REVIEW ARTICLE

miR-29 as Indicator of Health and Disease in Sports Medicine - A Review

Mania Roozbayani

1. Assistant Professor of Exercise Physiology, Department of Exercise Physiology, Borujerd Branch, Islamic Azad University, Borujerd, Iran.

***Correspondence:**
Mania Roozbayani, Assistant Professor of Exercise Physiology, Department of Exercise Physiology, Borujerd Branch, Islamic Azad University, Borujerd, Iran.
Tel: (98) 910 212 8472
Email: m.roozbayani@iaub.ac.ir

Received: 12 July 2018

Accepted: 25 August 2018

Published in November 2018

Abstract

Recent research is about the role of miR-29 accompanied by various conditions especially during the physical activity is a case of special attention, such as high intensity interval training (HIIT) and continuous aerobic training (CT) protective in heart, renal, lung, liver and even immune system adaptation. Since recent studies indicated the rolls of miR family on health and disease such as the effect of miR on health parameters evaluation and cardiovascular-respiratory, diabetic cardiomyopathy, diabetes, hypertension, myocardial infarction, gastric and breast cancer. Blocking harmful genes such as COL-1, CTGF, SMAD3, TGF-β, NFK-B and genes expression related to health such as miR-29 is a primary approach in treatment of some diseases. Meanwhile sports as HIIT and CT can be safe approach for genes expression related health and blocking harmful genes. This regulations applies by miRs especially miR-29 that is one mystery regulator in variety of diseases. We will give a brief account of relation between sports activities and miR-29 expression in this review.

Keywords: miR-29, Sports medicine, Health, Disease, Gene regulation

Introduction

miRs (microRNAs) are gene expression endogenous regulators by inhibiting translation or protein degradation. miRNAs mainly bind to the 3´ -untranslated regions (UTRs) of target RNAs, resulting in mRNA degradation or translation repression (1).

Recent studies indicated that miRs play a role in variety of diseases such as; coronary artery disease (CAD), cardiomyocyte insulin receptor knockout (CIRKO), cancers, diabetes, heart failure and factors increasing similar transforming growth factor-β (TGF-β), connective tissue growth factor (CTGF), diacylglycerol acyl transferase (DGAT), fatty acid, forkhead box O1 (FOXO1), histone deacetylase (HDAC), microtubule-associated protein 1A/1B-light chain 3 (LC3), smooth muscle actin d (SMAD) and lipoprotein lipase (LPL), mitogen-activated protein kinase (MAPK), myosin heavy chain (MHC), matrix metalloproteinase (MMP), mammalian target of rapamycin (MTOR), nuclear factor κB (NF-κB), oxidative phosphorylation (OXPHOS), phosphatidylinositol 3-kinase (PI3K), renin–angiotensin–aldosterone system (RAAS),

receptor for AGEs (RAGE), reactive oxygen species (ROS), sarcoplasmic/endoplasmic reticulum calcium ATPase (SERCA), intracellular adhesion molecules (ICAM-1) and increased expression of cell adhesion molecules (VCAM), macrophages, leucocytes and inflammatory cytokines (IL-1β, IL-6, IL-18, TNF-α and TGF-β1) (2-8). In other words often diseases are accompanied by gene expression global pattern changes which are supplemented by miRs.

This paper reviews miR-29 rollson health and disease in sports sciences and kinds of exercises especially its effect on heart diseases and diabetes.

What is miR

miRs are small non - coding and endogenous RNA molecules with 18-22 nucleotides and gene expression regulating and are encoded by short inverted repeats within the genome. The regulation of mRNA by miR has a potent effect on many cellular functions (9).

miR-125b, miR-146a-5p, and miR-29a-3p expressions were accompanied by persistent impaired endothelial function and altered pro-inflammatory gene expressions like NF-kB subunit p65. In this way it might be clear that miR expression may have several effects on proper actions in the cell regulation (10).

