20a-1 miR-103a miR-192	miR-451 miR-21 miR-146a miR-221	miR-1 miR-133a miR-206 miR-499	
Unspecified chronic exercise (endurance and/or resistance exercise)											
Bye et al., 2013 (77)	Observational	miRNAscreening: 12 males 12 and females 40–45 yrs miRNAvalidation: 38 males 38 and females 40–45 yrs Active vs. nonactive based on $\dot{V}O_2$max	Training included in lifestyle	Before the start of the exercise test measuring the subjects' $\dot{V}O_2$max -serum	720	Screening: Males and females: miR-210↓ miR-125a ↓ miR-652 ↑ Males only: miR-151↑ miR-29a↓ let-7d↓ Validation cohort: Males and females: miR-222↓ miR-210↓ Males only: miR-21↓	Women only: miR-210↓ miR-125a↓ miR-21↓				miR-125 in the validation cohort

Abbreviations: no, number; yrs, years.

‡Borderline significant miRNAs

Results of a literature review of intervention and observational studies investigating the impact of chronic PA on c-miRNA expression in humans.

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With regards to the type of exercise, we considered predominantly endurance exercises as exercises involving the whole body and increasing oxidative capacity and aerobic endurance (e.g., a marathon run), while resistance exercises were defined as exercises using machines, weights, or even individuals' body weight to stimulate muscle hypertrophy and increase muscular strength or power (e.g., leg press, squats, pull-ups). We highlight the distinctions between normally active and "trained" participants, based on the information provided by the studies. We considered the subjects trained if: (i) the subjects underwent a specific training program described in the study; (ii) a large bout of exercise, such as a marathon run, was included in the protocol as undergoing such an effort implies previous training (even though not always specified in the reviewed studies); (iii) the authors stated that the participants were "trained individuals" and/or part of a competitive program. We considered the subjects "untrained" or "normally active" if the participants engaged in recreational activity $\leq$ 4 hours per week and/or if specified in the study. In total, we included 5 studies examining normally active individuals and 10 studies investigating trained individuals, according to our criteria.

To facilitate comparisons across studies, we present the data for c-miRNAs that were examined in multiple studies. We first synthesize and discuss the results obtained for c-miRNA expression following acute PA, followed by a discussion and synthesis of results examining basal miRNA expression in response to chronic PA.

PA has also been shown to modulate miRNA expression within peripheral blood mononuclear cells (PBMC). PBMCs are leukocytes with a round nucleus, and comprise lymphocytes (T cells, B cells, and natural killer cells), monocytes, and dendritic cells (59). Similar to c-miRNAs, PBMC miRNAs can easily be detected by standard qRT-PCR techniques, but it remains controversial whether their expression is similar or not to whole blood miRNAs (60, 61). Thus, even though two different research groups found an impact of acute PA in circulating leukocytes (62–65), those results are not discussed in this review.

Results

We have identified a total number of 16 studies in our review, which are displayed in Tables 1–3. Among these studies, 14 investigated c-miRNA expression in response to a single bout of exercise (48, 49, 65–76), and six (49, 66, 71, 75, 77, 78) evaluated the impact of chronic exercise on c-miRNA expression.

Impact of acute physical activity on c-miRNA expression

Acute PA refers to a single isolated PA session. It is clear that a single bout of PA alters expression of several c-miRNAs shortly after its completion (Tables 1 and 2). However, the modalities of PA [frequency, intensity, timing and type (FITT)] and the individual's physical fitness levels (trained or untrained) may impact those changes. Modifications in several c-miRNAs are not always observed immediately after PA, but are seen only after 2–3 hours of rest. For example, Banzet and colleagues reported no changes in miRNA expression immediately after the completion of a single bout of eccentric exercise (30 minutes downhill walking) but observed an increase in miR-1, miR-133a, miR-133b, miR-499-5p, and miR-208b 6 hours post bouts of PA (68). These c-miRNAs then returned to baseline expression after periods of inactivity, which has been reported to be relatively slow in some studies (66–68, 70, 72). For example, decreased expression of c-miR-221 was still observed by Sawada and colleagues 3 days postcompletion of a resistance exercise session (67).

