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Research highlight

Physical activity responsive miRNAs – Potential mediators of training responses in human skeletal muscle?

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1. The basics of miRNA-mediated regulation

The plasticity of skeletal muscle is of utmost importance for responding to and coping with environmental demands that emerge from changes in physical activity patterns, nourishment, hormonal status, and health. As is well known, a sedentary lifestyle, aging, immobilization, and chronic diseases are associated with reduced muscle mass and function, while regular exercise improves muscle function and reduces the rate of decrement throughout life.[1] However, we do not have a complete understanding of the molecular factors controlling skeletal muscle adaptation to exercise stimuli. Recently identified microRNA molecules (miRNAs) have rapidly gained attention within the scientific community as modulators of muscle properties and potential therapeutic targets.[2]

miRNAs—short, conserved, non-protein-coding RNA molecules capable of repressing gene expression in a sequence-specific manner[3]—are found in a wide variety of life forms. Some miRNAs show cell type- or tissue-specific expression patterns, while others are expressed ubiquitously. Typically, miRNAs have intra- or autocrine functions, but they are also found in all body fluids. Currently it is not clear if miRNAs are actively secreted to the circulation to deliver endocrine functions, or whether they are passively released following cell damage. In short, miRNA-mediated regulation is complicated. miRNAs form regulatory networks in which one miRNA can modulate the expression of several targets, and each miRNA is regulated by other miRNAs or transcription factors. Furthermore, miRNAs are responsive to extracellular stimuli, such as physical exercise, steroid hormones, and nutritional factors. The miRNAs most abundantly found in cardiac and skeletal muscle are named myomiRs.[4] In addition to the regulation of muscle properties by exercise-responsive myomiRs, other muscle tissue-expressed miRNAs are likely to contribute to the plasticity of skeletal muscle, for example, in response to sex steroid hormones.

2. Exercise- and training-responsive miRNAs in skeletal muscle and circulation

2.1. Effects of exercise on miRNAs in skeletal muscle

Nielsen et al.[5] studied the effects of acute and chronic endurance exercise on the expression of myomiRs in skeletal muscle, discovering a significant increase in the expression of miR-1 and -133a and no change in the expression of miR-133b and -206 after a single bout of endurance exercise in untrained male subjects, but a decreased expression of miR-1, -133a, -133b, and -206 after a 12-week training period using the same single exercise test. Drummond et al.[6] showed a decrease in the expression of miR-1 after a single bout of resistance exercise combined with essential amino acid supplementation, while there was no effect on miR-133a and -206.

Davidsen et al.[7] showed that low and high responders to resistance exercise possess a diverse miRNA expression pattern; miR-378, -29a, and -26a were down-regulated in low responders, and miR-451 was upregulated. In this study, a correlation between muscle gain and miRNA expression was observed. Keller et al.[8] used a miRNA microarray to screen for the expression of miRNAs before and after endurance exercise training, showing a reduction for most of the studied miRNAs. The reduced expression after endurance training was further verified for miR-1, -101, -133a, and -455. Using top training responders only, Keller et al.[8] identified the training responsive transcriptome

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(TRT), which was studied for the miRNA target sites. According to the authors, 33 target sites were identified for the core regulators of TRT. These results indicate that miRNA-based regulation is involved in the muscular adaptation to training.

2.2. Effects of exercise on circulating miRNAs

Cell-free circulating miRNAs that are responsive to exercise stimuli have recently received attention as potential markers in cardiovascular adaptation to physical exercise. By studying endurance athletes before and after sustained aerobic rowing training, Baggish et al.[9] showed miR-146a, -222, -21, and -221 to be responsive to maximal acute exercise at baseline and the maintenance of elevated expression levels after a training period. miR-146a and -222 had increased expressions in response to acute exercise after a training period, while miR-21 and -221 remained at baseline levels. Furthermore, miR-20a was elevated after the training period but was not responsive to acute exercise, while miR-328, -210, and -133a were not responsive to either acute exercise or chronic training. Recently, Uhlemann et al.[10] demonstrated significant changes in circulating miR-126 and miR-133 levels in healthy individuals that depended on the exercise type. The level of miR-126, an indicator of endothelial damage, increased after a single maximal spiroergometry test and 30 min after 4 h cycling, whereas the level of miR-133, a marker of muscle damage, did not change. In contrast, after a marathon race, miR-126 and -133 levels were increased significantly. Interestingly, resistance exercise affected only the miR-133 level, increasing it immediately after a workout. According to the authors, maximal ergometric exercise tests and endurance exercise cause endothelial damage, whereas a marathon race induces damage in skeletal muscle cells as well, and resistance exercise has an effect only on the musculature. Therefore, circulating miRNAs may serve as indicators of muscle damage.

Circulating miRNAs can be delivered—in response to exercise—by muscle or other human tissues. In addition, the source of circulating miRNAs may be cells that are themselves part of the circulation. Such cells include different types of leukocytes, peripheral blood mononuclear cells (PBMCs), and natural killer cells (NKs, a fraction of PBMCs). Radom-Aizik et al.[11–13] used cycle ergometer exercise test (ten 2-min bouts with a 1-min rest interval) to study the exercise responsiveness of miRNAs in three different circulating cell populations. They reported exercise responsiveness for 38 miRNAs in neutrophiles,[11] 34 miRNAs in peripheral blood mononuclear cells,[12] and 23 miRNAs in natural killer cells,[13] three of which (miR-126, -130a, and -151-5p) showed a parallel response in all three cell populations. These studies suggest that the miRNA-mediated regulation of the innate immune system may be one of the mechanisms behind the health-promoting function of physical activity, although the miRNAs involved may vary in different leukocyte populations.

3. Future challenges

miRNAs are promising regulators of human muscle plasticity. Unfortunately, our current knowledge is too fragmented to predict whether the promises of miRNA testing can ever be fully exploited. Future research should focus on resolving the nature of the regulatory network formed by miRNAs and their targets. The age and gender of the participants, their training status, and the exercise type may affect the expression of miRNAs. To date, there have been no studies aimed at investigating the miRNA-delivered adaptation to physical exercise or training in young or older women. Therefore, it is unknown if gender-specific differences occur and if they may partially explain the phenotypic differences between female and male training responses. In order to understand the molecular control of miRNA regulation and their expressions in diverse populations and in response to different exercise types, comprehensive studies are needed.

The potential of miRNAs as therapeutic agents or diagnostic markers also needs further study. Circulating miRNAs have been proposed and studied as early diagnostic markers for acute myocardial infarction.[14] Whether miRNAs will ever be used in the diagnosis of harmful decrements in skeletal muscle prior to detectable functional or metabolic limitations remains to be seen. However, a better understanding of the connection between miRNA-mediated regulatory networks and physical fitness, physiological adaptation, and training ability will be of importance in order to maintain and improve human health amidst changing environmental demands.

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