

Commented on: Wang Lijun, MicroRNAs in heart and circulation during physical exercise

Comentário sobre: Wang Lijun, MicroRNAs no coração e circulação durante o exercício físico

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Wang *et al.* [1], recently published in the Journal of Sports and Health Science a review study entitled “**MicroRNAs in heart and circulation during physical exercise**” in which they summarize the regulatory role of small non-coding ribonucleic acid (RNA) molecules, the microRNAs (miRNAs), related to physiopathology in cardiovascular disease and cardiovascular responses to physical exercise.

MiRNAs are non-coding small sequences of RNA, 17 ~ 25 nucleotides [2], that can regulate gene expression by partially binding in 3' untranslated (3'UTR) regions of the messenger RNA (mRNA) inhibiting its translation [3]. It is known that different miRNAs can interact with a single mRNA, and mRNA can have its function altered by several miRNAs [4].

Thus, miRNAs, by regulating gene expression, can alter the cellular response by altering the health-disease relationship. Wang *et al.* [1] by summarizing the role of miRNAs in this process, they identify changes in specific miRNAs in various cardiac diseases, such as cardiac fibrosis, ischemia and reperfusion (I/R) injury, myocardial infarction and heart failure (HF), as well as addressing the expression of miRNAs in physiological hypertrophy.

In this commented article we covered the regulation of miRNAs in cardiac fibrosis, in I/R injury, added a topic to arterial hypertension system (SAH) and ended with HF, evidencing the epigenetic, counter-regulatory role of these molecules in disease and adaptation to exercise, regulating health-disease state.

Cardiac fibrosis

Cardiac fibrosis consists of a pathological increase in the synthesis of extracellular matrix proteins in the heart, that induces loss of diastolic function and later of systolic function. Cardiac fibrosis occurs in almost all cardiovascular diseases such as myocardial infarction (MI), systemic arterial hypertension (SAH), hypertrophic and dilated cardiomyopathy, being also a determinant to discriminate differentiates between pathological and physiological cardiac hypertrophy (CH) [5]. In myocardial-infarcted mice, cardiac miRNA-29 family expression decreased after 14 days. When miRNA-29b was inhibited, a marked increase in cardiac fibrosis and a cardiovascular worsening were observed [6]. The authors suggested that miR-

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NA-29 inhibition may be mediated by an increase in transforming growth factor beta (TGF- β), which also mediates several pathological processes in the heart, including cardiac fibrosis [7]. In contrast, aerobic exercise training increases the expression of miRNA-29a and miRNA-29c, and is able to negatively regulate the deposition of cardiac collagen in healthy female rats trained by swimming, with concomitant exacerbated cardiac hypertrophy by the increase in training volume, improved function, increased diameter of cardiac muscle cells. Thus, the involvement of the miRNA-29 family in the regulation of physiological hypertrophy induced by aerobic training, occurs in an opposite pattern to cardiovascular disease [8].

Ischemia and reperfusion injury

The ischemia and reperfusion injury (I/R) is a condition in which the cardiac tissue presents impaired blood flow and a after a resumption period, as coronary artery obstruction induced by myocardial infarction. This injury occurs due to the increase in reactive oxygen species, atherosclerosis, damaged calcium mechanism and inflammatory responses, and can leads to necrosis of the injured cells, edema, and a non-uniform restoration of blood flow to the damaged tissue [9,10]. In contrast, physical exercise can improve cardiac function after I/R injury.

Liu *et al.* [11] reported that the increase in miRNA-222 expression can reduce the adverse effects of I/R injury in mice that Swan or performed voluntary running for 4 weeks and showed that the increase in miRNA-222 has a protective effect against pathological cardiac remodeling. The authors produced a transgenic animal with overexpression of miRNA-222 to assess *in vivo* the effects of the expression of this miRNA on the cardiomyocyte. The cardioprotective mechanism of miRNA-222 related to I/R goes through the negative regulation of targets such as Homeodomain-Interacting Protein Kinases 1 and 2 (HIPK1, HIPK2), Protein binding to the homeobox telomer (HMBOX1) and the kinase inhibitor cyclin dependent (p27). These targets are related to the proliferative and hyperplastic phenotype of cardiac muscle cells, which shows the cardioprotective involvement of miRNA-222 in the increase in cardiac tissue size induced by aerobic physical training and in regenerative processes.