Muscle- or cardiac-specific miRNAs. In healthy individuals, muscle- or cardiac specific miR-1, miR-133, miR-206, miR-499, and miR-208 are expressed at low levels in the circulation, whereas miR-486 is generally found in higher concentrations (74, 79). In response to PA, several studies have shown an increase in the circulating forms of miR-1, miR-133, miR-206, miR-208, and miR-499 immediately after the completion of various PA modalities (FITT; refs. 48, 68, 70, 72, 73, 75, 76), and a decrease in miR-486 (66). It can be noted that specific exercise modalities appear to impact changes in miRNA levels. Banzet and colleagues found different c-miRNA expression patterns in normally active participants who underwent a downhill walk versus others who completed an uphill walk (68). Downhill walking is considered an eccentric exercise as the muscles actively lengthen during this effort, whereas uphill walking induces active shortening of the muscles and is thus considered a concentric exercise. Interestingly, Banzet and colleagues found significantly higher muscle/cardiac specific c-miRNA expression for participants who walked downhill compared with subjects walking uphill (68). Thus, these data suggest that the type of muscle contraction involved in the exercises impacts c-miRNA expression. Furthermore, data from various studies also suggests that muscle/cardiac c-miRNAs can be differentially expressed depending on PA's intensity. For example, when looking at c-miR-133, Uhlemann and colleagues showed that modifications in c-miR-133 expression in response to PA were correlated with phosphocreatine kinase (CPK) activity, a marker for muscle damages: the more damaging the exercise was, the most altered c-miR-133 expression was (48).

Modulations in muscle/cardiac c-miRNA expression postexercise appear to be temporary, yet the exact delay before a return to baseline values is unclear. When examining measures taken one day postexercise, most studies showed that muscle and cardiac specific c-miRNAs had returned to their basal value. Others, however, reported a decrease in expression of those c-miRNAs compared to immediately after exercise, but still significantly elevated compared to baseline values. Focusing on c-miR-1 for example, four studies found similar expression of this c-miRNA between preexercise and 24 hours postexercise (49, 68, 75, 76), while one other observed significantly higher expression compared with baseline value (but attenuated from expression measured immediately after exercise; ref. 70).

Interestingly, high interindividual variation in c-miR-499 expression has been reported in response to an acute bout of endurance exercise in two different studies (68, 72) which suggests that c-miR-499 is highly dependent on participants' characteristics, notably their training status. miR-499 is a cardiac-specific miRNA and studies have shown its circulating form may represent a marker of myocardial injury (80–84). Strenuous exercises such as marathon running can induce transient myocardial injuries (85–88), this risk being higher in less trained individuals (87, 89). Therefore, the interindividual variation observed in c-miR-499 expression following a marathon run may reflect variation in training among participants, and/or cardiac muscle exhaustion.

Other circulating miRNAs. Non muscle- or cardiac-specific c-miRNAs have also been reported to be impacted by acute PA, but the exact direction and magnitude of those changes remain

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unclear. Two different research groups observed an upregulation of c-miR-126, an endothelial-specific miRNA involved in angiogenesis (90), immediately after a single bout of PA (48, 72), while no statistical differences in c-miR-126 expression pre- and post-PA have also been reported (48, 69). Interestingly, Uhlemann and colleagues measured c-miR-126 expression before and after an acute bout of PA: subjects were either trained or untrained and the exercises which had to be completed varied among protocols in type, duration, and intensity (48). They observed an upregulation in c-miR-126 in response to a single maximal symptom–limited test performed by healthy individuals, as well as in trained men who underwent 4 hours of bicycling at 70% of their anaerobic threshold, and in trained runners who completed a marathon. However, Uhlemann and colleagues also reported no significant difference in c-miR-126 expression in trained subjects who performed a resistance training session compared with basal values (48). As miR-126 is an endothelial-specific miRNA, the authors explained the increase in c-miR-126 expression following acute exercise observed in three of their protocols by exercise-induced endothelial damages, while they suggested that the resistance exercise session, which resulted in unaltered c-miR-126 expression, did not cause such damages (48).

c-miR-146a, a miRNA known for playing a role in inflammation and immunity (91, 92) has also been found to be altered by acute PA; however, the effects appear to be highly dependent on the type of activity intervention. Two studies have reported an upregulation of this c-miRNA in response to a single bout of endurance exercise in trained individuals (49, 72), but Nielsen and colleagues observed opposite results with a decrease in c-miR-146a in response to a similar type of PA in normally active subjects (71). In contrast, Van Craenenbroeck and colleagues reported no change in c-miR-146a expression in response to a single maximal symptom–limited test, while Sawada and colleagues measured no alteration in c-miR-146a expression in healthy men immediately after they performed resistance exercise session but found a decrease in its expression three days postexercise (67). Interestingly, in trained athletes, Baggish and colleagues found an upregulation miR-146a in response to an acute bout of PA both before and after a training program, the magnitude of the elevation being higher after completion of the training program (49).