Role of miR-29 family on health and disease

The miR-29 family consists of four members with shared regulatory capacity, namely miR-29a, miR-29b-1, miR-29b-2 and miR-29c.Therefore miR-29 worth as being biomarker in health and diseases which attracted the attention of researchers recently (11). miR-29s were considered by broad gene expression at human (12) and mice (13,14) in variety organs. miR-29 family can be effective on three gene networks :a) cellular processes, connective tissues, b) cardiovascular and nervous systems, c) cancer and hematological function (15).

miR-29 is an effective treatment for fibrosis via down regulating of COL7A1 and inhibiting TGF-β in recessive dystrophic epidermolysis bullosa (RDEB) patients that was tested on mice. RDEB is a severe genetic skin disorder characterized by chronic skin blistering and abnormal wound healing too. The process cell mechanism shows that miR-29 directly regulates COL7A1 (in part via targeting the 3´ untranslated region [UTR]) and decreases SP1 expression (which leads to indirect regulation of COL7A1 transcription) (16).

miR-29 upregulation identified as one cardiac fibrosis regulation biomarker by genes reducing such as collagen, CTGF, TGF-B (8,9,17). Blocking COL-1 and CTGF is a primary approach for the treatment of diseases such as cardiac hypertrophy, diabetic cardiomyopathy and cardiac fibrosis (8,9). There are cytokines and growth factors linked with development of cardiac fibrosis (18,19) such as, IL-6 and CTGF that causes heart failure and miR-29 can suppress these factors (19-21). One other study revealed that miR-29a is upregulated and promotes self-renewal in AML and increases epithelial mesenchymal transition (EMT) and metastasis in breast cancer (22,23).

Silencing NMI expression from epithelial-like breast cancer cell lines induced molecular markers and morphological attributes of mesenchymal like phenotype as well as promoted the invasive ability of these cells. Systematically, loss of NMI had negative impacts on STAT5-driven expression of TGFβ signaling repressor, SMAD7. This allowed for aberrant manifestation of TGFβ-driven EMT (24)

Based on this developing body of compelling reports, it is apparent that loss of NMI expression during tumor progression may prompt EMT and metastases (25).

Kim et al. indicated that miR-29b is induced by c-Myc in HMEC cells (26).

miR-29b is also upregulated in canine breast cancer and multiple gene expression analyses indicate its up-regulation in this kind of cancer (27-29).

miR-29 family act as critical regulators of key processes in adaptive immunity (15). One study stated that miR-29a is up- regulated in aggressive B cell chronic lymphocytic leukemia (B-CLL), and further up-regulated in indolent B-CLL, compared to non-transformed B cells. This up-regulation can be a key event in transformation, as transgenic mice over expressing miR-29a/b-1 in B cells show an expansion of CD5+CD19+IgM+ B cells that is similar to the findings in indolent B-CLL (30).

Chen et al. stated that miR-29a and c has up-regulated effect in drug resistant breast cancer (31). Rostas et al. focused their studies on testing the ability of the miR-29 family in targeting NMI. miR-29 a, b, c identical sequences in the NMI 3′UTR with a slight alteration in their binding capacity based on variations outside the seed-sequence. To validate targeting of the NMI 3′UTR by miR-29, they copied the putative binding site of miR-29 into the pMIR-REPORT™ vector to generate pMIR-REPORT29-NMI (25). It is a cytokine (IL-2, IFNγ) inducible protein that interacts with several transcription factors such as STATs, cMYC, BRCA1, TIP60 and SOX10, all of which that have known as critical involvement in influencing tumor progression has a hung impact on tumor progression and stem-ness (32-37).

It was observed approximately 50% reduction in the activity of pMIR-REPORT29-NMI in MCF7 cells. There were not significant differences when activity of the miR-29 members was compared with each other, implying that they are capable of targeting NMI with comparable efficiency. The miRs target NMI specially (25).

miR-29 a and b expression levels in select cell types of reported epithelial or mesenchymal-like phenotype. MFC7, T47D and MDAMB-4 68 are epithelial like cells whereas MCF10CA.cl.a, MCF10CA.cl.d, MDA-MB-231 are tumorigenic, highly invasive (mesenchymal- like) and metastatic cell lines. (25,38,39).

