The potential implications of exercise-induced epigenetic modifications

Potencijalne implikacije epigenetskih modifikacija uzrokovanih vežbanjem

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Introduction

Genetics provides a versatile approach and highlights the mechanisms responsible for the successful sports phenotype. Despite the stability of the genome, the environment has a potential to act as a trigger for chemical changes that activate, or silence genes and so affect the phenotype. These changes could be reflected in the health beneficial epigenetic modifications that may leave a significant and permanent mark on the epigenetic profile of the individual. That means the epigenome in the adaptive response of the environmental sensitivity can adjust the metabolism and homeostasis. In contrast to some other environmental influences, exercise generates positive epigenetic changes that may be a contributing factor to improving health and better quality of life. Identification of the genetic background and the genetic determinants of variability in response to exercise is always a complex matter and sometimes exceeds the limits of known candidates genes and their gene expression. However, the individual molecular pathways information in the field of sports performance is still of paramount importance and it is one of the surest indicators of the direction and the framework needs to go. Sports scientists sometimes refer to the genetic basis of physical performance as a „biological counterpart to the holy grail“, arguing that a genetic composition is responsible for a large number of individual variations in the physical performance. But, it is quite clear that this molecular information acts dynamically in relation to the environment and these epigenetic shifts in response to the exercise are worthwhile because they can be used in some trials to improve health. So, the main goal is to translate the obtained changes in the desired metabolic response and to put that initial molecular signature to practical use.

Epigenetic mechanisms: interface between gene expression and environmental cues

In recent times, environmental factors are increasingly marked as important in determining the final phenotype. In this context, regular physical activity is recognized as available and convenient component that has epigenetic capacity with many positive implications on health. The unique plasticity of skeletal muscle and the specificity of its response to homeostatic perturbation enable the integration of a set of changes within the physiological stimuli in the phenotypic response. Improving the sports performance through training is achieved as a result of the transition of gene expression to generate changes in the composition and function of skeletal muscle as well as in other tissues. These epigenetic changes are not determined by the genetic code and occur in the DNA or chromatin’s structure and may affect the transcription of certain genes regardless of their primary sequence. The enhanced levels of gene transcripts can, in this manner, affect the synthesis and degradation of protein components by directly altering their normal function through changing the availability of substrate, or through an indirect mechanism.

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that conduct the altered expression of growth factors, receptors and to the altered activity at gene promoters resulting in the long-term functional and structural remodeling 3, 4. The most common epigenetic changes induced by exercise are the histone modifications, like methylation and acetylation, DNA methylation and expression of different types of miRNAs (miRNAs) 5.

What type of epigenetic mechanisms will prevail in the metabolic processes of muscle cells depends on the type, intensity, duration and frequency of exercise stimulus. The most common changes occur within the mitochondrial biogenesis and bioenergetics through different metabolic pathways of muscle fibers. As a consistent feature in many studies, the acute or long-term exercise impacts DNA methylation in a gene-specific mode. It has been reported that exercise increases the expression of many messenger RNA (mRNA) and the protein levels of genes that regulate mitochondrial function, including peroxisome proliferator-activated receptor-gamma coactivator 1-alpha (PGC-1α), mitochondrial transcription factor A (TFAM), peroxisome proliferator-activated receptor δ (PPAR-δ), pyruvate dehydrogenase kinase isoenzyme 4 (PDK4), etc. 6, 7. Using the human isolated contracting muscle and cultured myotubes, Barres et al. 8 demonstrated that the acute exercise changes the histone modifications, like methylation and acetylation, and found that ubiquitin-mediated proteosomal degradation of HDACs in the adaptive response to exercise, pointing out that this proteosomal degradation could take part in the adaptive response to the repeated exercise bouts.

Another epigenetic event that regulates gene expression is the histone post-translational modifications (PTMs). The histone modifications include a number of various posttranslational modifications to the lysine rich tails regions of histones, in particular H3 and H4 11, 12. The modifications like phosphorylation, ubiquitination, methylation and acetylation, and their effects on transcription are different. It is known that subfamily of histone deacetylases (HDACs) has an essential role in skeletal muscle physiology and regulates genes that comprise PGC-α, carnitinepalmitoyl transferase 1 (CPT-1), medium chain acyl-CoA dehydrogenase (MCAD), hexokinase II (HKII), glycogen phosphorylase, and ATP synthase β 13.

