Exercise for cardiac health and regeneration: killing two birds with one stone

Karine da Silva Verdoorn[1], Cristiane Matsuura[2], Juliana Pereira Borges[3]

[1]Physiology Department, Federal University of Rio de Janeiro, Macaé, Rio de Janeiro, Brazil; [2]Department of Pharmacology and Psychobiology, State University of Rio de Janeiro, Rio de Janeiro, Brazil; [3]Physical Education and Sports Institute, State University of Rio de Janeiro, Rio de Janeiro, Brazil

Correspondence to: Juliana Pereira Borges. Rua São Francisco Xavier, 524, sala 8133F – Maracanã, Rio de Janeiro, Brazil. Email: julipborges@gmail.com.

Provenance: This is a Guest Editorial commissioned by Editor-in-Chief Jianxing He, MD, FACS (Department of Cardiothoracic Surgery, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China).

Comment on: Shi J, Bei Y, Kong X, *et al.* miR-17-3p Contributes to Exercise-Induced Cardiac Growth and Protects against Myocardial Ischemia-Reperfusion Injury. Theranostics 2017;7:664-76.

Submitted Feb 24, 2017. Accepted for publication Mar 01, 2017.
doi: 10.21037/atm.2017.03.10
View this article at: http://dx.doi.org/10.21037/atm.2017.03.10

The benefits of exercise for cardiovascular health and improved cardiovascular disease outcome are undeniable. Experimental, epidemiological and clinical studies support exercise as an effective cardioprotective activity (1). Diverse exercise-induced acute and chronic adaptations have been described as underlying contributors for a cardioprotective phenotype (2). Yet, many questions remain unanswered: is there a critical amount and/or intensity of exercise to trigger the adaptations? Is there one main signaling pathway that orchestrates the resulting phenotype? If so, is it possible to therapeutically stimulate specific signaling pathways and thereby mimic the exercise stimulus?

In this sense, Shi and colleagues (3) have concentrated efforts on identifying exercise-induced signaling pathways responsible for physiological cardiac growth (including cardiomyocyte hypertrophy and proliferation) and, subsequently, testing if these pathways enhance cardiac regeneration after a myocardial insult. The authors targeted members of the miR-17-92 cluster, a microRNA (miRNA) (and passenger strands) family known for its regulatory effect on cell cycle, proliferation and apoptosis, and identified the passenger strand miR-17-3p as the only one with increased levels in murine cardiomyocytes after two different models of endurance exercise training (swimming and voluntary wheel running). The role of miR-17-3p in cardiomyocyte hypertrophy and proliferation was further confirmed by *in vitro* and *in vivo* analysis. In neonatal rat ventricular cardiomyocytes, gain-and loss-of-function tests confirmed miR-17-3p as a positive regulator of cardiomyocyte hypertrophy, proliferation and survival. In addition, through Luciferase reporter assay, TIMP3 and PTEN were identified as direct and indirect targets of miR-17-3p, respectively. Of note, TIMP3 inhibits cardiomyocyte proliferation via EGFR/JNK/SP-1 pathway (4), whilst PTEN antagonizes PI3K/Akt pathway, which is involved in cardiac physiological hypertrophy (5), and both are suppressed by miR-17-3p. *In vivo*, mice were injected with miR-17-3p antagomir for three consecutive days prior to exercise training, which attenuated exercise-induced cardiac hypertrophy, partially blocked the increase of proliferation markers and blunted elevation of contractile protein levels (α-actinin and cTnI). Elevating heart miR-17-3p, with its agomir, in untrained mice at a comparable level to exercise failed to induce physiological cardiac growth, however, it stimulated cardiomyocytes proliferation and attenuated cardiac apoptosis and fibrosis in mice submitted to ischemia/reperfusion injury. From these results, it seems clear that miR-17-3p plays a key role in physiological cardiac growth and may counteract adverse cardiac remodeling.