Zhong et al. stated that in human aortic endothelial cells (HAECs) 7 miRNAs were decreased: miR-29a-3p, let-7c, miR-889, miR-146a-5p, miR-502-5p, miR-138-1-3p, and miR-138-2-3p. Only miR-125b, miR-29a-3p, and miR-146a-5p had the consistent results in vitro and vivo. However, their present study shows transient high glucose causes sustained changes of miR-125b, miR29a-3p, and miR-146a-5p together with p65 during subsequent normal glucose. Only miR125b and miR-146a-5p could regulate the expression and nuclear translocation of p65 in HAECs (10).

Schmitt et al stated that miR-29a exhibits differential regulation in cell biology, tumor suppressing, immune modulating, and cardiovascular injury (40).

miR-29a targets expression of diverse proteins like transcription factors, methyl transferases, and others, which may take part in abnormal invasion, migration, or proliferation of cells and may cause development of cancer. Due to the complex modulation of miR-29a3p, they assumed that dysfunction of miR-29a-3pis the result rather than the cause of metabolic memory. Therefore, the expression of miR-29a-3p might be a useful predictive tool in metabolic memory (10).

miR-29 prevents of cardiac fibrosis progression by suppressing its target CDK2. AMPK activation, up-regulated p21 and p27 expression, inhibited CDK2 and cyclin E complex, finally suppressed cardiac fibrosis progression, and repressed HNF-4a expression, further down-regulated theTGF-b1 promoter activity, promoted miR-29 expression, and as a result prevented cardiac fibrosis development (41). Qi et al. stated that miR-29 prevents cardiac fibrosis development by suppressing its target CDK2. (42).

In animal models, it was observed that during pathological remodeling, when the expression of miR-29, decreases the repression of pro-fibrotic genes may be relieved, resulting in enhanced collagen synthesis and fibrosis (43).

Morita et al. stated that overexpression of miR-29 up-regulated the global DNA methylation level in some cancer cells and down-regulated DNA methylation in other cancer cells, suggesting that miR-29

suppresses tumorigenesis by protecting against changes in the existing DNA methylation status rather than by preventing methylation of DNA (44).

Role of mir-29 and other markers in physical activity

Physical inactivity (PA) implication on general health and well-being are clear (45).

Murach et al. stated the cycle training is an effective endurance exercise modality for promoting growth in middle-aged women, who are susceptible to muscle mass loss with aging (46). Exercise specially vigorous exercise increases the concentrations of cardiac damage biomarkers widely used in clinical routine practice, such as high-sensitive cardiac troponin T (hs-cTnT) or N-terminal pro-brain natriuretic peptide (NT-proBNP) (47).

Sports and exercises exert cardiac, renal, live rand immune system protective effects by miR-29 gene expression.

It was found that beside protein markers there are few DNA or RNA like markers which may be used as markers of health and disease in sports activity such as miR (48).

Li et al. suggested that miR-29 family can exert both transcription and/or translation regulation of CCND2 and E2F7 (49).

Aerobic swimming exercise induced physiological left ventricular (LV) hypertrophy, miR-21, miR-27a and miR-143 cardiac genes expression in vivo models (50,51) that miR-21 function is similar to miR-29. Therefore miRs circulate increasing by variety exercises succeed cardiac regenerative (52).

Calvo et al. stated that acute aerobic exercise induced a qualitative and quantitative alteration in the circulating profile of miRNAs. Regarding Marathon run, miR-21-5p, miR-27a-3p, miR-29a-3p, miR-30a-5p, miR-34a-5p,miR-126-3p, miR-142-5p, miR-143-3p, miR-195-5p and miR-199a-3p peaked immediately after the race. These miRNAs returned to baseline levels 24 hours after the race (53).