Similarily, changes in the circulating expression of miR-221 and miR-222, important players in vascular biology (93), have been reported, but high variations can be found between the studies (49, 67, 71). In response to a 60-minute cycle ergometer exercise bout below anaerobic threshold, c-miR-221 has been found to be downregulated in normally active participants by Nielsen and colleagues (71), as opposed to Baggish and colleagues who showed an upregulation of c-miR-221 expression in trained individuals following an acute exhaustive cycling exercise (49). When assessing the impact of a short exhaustive bout of PA on the c-miRNA expression, Sawada and colleagues did not report any changes immediately after PA completion, but found a decrease three days later (67). c-miR-222 expression in response to an acute bout of PA has only been investigated by two different studies: one of them showed an upregulation of this c-miRNA in trained men undergoing an exhaustive bout of exercise (49), while the other one reported no change in its expression between before and after a resistance exercise session (67). The differences observed between studies are likely attributable to differences in protocols, suggesting that alterations of c-miRNAs in response to acute PA are dependent on the dose and type of exercise (FIIT) as well as participants' characteristics (e.g., age, gender, fitness level, health status, personal history, diet, smoking habits, etc.).

Impact of chronic physical activity on c-miRNA expression

Chronic PA is defined as regular PA done over an extended time period (a minimum of several weeks). Interestingly, contrary to what is observed for c-miRNA expression following an acute bout of PA (Tables 1 and 2), there is a general trend for a downregulation of c-miRNAs expression in response to chronic PA (Table 3). Among the six different studies investigating the impact of chronic PA on resting expression of c-miRNAs we included in our review, four were intervention trials (49, 66, 71, 75) and two were observational studies (77, 78). The blood samples analyzed in those research projects were taken at rest, at least 12 hours after the last training session.

Muscle- or cardiac-specific miRNAs. Cardiac- or muscle specific c-miRNA expression changes in response to chronic PA are hard to measure because of their low concentrations in humans at rest, consequently, there are limited results thus far. For c-miR-1, one study reported no change between its resting expression before and after a 10-week marathon training period in either trained or untrained individuals (75), whereas two other research groups found its expression too low to interpret its measurement (66, 78). A trend towards a decrease in c-miR-133 expression in response to a supervised training on a cycle ergometer was found by Nielsen and colleagues (71), while other studies reported no changes (49, 75) or nondetectable amounts for the quantification of c-miR-133 (66, 78). Several studies measured the resting expression of c-miR-206 (66, 78), c-miR-208 (66), and c-miR-499 (66, 78) before and after a training period, but their expressions were too low to be interpreted. Finally, Aoi and colleagues found that a 4-week cycling program downregulates c-miR-486 basal expression (66).

Other circulating miRNAs. When evaluating c-let-7d expression, a miRNA that has a crucial role in cell division and differentiation (94, 95), Nielsen and colleagues showed a downregulation of its baseline expression after a 12-week training period (71) while Bye and colleagues' observational study (77) showed that subjects with high maximal oxygen uptake ($\dot{V}O_2$max; 145.2 $\pm$ 20.7 mL/kg$^{0.75}$/min) had a lower c-let-7d expression compared with individuals engaging in similar activity levels but with lower $\dot{V}O_2$max (101.1 $\pm$ 18.0 mL/kg$^{0.75}$/min).