Stimulation of physiological cardiac growth signaling cascades and prevention of cardiomyocyte loss in the context of myocardial injury and/or overload is an interesting approach to preserve cardiac function. Both, myocardial injury and pathological overload, elicit maladaptive cardiac remodeling leading to arrhythmia,

heart failure and ultimately myocardial insufficiency. In contrast, physiological cardiac growth enhances myocardial contractile function and confers resistance against pathological insults. The authors have been exploring this strategy with promising results (3,6,7). Although the concept of absent adult cardiomyogenesis has been outdated in the last years (8), strategies that boost myocyte proliferation and restore myocardial contractile function are extremely important to counteract ischemia/reperfusion injury, one of the main causes of chronic heart disease, that elicits substantial cardiomyocyte death and leads to cardiac fibrosis.

MicroRNAs are major regulators of biological processes and are known to modulate cellular responses to diverse stimuli (disease, exercise or status maintenance) (9). More recently, even its passenger strand, which formerly was believed to be degraded, has been identified as a bioactive molecule. This relatively novel class of molecules are being thoroughly investigated for its potential therapeutic use (10,11). Although miR-17-3p action inducing cell proliferation and survival had previously been described in murine prostate tumor (12,13), its role in cardiomyocytes and altered expression in response to exercise were first demonstrated by Shi and colleagues (3). The authors verified that miR-17-3p is downregulated in left ventricular samples of patients with dilated cardiomyopathy, and anticipated that with heart failure patients a single cardiopulmonary exercise test was able to increase serum miR-17-3p. This can be considered a first clue that cardiomyopathy patients could benefit from increased miR-17-3p expression. However, thinking of translating experimental findings into the clinic, immediate questions emerge: will acute exercise-induced increase in circulating miR-17-3p activate the cardiac physiological growth signaling pathways? Is there a necessary amount of exercise training to obtain the desired results? Induction of different sets of circulating miRNAs in response to acute and sustained exercise training have been reported (14). Intriguingly, the role circulating miRNAs play is still unclear. While serum miRNAs could be used as biomarkers of myocardial adaptations (or myocardial health status), knowing the exercise dose (intensity and frequency) necessary to stimulate cardiac physiological growth pathways in a pathological setting would be desirable.

Alternatively, miR-17-3p could be administered therapeutically, as experimentally tested by the authors. But then, will one specific miRNA (or passenger strand) induce efficient adaptations in humans or is a subset of miRNAs required? Although one miRNA targets multiple mRNAs, complex biological processes are rather regulated by several miRNAs, with complementary or concurrent functions. In a previous work of the same authors (5), miR-222 was similarly reported to modulate cardiomyocyte growth and proliferation, and protect the heart against ischemia/reperfusion injury. Both miR-222 and miR-17-3p when injected individually in untrained mice were not able to induce cardiac growth, and had their effect only partially blocked when repressed using its respective antagomir in exercised mice, but protected the heart against adverse remodeling after an ischemic insult. These miRNAs could be part of a larger synergistic network, in which the effect of one miRNA depends on the action of others. In this way, injecting one specific miRNA can induce different cellular responses or no response at all, depending on the cellular's pre-existing miRNA set or priming event (which could be an ischemic insult, disease or exercise). Furthermore, extra concern is warranted when putting this into perspective, exercise produces a systemic stimulus and thereby modifies miRNA expression in diverse tissues and cell types. Increased expression of miR-17-3p was detected specifically in cardiomyocytes and, interestingly, non-cardiomyocytes presented a, though not significant, decreased level of expression. As highlighted before by Uchida and Dimmeler (15), when it comes to systemically injecting miRNAs cell specificity must be guaranteed. Each miRNA has numerous downstream targets, many still to be identified, that could lead to undesired side effects. In line with this, miR-17-3p has been clearly related to growth, proliferation, invasion, and survival of different types of tumor cells (12,13). Moreover, it has been shown to suppress the expression of mRNAs responsible for the synthesis of antioxidant enzymes in human peripheral blood mononuclear cells and endothelial cells (16). And more importantly, an additional challenge is the potential of miRNAs to silence mRNAs that are not normally its target (11).