Xiao et al. stated that intermittent aerobic exercise through miR-29 a and miR-101a effect on TGFb, fos, Smad2/3, COL1A1 and COL3A1 in MI model of rats (54).

Aerobic trainings increase miR-29 expression and decreased collagen gene expression and concentration in the heart, which is relevant to the improved LV compliance and beneficial cardiac effects, associated with aerobic high performance training (55).

Russell et al. stated that short-term training increased miR-1 and -29b in trained man's skeletal muscles that evaluated via biopsy (56). Roozbayani et al. stated that miR-29 a expression is statistically higher in HIIT and CT group than control group. The miR- 29 expression was more in HIIT than CT (8,9).

miR-29 gene expression decreases fibroblasts, and have other components such as G protein coupled estrogen receptor (GPR30) that attenuates the adverse effects of estrogen loss on cardiac fibrosis and diastolic dysfunction (57).

The aerobic exercise training (AET) consisted of 10 weeks of 60-min swimming sessions, and 5 days/week AET counteracts CH in obesity. Meanwhile Cardiac miR-29 expression was decreased in control obese rats compared with the control lean rats group (58).Recent research revealed that miR-1 down regulates Pim-1 in STZ-induced Type 1 diabetic mice, and restoration of Pim-1 levels prevented cardiomyocyte apoptosis, ventricular dilatation and failure (59).

Cardiac miR-133 expression is increased in the alloxan-induced type 1 diabetes rabbit model, and miR-133 modulates connective tissue content by CTGF expression regulating, suggesting its and contributes to in diabetic hearts fibrosis induction in diabetic hearts (60,61).

New studies stated that miR-103, miR-107,miR-143, miR-181 and miR-802 in the regulation of systemic glucose metabolism and insulin sensitivity are effective, thereby miRs have important role in insulin resistance and type 2 diabetes pathogenesis (62-64). Aerobic swimming exercise stimulates cardiac

angiogenesis by miR-126 expression regulation in rats (65). miR-199a-3p exogenous administration promoted cardiac regeneration cell cycle in neonatal and adult mice (66). miR-222 causes cardiac growth and protect against pathological cardiac remodeling through exercise (53).

Conclusions

miRs can be effective on variety biological conditions. The miRs are numerous. Some of them have specific targets. miR-29 is effective on heart, liver, kidney, lung and hippocampus. The miR-29 major effect applied via three gene networks: a) cellular processes, connective tissues, b) cardiovascular and nervous systems, c) cancer and hematological function.