For c-miR-21, Nielsen and colleagues reported that baseline expression was decreased after chronic PA (71), while the results obtained from Bye and colleagues' observational study shows that independently of activity levels, individuals with high $\dot{V}O_2$max have decreased c-miR-21 basal expression compared with subjects with lower $\dot{V}O_2$max (77). However, Baggish and colleagues found an upregulation of c-miR-21 after 13 weeks of rowing training, while Wardle and colleagues reported no alteration in expression between athletes (endurance or resistance trained) and controls, but showed a significant increase in resistance trained individuals when compared with endurance athletes (72, 78).

c-miR-221 and c-miR-222 expression in response to chronic PA remains unclear. Baggish and colleagues reported increased expression of c-miR-222 after a 13-week training program (72), in line with Wardle and colleagues' findings when comparing endurance trained athletes with control individuals (78). However, Wardle and colleagues found a downregulation of

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c-miR-222 in resistance trained athletes, and Bye and colleagues' reported a decrease in c-miR-222 expression in individuals with high $\dot{V}O_2$max when compared with subjects with a lower $\dot{V}O_2$max (77, 78). Similarly, various results have been found for the changes of c-miR-221 expression in response to chronic PA: Baggish and colleagues reported an increase in its baseline expression after a training period (72), whereas Wardle and colleagues found no statistical differences between trained athletes (endurance or resistance) and controls, but a downregulation in resistance-trained athletes when compared with endurance-trained athletes (78).

Discussion

Potential impact of PA-induced c-miRNA changes on cancer risk, progression, and treatment

Overall, the current results available from the scientific literature suggest that several c-miRNAs are impacted by acute PA (miR-1, miR-133, miR-206, miR-208, miR-499, miR-486, miR-126, miR-146, miR-221, and miR-222) and/or by chronic PA (miR-133, miR-486, let-7d, miR-21, miR-222, and miR-221). Importantly both acute PA and chronic PA appear to induce changes in c-miRNA expression depending on exercise modalities and individuals' fitness status. While results to date are promising and suggest a clear impact of PA on miRNA expression, comparisons between studies are challenging and efforts should be devoted toward standardized protocols and procedures for miRNA collection, analysis, and reporting.

The studies included in this review suggest that PA modulates c-miRNA expression in healthy individuals. Several studies have also observed that PA can alter c-miRNA expression within disease populations such as patients with chronic kidney diseases (69) and prediabetic individuals (96). To our knowledge, however, no data exist regarding the impact of PA on miRNA in patients with cancer. PA also appears to be able to influence miRNA expression within organs other than skeletal muscles (97, 98). Taken together, these elements suggest that PA may influence c-miRNA expression in cancer patients, perhaps via c-miRNA intercellular communication. This hypothesized mechanism is illustrated in Fig. 1.

Throughout this section, we discuss how modulation of specific c-miRNA expression by PA might impact cancer risk, progression, and treatments, and provide some examples of promising early findings. Figure 2 presents hypothesized examples of how PA could impact cancer via c-miRNA modulation using c-miR-133, c-miR-221/222, c-miR-126, and c-let-7.

Impact of miRNAs on cancer risk and development. Multiple miRNAs are involved in DNA repair, checkpoint functions, tumor suppression, etc. (99), and their modulation by PA might play an important role in cancer risk and progression. For example, PA can alter c-miR-133 expression (48, 68, 70–73, 75, 76, 100), a well-known myoMiR participating in myoblast differentiation, which has also been identified as a tumor suppressor (101) in several cancers, including ovarian, colorectal, bladder, breast, prostate, and gastric cancers (100, 102–107). miR-133 has also been shown to be modified within muscle tissues in response to acute and chronic PA. More specifically, acute bouts of exercise seem to increase muscular miR-133 expression (108, 109), while training tends to decrease expression (108). These data suggest that miR-133 can translocate from muscle tissue to blood vessels, and that this miRNA can impact cancer progression as depicted in Fig. 1. Several studies suggest that miR-133 targets several oncogenes, such as the *EGFR* (100) and the insulin-like growth factor 1 receptor (IGF1R; refs. 107, 110). When activated, those oncogenes stimulate various pathways causing deregulation in several cell processes, eventually leading to carcinogenesis. For example, activation of EGFR pathway leads to the stimulation of intracellular signaling cascades such as the MAPK/ERK pathway, which plays a role in cell-cycle progression, differentiation, proliferation, and apoptosis (111, 112). When activated, the *EGFR* pathways also stimulate the PI3K/AKT cascade, known for its crucial role in regulation of apoptosis and protein synthesis (113, 114). An increase in c-miR-133 by PA originating from muscle tissue, may therefore impact tumor cells and regulate target oncogenes and associated pathways.

