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

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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),

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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).

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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

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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

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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.

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