References

1. Kong YW, Cannell IG, de Moor CH, Hill K, Garside PG, Hamilton TL, Meijer HA, Dobbyn HC, Stoneley M, Spriggs KA, Willis AE. The mechanism of micro-RNA-mediated translation repression is determined by the promoter of the target gene. Proceedings of the National Academy of Sciences. 2008;105(26):8866-71.
2. Westermann D, Rutschow S, Jäger S, Linderer A, Anker S, Riad A, et al. Contributions of inflammation and cardiac matrix metalloproteinase activity to cardiac failure in diabetic cardiomyopathy: the role of angiotensin type 1 receptor antagonism. Diabetes. 2007;56(3):641-6.
3. Tschöpe C, Walther T, Escher F, Spillmann F, Du J, Altmann C, et al. Transgenic activation of the kallikrein-kinin system inhibits intramyocardial inflammation, endothelial dysfunction and oxidative stress in experimental diabetic cardiomyopathy. The FASEB journal. 2005;19(14):2057-9.
4. Westermann D, Rutschow S, Van Linthout S, Linderer A, Bücker-Gärtner C, Sobirey M, et al. Inhibition of p38 mitogen-activated protein kinase attenuates left ventricular dysfunction by mediating pro-inflammatory cardiac cytokine levels in a mouse model of diabetes mellitus. Diabetologia. 2006;49(10):2507-13.
5. Westermann D, Van Linthout S, Dhayat S, Dhayat N, Escher F, Bücker-Gärtner C, et al. Cardioprotective and anti-inflammatory effects of interleukin converting enzyme inhibition in experimental diabetic cardiomyopathy. Diabetes. 2007;56(7):1834-41.
6. Rajesh M, Bátkai S, Kechrid M, Mukhopadhyay P, Lee WS, Horváth B, et al. Cannabinoid 1 receptor promotes cardiac dysfunction, oxidative stress, inflammation, and fibrosis in diabetic cardiomyopathy. Diabetes. 2012;61(3):716-27.
7. Roozbayani M, Peeri M, Agha-Alinejad H, Azarbayjani MA. Effect of Continues Training and High Intensity Interval Training on miR-29a and CTGF Gene Expression in Male Wistar Diabetic Rats' Heart Tissue. Iranian Journal of Diabetes & Obesity (IJDO). 2016;8(3).
8. Roozbayani M, Peeri M, Agha-Alinejad H, Azarbayjani MA. Type of Aerobic Training Effect on Cardiac Muscles MIR29A and Collagen I Gene Expression in Diabetic Male Rats. Iranian Journal of Diabetes & Obesity (IJDO). 2016;8(4).
9. Yang B, Lin H, Xiao J, Lu Y, Luo X, Li B, et al. The muscle-specific microRNA miR-1 regulates cardiac arrhythmogenic potential by targeting GJA1 and KCNJ2. Nature medicine. 2007;13(4):486.
10. Zhong X, Liao Y, Chen L, Liu G, Feng Y, Zeng T, et al. The microRNAs in the pathogenesis of metabolic memory. Endocrinology. 2015;156(9):3157-68.
11. Liston A, Linterman M, Lu LF. MicroRNA in the adaptive immune system, in sickness and in health. Journal of clinical immunology. 2010;30(3):339-46.
12. Liang Y, Ridzon D, Wong L, Chen C. Characterization of microRNA expression profiles in normal human tissues. BMC genomics. 2007;8(1):166.
13. Thomson JM, Parker J, Perou CM, Hammond SM. A custom microarray platform for analysis of microRNA gene expression. Nature methods. 2004;1(1):47.
14. Van Rooij E, Sutherland LB, Thatcher JE, DiMaio JM, Naseem RH, Marshall WS, et al. Dysregulation of microRNAs after myocardial infarction reveals a role of miR-29 in cardiac fibrosis. Proceedings of the National Academy of Sciences. 2008;105(35):13027-32.
15. Liston A, Papadopoulou AS, Danso-Abeam D, Dooley J. MicroRNA-29 in the adaptive immune system: setting the threshold. Cellular and Molecular Life Sciences. 2012;69(21):3533-41.
16. Oever MV, Muldoon D, Mathews W, Mc Elmurry R, Tolar J. miR-29 Regulates Type VII Collagen in Recessive Dystrophic Epidermolysis Bullosa. The Journal of investigative dermatology. 2016;136(10):2013.