Similarly, let-7 is a tumor suppressor and proapoptotic miRNA (115) whose expression is decreased in numerous cancers (116), and reported to be modulated in plasma by

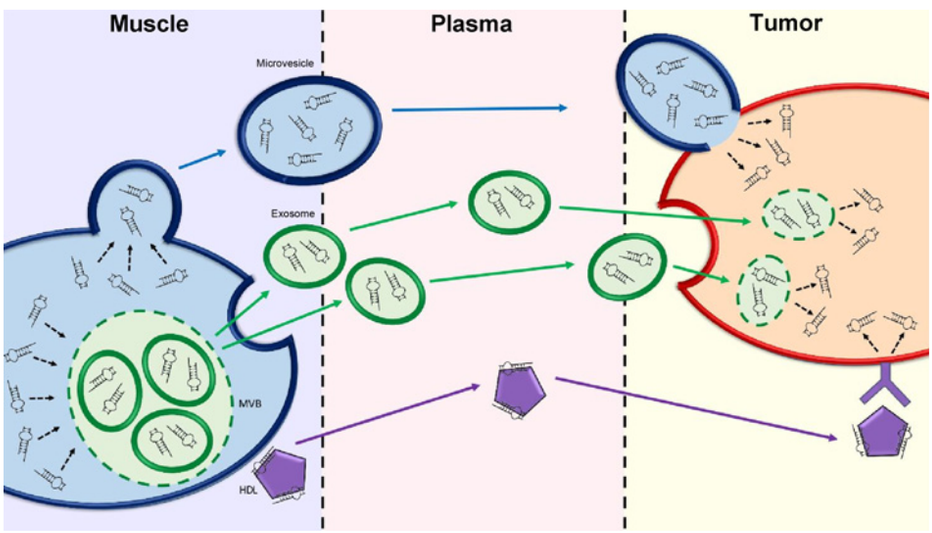

Figure 1.
Hypothesized pathways of miRNA transport from muscles to tumor cells via the circulation. miRNAs can be exported from one cell to another via plasma through various active transport systems including: exosomes developed within multivesicular bodies (MVB); released into the blood circulation after fusion of the MVBs with the plasma membrane; transport through protein or lipid-based complexes, such as HDL, and delivered to recipient cells. Abbreviations: MVB, multivesicular body.

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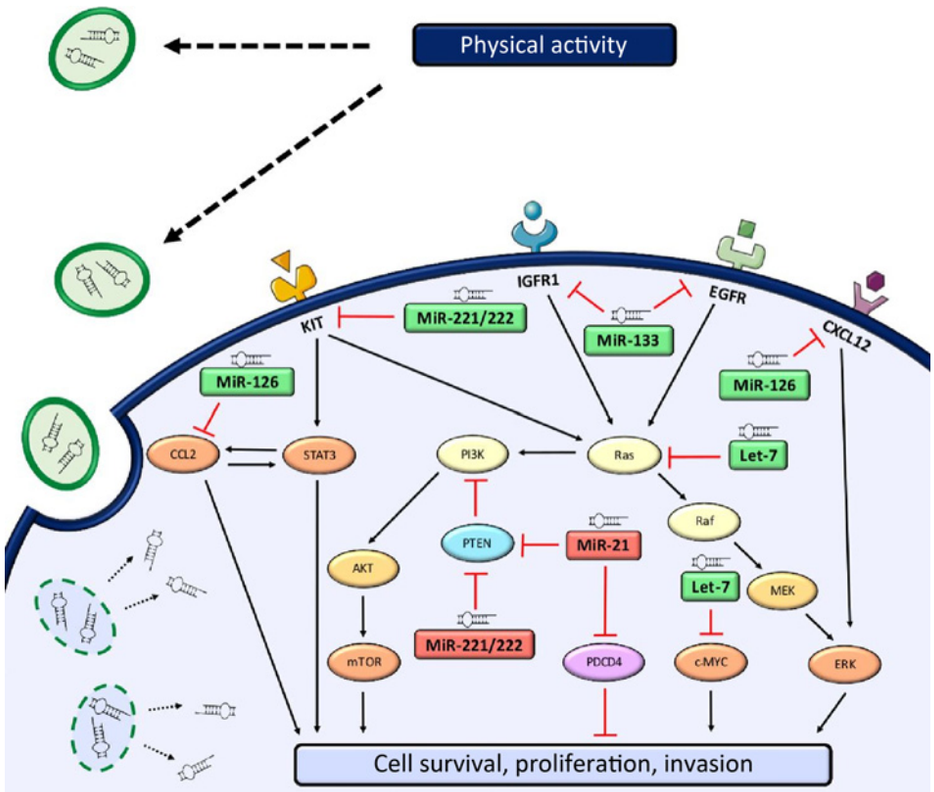