It is still not entirely clear about ubiquitination as a potential modification that may be part of the exercise adaptation. Pothoff et al. 14 studied this issue using an animal model and found that ubiquitin-mediated proteosomal degradation of HDACs in the adaptive response to exercise, pointing out that this proteosomal degradation could take part in the adaptive response to the repeated exercise bouts.

MiRNAs are a group of short (20–24 nucleotide) endogenous posttranscriptional regulators that are capable of blocking the translation of protein-coding genes 15, 16. They become more relevant in the regulation of cell- and tissue-specific gene expression including a role as potential biomarkers for the physiological and pathological conditions. Packed in the exosome vesicles, miRNAs are released to the circulation by nearly all cell types, including the skeletal muscles. The relevant literature data show that the most-studied miRNAs are miR-133a/b, miR-206, and miR-1, which are induced during differentiation of myoblasts into myotubes and are collectively referred to as the “myomiRs” 17. More recent studies of Nielsen et al. 18 determined that the endurance exercise and resistance training induce changes in the ci-miRNA human plasma signature. The studies showed that these changes were dynamic during the short period in the acute exercises and during the long periods of strenuous exercise. Another study of Davidsen et al. 19 reports that resistance exercise training leading to hypertrophy of human skeletal muscle is associated with selected changes in miRNA abundance. Their results indicate that miRNAs can play a major role in the phenotypic changes and noticeable intergroup diversity in a response to resistance training.

In addition, there are posttranscriptional changes in the metabolism of carbohydrates and fatty acids that occur immediately after a single bout of exercise as mitochondrial biogenesis which subsequently increases the requirements of oxygen utilization resulting in a drop in intracellular oxygen. Under these conditions of hypoxia, hypoxia-inducible factor 1 (HIF-1) a member of the HIF family of transcriptional activators which are essential for maintaining O2 homeostasis, switches on the transcription of genes encoding glucose transporters and glycolytic enzymes, acting together with PGC-1α and initiate the mechanism of gene expression that facilitates increased oxygen supply. This complex triggers the transcription of numerous hypoxia-responsive genes of metabolic processes that would be favorable in conditions of reduced oxygen 20. HIF1α regulates the gene expression through hypoxia response elements (HRE) present in the promoter regions of target genes. This binding can be affected through the DNA methylation and histone modification, which may maintain a favorable chromatin conformation around the HRE sites. In the presence of oxygen, HIF1α is regulated through hydroxylation, ubiquitination, and degradation by prolyl hydroxylase enzymes (PHD) 21. In the absence of oxygen, this is inhibited which allows for the HIF1α stabilization and activation. For these reasons, HIF can be considered not only an important oxygen sensor, but also an essential regulator of adaptation induced by exercise 22.

Epigenetic stability

Discussing all these exercise-induced epigenetic modifications, the logical question is how much these changes are stable, and what the factors that determine framework of epigenetic stability are. Many have attempted to investigate the stability and inter-individual variation in DNA methylation comparing changes in DNA methylation profiles during a