17. Van Rooij E, Sutherland LB, Liu N, Williams AH, Mc Anally J, Gerard RD, et al. A signature pattern of stress-responsive microRNAs that can evoke cardiac hypertrophy and heart failure. Proceedings of the National Academy of Sciences. 2006;103(48):18255-60.
18. Kapoun AM, Liang F, O'young G, Damm DL, Quon D, White RT, et al. B-type natriuretic peptide exerts broad functional opposition to transforming growth factor-β in primary human cardiac fibroblasts: fibrosis, myofibroblast conversion, proliferation, and inflammation. Circulation research. 2004 Mar 5;94(4):453-61.
19. Pathak M, Sarkar S, Vellaichamy E, Sen S. Role of myocytes in myocardial collagen production. Hypertension. 2001;37(3):833-40.
20. Daniels A, Van Bilsen M, Goldschmeding R, Van Der Vusse GJ, Van Nieuwenhoven FA. Connective tissue growth factor and cardiac fibrosis. Acta physiologica. 2009;195(3):321-38.
21. Koitabashi N, Arai M, Kogure S, Niwano K, Watanabe A, Aoki Y, et al. Increased connective tissue growth factor relative to brain natriuretic peptide as a determinant of myocardial fibrosis. Hypertension. 2007;49(5):1120-7.
22. Han YC, Park CY, Bhagat G, Zhang J, Wang Y, Fan JB, et al. microRNA-29a induces aberrant self-renewal capacity in hematopoietic progenitors, biased myeloid development, and acute myeloid leukemia. Journal of Experimental Medicine. 2010;207(3):475-89.
23. Gebeshuber CA, Zatloukal K, Martinez J. miR-29a suppresses tristetraprolin, which is a regulator of epithelial polarity and metastasis. EMBO reports. 2009;10(4):400-5.
24. Devine DJ, Rostas JW, Metge BJ, Das S, Mulekar MS, Tucker JA, et al. Loss of N-Myc interactor promotes epithelial–mesenchymal transition by activation of TGF-β/SMAD signaling. Oncogene. 2014;33(20):2620.
25. Rostas JW, Pruitt HC, Metge BJ, Mitra A, Bailey SK, Bae S, et al. microRNA-29 negatively regulates EMT regulator N-myc interactor in breast cancer. Molecular cancer. 2014;13(1):200.
26. Kim JW, Mori S, Nevins JR. Myc-induced microRNAs integrate Myc-mediated cell proliferation and cell fate. Cancer research. 2010:0008-5472.
27. Boggs RM, Wright ZM, Stickney MJ, Porter WW, Murphy KE. MicroRNA expression in canine mammary cancer. Mammalian Genome. 2008;19(7-8):561-9.
28. Iorio MV, Ferracin M, Liu CG, Veronese A, Spizzo R, Sabbioni S, et al. MicroRNA gene expression deregulation in human breast cancer. Cancer research. 2005;65(16):7065-70.
29. Mattie MD, Benz CC, Bowers J, Sensinger K, Wong L, Scott GK, et al. Optimized high-throughput microRNA expression profiling provides novel biomarker assessment of clinical prostate and breast cancer biopsies. Molecular cancer. 2006;5(1):24.
30. Santanam U, Zanesi N, Efanov A, Costinean S, Palamarchuk A, Hagan JP, et al. Chronic lymphocytic leukemia modeled in mouse by targeted miR-29 expression. Proceedings of the National Academy of Sciences. 2010;107(27):12210-5.
31. Chen GQ, Zhao ZW, Zhou HY, Liu YJ, Yang HJ. Systematic analysis of microRNA involved in resistance of the MCF-7 human breast cancer cell to doxorubicin. Medical oncology. 2010;27(2):406-15.
32. Bao J, Zervos AS. Isolation and characterization of Nmi, a novel partner of Myc proteins. Oncogene. 1996;12(10):2171-6.
33. Bannasch D, Weis I, Schwab M. Nmi protein interacts with regions that differ between MycN and Myc and is localized in the cytoplasm of neuroblastoma cells in contrast to nuclear MycN. Oncogene. 1999;18(48):6810.
34. Zhu MH, John S, Berg M, Leonard WJ. Functional association of Nmi with Stat5 and Stat1 in IL-2-and IFN γ-mediated signaling. Cell. 1999;96(1):121-30.
35. Li H, Lee TH, Avraham H. A novel tricomplex of BRCA1, Nmi, and c-Myc inhibits c-Myc-induced human telomerase reverse transcriptase gene (hTERT) promoter activity in breast cancer. Journal of Biological Chemistry. 2002;277(23):20965-73.
36. Schlierf B, Lang S, Kosian T, Werner T, Wegner M. The high-mobility group transcription factor Sox10 interacts with the N-myc-interacting protein Nmi. Journal of molecular biology. 2005 Nov 11;353(5):1033-42.
37. Zhang K, Zheng G, Yang YC. Stability of Nmi protein is controlled by its association with Tip60. Molecular and cellular biochemistry. 2007;303(1-2):1-8.
38. Devine DJ, Rostas JW, Metge BJ, Das S, Mulekar MS, Tucker JA, et al. Loss of N-Myc interactor promotes epithelial–mesenchymal transition by activation of TGF-β/SMAD signaling. Oncogene. 2014;33(20):2620.
39. Fillmore RA, Mitra A, Xi Y, Ju J, Scammell J, Shevde LA, et al. Nmi (N-Myc interactor) inhibits Wnt/β-catenin signaling and retards tumor growth. International journal of cancer. 2009;125(3):556-64.
40. Schmitt MJ, Margue C, Behrmann I, Kreis S. MiRNA-29: a microRNA family with tumor-suppressing and immune-modulating properties. Current molecular medicine. 2013;13(4):572-85.
41. Qi H, Liu Y, Li S, Chen Y, Li L, Cao Y, et al. Activation of AMPK attenuated cardiac fibrosis by inhibiting CDK2 via p21/p27 and miR-29 family