Figure 2.
Hypothesized mechanisms of action of PA on cancer risk and progression through c-miRNA modulation. Multiple c-miRNAs (miR-126, miR-221/222, miR-133, and Let-7) that impact pathways involved in cancer risk and progression have been shown to be altered by PA.

exercise (71, 77). While no direct evidence was identified in humans, in an animal model, breast tumor-bearing mice who underwent 5 weeks of interval exercise training (treadmill running) had increased let-7 expression within the tumor itself when compared with breast-tumor sedentary mice (117). Let-7 is known for inhibiting mRNA translation of well-known oncogenes, including the *RAS* family (*HRAS*, *KRAS*, and *NRAS*; ref. 13) and *c-MYC* (refs. 118, 119). When activated, *Ras* stimulates several signaling pathways, including MAPK cascade and PI3K/AKT (120), thereby influencing many cellular functions.

We must note the complex and often paradoxical role of miRNAs, with several miRNAs exerting stimulatory as well as inhibitory effects depending on cancer type or stage of the disease (121–123). miR-221 and miR-222 for example have a dual role: they can either act as tumor suppressors as oncogenes. On one hand, miR-221 and miR-222 have been found to relent cancer progression in several cancer types, and their expression in the circulation have been found to be altered by PA in several studies (49, 71, 72, 77, 78). In gastrointestinal stromal tumors, for example, miR-221 and miR-222 are thought to have prophylactic effects by negatively regulating the stem cell factor receptor KIT, and are found underexpressed in tumors when compared with healthy tissues (124–126). KIT is a receptor tyrosine-kinase (RTK), and its activation leads to the stimulation of several intracellular signaling pathways, including the STAT3, PI3K, phospholipase C (PLC), and the MAPK cascade (127–129). KIT promotes cell survival, proliferation, and motility (130), and its inhibition by miR-221 and miR-222 therefore contributes to carcinogenesis suppression. Modulation of those miRNAs by PA could thereby inhibit KIT activation, consequently lowering the risk of developing cancer.

On the other hand, miR-222 and miR-221 have been shown to act as oncomiRs in other cancer types. In lung and liver cancer for example, these miRNAs have been shown to inhibit the action of the PTEN, known to inhibit MAPK/ERK pathway, and the tissue inhibitor of metalloproteinases-3 (TIMP3), thereby enhancing cell proliferation and migration through PI3K/AKT pathway (131). The dual role played by miR-222 and miR-221 suggest that clarifying the influence of exercise modalities (endurance vs. resistance, short vs. long duration, regular vs. irregular training, etc.), tissue and/or cancer site of interest will be extremely important in subsequent research.

Impact of miRNAs on cancer invasion and metastasis. PA also modulates c-miRNAs involved in cell proliferation, invasion and metastasis (Fig. 2). For example, miR-21 is altered by resistance and endurance training (71, 72, 78) and is also known for participating in tumor invasion. In fact, *in vitro* studies have shown that in several cancer types, miR-21 knockdown mice displayed suppression of cell proliferation and tumor growth (132), as well as reduced invasion and metastasis (132–134). Furthermore miR-21 negatively regulates tumor suppressor programmed cell death 4 (*PDCD4*; ref. 135) and downstream signaling targets (136, 137) in colorectal cell lines. The results in this review (Tables 1–3) suggest that acute exercise can transiently upregulate c-miR-21 expression (65, 49), while chronic exercise (which reflects physiologic adaptations) can also lead to alterations in miR-21 expression within circulation

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(71, 77); however, the influence of chronic PA is less clear. By lowering miR-21 expression within cancer cells, PA may restore *PDCD4* and *PTEN* activation and limit cancer proliferation. This is supported by literature that suggests PA is able to modulate miR-21 within multiple tissues/fluids, for example muscle tissue in mice (138) as well as in plasma in healthy human subjects (49, 65, 71, 77, 78), as well as in tumors of breast tumor-bearing mice (Fig. 1; ref. 117).