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short-time to longer periods and concluded that some methylation marks showed considerable variation over time, while others are highly stable. In general, these processes are partly reversible, so that, for example, the histone modifications are in a continual state of change, whereas DNA methylation is considered more stable and long-term. However, the variations of methylation levels have a diverse range and are greatly affected by the gene structures and its genomic location. The epigenetic stability is defined as the persistence of modifications in the gene expression and/or epigenetic marks that influence the gene expression and such stability can exist at different temporal scales. It remains unclear whether the adaptive value of stable and unstable, or transient epigenetic changes may cause the long-term changes in phenotype. On the other hand, it is clear that the nature of the environmental impact that generate the epigenetic change is the most critical factor for the epigenetic stability. In support, recent advances in molecular biology have reported that epigenetic alterations induced by the environmental stressors, can create a persistent memory of the received signal called epigenetic memory. Interestingly, it is proposed that each of that stressors can promote specific alterations to the normal form of DNA methylation-epigenetic footprint, and further cause changes to the gene expression. Sharples et al., in attempt to explain the molecular and epigenetic mechanisms of skeletal muscle memory in humans, introduced the term “epi-memory”, studying the human skeletal muscle cells isolated from the different population by generation. They showed that muscle cells had a morphological memory and can retain molecular information of the acute early lifespan in different signaling proteins and that cells possess the ability of retaining elevated methylation for at least thirty cellular divisions. They further compared this type of muscle memory with the motor learning in which learning the motor skills incorporates specific templates of movement through repetition. This implies that their understanding, confirmation and refinement of epigenetic modifications can help in future with targeted therapies, for example, in repairing muscle growth and reducing the loss of muscle mass in the aging process.

The role of epigenetic changes in response to exercise and metabolic disorders

Although the research on molecular genetics of physical exercise and health-related outcomes is still in its infancy, we need to look at the bigger picture, to link all the known and valuable facts as well as to reinforce them in healthcare practice. Exercise is one of those external factors that can modify the expression of genes and that a cascade of epigenetic changes in different tissues can preserve and improve health. So, these epigenetic mechanisms can be used for the purpose of targeted benefits of exercise and can be incorporated in the exercise prescription.

There is no doubt that the physical activity and exercise play a pivotal role in the prevention and treatment of many metabolic disorders. Large part of individual differences in the weight loss response is attributable to genetic and epigenetic factors. Recent studies about the regulation of the epigenome in human adipose tissue show a general increase in the adipose tissue of DNA methylation in response to six months of moderate exercise consisting of spinning and aerobics. Two genes, HDAC4, a histone deacetylase and NCO2, a nuclear co-repressor, displayed the increased levels of DNA methylation and synchronous decrease in the mRNA expression in the adipose tissue in response to the exercise intervention as well as to increased lipogenesis. Also, this study establish the connection between the differential DNA methylation and mRNA expression in response to exercise, thereby they confirmed the relationship between methylation and altered metabolism through the gene expression. These results may be of clinical significance and the HDAC inhibitors perhaps can be applied in the treatment of obesity and T2D. Similarly, Wang et al. examined DNA methylation of peripheral blood leukocytes between obese adolescent and lean controls and identified two CpG sites in the UBASH3A gene and TRIM3 gene with roles in the immune function that were differentially methylated and that methylation changes may be associated with the pathogenesis of obesity.

Existing data strongly indicate that there is a link between the obesity, energy metabolism and epigenetic modifications and support the fact that the exercises induce the expression of a number of genes that regulate glucose uptake in the skeletal muscle, including GLUT isoform 4 (GLUT4), whose increased expression is further regulated by the transcription factor MEF2 (myocyte enhancer factor 2) and with coactivator protein PPARGC1A. In addition, an increase in the PGC1 expression generated by exercise is an important element for improving the insulin sensitivity in the skeletal muscle not only by increasing the glucose transporter expression (GLUT4) but also by increasing the mitochondria density and it is considered that exercises attenuate the epigenetic modifications at PGC1 and can lead to inhibition, or delay of type 2 diabetes onset.

Attempting to identify the epigenetic patterns which may predispose to type 2 diabetes (T2D), Nitert et al. demonstrated that exercises lasting for 6 months and consisting of endurance exercise of moderate intensity, in the people with type 2 diabetes (T2D), were associated with the epigenetic changes, citing the example of decreased DNA methylation of two key transcription factors involved in the glucose uptake in the muscle and respiratory metabolism (RUNX1 and MEF2A). They further reported on differential DNA methylation of mitogen-activated protein kinase (MAPK), insulin and calcium signaling genes concluding as possible that the exercise-induced epigenetic modifications reduce the future risk of T2D among the men with the positive family history (FH+).