MiRNA-208a is regarded the strongest candidate to become a pathological and related to physical training biomarker, due a close relationship with cardiac contractility and metabolism, and to be exclusively expressed by heart [12]. MiRNA-208a expression increases in the heart in patients with heart failure and hypertensive rats [9,13,14]. Currently, this miRNA is considered as an acute circulating biomarker of myocardial infarction, pathological remodeling, cardiac conductance and contractility, since it increases, through the repression of its various target mRNAs, the expression of β -type heavy chain myosin, a pathological marker [15]. On the other hand, after high-volume aerobic training in normotensive rats and concomitant with their physiological adaptations, such as HC, improvement in diastolic function and increase in oxygen consumption, there is a marked decrease in miRNA-208a expression, which makes it special attention in the regulation between physiological and pathological adaptive processes in the heart [16].

Systemic Arterial Hypertension

SAH is a syndrome characterized by high blood pressure values, above 139mmHg for systolic pressure and 89mmHg for diastolic pressure [17]. In Brazil, SAH affects more than 30% of the adult population, with prevalence among the elderly exceeding 60% [17]. The role of regular physical exercise stands out as a non-pharmacological measure for the treatment of SAH, since, can act by reducing sympathe-

tic nervous activity (ANS) [18], decreasing capillary rarefaction, which increases the cross-sectional area of capillaries [19]. These two physiological adaptations together contribute to the reduction of peripheral vascular resistance, consequently, reducing blood pressure values.

Santulli [20] summarizes the regulation of miRNAs in essential hypertension, in a study showing that there are changes in the circulating, urine and tissue miRNAs (c-miRNAs), in the heart, kidney, brain and blood vessels. Neves *et al.* [21] described a list of miRNAs that play a role in the pathogenesis of SAH and that have the potential to be regulated by physical exercise, especially miRNA-16, targeting Vascular Endothelial Growth Factor (VEGF), involved in angiogenesis.

MiRNA-155, which targets the endothelial nitric oxide synthase (eNOS) enzyme, regulates the production of endothelial nitric oxide (NO) involved in the process of dependent endothelial vasodilation [21]. The consequent changes of physical exercise in the regulation of miRNA-16 and miRNA-155, demonstrate again, how exercise is crucial in the treatment of SAH, since it promotes fundamental changes for angiogenesis, improvement of endothelial function, through NO, in addition to, reduces vascular peripheric ANS and vascular rarefaction.

Heart failure

Heart failure (HF) is a clinical syndrome characterized by decreased values of cardiac output and is the common final route of cardiovascular diseases [22]. The regular physical exercise deserves mention among the most effective therapies for the treatment of HF. Exercise training, in addition to causing a change in sympathetic nerve activity, helps to improve the shortening fraction of the cardiomyocyte and improves the cytosolic Ca⁺⁺ transient, improving the activity of the regulating proteins, such as the Sarcoplasmic Reticulum Ca⁺⁺ Pump (SERCA-2a) and Phospholamban [23].

To elucidate the exercise-induced miRNAs regulation in HF, Souza *et al.* [24] traced a miRNAs profile in Wistar rats submitted to surgical aortic stenosis and trained on a treadmill for 10 weeks. The trained rats showed improvement in systolic and diastolic functions and reduced atrial mass compared to untrained. The responsive miRNAs to the therapeutic effect of exercise, with a possible cardioprotective role in HF were miRNAs-21, -132, -155, -146b, -208b, -212, -214, studied as regulators of cardiac remodeling and function. Recently, the study by Correa *et al.* [25] showed, in patients with HF of functional classes II and III, who underwent aerobic training for 4 months, improved flow and vascular conductance, increased oxygen consumption, and vastus lateralis skeletal muscle hypertrophy. Skeletal muscle hypertrophy has been associated with an increase in muscle miRNA-1, which inhibits its target, the Homologous Phosphatase and Tensin Protein (PTEN), PTEN, in turn, inhibits the action of phosphoenositide-3 kinase, protein kinase B and Mammalian Rapamycin Receptor Target (PI3K-AKT-mTOR), an important protein synthesis pathway in physiological HC. Thus, physical exercise by increasing the expression of miRNA-1 indirectly stimulates protein synthesis. Another target of miRNA-1 is histone deacetylase 4 (HDAC-4), which, inhibited, facilitates the transcription of deoxyribonucleic acid (DNA), which improves muscle regeneration and atrophy in patients [25].

Conclusion

MiRNAs play a crucial role in the health-disease relationship and their expression can be regulated by physical exercise. As in the article by Wang *et al.* [1],

the role of miRNAs in some cardiovascular diseases and how exercise has therapeutic potential were addressed here.

In the future, new research may point to miRNAs as physiological markers in the health-disease relationship, as well as a therapeutic target for the control of several of these diseases.

Potential conflict of interest

No conflicts of interest with potential potential for this article have been reported.

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