The upregulation of c-miR-126 by acute PA (48, 72) might also represent a pathway through which PA impacts cancer progression. In breast cancer, miR-126 regulates the tumor microenvironment composition by directly inhibiting stromal cell–derived factor-1 alpha (CXCL12) expression and indirectly suppressing chemokine ligand 2 (CCL2) expression in cancer cells; ref. 139). These two chemokines play a role in recruiting stromal cells to the primary tumor microenvironment (140, 141), thereby leading to cancer cell invasion and metastasis. Therefore, the increase in c-miR-126 expression in response to acute PA followed by active transport into tumor cells could lead to inhibition of *CXCL12* and *CCL2*, consequently suppressing cancer expansion by modifying the tumor microenvironment composition (48).

Overall, PA-induced c-miRNA expression changes could have the potential to impact tumorigenesis and cancer development. Importantly, several studies suggest that reexpression of tumor suppressor miRNAs within tumor tissues can inhibit tumor growth, thereby representing a promising therapeutic tool against cancer (18, 142–144). For example, reexpression of let-7 within various tumor types have been proven to slow cancer growth (94, 145–147) and is thus considered a promising tool against cancers underexpressing let-7 family members (145, 148). Additional research, particularly large intervention studies in populations of cancer patients, is needed to determine the exact impact of PA on miRNA expression and potential roles in cancer therapy.

Limitations of the research to date

Investigating c-miRNAs in response to PA presents several challenges. First, to date, there are few studies that have compared similar c-miRNAs using comparable methods to enable direct comparisons across studies. Although some consistency has been observed for several c-miRNAs such as miR-133 (48, 70, 72, 73, 75, 76), contradictory results have often been observed. This inconsistency can largely be attributed to discrepancy in methods across studies, including: (i) differences in sample collection; (ii) postprocessing of samples, and (iii) the use of serum or plasma for miRNA extraction.

Different normalization strategies have been used between the reviewed studies. The current results available on c-miRNA expression changes in response to PA should therefore be carefully interpreted. For example, Nielsen and colleagues used a stable expressed c-miRNA to account for the biological variation between samples, whereas Baggish and colleagues used a synthetic spike in approach (71, 72). Some studies also included a hemolysis control phase in the study design, as it has been shown that hemolysis occurring during blood collection has substantial impact on the miRNA content in plasma/serum (149). This issue occurs because erythrocytes contain numerous miRNAs that unavoidably will contaminate a plasma sample if the erythrocyte bursts during sampling (150).

Another methodologic factor likely to impact the reliability of the results obtained from the various studies reviewed here is the fact that miRNA concentrations vary between serum and corresponding plasma samples (151). Analyzing and comparing miRNA expression from serum and plasma within or between studies should be done carefully.

To date, miRNA expression in response to PA has mainly been measured in the circulation and in muscles, but it would also be interesting to study the changes in miRNA expression in other tissues. More specifically, investigating miRNA expression after PA in target tissues, and more specifically tumor tissues, would provide novel data of how PA can impact cancer through miRNA modulation. Tissue-specific approaches would also aid in a better understanding of the role of c-miRNAs in specific cancer sites that may result in the development of targeted novel therapies.

Conclusions and future directions

PA represents a lifestyle behavior that influences the expression of several c-miRNAs, some of which have been associated with carcinogenesis and cancer progression. Our results suggest that alteration of miRNAs within the circulation is dependent on the type/modality/frequency of exercise as well as on the participants' characteristics. Furthermore, the evidence to date on c-miRNA expression in response to PA is limited by small sample sizes without standardized measures of miRNA or physical activity. miRNAs appear to have a meaningful impact on cancer risk and progression; however, the effect varies between cancer types. Therefore, it appears essential to provide a better understanding of how various types of PA in a specific population could impact c-miRNA expression: it could represent a useful tool for healthcare practioners in establishing and monitoring PA programs for patients with cancer.

Future research should focus on large epidemiologic studies with standardized blood storage and collection as well as standardized measures of c-miRNA expression and objective measures of PA. Additional consistency is needed to provide more meaningful conclusions as well as standardization of PA measurement. Further investigation into the effects of PA on miRNAs is necessary and could have implication both for cancer prevention, treatment, and survival outcomes.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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