pathways in rats. Molecular Therapy-Nucleic Acids. 2017;8:277-90.
42. Bauersachs J, Thum T. Biogenesis and regulation of cardiovascular microRNAs. Circulation Research. 2011;109(3):334-47.
43. Morita S, Horii T, Kimura M, Ochiya T, Tajima S, Hatada I. miR-29 represses the activities of DNA methyltransferases and DNA demethylases. International jomurnal of molecular sciences. 2013;14(7):14647-58.
44. Gråstén A. Children's expectancy beliefs and subjective task values through two years of school-based program and associated links to physical education enjoyment and physical activity. Journal of Sport and Health Science. 2016;5(4):500-8.
45. Murach KA, Walton RG, Fry CS, Michaelis SL, Groshong JS, Finlin BS, et al. Cycle training modulates satellite cell and transcriptional responses to a bout of resistance exercise. Physiological reports. 2016;4(18).
46. Scherr J, Braun S, Schuster T, Hartmann C, Moehlenkamp S, Wolfarth B, et al. 72-h kinetics of high-sensitive troponin T and inflammatory markers after marathon. Medicine and science in sports and exercise. 2011;43(10):1819-27.
47. Rostas JW, Pruitt HC, Metge BJ, Mitra A, Bailey SK, Bae S, et al. microRNA-29 negatively regulates EMT regulator N-myc interactor in breast cancer. Molecular cancer. 2014;13(1):200.
48. Li L, Sarver AL, Alamgir S, Subramanian S. Downregulation of microRNAs miR-1,-206 and-29 stabilizes PAX3 and CCND2 expression in rhabdomyosarcoma. Laboratory investigation. 2012:571.
49. Fernandes T, Soci UP, Oliveira EM. Eccentric and concentric cardiac hypertrophy induced by exercise training: microRNAs and molecular determinants. Brazilian Journal of Medical and Biological Research. 2011;44(9):836-47.
50. Ma Z, Qi J, Meng S, Wen B, Zhang J. Swimming exercise training-induced left ventricular hypertrophy involves microRNAs and synergistic regulation of the PI3K/AKT/mTOR signaling pathway. European journal of applied physiology. 2013;113(10):2473-86.
51. Liu X, Xiao J, Zhu H, Wei X, Platt C, Damilano F, et al. miR-222 is necessary for exercise-induced cardiac growth and protects against pathological cardiac remodeling. Cell metabolism. 2015;21(4):584-95.
52. de Gonzalo-Calvo D, Dávalos A, Fernández-Sanjurjo M, Amado-Rodríguez L, Díaz-Coto S, Tomás-Zapico C, et al. Circulating microRNAs as emerging cardiac biomarkers responsive to acute exercise. International journal of cardiology. 2018;264:130-6.
53. Xiao L, He H, Ma L, Da M, Cheng S, Duan Y, et al. Effects of mir-29a and mir-101a expression on myocardial interstitial collagen generation after aerobic exercise in myocardial-infarcted rats. Archives of medical research. 2017;48(1):27-34.
54. Soci UP, Fernandes T, Hashimoto NY, Mota GF, Amadeu MA, Rosa KT, Irigoyen MC, Phillips MI, Oliveira EM. MicroRNAs 29 are involved in the improvement of ventricular compliance promoted by aerobic exercise training in rats. Physiological genomics. 2011;43(11):665-73.