The findings of Shi and colleagues present a novel therapeutic possibility, nevertheless a long way to prove its safety and applicability for clinical use exists. Translating experimental findings into the clinic, even with safety proven agents, has been challenging (17,18). To date, physical exercise is a strongly recommended intervention with positive effects in the prevention and treatment of established cardiovascular diseases, that acts as a "master polypill" capable to strengthen the heart, improve blood pressure, tackle different risk factors and attenuate injury upon a stressful event (19). Shi and colleagues (3) reinforced

this concept by demonstrating that exercise elicits myocardial regeneration, through induction of signaling cascades that stimulate physiological cardiac growth and counteract adverse cardiac remodeling.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Mann N, Rosenzweig A. Can exercise teach us how to treat heart disease? Circulation 2012;126:2625-35.
2. Golbidi S, Laher I. Molecular mechanisms in exercise-induced cardioprotection. Cardiol Res Pract 2011;2011:972807.
3. Shi J, Bei Y, Kong X, et al. miR-17-3p Contributes to Exercise-Induced Cardiac Growth and Protects against Myocardial Ischemia-Reperfusion Injury. Theranostics 2017;7:664-76.
4. Hammoud L, Burger DE, Lu X, et al. Tissue inhibitor of metalloproteinase-3 inhibits neonatal mouse cardiomyocyte proliferation via EGFR/JNK/SP-1 signaling. Am J Physiol Cell Physiol 2009;296:C735-45.
5. Maehama T, Dixon JE. The tumor suppressor, PTEN/MMAC1, dephosphorylates the lipid second messenger, phosphatidylinositol 3,4,5-trisphosphate. J Biol Chem 1998;273:13375-8.
6. Boström P, Mann N, Wu J, et al. C/EBPβ controls exercise-induced cardiac growth and protects against pathological cardiac remodeling. Cell 2010;143:1072-83.
7. Liu X, Xiao J, Zhu H, et al. miR-222 is necessary for exercise-induced cardiac growth and protects against pathological cardiac remodeling. Cell Metab 2015;21:584-95.
8. Kajstura J, Urbanek K, Perl S, et al. Cardiomyogenesis in the adult human heart. Circ Res 2010;107:305-15.
9. van Rooij E, Sutherland LB, Liu N, et al. A signature pattern of stress-responsive microRNAs that can evoke cardiac hypertrophy and heart failure. Proc Natl Acad Sci U S A 2006;103:18255-60.
10. Pan ZW, Lu YJ, Yang BF. MicroRNAs: a novel class of potential therapeutic targets for cardiovascular diseases. Acta Pharmacol Sin 2010;31:1-9.
11. Dorn GW 2nd. MicroRNAs in cardiac disease. Transl Res 2011;157:226-35.
12. Yang X, Du WW, Li H, et al. Both mature miR-17-5p and passenger strand miR-17-3p target TIMP3 and induce prostate tumor growth and invasion. Nucleic Acids Res 2013;41:9688-704.
13. Shan SW, Fang L, Shatseva T, et al. Mature miR-17-5p and passenger miR-17-3p induce hepatocellular carcinoma by targeting PTEN, GalNT7 and vimentin in different signal pathways. J Cell Sci 2013;126:1517-30.
14. Baggish AL, Hale A, Weiner RB, et al. Dynamic regulation of circulating microRNA during acute exhaustive exercise and sustained aerobic exercise training. J Physiol 2011;589:3983-94.
15. Uchida S, Dimmeler S. Exercise controls non-coding RNAs. Cell Metab 2015;21:511-2.
16. Curti V, Capelli E, Boschi F, et al. Modulation of human miR-17-3p expression by methyl 3-O-methyl gallate as explanation of its in vivo protective activities. Mol Nutr Food Res 2014;58:1776-84.
17. Iliodromitis EK, Cohen MV, Dagres N, et al. What is Wrong With Cardiac Conditioning? We May be Shooting at Moving Targets. J Cardiovasc Pharmacol Ther 2015;20:357-69.
18. Hausenloy DJ, Yellon DM. The second window of preconditioning (SWOP) where are we now? Cardiovasc Drugs Ther 2010;24:235-54.
19. Sanchis-Gomar F, Fiuza-Luces C, Lucia A. Exercise as the master polypill of the 21st century for the prevention of cardiovascular disease. Int J Cardiol 2015;181:360-1.

Cite this article as: Verdoorn KS, Matsuura C, Borges JP. Exercise for cardiac health and regeneration: killing two birds with one stone. Ann Transl Med 2017;5(Suppl 1):S13. 10.21037/atm.2017.03.10