Other impacts of exercise-induced epigenetic modifications

The impact of exercise-induced epigenetic modifications appears to have multiple influences within all cells in organism. Accordingly, one of the exercise intensity benefits for the positive epigenetic changes in terms of mitochondrial...
biogenesis was shown by Edgett et al. 33, who concluded that  
the intensity-dependent increases in PGC-1α mRNA follow-  
ing submaximal exercise are mainly due to the increases in  
muscle induction. Furthermore, the blunt response of  
PGC-1α mRNA expression following the supramaximal ex-  
ercise may imply that signaling mediated activation of PGC-  
1α may also be blunted. According to the extensive interven- 
tional studies of Voisin et al. 34, the genes whose methylation  
levels change significantly after exercise in humans includ-  
the genes involved in particular cellular metabolic states (in- 
cluding PGC-1α, GLUD1, PKD-4, PPPAR-d, TFAM, ADIPO-  
R1, ADIPOR2 and BDKRB2), muscle growth (MEF2α),  
hematopoiesis is (RUNX1) and inflammation (ASC).  
Various studies have implied that epigenetic mecha- 
nisms also play a role in the definition of the onset of age-  
associated diseases and lifespan potential. Lopez-Otin et al.  
35 postulated some hallmarks of aging like genomic insta- 
ibility, telomere attrition, epigenetic alterations, etc., and sug- 
gested that exercise can influence, at least partly, most of  
these hallmarks. The relationship between the epigenetics  
regulation and aging is complex and controversial, depend- 
ning on the process hypo- or hypermethylation, on the type of  
cells, enzymes, but it seems that exercise can promote the  
protective effects and help to attenuate that age-  
deregulations 36, 37. Genomic imprinting is a unique epige- 
etic phenomenon that summarizes connection of inheritance  
with the environment and signifies the “genotype-  
dependent parent-of-origin” gene expression. The effect of  
parental origin refers to the genomic imprint, and methyla- 
tion is considered the main mechanism by which the expres- 
sion is modified. Such an expression of different alleles  
(mother or father) may take place in all cells and tissues, and  
it is believed that about 1% of the human genome is im- 
printed. These genes are of major importance in the medical  
context, regardless of their low percentage. In order to de- 
termine the impact of imprinted genes in human skeletal  
muscle, Brown 38 identified these genes and changes in DNA  
methylation associated with exercise. An important conclu- 
sion of this recent bioinformatics meta-analysis is that the  
modification of DNA methylation induced by exercise can  
slow down the aging process, but also to mitigate the occur- 
rence of certain health disorders.  
It is a well-established fact that the exercises, due to the  
increased metabolic demand, are associated with the in- 
creased formation of reactive oxygen species (ROS), but  
regular exercise reduces the prevalence of a wide range of  
ROS-associated diseases. Furthermore, the effects of exer- 
cise attend to be beneficial for the brain function and include  
the processes of neurogenesis via neurotrophic factors, in- 
creased capillarization, decreased oxidative damage and in- 
creased proteolytic degradation. It is known that the oxida- 
tive modification of DNA could lead to the increased apop- 
tosis and that impaired function could be the major factors  
related to the brain aging and neurodegenerative diseases 39.  
Moreover, the exercise-induced changes increase the resis- 
tance against oxidative stress, facilitates recovery from ox- 
idative stress, and attenuates age-associated decline in cogni- 
tion. In addition, some recent studies suggest a notable role  
of exercise on brain plasticity and cognitive health through  
the epigenetic modifications mostly by the action of brain-  
derived neurotrophic factor (BDNF) highly expressed in hip- 
pocampus 40.  