55. Russell AP, Lamon S, Boon H, Wada S, Güller I, Brown EL, et al. Regulation of miRNAs in human skeletal muscle following acute endurance exercise and short-term endurance training. The Journal of physiology. 2013;591(18):4637-53.
56. Wang H, Zhao Z, Lin M, Groban L. Activation of GPR30 inhibits cardiac fibroblast proliferation. Molecular and cellular biochemistry. 2015;405(1-2):135-48.
57. Silveira AC, Fernandes T, Soci ÚP, Gomes JL, Barretti DL, Mota GG, et al. Exercise training restores cardiac MicroRNA-1 and MicroRNA-29c to nonpathological levels in obese rats. Oxidative medicine and cellular longevity. 2017;2017.
58. Katare R, Caporali A, Zentilin L, Avolio E, Sala-Newby G, Oikawa A, Cesselli D, Beltrami AP, Giacca M, Emanueli C, Madeddu P. Intravenous gene therapy with PIM-1 via a cardiotropic viral vector halts the progression of diabetic cardiomyopathy through promotion of prosurvival signaling. Circulation research. 2011:CIRCRESAHA-110.
59. Xiao J, Luo X, Lin H, Zhang Y, Lu Y, Wang N, et al. MicroRNA miR-133 represses HERG K+ channel expression contributing to QT prolongation in diabetic hearts. Journal of Biological Chemistry. 2007;282(17):12363-7.
60. Duisters RF, Tijsen AJ, Schroen B, Leenders JJ, Lentink V, van der Made I, et al. miR-133 and miR-30 regulate connective tissue growth factor: implications for a role of microRNAs in myocardial matrix remodeling. Circulation research. 2009;104(2):170-8.
61. Jordan SD, Krüger M, Willmes DM, Redemann N, Wunderlich FT, Brönneke HS, et al. Obesity-induced overexpression of miRNA-143 inhibits insulin-stimulated AKT activation and impairs glucose metabolism. Nature cell biology. 2011;13(4):434.
62. Zhou B, Li C, Qi W, Zhang Y, Zhang F, Wu JX, et al. Downregulation of miR-181a upregulates sirtuin-1 (SIRT1) and improves hepatic insulin sensitivity. Diabetologia. 2012;55(7):2032-43.
63. Trajkovski M, Hausser J, Soutschek J, Bhat B, Akin A, Zavolan M, et al. MicroRNAs 103 and 107 regulate insulin sensitivity. Nature. 2011;474(7353):649.
64. DA JS, Fernandes T, Soci UP, Monteiro AW, Phillips MI, DE EO. Swimming training in rats

increases cardiac MicroRNA-126 expression and angiogenesis. Medicine and science in sports and exercise. 2012;44(8):1453-62.
65. Eulalio A, Mano M, Dal Ferro M, Zentilin L, Sinagra G, Zacchigna S, et al. Functional screening identifies miRNAs inducing cardiac regeneration. Nature. 2012;492(7429):376.
66. Liu G, Friggeri A, Yang Y, Milosevic J, Ding Q, Thannickal VJ, et al. miR-21 mediates fibrogenic activation of pulmonary fibroblasts and lung fibrosis. Journal of Experimental Medicine. 2010;207(8):1589-97.
67. Brown BD, Naldini L. Exploiting and antagonizing microRNA regulation for therapeutic and experimental applications. Nature Reviews Genetics. 2009;10(8):578.