There is no strong evidence to provide a direct connec- 
tion between the epigenetic modulation and changes in  
cardiovascular system induced by exercise, but recent data show  
that moderate exercise mitigate the age-dependent decrease  
in apoptosis associated protein (ASC) methylation, indicat- 
ing suppression of redundancy pro-inflammatory cytokines  
through just reduction of ASC expression 41. These epige- 
etic modifications just ensure proper function at the cellular  
level, due to the balance between the inflammatory response  
and anti-inflammatory genes, so any disruption of these epi- 
genetic mechanisms could lead to the development of ather- 
sclerosis and stenosis 42. Keeping in mind the fact that physi- 
cal activity can prevent many pathological epigenetic events,  
for example, through the increased expression of endothelial  
growth factor like (VEGF), as well as through the reduction  
of the many risk factors such as oxidative stress which are  
held responsible for cardiovascular disorders, many authors  
point out the role of exercise as a strong regulator of positive  
epigenetic modification 43–45. Many of these key regulators  
of epigenetic mechanisms are associated with the modifications  
of DNA and histones in endothelial cells, suggesting a direct  
protective role of physical exercise on endothelial function.  
It is believed that the role of free radicals in the modulation  
of extracellular matrix which is regulated by epigenetic  
mechanisms is very important and that they participate in the  
development of many pathophysiological processes. In this  
regard, the exercises improve the antioxidant capacity and  
maintains cellular oxidative balance, molecular structure and  
arichitecture of the extracellular matrix through the mediating  
signaling cascades. Precisely in this way, the epigenetic  
modification induced by exercises is a significant factor in the  
modification of the functional genome and heart and vascular  
beds 46. Baccarelli et al. 47 in an experimental work with ani- 
mals and humans argued that DNA methylation appears as  
a primary regulator of inflammation and atherosclerotic  
changes in peripheral blood leukocytes, and it is connected to  
several cardiovascular-related biomarkers that include ho- 
mozeste and C-reactive protein. In addition, referring to the  
epigenetics and the cardiovascular relation, miRNAs con- 
tribute to the process of myocardium remodeling through the  
different signaling pathways in condition of hypertrophy and  
neo-angiogenesis – “the athlete’s heart”, and thus protect the  
heart from fibrosis and pathological hypertrophy 48. How- 
ever, although a lot of factors are known and confirmed, fur- 
ther detailed investigations are required to explore other  
positive effects of epigenetic modulation induced by exercis- 
ing and to incorporate them into the improved prevention,  
risk assessment, risk stratification and treatment of cardio- 
vascular disorders.  

Finally, the most recent tightly controlled and extensive  
human study showed that 3 months of endurance training in  
the healthy human volunteers caused the substantial DNA  
methylation changes at about 5,000 sites across the genome  
and powerful gene expression 49. This study indicates that the
numerous changes in methylation were not a random and co-
incidental effect but more a well-controlled adaptive process
generated as a response to endurance exercises. Thus, the in-
creased methylation seemed to be related to remodeling of the
tissue and metabolism, while decreased methylation was related
to inflammation, and this can explain the benefits of exercise.
DNA methylation was predominantly changed in the enhancer
regions (short regions of DNA which activate gene transcription
from a distance) with structural improvement for binding of
myogenic regulatory factors (MRFs), myocyte enhancer factors
(MEFs) and ETS proteins, so it can be assumed that the training-
induced integrated epigenetic adjustment contributes to the het-
erogeneity in individual responses.

All of these data in the literature point out the existence of
particular regions in the genome that are sensitive to the
epigenetic modifications in response to exercise and there are
differences depending on the type, duration and intensity of
exercise. Future studies should investigate the stability of
those exercise-induced DNA methylation changes and the
possible effects of epigenetic alterations in different periods
of training, as well as the exercise program that includes dif-
ferent types of speed and effort.

Conclusions and future perspectives

By understanding the epigenetic changes which are im-
portant for responses of various phenotypes, it is logical to
expect that these valuable facts as part of important biologi-
cal adaptation can be used to improve the health of individu-
als. Epigenetics provide a scientific basis for how the train-
ing intervention and other external factors can reshape the
individual and provide the insight into the way the changes
in gene expression through a complex network of coordi-
nated pathways may affect the phenotype. Key epigenetic
elements are responsible for regulating adiposity, numerous
molecular pathways related to the inflammatory processes,
energy expenditure, and glucose homeostasis, so that the
molecular events within their physiological processes are
very powerful tool. It is conceivable that these observations
and health benefits about the epigenetic modification within
the different cells and tissues in response to exercise as read-
ily available and efficient form of behavior intervention,
could be combined for the valuable clinical information and
used in practice for health improvement in the future.

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